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Maternal mental health and memory (re)consolidation following a traumatic childbirth

Deforges Camille

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Institut universitaire de formation et de recherche en soins (Université de Lausanne) en collaboration avec le Département femme-mère-enfant (Centre hospitalier Universitaire Vaudois)

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Thèse de doctorat ès sciences de la vie (PhD)

présentée à la

Faculté de biologie et de médecine
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par

Camille DEFORGES

Psychologue diplômée de l'Université de Rennes 2

Jury

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Thesis abstract

Objectives: The overall aim of this thesis was to contribute to the development of clinical interventions to prevent or reduce maternal symptoms of childbirth-related post-traumatic stress disorder (CB-PTSD). To do so, it relied on the literature on memory (re)consolidation, which corresponds to a set of processes potentially involved in the development and maintenance of CB-PTSD. The ambition of this thesis was to translate the research on memory (re)consolidation, mainly based on laboratory studies, into applied clinical proposals. Several avenues were explored: **1.** Identifying factors that may modulate the consolidation of the traumatic birth memory (TBM) such as prenatal insomnia symptoms (Study 1), administration of nitrous oxide gas (N_2O) or morphine during childbirth (Study 2), and CB-PTSD symptoms; and **2.** Testing the effectiveness of brief visuospatial task-based interventions, which are assumed to interfere with the (re)consolidation of the TBM, in preventing (Study 3) or reducing (Study 4) CB-PTSD symptoms. **Methods:** Studies 1 (n = 1,610) and 2 (n = 2,070) were based on a prospective population-based cohort study (secondary data analyses), following women from pregnancy to eight weeks postpartum. Variables were measured via self-report questionnaires and patients' medical records. CB-PTSD was assessed at eight weeks postpartum. Study 3 (n = 144) is an ongoing multicentre, double-blind, randomised controlled trial (thus, results are not available yet). The intervention tested is delivered within six hours postpartum, and its effectiveness is primarily measured by a childbirth-related intrusive traumatic memories (ITMs) diary over the first week postpartum and an assessment of CB-PTSD symptoms at six weeks postpartum. Finally, Study 4 (n = 18) was a single-group pre-post study. The benefits of the intervention were measured with an ITMs diary over two weeks before and six weeks after the intervention, and CB-PTSD symptoms were measured with a self-report questionnaire, five days before and one month after the intervention. **Results:** In Study 1, prenatal insomnia symptoms were associated with CB-PTSD symptom severity, and this relationship was fully mediated by a negative subjective birth experience, as well as by postnatal insomnia symptoms. In Study 2, N_2O administration during childbirth predicted less severe CB-PTSD symptoms. This was marginally the case with morphine. However, both analgesics predicted more CB-PTSD symptoms when combined with very severe pain during childbirth. Finally, participants in Study 4 reported a large reduction in their number of ITMs, and it persisted for up to six weeks post-intervention. Their CB-PTSD symptoms were also greatly reduced. **Clinical implications:** The results of this thesis suggest a number of avenues for preventing or reducing CB-PTSD symptoms through brief, simple, cost-effective, and innovative interventions. These could potentially be implemented throughout the perinatal period and notably pave the way for pharmacological (Study 2) or psychological (Studies 1 and 3) strategies for CB-PTSD *prevention*, for which there is currently no evidence-based intervention.

Résumé de la thèse

Objectifs : Cette thèse visait à contribuer au développement d'interventions cliniques pour prévenir ou traiter les symptômes maternels du trouble de stress post-traumatique lié à l'accouchement (TSPT-A). Elle s'est appuyée sur les travaux sur la (re)consolidation de la mémoire, qui correspondent à un ensemble de processus suspectés d'être impliqués dans le développement et maintien du TSPT-A. Les deux axes de recherche étaient : **1.** Investiguer la relation entre des facteurs pouvant affecter la consolidation du souvenir de l'accouchement traumatique (SAT), tels que les symptômes d'insomnie prénatale (Étude 1), l'administration de protoxyde d'azote ou de morphine pendant l'accouchement (Étude 2), et les symptômes de TSPT-A ; et **2.** Tester l'efficacité de brèves interventions basées sur une tâche visuospatiale et interférant avec la (re)consolidation du SAT pour prévenir (Étude 3) ou traiter (Étude 4) les symptômes de TSPT-A. **Méthodes :** Les Études 1 (n = 1,610) et 2 (n = 2,070) étaient basées sur une étude de cohorte prospective suivant des femmes depuis la grossesse jusqu'à huit semaines postpartum. Les variables étaient mesurées par des questionnaires auto-reportés et les dossiers médicaux des participantes. Le TSPT-A était évalué à huit semaines postpartum. L'Étude 3 (n = 144) est un essai randomisé contrôlé multicentrique et en double-aveugle, en cours (résultat non disponibles). L'intervention testée est réalisée dans les six heures suivant l'accouchement, son efficacité est mesurée par un journal des souvenirs traumatiques intrusifs (STIs) liés à l'accouchement durant la première semaine postpartum, et une évaluation du TSPT-A à six semaines postpartum. Enfin, l'Étude 4 (n = 18) était une étude avant-après avec groupe unique. Les bénéfices de l'intervention étaient mesurés avec un journal des STIs durant deux semaines avant puis six semaines après l'intervention, et les symptômes de TSPT-A étaient mesurés cinq jours avant puis un mois après l'intervention, par questionnaire auto-reporté. **Résultats :** Dans l'Étude 1, les symptômes d'insomnie prénatale prédisaient la sévérité des symptômes de TSPT-A, et cette relation était médiatisée par une expérience subjective de l'accouchement négative, ainsi que par les symptômes d'insomnie postnatale. Quant à l'Étude 2, l'administration péri-partum de N_2O (et, marginalement, de morphine) prédisait des symptômes de TSPT-A moins sévères. Cependant, combinés à une très forte douleur pendant l'accouchement, ces deux analgésiques prédisaient des symptômes de TSPT-A plus sévères. Pour finir, les participantes de l'Étude 4 ont reporté une large et durable réduction du nombre de leurs STIs. Leurs symptômes de TSPT-A étaient tous fortement réduits. **Implications cliniques :** Cette thèse suggère de nombreuses pistes pour prévenir ou traiter les symptômes de TSPT-A, par des interventions globalement brèves, simples, peu coûteuses et innovantes. Ces dernières pourraient être implémentées tout au long de la période périnatale, et ouvrent la voie à des stratégies, pharmacologiques (Étude 2) ou psychologiques (Études 1 et 2), de prévention du TSPT-A - pour laquelle il n'existe pas d'intervention basée sur les preuves.

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List of abbreviations

ABC	Akershus Birth Cohort
ASD	Acute Stress Disorder
BIS	Bergen Insomnia Scale
BLA	BasoLateral Amygdala
CAPS-5	Clinician Administered PTSD Scale for DSM 5
CBI	Consolidation-Based Intervention
CB-IM	ChildBirth-related Intrusive Memory
CBI-VT	Consolidation-Based Intervention involving a Visuospatial Task
CB-PTSD	ChildBirth-related Post-traumatic Stress Disorder
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CONSORT	CONsolidated Standards Of Reporting Trials
CS	Conditioned Stimulus
DSM	Diagnostic and Statistical manual of Mental disorders
ECS	Emergency Caesarean Section
ED	Emergency Department
EFT	Emotion-Focused Therapy
EMDR	Eye Movement Desensitization and Reprocessing
EPDS	Edinburgh Postnatal Depression Scale
FOC	Fear Of Childbirth
IES	Impact of Event Scale
IM	Intrusive Memory (of trauma)
IQR	InterQuartile Range
ITT	Intention-To-Treat
LTP	Long-Term Potentiation
Mdn	Median
MINI	Mini International Neuropsychiatric Interview
N_2O	Nitrous Oxide Gas
NCT	National Clinical Trial number
NICE	National Institute for Health and Care Excellence
PCL-5	PTSD Checklist for DSM-5
PTSD	Post-traumatic Stress Disorder

RBI	Reconsolidation-Based Intervention
RBI-VT	Reconsolidation-Based Intervention involving a Visuospatial Task
RCT	Randomised Controlled Trial
REM	Rapid Eye Movement
RESI	Robust Effect Size Indices
RTM	Reconsolidation of Traumatic Memories
SBE	Subjective Birth Experience
SCL-A	Hopkins symptom CheckList - Anxiety scale
SD	Standard Deviation
SEM	Structural Equation Modelling
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
START	Swiss TrAumatic biRth Trial
TF-CBT	Trauma-Focused Cognitive Behavioural Therapy
TFP	Trauma Film Paradigm
TF-PT	Trauma-Focused Psychological Therapies
UCS	UnConditioned Stimulus
VWM	Visuospatial Working Memory
W-DEQ	Wijma Delivery Expectancy/experience Questionnaire - version A

List of figures and tables

I. Introduction

The perinatal period, although often anticipated with joy, involves an increased vulnerability to mental health problems (1-3) and childbirth, which is generally considered a wonderful and life-changing experience (4), can be highly distressing. As an illustration, 30-45% of women perceive their childbirth as a traumatic event (5-7). For some of them, this experience is the starting point for childbirth-related post-traumatic stress disorder (CB-PTSD) (introduced in Section I.A). To date, however, there is a lack of evidence-based interventions to support these women (Section I.B).

In a call for mental health science, several clinicians and neuroscientists noted that: "*Neuroscience is shedding light on how to modulate emotion and memory, habit and fear learning. But psychological understanding and treatments have, as yet, profited much too little from such developments* (8, p. 288). Hence, they concluded that: *"It is time to use science to advance the psychological* […] *treatment of those with mental-health problems*" (8, p. 288). Echoing these words, this thesis intends to contribute to the development of innovative and scientifically informed interventions (Box 1) to prevent or reduce maternal CB-PTSD symptoms. Preclinical evidence suggests that certain memory processes, like memory (re)consolidation (Sections I.C and I.D), may be a mechanism that could provide the basis for such interventions. Thus, the present work sought to translate these laboratory developments into the clinical context of CB-PTSD, with the primary goal of providing a benefit to women who will experience or have experienced a traumatic childbirth.

Box 1. What type of interventions will this thesis focus on?

In this thesis, the word "intervention" primarily refers to individual psychological interventions carried out by health professionals, which aim to prevent or reduce (CB-)PTSD symptoms. Pharmacological interventions will be marginally discussed because on the one hand, they provide insights into the functioning of psychological interventions and, on the other hand, Study 2 focused on the association between obstetrical analgesia and CB-PTSD symptoms.

A. Childbirth-related post-traumatic stress disorder

1. Definition

Post-traumatic Stress Disorder (PTSD) is a mental health disorder triggered by single or repeated traumatic events. Whether witnessed or directly experienced, these are defined as "*exposure to actual or threatened death, serious injury, or sexual violence*" in the 5th Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (9, p. 271). Since it may involve actual or perceived injury and life threat for the woman or the infant[1], childbirth can be qualified as a traumatic event and, therefore, result in CB-PTSD (10, 11). Importantly, although a majority of women going through a traumatic birth experience do not ultimately develop CB-PTSD (11), a significant proportion of them show distressing CB-PTSD symptoms without fulfilling all the CB-PTSD diagnostic criteria (see prevalence rates in Section I.A.3).

2. Symptoms

According to the DSM-5, PTSD (Box 2) consists of a combination of four symptom clusters, which are caused by the experience of a traumatic event (diagnostic criterion A) and last at least a month (criterion F). Symptoms experienced after three days but before one month post-trauma reflect acute stress disorder (ASD) (9), while those appearing after more than six months reflect delayed-onset PTSD. Importantly, symptoms must cause significant distress or impair women's functioning (criterion G).

1. **« Intrusion »** symptoms (criterion B, one symptom required) include trauma-related intrusive memories (IMs)[2] and recurrent distressing dreams. This symptom cluster also comprises emotional distress or physiological reactivity following exposure to trauma-related reminder cues, as well as dissociative reactions: in CB-PTSD, women may feel or act as if the childbirth is reoccurring. Childbirth-related IMs (CB-IMs) are presented in more detail in Section I.A.6.
2. Persistent **« avoidance »** (criterion C, one symptom required) of trauma-related stimuli can apply to memories, thoughts, feelings, places, people, situations or conversations. In CB-PTSD, avoidance may typically be expressed through the refusal to go to postnatal medical appointments. It may also apply to the infant, whose presence can be a distressing reminder of the birth (13). Crucially, avoidance symptoms can compromise women's ability to seek help.

[1] If childbirth may involve actual death, in this work I will focus on the experience of women who have given birth to a live baby.
[2] Childbirth may also trigger positive involuntary memories (12), but this is not the scope of the present thesis.

3. **« Negative alterations in cognitions and mood »** (criterion D, two symptoms required) comprise domination of negative emotions over positive ones, but also negative beliefs about the world, oneself or others, and trauma-related amnesia – although the latter show low correlations with other symptoms of PTSD (e.g., 14, 15), including in CB-PTSD (16). Women may show a marked decrease in interest in the activities they used to enjoy, or feel detached from others. They can also have distorted cognitions concerning the causes or consequences of the birth, leading to excessive (self-)blame. Overall, these symptoms are close to the depressive spectrum, perhaps accounting for some of the comorbidity of postnatal depression and CB-PTSD (17, 18).
4. Marked « **alterations in arousal and reactivity** » (criterion E; two symptoms required) include hypervigilance (potentially towards the child), difficulties concentrating or falling and staying asleep, irritability, exaggerated startle response and reckless or self-destructive behaviour.

In the presence of additional derealisation and depersonalisation symptoms, PTSD may be classified as dissociative. These dissociative symptoms, as well as mood alterations and concentration difficulties, can limit women's capacity to engage in interventions (19).

Box 2. Note on CB-PTSD and unrelated-to-childbirth PTSD.

Compared to unrelated-to-childbirth PTSD, CB-PTSD has singularities, which led certain authors to suggest that it should be considered as a distinct subtype of PTSD (20). For example, it is triggered by an event that is socially considered as positive, occurring in a unique hormonal context, and involving powerful and lasting bodily sensations (20). Furthermore, some symptoms of PTSD have a different connotation during the perinatal period: irritability or sleep difficulties, for example, are common regardless of the birth experience. As for hypervigilance, it seems to some extent adaptive that it increases when taking care of a newborn (21, 22), which may explain why hyperarousal symptoms are frequent in all mothers, and show poor specificity to identify those who are traumatised (21). On the contrary, intrusion symptoms would be more frequent in mothers with childbirth-related post-traumatic stress than in those with unrelated-to-childbirth post-traumatic stress (23). Another interesting point is that, in CB-PTSD, a recent factor analysis did not find four symptom clusters, as described in the DSM-5, but two: one corresponding to childbirth-related symptoms (e.g., childbirth-related distressing dreams, IMs and avoidance), and one to "general" symptoms (e.g., alterations in arousal and low mood) (16, 24, 25).

However, to date, CB-PTSD is not classified as a distinct PTSD subtype in the DSM-5 (9). Furthermore, CB-PTSD and unrelated-to-childbirth PTSD have many commonalities, sharing some risks factors (17, 23) and treatment responses (1, 26). Thus, childbirth appears to be a highly relevant study model for PTSD research, especially given that it is one of the most standardised real-life traumatic events: the population is relatively homogeneous (women, aged between 15 and 45 years) and, in Western countries, peri- and post-traumatic environments are generally standardised (a care setting). Therefore, while findings on CB-PTSD interventions may not be directly generalisable to all unrelated-to-childbirth PTSD (and vice-versa (27)), there are good reasons to believe that they can enrich research on single-event trauma, and benefit other populations.

3. Prevalence

In community samples, 3-6% of women develop CB-PTSD (28, 29), and this percentage rises to 16-19% in high-risk samples (e.g., in case of premature birth, pregnancy complications or emergency caesarean section (ECS)) (28, 29). With 140 million annual births worldwide (30), CB-PTSD would thus affect around seven million women each year. This number is expected to further increase due to the rise of certain obstetric risk factors, such as advanced maternal age and obesity (31). In addition, a substantial 10-32% of women suffer from clinically significant CB-PTSD symptoms despite not reaching the diagnostic cut-off[3] (18, 32-34). Given that subthreshold PTSD is associated with functional impairment (35), distress and suicidal ideation (36), these women also need to be considered, as they may require professional support (35, 37).

4. Consequences

The most obvious consequence of CB-PTSD is **maternal psychological distress**, which may disrupt everyday functioning and even lead to suicidal thoughts (4, 16). CB-PTSD is also associated with lower **couple relationship satisfaction**, even at two years postpartum (38). Women having experienced a traumatic birth report avoidance of sexual intercourse, tensions within the couple, feeling neglected by their partner, or being too exhausted to support him/her, which may eventually lead to relationship breakdown (39, 40). CB-PTSD also affects the whole **family structure**, as traumatised women may develop secondary tokophobia, i.e., severe fear of childbirth, and may postpone or even abandon the idea of having other children (see (4) for an overview). In **future pregnancies**, these women are at higher risk of pregnancy complications (41) and negative birth outcomes, such a low birth weight (42), and are less likely to **breastfeed** (4, 42).

Maternal PTSD, whether caused by childbirth or not, may also have consequences for the **child**, as it is associated with more hostile and insensitive parenting behaviour, disrupted bonding, and a lower quality of mother-child relationship (43, 44) - although contradictory findings have been reported (43, 45). When specifically elicited by childbirth, maternal PTSD symptoms are associated with delayed child socio-emotional development (e.g., self-

[3] Hence, studies classically distinguish the measurement of CB-PTSD symptom *severity*, which corresponds to a continuous score, from the *diagnosis* of CB-PTSD, which yields a dichotomous variable.

regulation, compliance) and sleep difficulties (4, 42). The **mother-child attachment relationship** has also been found to be more compromised in women with CB-PTSD than in those with unrelated-to-childbirth PTSD (46), which may be due to the fact that, in the former, the child acts as a constant reminder of the traumatic event. In sum, like most perinatal mental health problems, CB-PTSD concerns parents as well as children. As an illustration, in the United Kingdom, perinatal mental health problems (including CB-PTSD) **cost** £8.1 billions per one-year cohort of births, and 72% of this amount is linked to their adverse effects on the child (47). Thus, interventions tackling CB-PTSD symptoms may not only alleviate parental suffering: they could also benefit children by stemming the intergenerational transmission of stress and trauma - i.e., the negative effects of biological changes triggered by parental exposure to a traumatic stressor on the child (48-50).

5. Risk factors

Identifying CB-PTSD risk factors is a necessary step to develop relevant interventions and target women who would benefit most. In 2016, Ayers and colleagues conducted a meta-analysis on CB-PTSD risk factors (17), and included those most strongly associated with CB-PTSD in an adapted version of the diathesis-stress model[4] (Figure 1). In their model:

1. **Vulnerability factors (Prenatal risk factors)** were depression, fear of childbirth (FOC), complication in pregnancy, and history of PTSD or psychological problems (including anxiety).
2. **Risk factors in birth** were negative birth experience, operative birth (caesarean section or assisted vaginal birth involving instruments such as forceps or vacuum), lack of support, and dissociation. Negative birth experience encompassed both the subjective birth experience (SBE), in particular negative emotions and lack of control and agency, and the objective birth experience. SBE was the second most important risk factor for CB-PTSD, thus illustrating that CB-PTSD is not only about objective life threat: childbirths without any apparent complication trigger CB-PTSD while, on the contrary, dramatic medical complications may not necessarily be experienced as traumatic (28).

[4] In the diathesis-stress model, disorders are assumed to result from a combination of prior vulnerabilities (e.g., psychological, environmental or biological factors) and stressful circumstances, such as a distressing birth.

3. **Postnatal factors** were depression and other co-morbid symptoms, stress, and poor coping strategies.

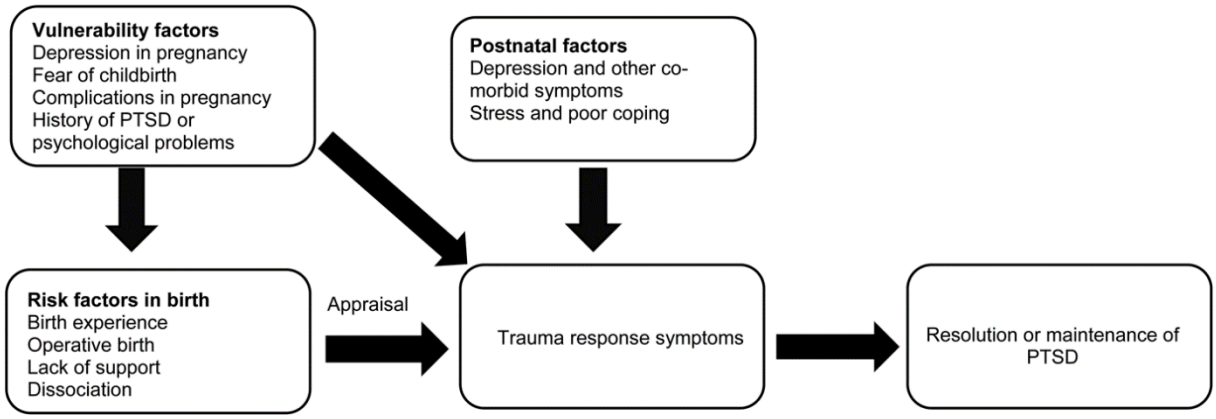

Figure 1. "*Revised diathesis–stress model of the aetiology of birth-related post-traumatic stress disorder (PTSD)*". Figure reprinted with permission from Ayers et al. (2016) (17, p. 1,130).

Beyond Ayers' model, there is consensus in the CB-PTSD literature on the above-mentioned factors (10, 33, 44, 51-54), although others, such as labour pain, have also been identified (17, 33, 54). It should also be noted that most studies on CB-PTSD measure symptoms within the first weeks or months postpartum, but rarely beyond the first year. Yet, the weight of risk factors may potentially vary depending on the considered timeframe (see 11, 55). Overall, while Ayer's model suggests that tackling CB-PTSD is challenging, the multiplicity of at-stake factors is also encouraging, because it indicates the variety of interventions that could be developed.

6. Intrusive memories of trauma

One of the symptoms of PTSD that may be particularly relevant to target in interventions is IMs. Often qualified as a hallmark of trauma-related disorders (e.g., 56, 57), IMs are repeated, involuntary and distressing sensory-perceptual fragments of the trauma memory (9, 58, 59), which can be associated with a strong physiological arousal (e.g., increased heart rate, sudden sweating) (60). They may be so vivid and immersive that the traumatic event seems to be happening again, "here and now" (61, 62). The "nowness" quality of these intrusive images has even been proposed to be pathognomonic for the traumatic stress response[5] (63).

[5] Although involuntary mental images or memories can be observed in other mental health disorders (56), IMs and CB-IMs always refer to trauma-related intrusive memories in this thesis.

Mostly visual (59), IMs can also be sounds, thoughts, tastes, smells, or even bodily sensations. They can be triggered by external or internal stimuli (e.g., seeing a pregnant friend, hearing infant crying, having perineal tear-related pain), or may even pop up without individuals being aware of the trigger. They generally reflect the most distressing moments of the trauma, called "hotspots" (35, 64) (as illustrated in Box 3). A British cross-sectional study found that birth-related hotspots mostly fall into three main categories: 1. Interpersonal difficulties (36.6%), comprising the feeling of being unsupported or put under pressure during birth, 2. Obstetrical difficulties (36%), such as pain, and 3. Infant-related events (separation, health problems) (27.4%) (65).

Box 3. Examples of CB-IMs.

The following [translated] CB-IMs, which were reported by participants in Study 4, illustrate what distressing involuntary memories concretely look like:

1. "*My son is vomiting blood, it's dripping into his ear*".

2. "*Voices of the midwives, word for word: 'It seems like you don't want her to come out'*".

3. *"I feel the blade in my lower abdomen*".

4. "*The baby is lying on me and does not breath, does not move. I shout to the doctors. They take him away, turn on the paediatric alarm. I call* [my son] *by his name to wake him up, I hear the nurses shouting*".

5. "*I am alone with the pain, I am afraid to die*".

IMs can be viewed in the light that recalling a life-threatening event when exposed to a seemingly related cue is adaptive (59). As an illustration, the warning signal hypothesis of Ehlers et al. (2002) (59) proposes that the content of IMs often includes elements that closely precede the traumatic event itself (e.g., the ECS announcement or the face of the anaesthetist entering the delivery room), which would indicate the imminence of danger if they were seen again. Nevertheless, if IMs are accompanied by invasive negative emotions, or if they are triggered by trauma-unrelated cues because of fear overgeneralisation, they can become problematic. Crucially, they could also insidiously contribute to the development and maintenance of other PTSD symptoms (58, 66). For instance, they may reactivate a sense of threat and thus sustain avoidance (cluster C), hypervigilance (cluster E), sadness or anger (cluster D), but also disrupt concentration and sleep (cluster E) (e.g., 67). A recent laboratory study also suggested that, through a regular rehearsal of the trauma memory, IMs may prevent its normative decay (68), which could explain why they appear as a predictor of PTSD (66, 69). For all these reasons, IMs therefore be highly relevant targets for interventions aimed at preventing or tackling CB-PTSD symptoms (63, 70, 71).

7. Theoretical considerations related to trauma memory

IMs are involuntary manifestations of the trauma memory, which integrates elements from both declarative memory, notably episodic memory (i.e., the conscious memory of an experienced event), and non-declarative memory, including reflexes and aversive conditioning (60) (Box 4). Crucially, evidence suggests that it is possible to target the involuntary expression of trauma memories, especially IMs, while preserving voluntary access to it (60). This has been found in multiple laboratory studies based on the trauma film paradigm (75-77) (Box 4).

Box 4. Studying IMs and PTSD symptoms.

Studying PTSD in clinical samples has many practical and ethical limitations. By triggering "PTSD-like" symptoms and enabling PTSD modelling, laboratory paradigms allow crucial advances in the understanding of this disorder.

1. The **fear conditioning paradigm** (72) is extensively used to study associative fear learning, considered as a fundamental mechanism in PTSD (see Section I.C). Participants, whether humans or nonhuman animals, are repeatedly exposed to a neutral stimulus, the conditioned stimulus (CS) (e.g., a tone or a neutral room), paired with an inherently aversive stimulus, the unconditioned stimulus (UCS) (e.g., an electric shock). After several simultaneous presentations of the CS and UCS, participants learn the association between both stimuli. Consequently, the CS becomes aversive in turn and triggers a conditioned fear response, typically measured with freezing or avoidance behaviour in rodents, or skin conductance response or acoustic startle reflex in humans.

2. The **trauma film paradigm (TFP)** (73, 74) is specifically helpful to model IMs. (Human) participants are exposed to a film containing traumatic footage. This trauma film is likely to elicit IMs in the subsequent days, which participants are generally asked to report in a daily diary. An interesting feature of the trauma film is that it contains complex traumatic material. Thus, by asking participants to recall or recognise its content several days later, it is possible to test whether a manipulation aimed at preventing or treating IMs preserved the declarative memory, a crucial requirement for PTSD interventions.

Cognitive models of PTSD provide insight into the trauma memory nature. In Ehlers and Clark's model (2000) (78) (Appendix A), which has been validated in the context of CB-PTSD (79), the appraisal of the traumatic event or its consequences keeps producing a sense of current threat, while the trauma memory is fragmented, uncontextualised and poorly integrated. Furthermore, it is characterised by a precedence of sensory aspects, as illustrated by a recent cross-sectional study on traumatic childbirth narratives (80). Because of these characteristics, the involuntary expression of the trauma memory, i.e., IMs, can be very easily triggered, even by stimuli that are not the same as those encountered during the traumatic event (e.g., intestinal pain reminding of uterine contractions). A compelling hypothesis, which has received empirical support (81, 82) and can also be found in other models (19, 83, 84), is

that IMs would result from the precedence of perceptual or data-driven processing of the traumatic event over conceptual processing, which is involved in reasoning and attribution of a meaning to the event (84). This would typically explain the association between enhanced perceptual priming and recurrent IMs (85, 86).

Another interesting model is the fear network or trauma memory network model of Foa and Rothbaum (1998) (87-89) (Appendix B). This states that, because of a high emotional and physiological arousal during the traumatic event, the trauma memory cannot be processed as an ordinary memory would be (88) - functional magnetic resonance imaging studies have since suggested that neural activity is indeed different when exposed to a scene that will trigger subsequent IMs, compared to a scene that will not (90-93). Instead of being integrated into episodic memory, the trauma memory would be stored in a fear network, in a disorganised and piecemeal form. This network comprises trauma-related sensory information, details about physiological, emotional, behavioural and cognitive responses to the threat, as well as information about the meaning (e.g., "*The fact that I had an ECS means that I am a bad mother*") (19). The storage of all these elements in a compact network, where they are strongly interconnected, would explain why being exposed to a trauma-related cue can reactivate any aspect of the trauma memory. However, as we will see in Section I.D, the strong connections within the fear network may be used in future interventions to target the whole trauma memory.

B. CB-PTSD interventions

As detailed in Section I.A, CB-PTSD affects a significant proportion of women, and has multiple deleterious consequences for them and their families. Thus, interventions preventing or reducing CB-PTSD symptoms are highly needed. As suggested in Ayer's model (17), such interventions can potentially be implemented before, during and after birth. Each of the studies of this thesis focused on one of these time points, making a distinction between the early and late postnatal period - the latter beginning at one month postpartum, when PTSD can be diagnosed. This section gives a brief overview of the available interventions to date, dividing them according to the time point of implementation and the corresponding type of prevention (Box 5). Rather than drawing up an exhaustive inventory of existing interventions, the aim is first and foremost to identify what is still lacking and, consequently, what could be the subject of future interventions.

Box 5. Three types of preventive interventions.

Preventive interventions can be divided into three categories, which correspond to different stages of development of the targeted disorder. According to the American Psychological Association, **primary preventive interventions** aim to "*promote and lay a firm foundation for mental, behavioral, or physical health*" so that the disorder does not develop (94). For CB-PTSD, primary prevention would typically apply to the prenatal period (see Study 1). **Secondary preventive interventions** aim to "*prevent the development of more serious dysfunction or illness*", in individuals with early psychological symptoms (95). They are for instance appropriate for women within the first postpartum days, who report that their childbirth experience was traumatic (see Study 3). Finally, **tertiary preventive interventions** attempt to "*minimize negative effects, prevent further disease or disorder related to complications, prevent relapse, and restore the highest physical or psychological functioning possible*" (96). They would for instance be appropriate for mothers who recovered from CB-PTSD but show significant distress during their next pregnancy (see Study 4).

1. Prenatal preventive interventions

CB-PTSD has well-known risk factors and is triggered by a predictable event, childbirth, which usually occurs after regular contact with health professionals. Consequently, it is ideally suited for primary preventive interventions. Yet, these are scarce, if not non-existent: a recent systematic review, for example, could not find any interventional studies on CB-PTSD primary prevention (97). However, several avenues have been proposed.

1. **Improved birth preparation**, including the development of a birth plan, may contribute to the prevention of CB-PTSD by promoting more realistic representations of childbirth (4). It is true that elaborating a birth plan is associated with greater birth satisfaction (98, 99, but see also 100), and respect for the birth plan is a protective factor against CB-PTSD symptom development (55). Given that birth plans cannot always be followed (101), it has also been suggested to promote "birth flow charts", which would include maternal wishes under different scenarios (e.g., induced labour, preterm birth) (35).
2. **Emotion-Focused Therapy** (EFT) has been suggested to prevent CB-PTSD and traumatic birth experiences when proposed before birth, or even before conception (102). EFT is partly based on the attachment literature, and is aimed at recognising, accepting and, if necessary, transforming difficult emotions. In principle, it could be well adapted to the perinatal period - which was not its initial focus.

Yet, to my knowledge, there are no interventional studies that tested the effectiveness of these two strategies for CB-PTSD primary prevention, although one randomised controlled trial (RCT) with childbirth experience as an outcome of birth plan implementation is currently underway (103).

In other populations, such as service members and firefighters, a recent systematic review and meta-analysis spotted only six RCTs testing interventions to prevent PTSD prior to the occurrence of the traumatic event (104), but none was found to be more effective than usual care – although one study found that attention bias modification training[6] mitigated the prevalence of PTSD diagnosis (105). Furthermore, all these interventions targeted samples at-risk of work-related trauma exposure and may therefore not necessarily be suitable for pregnant women.

A first step in developing evidence-based prenatal interventions against CB-PTSD development would be to identify risk factors that can be addressed during pregnancy. Ayers' model (2016) (17) provides several ideas, but there may be additional avenues. **Antenatal insomnia symptoms** (Box 6), for instance, could be relevant targets for CB-PTSD prevention (see Study 1). Indeed, in other populations, pre-traumatic insomnia symptoms predicted subsequent PTSD symptoms, whether in service members (106, 107), civilians (108, 109) or healthy volunteers (110) - although one longitudinal study in combat veterans did not find such association (111). Importantly, the association between pre-traumatic insomnia and PTSD symptoms seems to persist when controlling for other pre-traumatic psychological symptoms with well-established links to insomnia, such as depression, anxiety, and PTSD (e.g., 107). Consequently, prenatal insomnia may be an independent risk factor for CB-PTSD symptom development.

Box 6. Insomnia.

According to the DSM-5, insomnia is characterised by complaints of dissatisfaction concerning sleep quality or quantity, combined with difficulties to fall or stay asleep, or early-morning awakening without being able to go back to sleep (9). Despite adequate opportunities for sleep, these troubles are lasting (≥ 3 months, or ≥ 1 month in case of episodic insomnia), frequent (≥ 3 nights/week) and result in significant distress and/or impairment in functioning.

[6] The attention bias modification training is a computer-based method inducing attention to minor threats and thus expected to "*facilitate protective forms of threat processing during combat by countering maladaptive threat-avoidance patterns*" (105, p. 2,628).

However, the evidence to date is of relatively low quality. Indeed, in the above-mentioned studies on civilians, measures of pre-traumatic insomnia are retrospective and/or reconstituted from different instruments or single-item questions (108, 109) - this last point applies to studies on service members as well (106, 111). Moreover, the validity of these results for women during the perinatal period is unclear, especially as most studies focused on service members, who are in the overwhelming majority males, and evidence suggests that sex could moderate the association between sleep and PTSD (112, 113).

It would be particularly important to know whether prenatal insomnia symptoms, sometimes considered "normative", are a risk factor for CB-PTSD because, according to recent meta-analyses, they affect 39.7-42.4% of women during the third trimester of pregnancy (114, 115). In this population, prenatal insomnia symptoms may be caused by pregnancy- and childbirth-related ruminations (116). It could also reflect FOC, which is higher in pregnant women reporting insomnia symptoms than in those who do not (117), and is a major risk factor for CB-PTSD (17, 118). Just like in other populations, insomnia symptoms are strongly associated with anxiety and depression symptoms in pregnant women (117, 119, 120). However, their prospective association with CB-PTSD as well as the mechanisms underlying this potential association (Box 7) has received little attention.

Box 7. By which mechanisms could prenatal insomnia affect CB-PTSD?

Several mechanisms may explain the association between pre-traumatic insomnia symptoms and PTSD, including the following:

1. **Pre-traumatic insomnia fosters maladaptive responses to trauma** by impairing emotional regulation, altering cognitive functioning (108, 121-123) and ultimately facilitating fear learning (124), thus increasing the traumatic event's psychological impact. This first pathway may explain why subjective peritraumatic distress mediated the relationship between prior insomnia and PTSD-like symptoms after exposure to a trauma film (110) – however, this was not found in clinical setting (109). In women during the perinatal period, antenatal insomnia may therefore result in negative SBE, which has consistently been reported as a major risk factor for CB-PTSD (17, 125).

2. Given that insomnia is often chronic (and common postnatally (126, 127)), **individuals with pre-traumatic insomnia symptoms may also have post-traumatic insomnia, which contribute to PTSD symptoms aggravation or maintenance** (128, 129). This has notably been shown in CB-PTSD, as a prospective cohort study found that insomnia symptoms at eight weeks postpartum was a maintaining factor of CB-PTSD at two years postpartum (130). The association between post-traumatic insomnia and PTSD may notably be due to disrupted memory consolidation (defined in Section I.C) or impaired fear extinction and safety learning (122, 124, 131-135). Thus, post-traumatic insomnia may be a crucial confounder and explain the observed association between pre-traumatic insomnia and PTSD. Paradoxically, to my knowledge, it has not been taken into account in aforementioned studies, although this appears to be a key question to clarify the relevance of insomnia-focused primary interventions for (CB-)PTSD.

2. Peripartum preventive interventions

If prenatal interventions to prevent CB-PTSD are lacking, so too are peripartum interventions. In 2018, a systematic review of the literature did not find any interventional studies on CB-PTSD prevention during childbirth (97). Since then, a pilot study tested the use of **visual biofeedback via ultrasound** (136). In this intervention, 26 low-risk nulliparous women giving birth by vaginal delivery saw, on an ultrasound screen, the movements of their foetus in the birth canal during the second stage of labour, i.e., when the cervix is fully dilated and the parturient pushes until the infant's birth. Initially intended to improve maternal pushing under epidural, the procedure also reduced, through a double mediation, CB-PTSD symptoms. Specifically, it improved feelings of maternal connectedness to the newborn, which reduced childbirth-related ASD symptoms at two days postpartum and, in turn, reduced CB-PTSD symptoms. These preliminary data could therefore potentially lead to a CB-PTSD preventive intervention during childbirth, although it could probably only be offered to women with low obstetrical risk, giving birth vaginally.

As reflected by Ayers' model (2016) (17), a possible approach to develop CB-PTSD preventive interventions during childbirth would be to target peripartum risk factors, notably lack of support. In this regard, a Cochrane systematic review reported that women receiving **continuous support** during childbirth, i.e. giving birth in the presence of a person whose sole responsibility is to support and comfort them, were less likely to report negative feelings concerning their birth experience (137) or childbirth-related dissatisfaction (138). They were also less likely to have an operative birth, which is another risk factor for CB-PTSD (17). However, interventional studies have not yet examined the associations between continuous support during childbirth and CB-PTSD symptoms.

One of the reasons why there are no interventions to prevent CB-PTSD during childbirth is probably that the peripartum risk factors identified so far, such as operative delivery, are not modifiable. Furthermore, interventions that could be devised are difficult to test and implement in the delivery room, for many practical, ethical, or medical reasons. It therefore seems necessary to identify factors on which it would be simpler to intervene, typically by modifying procedures already common during childbirth, rather than by adding new ones. In particular, the choice of **analgesia**, which concerns a vast majority of parturients, seems an interesting avenue to explore (see Study 2).

3. Postnatal preventive interventions

Intervening during the first hours and weeks postpartum, before CB-PTSD symptoms are settled, has the advantage of limiting the consequences of a traumatic birth experience by lessening its impact on maternal functioning. Crucially, this may help to prevent the intergenerational transmission of stress and trauma. Moreover, at this stage, it is easier to identify the at-risk women that would benefit from preventive interventions, because childbirth circumstances are known and the SBE can be assessed (see 139, 140, and 141 for examples of used screening questions). Furthermore, parents are often still surrounded by healthcare professionals, making interventions easier to implement.

Following the chronological sequence of the postnatal period, the earliest tested intervention to prevent CB-PTSD symptoms was based on the implementation of the different stages of the "**magical hour**", which corresponds to the first hour postpartum, during which the child would go through nine distinct stages (including crying, relaxation, awakening, crawling, suckling). A RCT found that, in women who had experienced a traumatic birth, those who were encouraged to go through each stage of the "magical hour" had significantly less severe CB-PTSD symptoms at three months postpartum than women who had received only routine care, including skin-to-skin contact (140).

Four RCTs, including two in a high-risk population (operative birth and self-reported traumatic birth experience), tested the effectiveness of a **midwife-led debriefing** in the first few weeks postpartum, mostly in the first 72 hours (142-145). This type of intervention aims to help women process their birth experience by selectively focusing on their thoughts and feelings, normalising them, and educating women about future emotional difficulties they might face, as well as how to deal with them. Overall, these RCTs did not yield results in favour of midwife-led debriefing, as this did not affect CB-PTSD diagnosis, and only one study found reduced CB-PTSD symptom severity (97). Three reviews, including a Cochrane systematic review, shared this conclusion and stated that there is no evidence to support psychological debriefing, whether midwife-led or not[7] (146-148).

Results regarding **structured psychological interventions** offered in the first postpartum weeks, which may include psychological first aid or repeated counselling sessions, are also

[7] Please note that some reviews included, at least partially, the same studies.

mixed. A systematic review (97) identified five RCTs that tested this type of intervention in high-risk samples (premature birth, infant hospitalisation in neonatal intensive care unit, ECS). Of these five studies, three reported that women who received the intervention had fewer or less severe CB-PTSD symptoms, but the review authors indicated that it is difficult to draw firm conclusions due to the moderate level of evidence. Furthermore, these interventions as well as their timing of implementation were notably heterogeneous.

Expressive writing, which involves writing for 15-20 minutes regarding childbirth-related emotions, thoughts and feelings, was also tested for CB-PTSD symptom prevention in three RCTs (149-151). Overall, in low-risk samples, expressive writing within the first postpartum days led to reduced CB-PTSD symptoms at three months postpartum, compared to neutral writing (149, 150). It yielded similar results in a high-risk sample, compared to treatment as usual (151). More recently, a meta-analysis assessing expressive writing effectiveness reported that it was efficient at reducing PTSD symptoms, in particular when done through multiple sessions (152). However, it should be noted that, of the eight RCTs integrated in this meta-analysis, only four targeted mothers during the first postpartum month. Indeed, two offered the intervention in the late postpartum period, and two targeted infertile women. This means that some studies did not test expressive writing as a prevention but as treatment for PTSD symptoms.

Eye Movement Desensitization and Reprocessing (EMDR) has also been explored for preventive purposes. With this technique, patients are asked to bring back trauma-related sensations or thoughts while receiving a bilateral stimulation (e.g., through eye movements). In mothers with birth-related stress symptoms, a 90-minute long EMDR session within the first postpartum days significantly reduced the proportion of women with clinically relevant CB-PTSD symptoms at six weeks – by 12 weeks, symptoms were low in both the EMDR and control groups. (153).

Beyond all these tested interventions, other techniques to prevent CB-PTSD symptom development during the early postnatal period, such as **oxytocin intake** (154), **EFT** (102) or **internet-based cognitive behavioural therapy** (CBT) (155) have been proposed, but they have not been properly tested yet. Notably, a large RCT tested a **self-help material** (leaflet and online film) aimed at preventing CB-PTSD development in high-risk women, but it was not efficient when compared to usual care (139). Overall, de Graaf et al. (2018) concluded

their systematic review on preventive interventions for CB-PTSD by saying that "*current research shows that interventions to prevent PTSD or PTSD symptoms in an unselected group of postpartum women have not been proven effective, with the exception of expressive writing tasks*" and that "*inconclusive results were found in selected groups*" (97, p. 653).

4. Postnatal therapeutic interventions

After the first month postpartum, interventions for women with traumatic birth experiences no longer seek to prevent but to reduce CB-PTSD symptoms. As with unrelated-to-childbirth PTSD, the National Institute for Health and Care Excellence (NICE) recommends **EMDR** and **Trauma-Focused CBT** (TF-CBT) in women with CB-PTSD – conversely, it discourages high-intensity interventions focusing on birth reliving (i.e., detailed narration in first person and present tense of the birth) (1). TF-CBT comprises a vast array of cognitive, behavioural and emotional techniques aimed at working on the processing of trauma memories, and trauma-related hotspots, making sense of their traumatic experience and identifying both deleterious patterns of thinking and helpful coping strategies. It can either be proposed one-to-one, in a group or online, and requires multiple sessions (156). All these techniques can be reunited under the banner of **Trauma-Focused Psychological Therapies** (TF-PT) (157), which also include exposure therapy (Box 8) and EMDR (156).

A systematic review and meta-analysis on TF-PT for CB-PTSD showed that these therapies (which included expressive writing as it was considered as a form of exposure therapy by the authors) effectively reduce CB-PTSD symptom severity up to six months postpartum, in both high- and low-risk samples (156). However, there was no evidence suggesting that TF-PT improved recovery from CB-PTSD diagnosis. Furthermore, it should be noted that, of the 11 studies kept in the analyses, at least six proposed the intervention within the first postpartum month – thus rather as a prevention than as a treatment (156). The results of this meta-analysis were congruent with the conclusions of two systematic reviews on CB-PTSD treatment, which concluded that EMDR and CBT were the most promising therapies, although the evidence is still limited due to the small number of published studies (158, 159). Notably, this is true for EMDR, as the two available studies respectively included three and four women (160, 161), although at least three RCTs are currently ongoing (162-164). One of these reviews additionally stated that there was some preliminary evidence in favour of the **debriefing** (k = 1), if offered on request, and **expressive writing** (k = 1) (159). However, for

all techniques, very few studies were available and this third systematic review concluded that there is little definitive evidence regarding the effectiveness of psychological interventions for CB-PTSD treatment (159).

Box 8. Exposure therapy and its limitations.

Exposure therapy comes from the conditioning research field, and seeks to obtain fear extinction. It is based on the observation that repeated exposure to unreinforced CS (i.e., no longer associated with the UCS, such as an account of the traumatic experience) leads to a reduction of the fear response and its behavioural expression (165). Exposure therapy is one of the most effective and recommended PTSD treatments, and is considered as a "gold standard" (166). However, it would only produce a new memory trace *inhibiting* the original fear memory, which still exists and may therefore resurface (167, 168). Consequently, patients may experience a **reinstatement** of problematic fear-related behaviours when exposed to a CS in presence of the UCS, a **renewal** if they encounter the CS in a different context to the one worked on in therapy, and even a **spontaneous recovery** of the fear response over time (168). Moreover, in real-world settings, important **drop-out rates** have been reported in exposure therapy (169). Finally, this technique requires highly-trained clinicians, which limits its availability for individuals with PTSD.

The question of the relevance of all these therapies for pregnant women suffering from CB-PTSD related to a previous traumatic childbirth experience remains open. Considering that a history of PTSD and FOC can be the direct result of a traumatic childbirth experience and are two major risk factors for CB-PTSD (17, 54), it seems appropriate to intervene during pregnancy, which can reactivate old traumas. On the other hand, the consequences of foetal exposure to stress that these therapies may generate, including cortisol release, is unknown (4, 170). A recent systematic review concluded that treatment of PTSD during pregnancy is "*mostly likely safe*" (171, p. 11), while noting that there are few studies on this issue.

At the end of this brief overview of interventions for CB-PTSD prevention or treatment, it appears that *preventive* interventions are lacking, especially before and during childbirth (97, 172). Yet, they could be particularly suitable, notably because birth can be somewhat anticipated and usually occurs after regular medical follow-ups. Ideally, future preventive interventions should be simple to implement, manageable for non-mental health professionals (since they are present during this period anyway), and universal, i.e., not requiring local language skills, in order to be accessible for migrants (for information, 39.6% of the children born in Switzerland have a foreign mother (173)).

As for CB-PTSD *treatment*, the range of available techniques is broader, but the reviews cited above emphasise that there is still too little evidence available[8], and existing TF-PT may not be sufficient to bring women's symptoms below the PTSD diagnosis threshold (note that, even below the threshold, women may still suffer). Additionally, most of them require in-depth and potentially repeated evocation of the birth, through multiple sessions. This can compromise compliance, since CB-PTSD is characterised by avoidance symptoms. Thus, there is a need for other forms of intervention, especially brief ones, which could enrich the list of available clinical tools and have long-term benefits for women.

C. Memory consolidation

1. Definition

Memory consolidation, which corresponds to a set of time-dependent molecular and cellular processes of stabilisation of memories into long-term memory (174, 175), could be the starting point for the development of new preventive interventions for CB-PTSD[9]. Indeed, during its consolidation, which lasts a few hours (Box 9), the memory of an event that has just been experienced is not yet fixed, and would still be malleable (174, 177). Its long-term memory characteristics, such as its vividness, would be modulated during this consolidation phase, depending on different variables such as emotional arousal or hormonal activity (174). Evidence for memory consolidation mostly comes from studies showing that learning can be impaired or enhanced with appropriate manipulation (e.g., competing learning, amnestic agent), if the latter is carried out after memory acquisition but not beyond a few hours, i.e., within the so-called memory consolidation window (174, 178). This potentially means that memory consolidation is a window of opportunity for PTSD prevention, during which (trauma) memories are sensitive to interference (60), and beyond which they are durably settled.

[8] It should be noted that the distinction between prevention and treatment interventions in the postpartum period, although based on the DSM-5 criteria for PTSD, is somewhat artificial: several techniques seem to be suitable both before and after the first month postpartum, such as EMDR or expressive writing. In fact, some literature reviews have mixed the two time points (e.g., 156).
[9] Please note that, to my knowledge, only one study was specifically interested in CB-PTSD and memory (re)consolidation (176) This is why Sections I.C and I. D strongly draw on other populations and data on unrelated-to-childbirth PTSD, rather than CB-PTSD and the perinatal context.

Box 9. Synaptic and system consolidation.

Memory consolidation comprises two consecutive phases: **synaptic** and **system consolidation**. In this thesis, the term « memory consolidation » refers to the first one, which occurs within the first hours following any event, because it is during this early stage that memory would be malleable and responsive to interventions (60, 178). It is often said that memories are labile during approximately six hours following encoding (179) which corresponds to the consolidation window, but its exact duration is unknown and may vary across species or memory types. Rather than a binary state (malleable *vs.* not malleable), memories may progressively become insensitive to interference, as synaptic consolidation continues.

For information, system consolidation rather corresponds to a long-term process whereby memories become less hippocampus-dependent and are reorganised into different brain circuits, notably the neocortex – however, neocortical areas are already implicated in memory consolidation within minutes following encoding (178). System consolidation can take months or even years.

It is not the purpose of this thesis to produce an inventory of the neurobiological processes at work during memory consolidation, nor would this be my area of expertise. However, in order to design sound clinical interventions, it is necessary to be aware that memory consolidation is thought to be, *inter alia*, underpinned by long-term potentiation (LTP). LTP is a cerebral activity-based synaptic reinforcement. In other words, it strengthens the links between neurons that have been co-activated during an event, making them more likely to fire in synchrony, which consolidates the established connection. By promoting neuroplasticity, LTP is thought to be one of the neurobiological mechanisms underlying memory consolidation, particularly in the hippocampus (174), a key brain structure for the formation of new memories. Importantly, the late-phase LTP would be crucial for lasting memory consolidation and relies on protein synthesis (180), which could thus be a target for interventions on trauma memories (Sections I.C.3 and I.D.3).

• Stress response, hormones and memory consolidation

Converging evidence suggests that the stress response (Box 10), which typically occurs during a traumatic birth, enhances memory consolidation (181). Indeed, in rodents, **noradrenalin** or β-adrenergic receptor agonists favour memory consolidation of aversive learning and fear conditioning, while β-adrenergic receptors antagonists have an opposite effect and disrupt fear memory formation (182). Similar results have been observed for associative fear learning and fear generalisation in humans (182-184). As for **cortisol**, it would particularly enhance the memory consolidation of fearful or emotional events (182, 185), by acting directly on the hippocampus, which is rich in glucocorticoid receptors. Indeed, several studies found that glucocorticoid receptor agonists promote memory consolidation,

both in rodents and humans, particularly in women over men (181, 182). However, cortisol may have different effects on memory, depending on the memory stage: while enhancing memory consolidation during stress exposure, it would, on the contrary, impair retrieval (186, 187). Note that, in addition to enhancing memory consolidation *during* stress exposure, *post-traumatic* cortisol release would promote stress response termination, and homeostasis reinstatement (188-191). Thus, it must be released in sufficient quantity to regulate and shut down the stress response, and to allow recovery (192) – this may explain why individuals with established PTSD actually have lower levels of cortisol than trauma-exposed individuals who do not develop PTSD (193), although findings are inconsistent (194-198). Interestingly, during the stress response, the action of stress hormones is co-modulated, i.e., the effect of glucocorticoids on memory consolidation depends on the noradrenergic activity (199, 200).

Box 10. The stress response.

The stress response mostly consists of two processes: 1. The almost instantaneous activation of the **sympathetic nervous system**, which allows the secretion of noradrenalin, involved in the "fight or flight" response, and 2. The activation of the **hypothalamic-pituitary-adrenal** axis, responsible for the release of glucocorticoids, including cortisol – corticosterone in rodents – which reaches its peak blood levels 10-30 minutes after stressor onset (201). Importantly, as mentioned above, cortisol secretion is also necessary for the termination of the stress response.

The stress response also involves the amygdala, which is itself connected to the hippocampus, and whose activation modulates the consolidation of all emotionally arousing memories. In other words, the consolidation of emotional memory is enhanced via the implication of the amygdala, or more specifically, the basolateral complex of amygdala (BLA), which is triggered by noradrenergic activity. For instance, β-noradrenergic activation of the BLA results in a more intense post-learning hippocampal activity (see 200 for an overview). Similar effects have been observed with glucocorticoids, whose memory consolidation enhancing action depends on noradrenergic activation of the BLA (202). In sum, BLA would potentiate the effects of stress hormones on memory consolidation, through its interaction with the hippocampus (187, 200, 202).

Beyond the stress it can generate, childbirth triggers the release of **oestrogen**, **oxytocin**, **endorphins**, and **prolactin** (203, 204). Their role in memory consolidation is not well-determined yet. For instance, oestradiol (a form of oestrogen), is thought to facilitate memory consolidation (205), although its association with IMs is unclear (58, 206). This has led oestrogen to be considered as a vulnerability factor, which may explain why women are at greater risk of developing PTSD symptoms, including IMs, than men (207-210). However, Wegerer et al. (2014) (211) showed a negative association between intrusive memory frequency and oestradiol levels in healthy women exposed to an analogue trauma. Oxytocin, for its part, is said to have variable effects on memory consolidation: in rodent and birds, it tends to inhibit learning, although some opposite results have also been reported (212).

Indeed, it would tend to disrupt the LTP (212). There is little or no research on the effects of endorphins on memory consolidation. However, as it is an endogenous opioid, it can be hypothesised that its effects may be related to those of other opioids such as morphine, which would tend to limit the release of noradrenalin in the event of stress, and thus limit the consolidation of fearful memories (213). Conversely, prolactin is thought to promote memory consolidation and increase hippocampal synaptogenesis (214). Of course, these are only scattered results: as far as I know, there is no research on the joint effects of these hormones on memory consolidation. Reviewing the state of the art on the relationships between sex hormones and memory consolidation is out of the scope of this thesis, but it should be noted that, compared to other potentially traumatic events, birth takes place in a very unique hormonal context.

- **Sleep and memory consolidation**

Evidence shows that memory consolidation processes are not only time-dependent, but also sleep dependent (122). Indeed, on the one hand, it has been observed that sleep favours memory consolidation (but see 215) and, on the other hand, that sleep deprivation would limit its consolidation (122), especially in the short term (132). A large number of studies have highlighted the role of sleep in the consolidation of declarative memory, particularly for items with emotional valence (132). To illustrate, a laboratory study found that men who slept after learning neutral and emotional texts remembered the emotional texts better, four years later, than those who had not slept after learning similar texts (216). Interestingly, the two groups did not differ with regard to the neutral texts, thus suggesting a selective effect of sleep on the consolidation of emotional material. This would notably apply to fear learning (122), although the "sleep to remember, sleep to forget" hypothesis proposes that sleep also contributes to the "depotentiation" of the affective tone associated with an event (122, 131), thus potentially preventing the development of maladaptive stress responses. Importantly, sleep would also promote binding of information with its context, regardless of the associated emotional value (122).

The respective role of the sleep stages in memory consolidation is still under debate (122, 178, 217, 218), but it has been suggested that consolidation especially occurs during slow wave sleep and rapid eye movement (REM) sleep (Box 11). In healthy participants, for example, fear learning has been found to be improved after a night of sleep, compared to

wakefulness, and the strength of the memory was positively correlated to the amount of REM sleep in the post-learning night (219, 220). One potential explanation for the enhancing effect of sleep on memory consolidation could be that specific offline processing of memories occurs during the first post-training night, strengthening newly established neuronal connections (122, 217). Post-training sleep, for instance, is characterised by the activation of similar firing patterns as those implicated in the initial learning (178), in particular in hippocampal and cortical cells (217, 221, 222). In parallel, sleep also would favour the sorting of information and, in particular, the forgetting of irrelevant material, by a "synaptic downscaling" (217, 222, 223). Overall, if sleep after a traumatic event modulates memory consolidation and the resulting fear learning, it could be a target for PTSD preventive interventions.

Box 11. Sleep stages.

A typical night's sleep consists of four to six cycles, each of which includes different sleep stages. A distinction is made between **REM** and **non-REM sleep**. The former is associated with intense muscle atony, bursts of rapid eye movement and vivid dreams (132). As for non-REM sleep, which can also include dreaming (224), it is itself composed of three stages, numbered from the lightest to the deepest: **N1, N2, N3**. N3 is also called "deep sleep" or "**slow wave sleep**" because it is characterised by delta waves in the electroencephalogram.

2. Memory consolidation and PTSD

The experience of a traumatic event, i.e., one that involves actual or threatened death (9), will tend to trigger a strong stress response, which we now know will result in enhanced memory consolidation. In the end, could PTSD be the result of an intense peri-traumatic arousal, resulting in an "overly" consolidated traumatic memory? Are the persistence of trauma memory and the intense physiological and emotional responses it triggers, the consequences of an "excessive" stress response? Is PTSD the pathological expression of learning mechanisms that were originally intended to allow better adaptation to the environment, by favouring the retention of information relevant to survival? This hypothesis is already decades old: in 1989, the American psychiatrist Roger K. Pitman proposed that, because of the extreme stress response they trigger, traumatic events are "overconsolidated" in memory (which he had previously called "superconditioning") (225). Regarding PTSD, he concluded that: « *Extreme activation of an adaptive mechanism may produce not adaptation, but pathology*" (225, p. 222).

Since the 1990's, a large body of literature has confirmed that, when administered during the consolidation window, amnestic agents (e.g., protein synthesis inhibitors), behavioural manipulations (e.g., stress paradigm), or drugs that either stimulate or block stress hormone release (e.g., yohimbine, propranolol) modulate fear learning and subsequent fear responses, as well as PTSD symptoms and IMs (e.g., 60, 183, 185, 226, 227). Furthermore, observational clinical studies have reported that trauma-exposed individuals showing increased sympathetic nervous system activity during the peri- and early post-traumatic period were at higher risk of developing PTSD (228-230), although contradictory findings have also been reported (231). Reinforcing this hypothesis, substantial evidence suggests that peritraumatic emotional arousal, including the subjective trauma experience, is predictive of PTSD symptom development (17) and IMs (232). One can assume that the association between the subjective trauma experience and subsequent PTSD symptom development is related to the fact that the former is, at least partially, a psychological reflection of the stress response.

Since the overconsolidation hypothesis, the theorisation of PTSD has undergone numerous developments, as illustrated by the cognitive models in Section I.A.7. Some apparently contradictory clinical phenomena are still poorly understood from a biological point of view, such as the fact that trauma memory is sometimes fragmented, blurred or completely forgotten (83). However, the hypothesis that trauma memory consolidation disturbances are strongly implicated in the development of PTSD symptoms has received support, with some authors referring to PTSD as a "memory disorder" (e.g., 233)[10].

Overall, many mechanistic questions remain unanswered but, if we adopt a pragmatic posture, several lines of evidence could inform future (CB-)PTSD preventive interventions:

1. Memories are particularly malleable during the first hours after encoding, when memory consolidation occurs (60, 174).
2. The latter is enhanced in case of stress and/or intense emotion (60, 234), such as during childbirth.
3. Through behavioural or pharmacological manipulations during the consolidation window, it is possible to modulate fear learning and, ultimately, to reduce the fear response (226).
4. PTSD would result from maladaptive fear learning (185, 225, 226, 235-238)[11].

[10] It has also been suggested that other processes, such as disrupted encoding or extinction (124, 191) could be implicated in PTSD pathogenesis - note that these proposals are not necessarily mutually exclusive.
[11] Although clinically other negative emotions are reported, such as shame or anger.

Therefore, memory consolidation following a traumatic event may be a judicious target for CB-PTSD preventive interventions.

3. Memory consolidation-based interventions

Despite a growing number of laboratory studies suggesting the relevance of targeting memory consolidation to prevent PTSD, translating these findings into clinical interventions is not straightforward. Firstly, some of the drugs used to interfere with memory consolidation in rodents, such as the protein synthesis inhibitor anisomycin (239), are, at equivalent doses, toxic to humans. Furthermore, many (non-human) animal studies infuse these drugs into specific neural regions, which implies unsuitable surgical procedure for human treatment. Additionally, while it is absolutely crucial, for obvious ethical and legal reasons (e.g., reliability of potential testimonies), that consolidation-based interventions (CBIs) leave the ability to voluntarily access the memory intact, this is difficult to ascertain from rodent experiments. Finally, CBIs must be carried out within the first few hours following a traumatic event, which often means that they have to be adapted to medical contexts and to potentially distressed individuals.

a. Pharmacological CBIs

Most of the pharmacological blockades being explored to prevent PTSD within the memory consolidation are aimed at regulating the stress hormone activity. This is notably the case for **propranolol**, a β-adrenergic antagonist, which has been proposed to interfere with memory consolidation by reducing the noradrenergic activity and sympathetic arousal (191, 240). Propranolol-based CBIs have been tested in a variety of populations, from healthy volunteers to real-life trauma survivors (241). It had shown promising results in the laboratory, where healthy participants receiving propranolol within the consolidation window remembered less aversive material and showed reduced physiological fear responses compared to those receiving a placebo (242). One study by Kamboj et al. (2020) (76) also found that healthy women receiving propranolol immediately after watching a trauma film reported 42% fewer IMs in the subsequent week, compared to those who had received a placebo. Importantly, their declarative memory of the film was not affected (76). However, overall, the effectiveness of propranolol for the prevention of PTSD symptoms in trauma-exposed individuals is inconclusive, as noted by three meta-analyses (241, 243, 244) - although it is noteworthy that

two of these reviews intermixed interventions testing propranolol within and beyond the consolidation window, which limits the interpretation of results.

Glucocorticoids, in particular the exogenous cortisol **hydrocortisone**, are also considered for CBIs because they may promote stress response termination. Indeed, lower cortisol levels in the early aftermath of a real-life or analogue trauma predicted subsequent PTSD symptoms (192, 210, 245-247) – and were associated with peritraumatic data-driven processing, which brings us back to the cognitive models of PTSD (78). Hydrocortisone has notably been tested in the lab, where it reduced IMs by 55% within the first week following viewing a trauma film, relative to a placebo. In trauma-exposed individuals, hydrocortisone currently appears as the most promising drug for early secondary prevention of PTSD symptoms, as concluded by five systematic reviews and/or meta-analyses (104, 241, 243, 244, 248). However, some of these reviews also intermixed different time points, including studies on hydrocortisone administration during and beyond the consolidation window. Furthermore, there is still limited data available: the most recent review identified only six studies (243).

The study of the effects of opioids and opiates[12] on memory consolidation has produced rather contradictory results (249). However, it has been suggested that **morphine**, by reducing noradrenalin production, may interfere with memory consolidation (250). Laboratory studies on rats suggested that early morphine injection impair fear acquisition and reduce fear responses (251-253), while opioid antagonists, such as naloxone, would on the contrary promote fear learning (254). From a clinical point of view, it would be crucial to know whether morphine has incidental effects on memory consolidation and PTSD symptom development, because it is routinely used in intensive care units, military medicine and on labour wards, and is thus administered to populations at risk of developing PTSD. To the best of my knowledge, there are no RCTs studying that question. However, observational data provides preliminary results. In service members, two retrospectives studies found that individuals who received morphine within the first post-injury hours were less likely to develop PTSD, compared to service members who did not receive morphine (255) or who received fentanyl, another frequently used opioid (256). However, one study did not find such association (257). Among civilians, receiving opiates, including morphine, within the 48 hours following a traumatic injury was associated with less severe PTSD symptoms (213, 250).

[12] Opiates, such as morphine and codeine, are naturally derived from the opium poppy. The term "opioid" more broadly refers to substances binding to opioid receptors in the brain and having similar pharmacological properties as opiates.

Additionally, the duration of opiate administration after acute lung injury was a protective factor against subsequent PTSD symptoms, despite the fact that, paradoxically, a high daily opiate dose was a risk factor (258). In children with burns or injury, receiving high doses of morphine during hospitalisation was also associated with reduced subsequent PTSD symptoms (259-261). Similar results were found with opiates, even up to four years after a serious burn (262). Importantly, morphine does not only affect adrenergic activity but also has potent analgesic properties. Thus, given that peri-traumatic pain is a risk factor for PTSD (17, 250), its benefits, which remain to be confirmed, may not be due to its effects on the stress response and trauma memory consolidation, but to its pain-relieving action. This hypothesis is challenged by the fact that, in rodents, morphine administration reduced subsequent fear responses, even when administered after the end of the painful stimuli (263). Moreover, one observational study in civilians also found that morphine was protective against PTSD symptoms, regardless of pain (250). However, the lack of data precludes firm conclusions.

Surprisingly, **nitrous oxide gas** (N_2O), also known as laughing gas, has rarely been studied for its potential to prevent PTSD by interfering with trauma memory consolidation. Yet, in addition to its GABAergic and opioid activity, N_2O is suspected to be an antagonist of *N*-methyl D-aspartate receptors (264, 265), which are critically involved in LTP and memory consolidation (266). In the laboratory, N_2O inhalation impaired learning in both rodents (267) and humans (268, 269). Furthermore, one laboratory study found that N_2O inhalation following exposure to a trauma film sped up the reduction of IMs during the subsequent week, compared to placebo medical air (75). Notably, participants from the N_2O group showed intact recall of the trauma film, although it is important to specify that those showing high dissociation before viewing the film had an increased number of IMs. Taken together, these very preliminary findings suggest that N_2O may be a good candidate for CBIs.

Other pharmacological blockades have been considered for PTSD prevention, such as **ketamine, oxytocin, fish oil, imipramine**, and **serotonergic reuptake inhibitors,** but findings are mixed and research is still in its infancy (191, 192, 240, 244). According to the abovementioned meta-analyses, no drug has sufficient evidence to justify its use within the consolidation window and, indeed, for the moment, NICE guidelines advise against drug use for PTSD prevention (26). Furthermore, not all of them are compatible with breastfeeding or adapted to the early postpartum physiology. For all of these reasons, it is thus of interest to also consider behavioural CBIs.

b. Behavioural CBIs

A systematic review of RCTs testing preventive interventions for PTSD, by Bisson et al. (2021) (104), spotted only three non-pharmacological interventions proposed less than eight hours following the traumatic event, i.e., potentially within the consolidation window (176, 270, 271). According to their authors, they all employed a visuospatial task to interfere with memory consolidation. In addition to relying on a visuospatial task, the primary study outcome of two out of the three studies was the number of IMs in the first post-traumatic week.

• Principle of a visuospatial task-based intervention

The idea of using a visuospatial task during the memory consolidation window to specifically prevent IMs development stems from several observations:

1. IMs would result predominantly from sensory processing during the traumatic event (see Sections I.A.6 and I.A.7), and are mostly visual (59), i.e., mental imagery-based (70).
2. The working memory, which is involved in temporary information processing, especially of traumatic images, has limited resources (272, 273).
3. Information is processed in the working memory according to its modality, i.e., visuospatial information will mobilise the visuospatial resources of the working memory (274, 275).

Therefore, engaging in a visuospatial task within the memory consolidation window may prevent IMs development, by taxing the visuospatial resources of the working memory that would otherwise be allocated to the consolidation of the visual aspects of the trauma memory, i.e., the traumatic images appearing in IMs (276, 277). In other words, a visuospatial task may create a sensory modality-specific interference with the consolidation of traumatic images (although this can be discussed, as illustrated in the following paragraphs), thus resulting in fewer IMs and, subsequently, in reduced PTSD symptoms. From a neuroscientific perspective, the induced cognitive interference might be the consequence of an overloaded recruitment of the same neural populations (272) that are necessary, both to process the distressing traumatic visual images and to carry out the visuospatial task.

The idea of a visuospatial interference is based on findings on memory consolidation, which come from neurosciences, and findings on the working memory, which come more from cognitive psychology. Working memory is a component of short-term memory. It has notably been theorised and studied by Baddeley and Hitch (278), and is involved in information processing and manipulation (273). It has several components, including (but not limited to) verbal working memory (or phonological loop), which processes verbal material, and visuospatial working memory (VWM) (or visuospatial sketchpad), which processes visuospatial material (273) (see Appendix C). Since its initial conceptualisation, working memory has been the subject of intense research, numerous developments, and has received empirical support (279). Beyond the existing debates, there is some consensus on its links to long-term memory, its limited capacities, and its distinct processing of visual *vs*. verbal material (272, 273, 275, 277), three features that are of particular interest in the framework of CBIs.

An important point is that the VWM is constantly occupied, and holds visuospatial information for a limited duration of time (273). Therefore, the distressing traumatic images are not necessarily being processed in the VWM throughout the whole memory consolidation window. In order to interfere with their stabilisation into long-term memory, it has therefore been proposed that the visuospatial task should be performed after exposure to brief memory reminder cues that would "activate" these distressing images (276, 280). Indeed, unlike pharmacological CBIs, which for example lead to a global regulation of the adrenergic activity and thus indiscriminately affect the different brain areas, this type of behavioural CBI must, in order to be effective, selectively focus on the targeted aspect of the memory, in this case the distressing images. With the reminder cues, CBIs involving a visuospatial task (CBIs-VT) bring traumatic images back into the VWM focus, so as to make them vulnerable to subsequent visuospatial interference (277). The translation of consolidation findings into behavioural interventions to prevent PTSD thus necessitates ensuring that traumatic images are accessible beforehand.

- **Laboratory findings**

In the laboratory, one of the most widely tested visuospatial tasks to engage the VWM is the **computer game Tetris**, which requires the player to move and rotate geometrical shapes under time pressure (Box 12). Indeed, several laboratory studies found that healthy volunteers playing Tetris for 10 to 30 minutes within the six hours following the trauma film viewing had fewer IMs during the subsequent week, compared to those who had not played (e.g., 276, 280, 281, 282) - see also (283) for a study on positive involuntary images. Prior to playing Tetris, participants performed a brief memory reminder task (e.g., watching still images from the trauma film like in (276, 281), which was also proposed to the control group in some studies (276, 280)).

Box 12. Tetris.

In the Tetris game, seven differently shaped, colored geometric blocks randomly fall one by one from the top to the bottom of the screen (Figure 2). Players can rotate the blocks, accelerate their fall or move them to the right or left. Their objective is to create complete horizontal lines at the bottom of the screen, with the blocks. When a line is complete, it disappears and the player earns points. The game is over if the blocks pile up so high that they touch the top of the screen. In Marathon mode, which is used in Studies 3 and 4 of this thesis, the blocks fall faster and faster, which allows the task to be adapted to the level of the players - players will go far enough in the game for the blocks to fall at a challenging pace. To the best of my knowledge, Tetris is always played on handheld devices.

Figure 2. Screenshot of Tetris 3DS, the version used in Studies 3 and 4.

Interestingly, slight variations from the original procedure, e.g., no reminder task or engagement in Tetris before or immediately after the film (instead of 30 minutes and 4 hours later, like initially tested (276, 280)) made it ineffective (284, 285), thus suggesting that "playing Tetris" is not sufficient to prevent IMs. Tetris-based interventions in fact consist of a whole procedure, comprising several important and distinct components including memory reminder cues, appropriate timing, and a sustained Tetris gameplay (176, 280). These encouraging preliminary findings (see also Engelhard, van Uijen and van den Hout (2010) (286), who found benefits of a Tetris-based procedure on startle response) received a lot of

attention, as participants in the Tetris groups showed intact voluntary memory, i.e., their performance on film-related recognition or recall task was equivalent to that of the control groups (77, 276, 280, 282). Therefore, they confirmed that CBIs-VT selectively target involuntary memory expression, i.e., potential IMs in PTSD, while preserving the declarative memory (see 60).

It should be noted that the exact mechanisms of Tetris-based interventions are not yet established. Since the first laboratory studies, the fact that Tetris engages visuospatial resources has been substantiated by experimental (287) and neuroimaging (288) studies. In principle, other visuospatial tasks such as finger tapping or even eye movement could have comparable effects, as it is the case in several studies (286, 289-292) – some are even specifically developed for therapeutic purposes (293, 294). However, some tasks assumed to engage visuospatial resources did not show effectiveness (281, 294, 295), and the factors explaining these differences are unclear. Furthermore, the sensory modality specificity hypothesis would predict that non-visuospatial tasks would not prevent or reduce the number of IMs, but studies yielded inconsistent results. On the one hand, some studies, indeed, found that verbal tasks were ineffective (292) or even detrimental, as they led to more subsequent IMs (276, 296). Moreover, one study on auditory IMs actually showed a benefit of a concurrent verbal task (i.e., a reduction in subsequent auditory IMs), which was also in line with the modality specificity hypothesis (297). On the other hand, several studies found that verbal (or, at least, non-visuospatial) tasks reduce subsequent IMs (291, 298) - see also (299, 300). Clarifying the mechanisms involved in CBIs-VT would be an important step towards understanding these inconsistencies, isolating the determining parameters, and thus developing the most effective clinical interventions possible.

- **Clinical studies**

Two of the three clinical RCTs testing a CBI-VT included in the aforementioned systematic review of Bisson et al. (2021) (104) are translational proof-of-principle studies, which tested Tetris-based CBIs within the six first hours following exposure to a real life traumatic event (176, 270). One study by Iyadurai et al. (2018) (270) proposed the intervention to motor vehicle accident survivors, while they were waiting in the hospital emergency department (ED). In the intervention group (n = 37), participants started with a brief reminder task (think of the accident, mention the worst moments to the researchers), and then were instructed to

play Tetris for 20 minutes. In the control group (n = 34), participants wrote down what they had done since their arrival at the ED, for 20 minutes as well. Compared to the control group, intention-to-treat (ITT) analysis showed that participants in the intervention group reported 62.47% fewer IMs within the first post-traumatic week (primary study outcome), as well as reduced re-experiencing symptoms at one week post-trauma. Effect sizes were medium for both outcomes, respectively d = 0.67, [95% *CI*: 0.18, 1.14], and d = 0.54, [95% *CI*: 0.09, 1.01]). However, the groups did not differ for the other symptom clusters at one week, nor at one month post-trauma.

Since the publication of Bisson et al.'s systematic review (104), two RCTs testing a similar intervention in an ED were launched. One was prematurely interrupted due to the COVID-19 pandemic (301). The second was an exploratory RCT, which aimed to overcome the limitations of Iyadurai et al. (2018) (e.g., short follow-up) and included survivors of more diverse traumatic events (e.g., domestic accident, assault) (302). Participants from the control group listened to a podcast. A notable difference with the other RCTs testing a CBI-VT is that participants could receive the intervention up to 72 hours post-trauma, which means that some were certainly no longer in the memory consolidation window – rather, due to the inclusion of a reminder task in the intervention group, in the memory *re*consolidation window (Section I.D), which limits results interpretation. Compared to the control group (n = 19), participants from the intervention group (n = 22) reported 47.77% fewer IMs over the first post-traumatic week (ITT analysis; primary study outcome), with a small to medium effect size, d = 0.43 [95% *CI*: −0.23, 1.08]. The number of IMs during the 5th post-traumatic week was also significantly lower in the intervention group compared to the control group. There were no differences in terms of ASD symptoms at one week or PTSD symptoms at one month and six months post-trauma.

The second RCT mentioned in the systematic review of Bisson et al. (2021), by Horsch et al. (2017) (176), is of particular interest for this thesis, given that the intervention was offered to women who had an ECS, and were thus at risk of developing CB-PTSD symptoms. Participants in the intervention group played Tetris for 15 minutes (n = 29), while those allocated to the control condition received only routine postpartum care (n = 27). The intervention did not comprise a reminder task because it was carried out in the maternity unit, which was hypothesised to be a reminder cue in itself. Compared to the control group, the intervention group had 48.27% fewer CB-IMs over the first postpartum week (ITT

analysis; primary study outcome), with medium effect size, *d* = 0.647 [95% *CI*: 0.106, 1.182]. No other group difference was found in terms of ASD symptoms at one week or PTSD symptoms at one month postpartum with ITT analyses. However, in the per protocol analyses, participants from the intervention group had lower ASD re-experiencing symptoms at one week, and were also significantly less likely to fulfil the CB-PTSD diagnostic criteria or avoidance cluster criteria at one month postpartum. Overall, the results are very exciting for CB-PTSD prevention, although it should be noted that the study had several limitations, notably: 1. A passive control group, 2. No blinding for participants or researchers, 3. Relatively short follow-up, which does not capture long-term effects of the intervention, in particular with regard to child development, and 4. Self-reported CB-PTSD symptoms. Finally, the sample size, adapted to detect differences for CB-IMs during the first postpartum week, may have been insufficient to detect a difference in the diagnosis of CB-PTSD in the ITT analysis. Thus, a larger RCT with a stricter design may, by overcoming these limitations, provide crucial evidence on the relevance of this CBI-VT to prevent CB-PTSD.

The third RCT testing a CBI-VT included in the systematic review of Bisson et al. (2021) proposed that trauma survivors immerse themselves in a fictional universe through virtual reality, SnowWorld, in which they could walk around or throw snowballs at snowmen (271). The intervention was also proposed in an ED, but within eight hours following the traumatic event. Participants who had received the intervention (*n* = 36) did not show reduced PTSD symptom severity at six months post-trauma, compared to routine care (*n* = 41). However, the procedure differed in several respects from the Tetris-based interventions, notably in terms of: 1. Visuospatial task duration (on average only eight minutes in SnowWorld), 2. Reminder task (there was no reminder task in this RCT), 3. The nature of the task, which seemed less demanding because, in SnowWorld, there was no performance goal, it was possible to remain passive in the game world, and there were no instructions promoting engagement of visuospatial resources - although this was not the case for all RCTs based on Tetris either (e.g., 270). Moreover, and crucially, SnowWorld was labelled by the authors as a visuospatial task but, as far as I know, no study showed that it actually engages VWM resources.

Overall, a recent meta-analysis on consolidation-based RCTs concluded that CBIs involving Tetris have a small positive effect to prevent IMs during the first week post-trauma, but have not been shown to effectively prevent PTSD at one month post-trauma (243). Authors argue

that none of the three included trials (176, 270, 302) were powered to detect overall PTSD symptom reduction, and that larger clinical trials are thus urgently needed. As mentioned for Horsch et al. (2017) (176), these three studies are an important step toward single-session low-risk and inexpensive CBIs to prevent PTSD, but show several limitations which are common in proof-of-principle RCTs (e.g., passive control group, no blinding). Thus, larger RCTs with stricter design could lead to significant research and clinical advances.

Another critical step would be to find a way to make these CBIs-VT, which show promising results, accessible beyond the first post-traumatic hours. Indeed, most trauma-exposed individuals cannot receive such emergency interventions, because they are not seen on time or are too injured, shocked, or preoccupied to engage in a visuospatial task. Moreover, early detection of those at risk of developing PTSD is not 100% reliable. In the context of childbirth, for instance, even women without apparent risk factors and reporting a positive SBE may develop CB-PTSD. This is where memory reconsolidation comes in.

D. Memory reconsolidation

1. Definition

For decades, it was thought that, once consolidated, memories were fixed forever (168, 303). However, even after months or years, memories may, through their reactivation, transiently become malleable and labile again (304-307). The hypothetical process of memory restabilisation into long-term memory is named memory reconsolidation (308, 309) and, in many ways, resembles the initial memory consolidation. For instance, just like consolidation, memory *re*consolidation would be a time- and sleep-dependant process, lasting only a few hours (168, 310-312). Although debated, biological mechanisms of reconsolidation are thought to partially overlap with those involved in memory consolidation (i.e., protein synthesis, synaptic plasticity) (307, 313-316) (317, 318). In the end, the main difference between memory consolidation and memory reconsolidation is that the former corresponds to memory stabilisation following the experience itself, while the latter follows memory reactivation.

The evidence in favour of memory reconsolidation is also reminiscent of the one in favour of memory consolidation. In one word, it is based on a set of studies showing that a memory or

learning can be modulated (weakened or strengthened) when an appropriate manipulation, whether pharmacological (e.g., a protein synthesis inhibitor) or behavioural (e.g., a competing learning), is offered shortly after memory reactivation (e.g., via trauma narratives, unreinforced CS presentation) (307, 315, 319). The seminal study by Nader, Schafe and Le Doux (2000) (320) is a good illustration: first, researchers induced fear conditioning in rats, by pairing tones with shocks. Then, they exposed the rats to a tone alone (= reactivation of the memory with the unreinforced CS), before administering either a protein synthesis inhibitor or artificial cerebrospinal fluid (placebo) in the lateral amygdala. Twenty-four hours later, rats who had received the protein synthesis inhibitor showed reduced freezing behaviour when exposed to the tone. Notably, there was no effect if the drug was administered beyond six hours after memory reactivation. This result suggested that reactivated memories need *de novo* protein synthesis to be restabilised into long-term memory. Since this publication, numerous laboratory studies have reproduced and reinforced this conclusion, across different experimental settings and species, from nematodes to rabbits and humans - notably for episodic memories (309, 313, 319, 321).

One may wonder what the function of memory reconsolidation is. What is the point of making stored information malleable and sensitive to interference again? The dominant hypothesis is that this allows us to update memories, by integrating relevant new elements present at the time of memory reactivation, strengthening or revising existing learning, and, in the end, allowing constant adaptation to a changing environment (226, 307, 322). This is why some authors speak of "reconsolidation update mechanisms" (277, 323). Indeed, during the reconsolidation window, opening within minutes following memory reactivation (306), memories can reconsolidate unchanged, strengthened, or weakened (56, 60, 168, 324), depending on what happens when they are labile. In principle, memories could go through a process of reactivation-reconsolidation multiple times (Figure 3), thus ensuring their relevance and up-to-dateness (325).

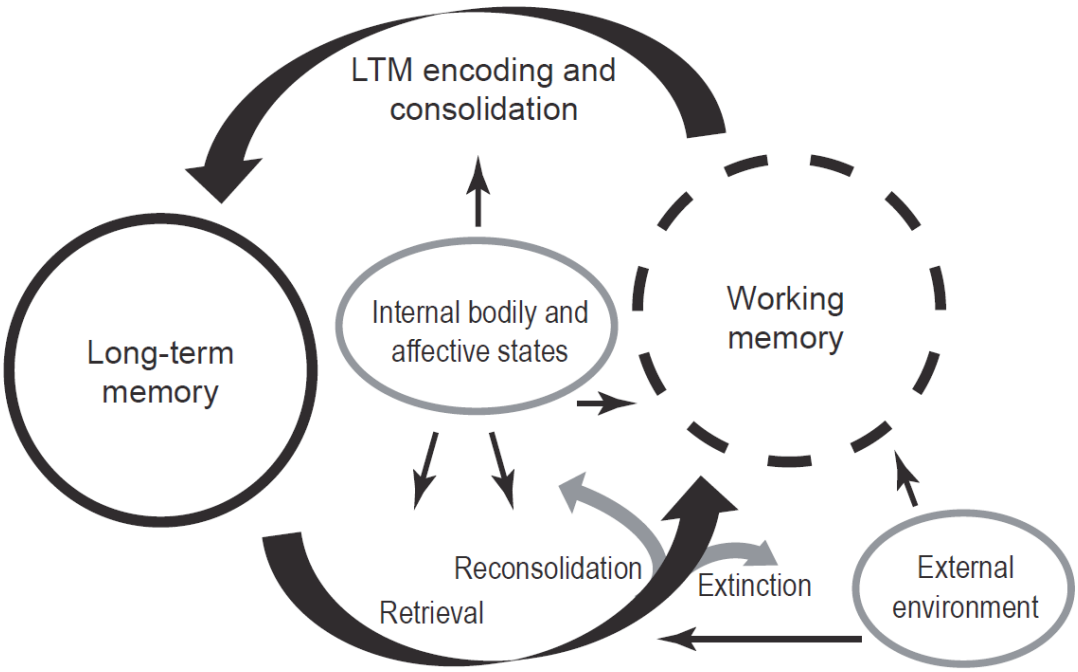

Figure 3. "*Interactive interplay in memory formation, maintenance, and modification. When initially acquired, memories are fragile and short lived. Some items or events may only be required for a brief moment and thus may be only temporarily maintained in working memory. Others may enter the process of consolidation and be stored in long-term memory. Upon retrieval, a consolidated memory* [...] *may re-enter working memory and be temporarily put to use or trigger mechanisms of extinction or reconsolidation*". Figure reprinted with permission from Visser et al. (2021) (56, p. 151).

Importantly, it should be noted that memory reconsolidation processes are a hot topic for psychologists and neuroscientists, and they are still debated. Some of the reasons for this dissensus include replication failures (e.g., 326, 327, 328), which would be under-represented in the rodent literature due to significant publication bias (as has been specifically highlighted in this research field (329)), and inconsistencies across memory types (226). This has led some researchers to propose alternative explanations, such as state-dependent learning, which postulates that pharmacological interventions induce physiological changes on which future memory retrieval will depend (see 307, 313, and 330 for a synthesis of the debate). On the other hand, it has been argued that, while replication failures and conflicting results may reflect the fact that this research field is still emerging (e.g., conditions allowing memory reactivation are not well understood yet (307)), the memory reconsolidation hypothesis is the one that currently best explains the observed data (308). One of the major difficulties encountered in the field is that, for the moment, it is not possible to measure memory reconsolidation by direct observation of the lability of the memory trace - and barely of the memory trace itself (331), although electroencephalography could be used to distinguish the retrieval of consolidated *vs*. reconsolidated memories (332). Therefore, the effects of a

manipulation are inferred from the supposed expression of memories (60). However, these indicators only confirm that a manipulation has worked in accordance with the assumed mechanisms, but not what has *actually* happened in the brain[13]. The most that can be said is that the results are "consistent with" the reconsolidation hypothesis (319). To some extent, this also applies to CBIs, notably those implicating behavioural tasks.

Admittedly, memory reconsolidation is speculative. In this thesis, however, the aim is not to take a stand in neuroscientific debates, which are far beyond its scope, but to focus on potential clinical applications. The reconsolidation hypothesis can be of great help in understanding certain clinical mechanisms. For example, it potentially explains why intrusive memories prevent the normative decay of trauma memory: by repeatedly inducing cycles of reactivation-reconsolidation, they could contribute to reinforcing the memory (68). Although it will be imperative to better understand their mechanisms in the future, reconsolidation-based interventions (RBIs)[14] thus seem to have a strong translational potential for tackling maladaptive emotional memories and to be an interesting avenue for developing treatments for CB-PTSD symptoms.

2. Translation to the clinic

Clinically, the reconsolidation hypothesis suggests that there may be not one but two windows of opportunity to target memories: their consolidation, and their reconsolidation (Figure 4). Thus, clinicians could attempt to use the reconsolidation-update mechanisms of memory, described as a fundamental property of memory (312), to the advantage of patients suffering from disorders involving maladaptive memories, such as PTSD, but also phobias and substance use disorders (319). The exciting objective would be to develop innovative and efficient therapeutic interventions harnessing the « *dynamic nature of memory* » (334, p. 1). As mentioned above, reactivated memories can reconsolidate strengthened, weakened, or unchanged. In the case of PTSD, it would therefore be possible, by reactivating the traumatic memory, to interfere with its reconsolidation and thus, to reduce its negative impact (335).

[13] For this reason, the terms "putative" or "assumed" memory reconsolidation processes can be found in the literature. In this thesis, these adjectives will not be used in order to increase the readability.

[14] In this thesis, reconsolidation-based interventions are considered as such if their design is explicitly grounded in the reconsolidation hypothesis. The term therefore does not apply to interventions that could *a posteriori* be hypothesised to rely on memory reconsolidation-update mechanisms, such as EMDR or some TF-CBT. See (333) for a discussion on memory reconsolidation processes in behavioural therapy, cognitive-behavioral therapy, emotion-focused therapy, and psychodynamic psychotherapy.

Such RBIs would be a breakthrough clinical advance and could overcome the limitations of exposure, since it is not a matter of creating a new inhibitory trace but of targeting the original one (168) – see (331) for an example of laboratory study showing that fear reduction can involve the original memory trace. In doing so, such an intervention would potentially have long-lasting and robust effects on PTSD symptoms. This prospect obviously interests PTSD clinicians and researchers: « *Novel pharmacological and psychotherapeutic approaches that target memory reconsolidation (sometimes referred to as "memory therapeutics") need to be moved toward the top of the priority list*" (336, p. 344).

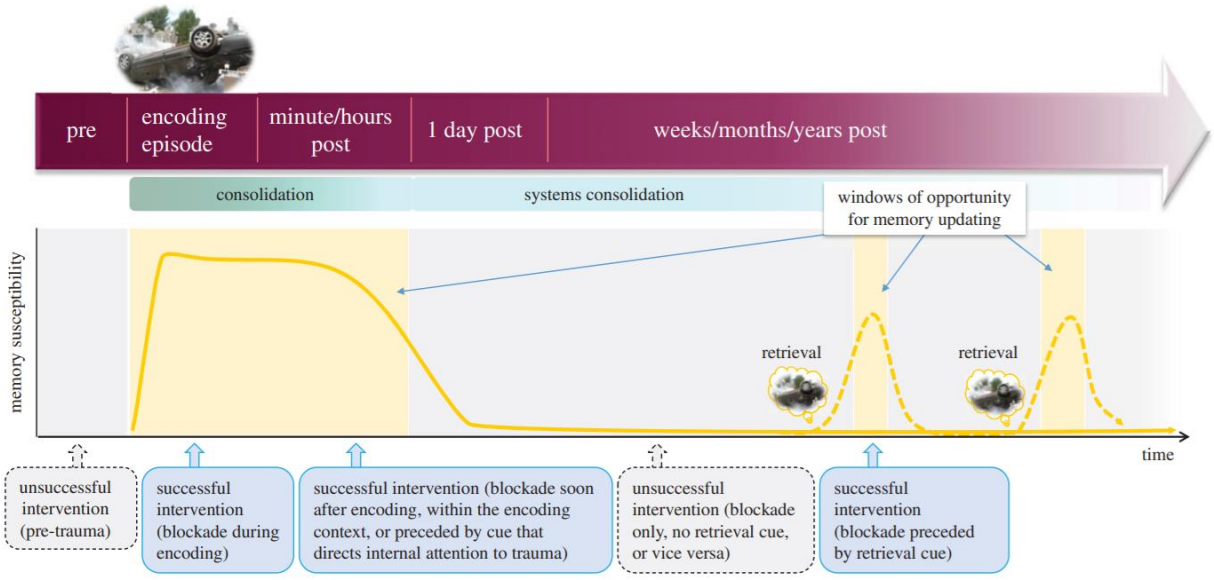

Figure 4. "*In the hours after an experience, memories are believed to go through an initial labile phase, before being stored into stable long-term memory, i.e. consolidation. The purple arrow depicts different time intervals with respect to the encoding of an aversive episode. Green gradients below indicate the putative processes of memory encoding and consolidation that occur during these different intervals, with systems consolidation referring to process by which memories become less hippocampus-dependent and integrated into a wider semantic network* [...]. *(Certain aspects of) memories* [...] *may become transiently malleable upon their reactivation, rendering them susceptible to interference or updating before returning to a fixed state, a process referred to as 'reconsolidation'. This offers a second window of opportunity to interfere with consolidated memory (shown by yellow background shaded areas). Successful interventions (blue arrows) need to be timed such that the blockade interferes with memory when it is in an active, susceptible state (indicated by the dotted yellow line)—either in the first hours after an experience, or at later time intervals after a retrieval procedure (e.g. reactivation through reminder cues)* [...]. *Unsuccessful interventions, timed when memories do not yet exist, or are in a fixed state (i.e. not recently retrieved), are indicated by grey arrows with dotted outlines*." Figure reprinted with permission from Visser et al. (2018) (60, p. 7).

Over the last years, numerous studies have therefore sought to develop RBIs (168, 226, 319), which are all articulated around two main and consecutive steps: 1. **Trauma memory reactivation**, for instance through its narration (337), and 2. **Trauma memory**

reconsolidation interference, which often involves techniques previously explored for CBIs (243). However, each of these steps has many translational challenges.

a. The challenges of reactivating a memory

Evidence suggests that memory retrieval is insufficient to reactivate a memory and to trigger a cycle of memory labilisation-reconsolidation (335, 338). This could be due to the function of memory reconsolidation, which is to keep memories up to date: it can be hypothesised that, without a worthwhile reason, such as the presentation of new relevant information to be integrated into the memory, it is unjustified for the organism to engage in a costly labilisation-reconsolidation cycle. Conversely, it seems advantageous to protect memories and learning, some of which are vital, by protecting them and limiting their malleability in most circumstances (339). In any case, several putative conditions would determine whether the memory is only retrieved or reactivated and labilised. These are called "boundary conditions". In order to keep this section as concise as possible, only those that have a direct implication on the methodology of the studies of this thesis will be mentioned here, but the reader is invited to peruse Treanor et al. (2017) (339) and Haubrich and Nader (2018) (312) for complete reviews.

1. The **duration of the memory reactivation session** would be a first boundary condition. A too short session may not be sufficient to elicit memory reactivation, whereas a too long one may trigger extinction (277, 340, 341). Indeed, memory reactivation-labilisation and memory extinction are suspected to be mutually exclusive and separated by an insensitive “limbo state” that does not allow memory reactivation either (342). Furthermore, the adequate duration of reminder cues may vary depending on other factors, such as the age of the memory or the duration of the initial learning (339, 343).
2. The **reminder cue specificity**, i.e., a strong similarity between cues used to trigger memory reactivation and the original trauma memory, is important because reminder cues that are too different may create a new memory trace instead of reactivating the one that we seek to labilise (339, 344, 345). Consequently, in RBIs targeting a trauma memory, personal narratives, whether oral or written, are often used as reminder cues (e.g., 243, 337, 346, 347). By definition, personal narratives are very specific.

3. The **context specificity** condition posits that memory reactivation will be facilitated in the same environment as the one where the initial trauma occurred (312, 339, 340, 345, 348). Supposedly, this is important, as it contributes to the global reminder cue specificity of the reactivation session. Context specificity is a relatively easy condition to meet in the laboratory, as rodents are simply placed in the same box as the one in which they received the initial conditioning. This also applies to humans who can, for instance, come back to the room where they initially watched the trauma film. In contrast, this condition could pose major limitations for the translation to the clinic, as it may be very difficult to return to the traumatising context. Indeed, this may not be possible for practical reasons (e.g., a veteran who has been traumatised in another country). Moreover, revisiting the place where the trauma occurred may be too distressing for the patient, which is ethically unacceptable and could compromise the patient's ability to engage in the intervention procedures. To my knowledge, context specificity has never been harnessed in RBIs for PTSD. In the case of CB-PTSD, however, it may be considered because the trauma context, i.e., the maternity ward, is easily accessible.
4. **Strength** and **age of the memory** are two additional boundary conditions to take into account. Indeed, strong and old memories are assumed to be more resistant to memory reactivation (313, 319, 339) (but see 321), in particular if regular IMs tend to reinforce the memory (68). Thus, they may necessitate a longer and/or more engaging reactivation session, which may risk inducing extinction (340, 349).

Given that PTSD results from particularly strong and lasting trauma memories, and that patients may only been seen years later, boundary conditions probably have particularly important implications in the context of clinical interventions. A crucial question for the translation to the clinical setting is whether recounting specific points of the traumatic experience can reactivate the whole memory. Current evidence is mixed (168, 344, 350). In human episodic memory, narratives would be more responsive to RBIs, compared to lists of elements, which is assumed to be due to the "cohesive nature" of narratives (321), making story components more closely linked to each other. Some evidence from laboratory studies on fear conditioning in humans also suggests that RBIs can have a fear reduction effect on stimuli that were not directly reactivated but semantically linked (e.g., new pictures of different spiders than the one which was initially used for fear conditioning) (351) which is very encouraging for translation. This is in line with what would have been expected in the

fear network model (84, 87) (presented in Section I.A.7 and Appendix B): the elements of the trauma memory are so closely interconnected and associated in PTSD, especially in a single-event trauma such as a childbirth, that even an incomplete account may reactivate the whole memory.

Overall, there are many important conditions for reactivating a memory and rendering it labile. Without a successful memory reactivation, it is impossible to interfere with its reconsolidation. However, the work on boundary conditions is still in its infancy, and many questions remain unanswered: boundary conditions may vary across species, memory types, thus « *there is* […] *no single, universally effective reactivation procedure that always induces reconsolidation* » (165, p. 4). Additionally, current knowledge is largely based on laboratory studies, particularly in rodents. However, their translation to the clinical context of PTSD is not so straightforward. "Old" laboratory memories, for instance, are only a few days old (e.g., 321, 340), whereas in PTSD, traumatic events may have occurred decades ago. The discrepancies between laboratory and clinical conditions could therefore hinder the development of RBIs.

b. The challenges of interfering with the reconsolidation of a memory

Once a memory is successfully reactivated, interfering with its reconsolidation brings its own set of challenges. The first is the intervention timing: indeed, evidence suggests that the reconsolidation process lasts a few hours (60). In rodent studies, reconsolidation blockades seem not to be efficient anymore beyond six hours post-reactivation (320, 352). However, the exact duration of the reconsolidation window in humans having reactivated episodic memories with a fear component is unknown, which suggests that the blockade should be offered as quickly as possible. On the other hand, it has been hypothesised that a reactivated memory is not immediately labile and that it takes about 10 minutes to allow for memory labilisation (306). This has led some authors to include a 10-minute "filler task" (e.g., rating music pleasantness, watching a TV show) between the memory reactivation session and the interference task (e.g., 300, 323, 353). However, the rationale for that time gap is not entirely clear, as I am not aware of a study demonstrating that reconsolidation blockades do not work if proposed before these 10 minutes. On the contrary, some studies did not include a filler task but still found that their reconsolidation blockade was efficient (299, 337). Therefore, to date,

the 10-minute time gap between reactivation and reconsolidation interference looks more like a precautionary principle than an evidence-based principle.

The evaluation of the effect of reconsolidation blockades is also limited by the fact that, as explained above, a marker of memory lability has not been found yet, which considerably hinders data interpretation and tends to limit research to a trial and error approach. It becomes impossible to draw targeted conclusions about reactivation or reconsolidation blockades: in case of a negative result, it may well be that only one part of the procedure has failed (either memory reactivation or interference with the memory reconsolidation), without knowing which one.

3. Memory reconsolidation-based interventions

a. Overview of tested RBIs

Over the last decade, a growing number of studies testing RBIs, both in healthy volunteers and clinical samples, has been published. Because of the assumed similarities between memory consolidation and reconsolidation, some blockades that were tested to interfere with the former are now tested on the latter. This is typically the case of **propranolol**, a single administration of which showed promising results in healthy participants exposed to negative emotional material (242, 354), reducing fear response while leaving declarative memory intact (165, 355). Indeed, propranolol, when reaching its peak concentration during the memory reconsolidation window, appears to dampen physiological responses (e.g., skin conductance and heart rate) to trauma-related material, as well as to reduce PTSD symptom severity (356, 357). It has also been tested in a multiple-session design (i.e., one weekly intervention combining trauma memory reminder cues and propranolol administration, over 6 weeks (358)) in a sample of treatment-seeking patients with PTSD, who showed reduced PTSD symptom severity compared to the placebo group. However, most reviews highlight that the existing few studies have significant limitations (very small sample sizes, short follow-ups), and that contradictory findings have also been reported (347, 354, 359, 360). Furthermore, one very recent systematic review and meta-analysis, which only integrated RCTs conducted on PTSD patients, found no effect of propranolol-based reconsolidation interventions on PTSD symptoms (243).

Another commonly studied RBI is the **reactivation-extinction procedure**, also named post-retrieval extinction (349). In a word, it is an extinction training offered after exposure to a brief reminder cue seeking to reactivate the targeted memory. By carrying out the extinction training within the reconsolidation window, this technique would allow the inhibitory trace to be directly integrated into the original trauma memory trace. Initially tested on rodents (352), reactivation-extinction has also shown encouraging results on the fear memories induced by fear conditioning in humans (360, 361) with effects lasting up to 18 months (362), despite notable replication failures (168, 326, 363). As far as I know, the few clinical studies available are designed for patients suffering from phobia or substance use disorder, but not from PTSD symptoms.

While propranolol and reactivation-extinction seem to be the two most studied techniques to interfere with the reconsolidation of negative emotional memories (360), other single or multiple session blockades are also under investigation, such as **rewinding techniques** (364), **metyrapone** (365), or **electroconvulsive shocks** (366). Some of them, like the **Reconsolidation of Traumatic Memories** (RTM), a multiple-session therapy combining brief trauma narratives with distancing exercises (e.g., imagining traumatic scenes displayed in black and white on a movie theatre screen) have been reported as particularly promising in a recent systematic review and meta-analysis, although available RTM RCTs were rated as being at high risk of bias (243). As mentioned before, these are all interventions that are *assumed* to be based on the reconsolidation of memory. In some cases, the research teams have done rigorous investigation work in the laboratory (e.g., studying all the components separately (319) - which is almost impossible to do in a clinical setting) to strengthen the reconsolidation hypothesis; however, this is not always the case (319). It is not within the scope of this thesis to review all the RBIs, but, if interested, the reader is invited to look at the reviews available on this subject, notably Kroes et al. (2016) (359) and Elsey, Van Ast and Kindt (2018) (319), a very thorough review of RBIs across memory types.

b. RBIs involving a visuospatial task

In the midst of these preliminary studies, RBIs involving a visuospatial task (RBIs-VT) could be an interesting alternative. Indeed, they would have the advantage of being easily accessible (since there would be no specific medical contraindications) and they would not necessarily require highly trained clinicians, such as with RTM or reactivation-extinction - although

following rigorous procedures remains crucial. Moreover, they could be suitable for a single-session format and thus be attractive for patients, as they would only require a very brief exposure to the trauma memory (in RTM and reactivation-extinction, the blockade phases involve prolonged contact with the trauma-related material).

- **Laboratory findings**

The idea of combining the reconsolidation framework with an interfering visuospatial task such as Tetris emerged a few years ago, and resulted in three TFP-based laboratory studies on healthy volunteers (299, 300, 323). All of them started with the viewing of a trauma film, followed 24 to 96 hours later by the intervention. The tested intervention involved: **1. A memory reactivation phase**, consisting of exposure to images extracted from the trauma film during 19-28 seconds, **2. A memory labilisation phase** (except for one study (299)), with a 10-minute filler task, **3. A memory reconsolidation interference phase**, during which participants played Tetris for 10 to 15 minutes (with instructions to promote mental rotation in two studies (300, 323)). From the initial trauma film viewing to up to one week post-intervention, participants filled in a daily diary in which they reported their film-related IMs. The three studies found that participants who received the intervention had significantly fewer IMs in the post-intervention days of the diary, compared to participants who did not receive it or those who received an incomplete intervention (i.e., no Tetris or no prior reactivation) (299, 300, 323). One study also found that IMs were less easily triggered at one week post-intervention (323). In the two studies which tested it, participants from all groups had similar scores on the film recognition task (299, 323), thus suggesting that the declarative memory of the trauma film was unaltered by the interventions.

Importantly, the data from the study that tested the intervention at 24 hours post-film viewing were later reanalysed by an external research team, who suggested that the observed improvements were due to a simple Tetris effect, regardless of the presence of the prior reminder task (367). It has been suggested that the study may have been underpowered to detect interactions between conditions (349). However, in light of the work on the context specificity boundary condition, it may simply be that participants in the "Tetris only" group still had their memory reactivated by returning to the research laboratory where they had previously been exposed to the trauma film. Thus, unbeknownst to the researchers, they would still have received a full intervention, including a memory reactivation phase (i.e., being

in the trauma context) and a visuospatial task. Alternatively, given the current scientific evidence, one can wonder whether the 24-hour delay is sufficient, in humans, to speak of memory reconsolidation. Most probably, memory consolidation is a continuous process that does not stop exactly at six hours, and it is possible that *consolidation*-based interventions involving a visuospatial task are still effective at 24 hours post-trauma. However, it is difficult to know which hypothesis is valid because the other two studies that tested the interventions at 72 and 96 hours post-film viewing did not include a group that only played Tetris (the control groups only did the reactivation phase).

• Clinical studies

RBIs-VT in clinical samples are extremely sparse. An open label case series on 20 inpatients with PTSD following multiple traumatic events tested a multiple-session intervention combining the written description of a specific IM with a 25-minute long Tetris gameplay (337). The multiple-session allowed targeting IM in turn, which seems adapted for multiple event-traumas, given that reactivating all the trauma memories in one session is not possible. From pre- to post-intervention, the number of the targeted IMs was reduced by 64%, versus 11% for the non-targeted IMs ones, suggesting that the intervention specifically affected the reactivated trauma memories. The remaining 11% may be due to the fact that inpatients received the intervention while receiving other PTSD-related care in parallel, which could explain why seven participants also reported at least 50% reduction in their total PTSD score. In addition to this study by Kessler et al. (2018) (337), three additional very small studies (one case study and two single case series with three and four participants, all involving multiple Tetris sessions) found that a similar RBI-VT led to a reduction of the number of IMs and of PTSD symptoms (368-370). All participants involved in these studies had IMs linked with several traumatic events.

4. Future directions and needs

As illustrated in the previous section, there are few clinical studies testing a RBI-VT, although the main one by Kessler et al. (2018) (337) showed encouraging results. Beyond its effects on the number of IMs, which are to be confirmed in further studies, many questions remain. Firstly, none of the above-mentioned studies tested the intervention on IMs linked with single-event traumas, such as traumatic childbirth. Yet, single-event traumas have

specificities that could be used to advantage with a RBI-VT. For example, rather than targeting IMs one by one, across multiple sessions, it might be possible to draw on the strong relationships between the different elements of the single trauma memory network (87, 321) to aim for a global memory reactivation. Secondly, the benefits of RBIs-VT on the overall severity of PTSD symptoms have not been studied, bearing in mind that participants in Kessler et al. (2018) (337) were receiving other PTSD-related care in parallel to their participation. Thirdly, there are no data on the effects of RBIs-VT on the qualitative characteristics of IMs, whereas this would allow a better understanding of the benefits of IMs on patients' daily lives. Indeed, IMs are not only characterised by their number or frequency, they can also have variable impacts according to their associated distress or their "nowness" (Section I.A.6). Furthermore, both IMs-related distress and nowness have been reported to be predictors of concurrent and subsequent PTSD symptom severity (61). Fourthly, according to the sensory modality hypothesis, IMs having a visual component would be more responsive to such interventions than those with other sensory modalities, but, as far as I know, this has not been tested. Measuring the sensory modality of IMs following RBIs-VT may thus provide insights on potential mechanisms of the intervention.

E. Overarching aim of this thesis

The overarching aim of this thesis is to contribute to the development of innovative clinical interventions to address maternal symptoms of CB-PTSD. It is part of a global research trend in the memory (re)consolidation field, which seeks to translate fundamental research and laboratory findings into applied proposals, directly benefiting the mental health of women (at risk of) experiencing CB-PTSD symptoms. While taking into account the specificities of the perinatal context, all the studies in this thesis were conducted with an eye on the potential interest of CB-PTSD studies for other populations having PTSD symptoms. Ultimately, their aim is to participate in the development of preventive or therapeutic interventions that draw on the most recent available evidence. However, it is perhaps useful to point out that, while these studies are based on the hypotheses of memory (re)consolidation, and while they hope to provide some relevant data to inform mechanistic discussions, they have neither the ambition nor even the possibility, due to their clinical nature, to formally identify the at-stake mechanisms. Although it is obviously essential to understand them, we believe that "*the clinical utility of a* [re]*consolidation-based procedure does not necessarily stand or fall on whether or not it represents a definitive demonstration of* [re]*consolidation, but on whether it*

can produce the desired outcome: effectively alleviating the burden of mental illness" (319, p. 841). Beyond the overarching aim of developing interventions to prevent or reduce maternal CB-PTSD symptoms, the four studies of this thesis (Figure 5), which span, in chronological order, the four time points of the perinatal period, have two more specific objectives:

1. **OBJECTIVE 1:** To identify factors that may modulate the consolidation of traumatic childbirth memory and on which it would be possible to intervene to prevent the development of CB-PTSD symptoms.
    - **Objective 1.1 (Study 1, primary prevention):** To investigate the association between prenatal insomnia symptoms and CB-PTSD symptoms, with a prospective cohort study.
    - **Objective 1.2 (Study 2, primary and secondary prevention):** To investigate the association between morphine and N_2O intake during childbirth and CB-PTSD symptoms, with a prospective cohort study.
2. **OBJECTIVE 2:** To develop and test the effectiveness of interventions that would interfere with the (re)consolidation of traumatic childbirth memory to prevent or reduce CB-PTSD symptoms.
    - **Objective 2.1 (Study 3, secondary prevention):** To test and confirm the effectiveness of a CBI-VT to prevent CB-PTSD symptom development, with a multicentre, double-blind RCT.
    - **Objective 2.2 (Study 4, treatment):** To develop and test the effectiveness of a RBI-VT to reduce CB-PTSD symptoms, and particularly CB-IMs, with a single-group pre-post study.

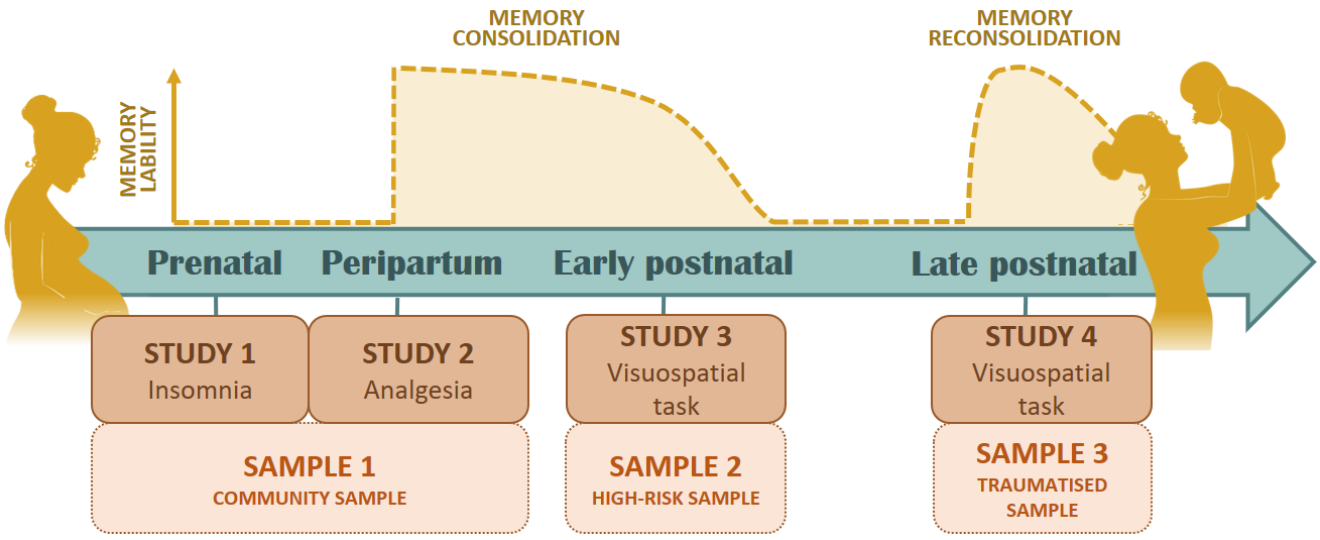

Figure 5. Overview of the thesis studies.

II. Thesis studies

A. Study 1 - The association between prenatal insomnia and CB-PTSD symptom severity: a prospective population-based cohort study

Study 1 (371) has been accepted and will be published in the *Journal of Affective Disorder* in December 2021. The article can be found in Appendix D (and the supplementary material in Appendix E). Please note that Study 1 was not initially planned. It was carried out in place of a study on sleep within the memory consolidation window, presented during the mid-thesis examination, as the data collection for the latter was interrupted by the COVID-19 pandemic.

1. Background and aims

Prenatal insomnia symptoms may be a risk factor for subsequent CB-PTSD symptoms, and thus a relevant target for CB-PTSD primary preventive interventions. This study aimed to examine the association between prenatal insomnia symptoms at 32 weeks of pregnancy and CB-PTSD symptom severity at eight weeks postpartum, while controlling for factors that may influence one or both of these variables, namely prenatal psychological symptoms (depression, anxiety, PTSD, FOC), childbirth-related factors (SBE, birth medical severity) and postnatal insomnia symptoms. It was hypothesised that more severe prenatal insomnia symptoms would predict more severe CB-PTSD symptoms, and that this prospective association would be fully mediated by postnatal insomnia symptoms and a negative SBE (see Box 7, Section I.B.1).

2. Methods

Study sample and procedure: The data were derived from a large population-based prospective cohort study, the Akershus Birth Cohort (ABC). Women planning to give birth at the Akershus University Hospital (Norway) between November 2008 and April 2010 were eligible to participate if they could fill in questionnaires in Norwegian. Recruitment took place at 17 weeks of pregnancy, during the routine foetal ultrasound examination. Participants completed paper questionnaires at 17 weeks and 32 weeks of pregnancy, as well as eight weeks and two years postpartum – the latter were not used in the present study. Those who

delivered between May 2009 and September 2010 answered additional questions related to childbirth-related pain and SBE, at 48 hours postpartum. The ABC study was approved by the Regional Committee for Medical and Health Research Ethics (approval number S-08013a), and all participants provided written informed consent.

At 17 weeks of pregnancy, 3,752 participants initially completed the questionnaires, but 131 were excluded due to obstetrical complications or to a new address. For the present secondary analyses, participants were further excluded if they had: 1. Taken sleeping pills over the last 10 weeks of pregnancy, 2. Missing data in the questionnaires of interest, 3. Unavailable hospital birth record. The final sample consisted of 1,610 participants (see study flowchart, Appendix D, Figure 1).

Measures: CB-PTSD symptoms at eight weeks postpartum were measured with the Impact of Event Scale (IES) (372). The IES is a 15-item self-report questionnaire, each item having four response categories. It has been validated in postpartum women (373), and participants were instructed to complete it in relation with their last birth. In the original scoring, a total score (range: 0–75) above 34 indicates probable PTSD (374). Insomnia symptoms were assessed at 32 weeks of pregnancy and eight weeks postpartum, with the Bergen Insomnia Scale (BIS) (375). It is a validated six-item self-report questionnaire assessing the frequency of insomnia symptoms per week, over the past month. The BIS is based on DSM-IV-TR, and higher total scores (range: 0–42) reflect more severe insomnia symptoms.

As for the other study variables, prenatal PTSD symptoms were measured at 17 weeks of pregnancy, with an eight-item PTSD symptom checklist derived from the Mini International Neuropsychiatric Interview (MINI) (376). Participants reported whether they had any symptoms on the checklist over the past month, in relation to a dramatic or terrifying event they might have experienced (total score range: 0–8). Prenatal depression symptoms, prenatal anxiety symptoms, as well as FOC, were all assessed at 32 weeks of pregnancy with validated self-report questionnaires, respectively the Edinburgh Postnatal Depression Scale (EPDS) (377), the anxiety scale of the Hopkins Symptom Checklist (SCL-A) (378), and the Wijma Delivery Expectancy/Experience Questionnaire version A (W-DEQ) (379). SBE was measured at eight weeks postpartum, with three self-report Likert scales assessing 1. The overall SBE, 2. To what extent participants felt frightened and 3. Well taken care of during childbirth. Finally, based on hospital medical records, a dichotomous variable was created to

reflect birth medical severity, distinguishing participants whose birth involved vacuum, forceps or ECS from the others. Please see Appendix D (Section 2.2) for further details on each of the study measurements, including socio-demographic ones.

Data analysis: Given that a Structural Equation Modelling (SEM) (380) approach was planned, and in order to obtain appropriate numeric scores, all the aforementioned questionnaires were statistically treated using item response models (IES, MINI checklist, EPDS, SCL-A) or factor techniques (BIS, W-DEQ, SBE questions). Please see Appendix E for a detailed description of statistical treatments applied to the questionnaires.

A piecewise SEM (381), using the piecewise SEM R package (382) on R version 4.0.4 (383), was used to examine the association between prenatal insomnia symptoms and CB-PTSD symptom severity. The first developed model (M1) included eight associations between the different study variables, seven that were theoretically expected and one for statistical reasons (repeated measurement of insomnia). The model's global fit was examined with Fisher's *C* statistic and admissible but non-included associations were tested, for each model, through a set of directed separation tests (384). Depending on the latter, additional significant associations were progressively included (high criterion values first), resulting in a sequence of increasingly complex models. A good predictive model of CB-PTSD symptom severity was pre-defined as 1. Being inclusive, 2. Being parsimonious, 3. Including only statistically significant associations, and 4. Showing a good fit (see details in Appendix D, Section 2.3.2). Effect sizes were expressed with Cohen's f^2 indices (385), except for predictors of CB-PTSD which were calculated with squared Robust Effect Size Indices (RESI) (386) due to the strong bimodal zero-inflated distribution of IES scores.

3. Results

Sample description: At the time of their childbirth, the majority of participants were married or cohabiting (n = 1,565, 97.25%), the mean age was 31.29 years (SD = 4.54), 50.4% of them were nulliparous (n = 812), and 20.3% of the deliveries involved vacuum, forceps or ECS (n = 327). Finally 1.9% of participants had probable CB-PTSD at eight weeks postpartum (n = 30), according to the original IES scoring (see Appendix D, Table 1, for a full description of the study sample).

Prediction of CB-PTSD symptom severity: M1 did not show acceptable fit (Fisher's C = 946.444, d.f. 36, p < .001), although all regression coefficients, notably the association between prenatal insomnia symptoms and CB-PTSD symptom severity, were significant *(*p < .001). The sequential addition of admissible associations led to an acceptable model, M12 (Fisher's C = 20.458, d.f. 14, p = .116), within which the association between prenatal insomnia and CB-PTSD symptom severity was not significant anymore (β = -0.0016, s.e. = 0.0160, d.f. 1603, t = -0.1021, p = .919). The latter was thus removed given that the reduced model, M13, did not significantly differ from M12 ($\chi^2(2)$ = 0.397, p = .82) (see model comparison in Appendix D, Table 2). M13 met all the aforementioned quality criteria, in particular a satisfying global fit (Fisher's C = 20.855, d.f. 16, p = .184) (see Appendix D, Tables 3 and 4). In this final model, as predicted, the prospective association between prenatal insomnia symptoms and CB-PTSD symptom severity was fully mediated by postnatal insomnia symptoms and a negative SBE (Figure 6, next page). All associations implicating insomnia symptoms had small or very small effect sizes (Appendix D, Table 4). Furthermore, prenatal psychological symptoms (depression, anxiety, PTSD and FOC) all predicted prenatal insomnia symptoms as well as postnatal insomnia symptoms (except for depression), thus confirming their importance as covariates.

4. Conclusion

This study suggested that prenatal insomnia symptoms may be a risk factor for subsequent CB-PTSD symptom severity, via two pathways. First, through their association with a negative SBE and, second, through their association with postnatal insomnia symptoms, as both SBE and postnatal insomnia were predictive of more severe CB-PTSD symptoms. Another important point is that the results highlight the importance of post-traumatic insomnia as a confounder, something which had never been, to my knowledge, taken into account in studies on pre-traumatic insomnia and PTSD. Clinically speaking, this study tentatively suggests that prenatal insomnia symptoms may be a relevant target for CB-PTSD primary prevention. However, given that effect sizes were all small or very small, further studies would be necessary to clarify whether interventions reducing prenatal insomnia symptoms such as CBT for insomnia, which is still not widely prescribed but yet recommended as first line treatment for chronic insomnia (387, 388), do yield significant benefits or not.

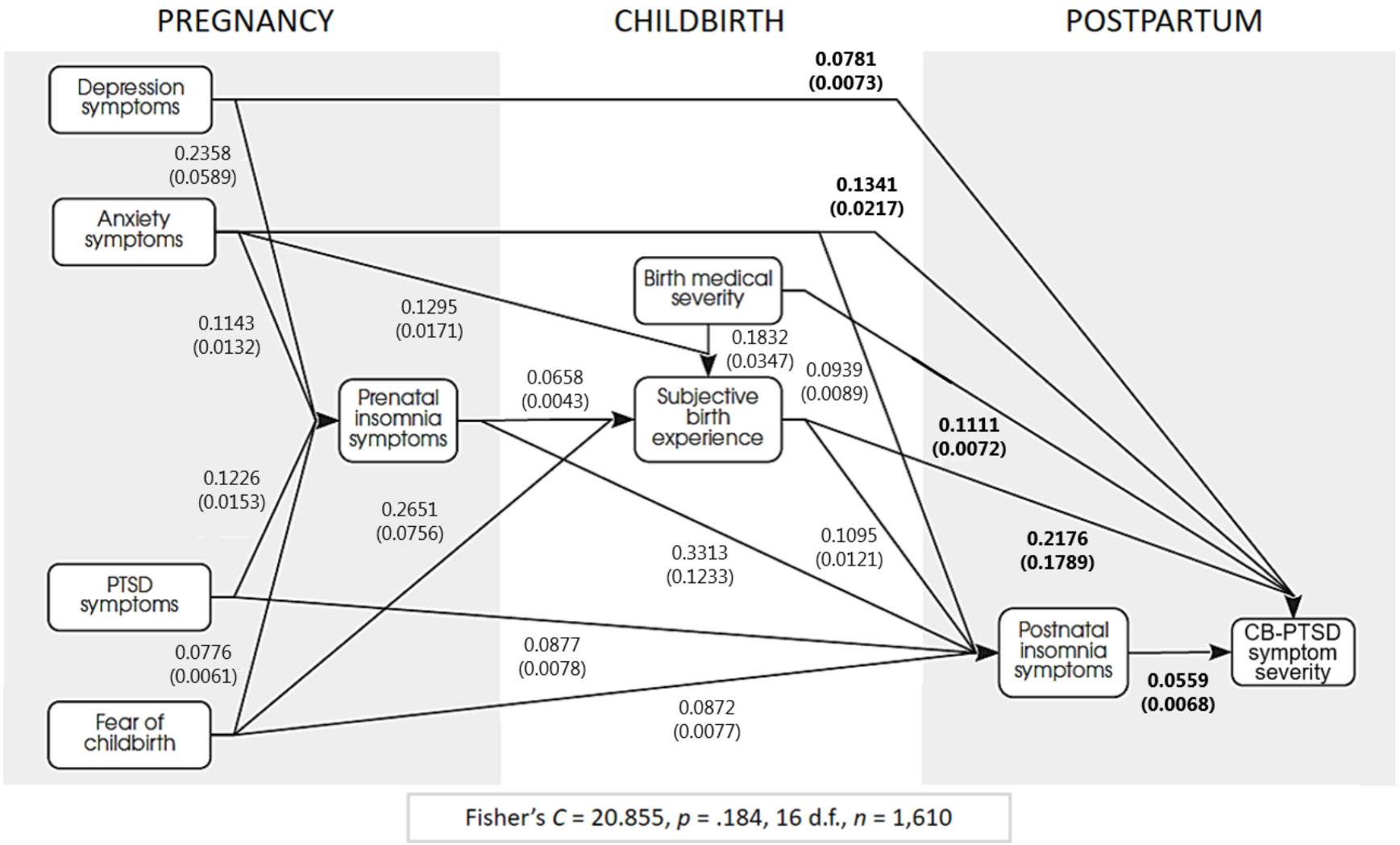

Figure 6. Final model (M13) describing prospective associations between prenatal insomnia symptoms and CB-PTSD symptom severity.
Note. CB-PTSD = Childbirth-related PTSD. Subjective birth experience is negatively oriented. Only the statistically significant pathways are shown. For each of them, standard estimates and effects sizes (Cohen's f^2 indices (385), in brackets) are indicated. For associations implicating CB-PTSD symptoms (in bold), for which a log link function was used in the Tweedie model, only the unstandardised coefficients are reported. Corresponding effects sizes (in bold, in brackets) are expressed with squared Robust Effect Size Indices (RESI) (386), also readable on a Cohen's f^2 scale (small effect: 0.02, medium effect: 0.15, strong effect: 0.35.

5. Personal contribution

I had the original idea for this study, and significantly contributed to its conception. I coordinated the data sharing between Norway, Switzerland, and France and extracted the dataset. I coordinated the statistical analyses, which were carried out by a statistician, and was highly involved in the data interpretation. Except for sections linked with the statistical analyses, I drafted the manuscript. I was also responsible for the entire publication process.

B. Study 2 - The association between early administration of morphine or nitrous oxide gas and CB-PTSD symptoms: a prospective population-based cohort study

Study 2 (389) was published in the *Journal of Affective Disorders*, in February 2021. The article can be found in Appendix F (and the supplementary material in Appendix G).

1. Background and aims

Commonly used during childbirth, morphine and N_2O may incidentally prevent the development of subsequent CB-PTSD. The two main reasons for making this hypothesis are that: 1. Both analgesics may interfere with the consolidation of the childbirth memory ("memory consolidation interference assumption", see Section I.C.3.a) and 2. Both aim at reducing childbirth-related pain, which is a risk factor for CB-PTSD (17, 33, 54) ("pain relief assumption"). If proven correct, this may pave the way for pharmacological prevention of CB-PTSD and inform parturients' and clinicians' choices regarding obstetrical analgesia. The objective of Study 2 was thus to investigate the association between analgesics intake (morphine and N_2O) during childbirth and CB-PTSD symptoms at eight weeks postpartum, whilst controlling for labour pain, prenatal PTSD symptoms and birth medical severity. These two last covariates where chosen because they are important risk factors for CB-PTSD and birth medical severity may also affect analgesics intake. It was hypothesised that receiving either of these drugs would predict reduced CB-PTSD symptoms.

2. Methods

Study sample and procedure: Like Study 1, Study 2 was derived from the ABC study. The reader is therefore referred to the method section of Study 1 for further details on this cohort and its time points. The main difference from Study 1 is the exclusion criteria, which were: 1. Missing data in the 8-week questionnaire, 2. Administration of pethidine, general anaesthetics (narcosis), or opiates other than morphine during childbirth, as these drugs may have independent effects on CB-PTSD symptom development, and 3. Unavailable hospital birth record. The final sample consisted of 2,070 participants (see study Appendix F, Figure 1).

Measures: CB-PTSD symptoms, prenatal PTSD symptoms and birth medical severity were respectively measured at eight weeks postpartum, 17 weeks of pregnancy and at birth, like in Study 1. They were measured in the same way as described for Study 1. Information regarding morphine and N_2O intake during childbirth was extracted from the hospital birth records: a dichotomous variable was created for each analgesic, depending on whether they had been used during the birth or not. Note that both were administered during labour. Morphine was injected intramuscularly, while 30 to 50% N_2O was given via an inhalation mask that participants could use as needed. Pain during labour was measured at eight weeks postpartum, with the following question: "*How much pain did you feel during labour?*", on a 11-point scale, from 0 ("*No pain at all*") to 10 ("*Most intense imaginable pain*"). The same question was also asked at 48 hours postpartum, but only the eight-week measurement was used because of a larger sample size available (2,070 *vs.* 682 participants). However, pain ratings from both time points were highly correlated ($r = .76$, $p < .01$) and indicated good test–retest reliability (intraclass correlation = .88, $p < .001$).

Data analysis: The total scores of CB-PTSD symptoms and prenatal PTSD symptoms were statistically treated in the same way as in Study 1 (see Section II.A.2 and Appendix E, Section 1.1). Because of a zero inflated distribution of the CB-PTSD scores, which was also Gamma-like skewed, a Zero-inflated Tweedie compound Poisson model (390) was chosen. This model comprised two sets of regressions, resulting from its two components: 1. A zero inflation model, to predict the presence *vs.* absence of CB-PTSD symptoms and 2. A Tweedie compound Poisson model, to predict CB-PTSD symptom severity. All analyses were carried out with the 'cplm' R package (390), using R version 4.0.4 (383). For each of the two aforementioned components, four models of increasing complexity were tested (i.e. from a reduced model including only main effects, to a full model including main effect as well as first and second

order interactions, see Appendix G, Section 3, for a full description). This resulted in 16 models, which were compared using the Akaike Information Criterion (391). RESI (386) were calculated for each coefficient of the best model.

3. Results

Sample description: The study sample had very similar characteristics to that of Study 1, in terms of marital status, age, parity, birth medical severity and proportion of participants with probable CB-PTSD. During childbirth, 59.2% of participants had received N_2O only (n = 1,225), 0.8% had received morphine only (n = 17) and 1.5% had received both analgesics (n = 32). The remaining 38.5% of participants had received neither (n = 796), and reported significantly less pain during labour than those who received N_2O only ($p < .001$) or both N_2O and morphine ($p < .01$) (see Appendix F, Tables 1 and 2, for a full description of the study sample).

Prediction of CB-PTSD symptoms: The best model included only a main effect on the zero inflation component, and main and first order interactions in the Tweedie component (see model comparison in Appendix G, Table S1). In the zero inflation component (Appendix F, Table 3.a), the presence of CB-PTSD symptoms was predicted by more prenatal PTSD symptoms, more severe labour pain, and birth medical severity, which reinforced the relevance of these variables in the analyses. However, only pain was close to a noticeable effect size (S = 0.0978). In the Tweedie component (Table 1), N_2O intake predicted lower CB-PTSD symptom severity (β = -0.4062, $p < .001$), with a small to medium effect size (S = 0.1121). A similar tendency appeared for morphine, but the coefficient was not significant (β = -0.8454, p = .064) and the effect size was null to small (S = 0.0290) (Table 3.b). There was also a positive interaction between both analgesics and labour pain, with small to medium effect size for N_2O (S = 0.1179) and null to small effect size for morphine (S = 0.0326). This means that participants receiving one of these two drugs developed more severe CB-PTSD symptoms if they experienced severe labour pain. As illustrated by Appendix F (Figure 3), the administration of morphine, N_2O or both predicted more severe CB-PTSD symptoms from a pain rating of about 9 out of 10.

Table 1. Estimated coefficients on the Tweedie regression model of CB-PTSD symptom severity.

	Estimate[a]	Std. Error	z value	Pr(>|z|)	RESI[b]
(Intercept)	0.4168	0.0469	8.8948	0.0000***	0.2111
Prior PTSD	0.0785	0.0521	1.5067	0.1319	0.0196
Pain	-0.0004	0.0062	-0.0594	0.9527	0.0000
Birth Medical Severity	0.0305	0.0917	0.3325	0.7395	0.0000
N_2O	-0.4062	0.0841	-4.8291	0.0000***	0.1121
Morphine	-0.8454	0.4568	-1.8507	0.0642	0.0290
Prior PTSD x Pain	0.0072	0.0070	1.0286	0.3037	0.0000
Prior PTSD x Birth medical severity	-0.0306	0.0451	-0.6776	0.4980	0.0000
Prior PTSD x N_2O	-0.0402	0.0407	-0.9872	0.3236	0.0000
Prior PTSD x Morphine	-0.0637	0.1210	-0.5260	0.5989	0.0000
Pain x Birth medical severity	0.0217	0.0119	1.8258	0.0679	0.0373
Pain x N_2O	0.0514	0.0101	5.0820	0.0000***	0.1179
Pain x Morphine	0.0999	0.0508	1.9655	0.0494*	0.0326
Birth medical severity x N_2O	-0.0580	0.0586	-0.9901	0.3221	0.0000
Birth medical severity x Morphine	-0.0065	0.1575	-0.0411	0.9672	0.0000
N_2O x Morphine	0.0390	0.1462	0.2668	0.7896	0.0000
Dispersion parameter :	0.19617				
Index parameter :	1.8681				

Note. RESI = Robust Effect Size Index; N_2O = Nitrous oxide gas.

[a] Estimates represent unstandardised β values.
[b] Interpretation of Robust Effect Sizes (RESI) (386): [0;0.1]: None-Small,]0.10;0.25]: Small-Medium,]0.25;0.4]: Medium-Large.

* $p < .05$, ** $p < .01$, *** $p < .001$.

4. Conclusion

In this study, N_2O intake during childbirth was associated with reduced CB-PTSD symptom severity at eight weeks postpartum. This was not the case for morphine, but the *p*-value was small and only 49 participants of the sample had received morphine, thus we may have lack of power for this analgesic. Both analgesics were associated with more severe CB-PTSD symptoms in women who reported very severe labour pain, which will be necessary to

understand before considering the use of these drugs for pharmacological prevention of CB-PTSD.

5. Personal contribution

I had the original idea for the study, and was highly involved in its conception. I coordinated the data sharing between Norway, Switzerland, and France, and extracted the dataset. I coordinated the statistical analyses, which were carried out by a statistician, and significantly contributed to the data interpretation. Except for sections linked with the statistical analyses, and some elements of the method section, I drafted the manuscript. I was also highly involved in the whole publication process.

C. Study 3 – The study protocol for the Swiss TrAumatic biRth Trial (START): a double-blind multicentre RCT

Study 3 (141) was published in *BMJ Open*, in December 2019. The article can be found in Appendix H.

1. Background and aims

Horsch et al. (2017) (176) showed that, compared to routine care, women receiving a CBI-VT within six hours following their ECS had fewer CB-IMs during the first postpartum week, and were less likely to fulfil the CB-PTSD diagnostic criteria at one month. As discussed in Section I.C.3.b, this proof-of-principle study had several limitations, including a passive control group and an open-label design. Study 3 corresponds to the study protocol of a large, multicentre double-blind RCT, the Swiss TrAumatic biRth Trial (START). Its main objective was to test the effects of that same CBI-VT on the presence and severity of CB-PTSD symptoms at six weeks postpartum. By revising the design of Horsch et al. (2017) (176), we hope to overcome the aforementioned limitations. START also aims to test the CBI-VT effects on a vast array of family outcomes, including parental psychological and physiological outcomes, maternal sleep, mother-infant interaction, and infant development and physiology. Given the amount of outcomes measured and the scope of this thesis, this section will mainly focus on measures relating to CB-PTSD symptoms. Please note that the data collection was delayed by one year due to the COVID-19 pandemic and is still ongoing, thus no results are available yet.

2. Methods

Study sample: Eligible women must have 1. Had an ECS at ≥ 34 weeks of pregnancy at the Lausanne or Geneva University Hospital, 2. Given birth to a live baby, 3. Indicated that they had experienced a traumatic childbirth (according to four screening questions described in Appendix H), 4. Given their written consent. Exclusion criteria are: 1. Insufficient French language-skills, 2. Established intellectual disability or psychotic illness, 3. Severe maternal or infant illness, 4. Infant requiring intensive care and 5. Alcohol abuse and/or illegal drug use during pregnancy. If women agree, their partner is also invited to participate in the study, although he/she is not offered the intervention – his/her data is collected for observational purposes. Partners are eligible if they attended the birth, have sufficient French language skills, and give written consent. START was approved by the Human Research Ethics Committee of the Canton de Vaud (study number 2017-02142), and was registered on Clinicaltrials.gov prior to data collection starting (trial number NCT03576586). An *a priori* power analysis, based on Horsch et al. (2017) (176), indicated that recruiting n = 120 participants would be necessary to detect a group difference of d = 0.30 on the primary outcome (CB-PTSD symptoms at six weeks postpartum), (80% power, α = 0.05, two-sided). Further power analyses showed that, applying the same criteria, this sample size would be sufficient to detect group differences for secondary outcomes – the results ranged between n = 56 and n = 84. Expecting a drop-out rate of 20%, the objective is to recruit n = 144 participants.

Procedure: Eligible women are approached by a midwife or nurse within the first postpartum hours. After signing their informed consent, participants are randomly allocated to the intervention *vs*. attention-placebo control group, at a 1:1 ratio. The block randomisation is computer-generated (block of sizes 2, 4 and 6 over 144 participant per stratum, stratified by research centre). For each condition, the task is carried out with the midwife or nurse, so that both the participants and the research team remain blind. The visuospatial or attention-placebo tasks are proposed once all important routine care is completed and the participant is settled, with her infant. After a three-minute training, participants allocated to the intervention group are instructed to continuously play Tetris for 15 minutes on a handheld gaming device, while using mental rotation, as described in Horsch et al. (2017) (176). No prior childbirth reminder task is included, as participants are still in the trauma context, i.e.,

the maternity ward. Participants allocated to the control group are asked to briefly write down what they do and for how long (e.g., "*texting my mother, 2 minutes*"), for 15 minutes as well. Given that there is no available preventive treatment that could be used for the control group, this writing activity was chosen because it appeared *a priori* as harmless. Importantly, it was matched with the intervention activity for the following criteria: 1. Carried out within the six first hours postpartum, on the maternity ward, 2. Lasts 15 minutes, 3. Delivered by the midwife or nurse, 4. Contains structured standardised instructions. Once the activity is done, the follow-up takes place during the first postpartum week, at six weeks postpartum, and at six months postpartum.

Measures and outcomes: The primary study outcomes are group differences in the presence and severity of maternal CB-PTSD symptoms at six weeks postpartum. They are assessed with the Clinician Administered PTSD Scale for DSM 5 (CAPS-5) (392, 393), a standardised clinical interview, and the PTSD Checklist for DSM-5 (PCL-5) (394), a 20-item self-report questionnaire. The PCL-5 allows the calculation of a total score (range 0–80), but also of the four PTSD symptom cluster scores. It can also be used to assess probable PTSD diagnosis. Secondary and other outcomes are notably measured via validated self-report questionnaires, physiological measurements (salivary cortisol; hear rate), actigraphy, and video recording. One outcome that is particularly worth mentioning within the context of this thesis is the number of CB-IMs within the first postpartum week, which is reported by participants in a daily diary (176, 323). All the measurements are further described in Figure 7 but also in Appendix H (Tables 1 and 2).

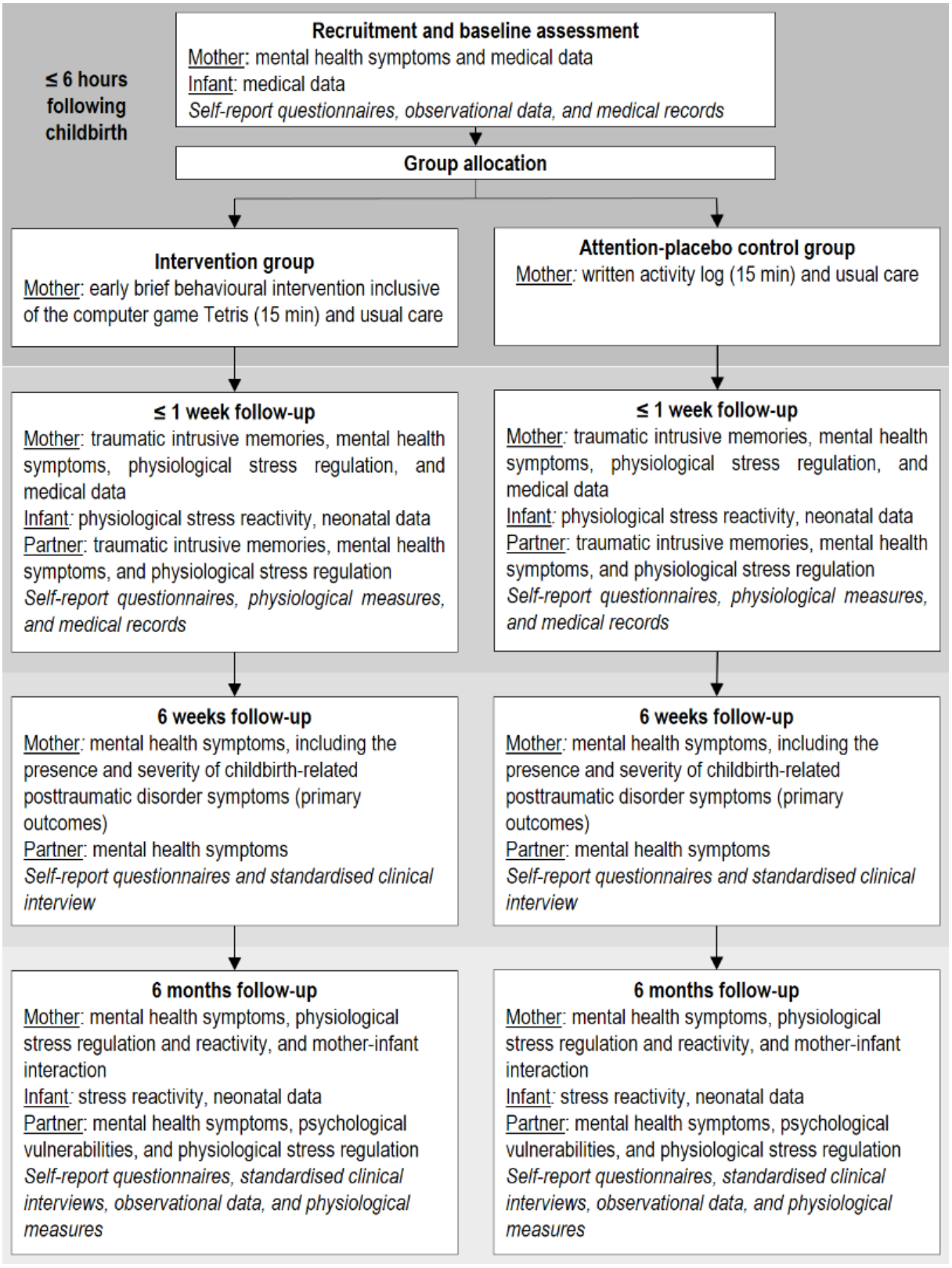

Figure 7. Flowchart of study procedures. Figure reprinted and adapted with permission from Sandoz (2021) (395).

Note. Measurements are reported in italics.

Planned analyses: For the primary outcomes, i.e., scores on the six-week PCL-5 and CAPS-5, group differences will be examined with separate linear regression analyses, controlling for recruitment centre and baseline values. Relevant covariates, such as maternal parity, will be first identified with univariate tests. Group differences in term of proportion of participants meeting the CB-PTSD diagnostic criteria will be investigated with logistic regression analyses, using the same procedure as described above to identify covariates. This will also be the case for differences between groups and across time, for the secondary and other outcomes. If conducted, *posthoc* exploratory analyses will be described as such in publications. Missing data will be managed with multiple imputation methods.

3. Conclusion

Given its strict design and rigorous procedures, START is expected to provide high-quality evidence on the effectiveness of a CBI-VT to prevent CB-PTSD. If results are in favour of the tested intervention, the next step would then be to implement CBI-VT in maternity wards. In the view of all the psychological and physiological measurements, START is also very likely to improve the global understanding of the effect of such an intervention on other family outcomes, and thus address an important gap in the literature.

4. Personal contribution

I was highly involved in the establishment and refinement of the study procedures, and in the writing of the manuscript. As part of my PhD, I have significantly contributed to the study coordination, notably the participant recruitment, data collection and management, but also the ethics committee procedures as well as the training and/or supervision of research collaborators (interns, research midwives, research assistants) and clinical partners (midwives, nurses, obstetricians).

D. Study 4 - Reducing childbirth-related intrusive memories and PTSD symptoms via a single-session behavioural intervention including a visuospatial task: a proof-of-principle study

Study 4 is currently under review in the *Journal of Affective Disorders*. The submitted manuscript is available in Appendix I (and the supplementary material in Appendix J).

1. Background and aims

This translational proof-of-principle study aimed to develop and test the effectiveness of a RBI-VT in reducing CB-PTSD symptoms, in particular CB-IMs. The intervention was inspired by Horsch et al. (2017) (176), and incorporated adaptations based on the available evidence on memory reconsolidation and PTSD. These modifications were intended to make the intervention appropriate for CB-PTSD treatment – rather than prevention. Notably, the boundary conditions (Section I.D.2.a) were taken into account during the memory reactivation phase, which took place at the maternity ward where participants had given birth (context specificity condition) and included their own childbirth narratives (reminder cue specificity condition). Several questions were asked to participants in order to assess the fulfilment of these conditions. Furthermore, based on the assumptions that elements of a single-event trauma memory are strongly interconnected (87), the reminder task did not only include the narration of one hotspot, like in prior studies testing a RBI-VT (e.g., 337), but also involved a brief account of the whole birth. This was proposed in order to make the entire childbirth memory accessible to the memory reconsolidation interference task, which was thus expected to reduce all CB-IMs, rather than a specific one. In this single-group pre-post study, it was hypothesised that, compared to pre-intervention measurements, 1. Participants would report fewer CB-IMs during the first two post-intervention weeks (primary study outcome), and that this reduction would be stable up to six weeks post-intervention, 2. CB-PTSD symptom severity would be reduced at one month post-intervention. Furthermore, intervention acceptability was expected to be high.

2. Methods

Study sample: Eligible women had to 1. Have given birth at the Lausanne University Hospital more than six weeks ago, 2. Have had at least two CB-IMs over the last week, 3. Be able to distinguish CB-IMs from other potential IMs, 4. Give their written consent. Exclusion criteria were: 1. Stillbirth, 2. Insufficient French language-skills, 3. Severe maternal or child illness, 4. Established intellectual disability or psychotic illness, 5. Alcohol abuse and/or illegal drug use, 6. Ongoing childbirth-related psychological treatment. To avoid a floor effect, participants

who had less than two CB-IMs over the two weeks prior to the intervention were further excluded (see study flowchart, Appendix I, Figure 1). The study was approved by the Human Research Ethics Committee of the Canton de Vaud (study number 2019-01435), and was registered on Clinicaltrials.gov before data collection started (trial number NCT04286724). Based on prior studies on a similar population (141, 176), the *a priori* power analysis showed that a sample size of n = 18 would be sufficient to detect a 35% reduction (corresponding to a d = 0.70) on the primary study outcome (80% power, α = 0.05, two-sided). Expecting a 20% drop-out rate and 20% of secondary exclusion, we initially intended to recruit 25 participants. However, both the drop-out rate and the secondary exclusion were overestimated. In total, as required, 18 participants received the intervention and none of them dropped out.

Procedure: Over the two pre-intervention weeks, participants completed a daily diary (diary 1), in which they reported their CB-IMs. Their CB-PTSD symptoms were measured five days before the intervention, i.e., close to the intervention day, but not on the same day to avoid interference with trauma-related memory processes.

On the intervention day, I, as the study psychologist, met participants in a neutral administrative building of the Lausanne University Hospital. For the memory reactivation phase, we went together to an examination room of the maternity ward where the participant had given birth, and they orally narrated their childbirth during 5-7 minutes (reminder task 1), as well as the moment corresponding to their most frequent CB-IM during 3-5 minutes (reminder task 2). While going back to the neutral building, ten minutes elapsed, thus supposedly allowing for memory labilisation. During the memory reconsolidation interference phase, participants played Tetris for 20 minutes, under the same condition as in Study 3 (three-minute training session, mental rotation instructions).

After the intervention, participants completed two CB-IMs diaries, one during the two post-intervention weeks (diary 2), and one during the 5th and 6th post-intervention weeks (diary 3). CB-PTSD symptoms were assessed again at one month post-intervention. The study ended after the completion of diary 3, with an audio-recorded study phone call including acceptability questions and study debriefing.

Measures: CB-IMs were self-reported in a daily diary, similar to that used in other studies testing CBIs- and RBIs-VT (176, 323). For each CB-IM, participants reported their time of

occurrence, content, and other qualitative characteristics described in Appendix J. They were notably asked to indicate the sensory modality of each CB-IM (visual, auditory, gustatory, olfactory, proprioceptive, tactile, nociceptive). CB-PTSD symptoms were assessed with the PCL-5 (394), just like in Study 3. Reminder cue specificity was measured at the end of the memory reactivation phase ("*To what extent did you narrate your childbirth in a way that is faithful to your actual childbirth experience? (In other words, is what you have told similar to your experience, or is it very different?)*" on a 10-point scale from 1 ("*not faithful at all/does not correspond at all*") to 10 ("*extremely faithful/completely corresponds*")), along with memory vividness, rated from 0% ("*not at all vivid/intense memory*") to 100% ("*extremely vivid/intense memory*"). Context specificity was assessed at the end of diary 2, with a single-item question ("*How much did the maternity ward remind you of your childbirth?*", on a 10-point scale from 1 ("*not at all*") to 10 ("*very strongly*")). Intervention acceptability was assessed on a 10-point scale from 1 ("*not at all acceptable*") to 10 ("*extremely acceptable"*). Participants also indicated to what extent they would recommend the intervention to a friend, on a 10-point scale from 1 ("*no, not at all*") to 10 ("*yes, absolutely*"), and if they would be willing to participate in a second session. The study included several other measurements, such as pre-intervention depression symptoms, mental health history, emotional arousal during the intervention or socio-demographics measurements, which are fully described in Appendix I, Section 2.3 and Appendix J, Section 1. To illustrate and enrich the results, some of the participants' quotes, retrieved from the last study phone call were also reported in Appendix J.

Data analysis: Two independent trained psychologists rated whether each diary entry was indeed a CB-IM. They reached 100% agreement, and the final analyses were carried out on 350 CB-IMs (out of 360 diary entries). There was no missing data. A Friedman test was used to compare the number of CB-IMs across the three diaries, and it was completed with Wilcoxon signed-rank tests with a Bonferroni correction for pairwise comparisons. Effect sizes were calculated with the following formula: $r = Z/\sqrt{N}$ (396), where values under -0.5 indicate large effect sizes. The sensory modality of CB-IMs were recoded as 1 if they included a visual component (i.e., at least one of the sensory modalities was visual) and 0 if not. Its analysis was conducted on the 211 CB-IMs reported by the 10 participants who had CB-IMs in the three diaries. Poisson generalised linear mixed-effects models, including participants as the random effect, were used to investigate the moderation effect of the type of CB-IMs (with *vs.* without a visual component) on the change of the number of CB-IMs over the diaries.

Differences in the severity of CB-PTSD symptoms between pre- and post-intervention were examined with paired *t*-tests. In a *post-hoc* analysis, the change in the number of participants meeting CB-PTSD diagnostic criteria over time was tested with a McNemar's test with continuity correction. Analyses were carried out with IBM SPSS 27 and R version 4.0.5 (383). To further quantify the intervention effects, the number of participants experiencing at least a 50% reduction of their CB-IMs or total CB-PTSD symptoms between the pre- and post-intervention measurements was also indicated (as in Kessler et al. (2018) (337)). One participant did not comply with the intervention instructions, as shown by her own statement and her response to the reminder cue specificity question, on which she appeared as an extreme outlier (more than three interquartile ranges (*IQR*) above quartile 3). She was thus excluded from the analyses but her data are reported in Appendix J, Section 3.

3. Results

Sample description: On the day of the intervention, mean participant age was 33.55 years (*SD* = 6.35) and the traumatic childbirth had occurred between seven months and 6.9 years ago (*Mdn* = 2.01 years, *IQR* = 2.23). Before the intervention, eight participants had a probable CB-PTSD diagnosis and the mean depression score was above the clinical cut-off. Four participants had previously received a psychological treatment linked to their traumatic birth experience, such as EMDR (see full sample description in Appendix I, Table 1).

CB-IMs: The median (*IQR*) number of CB-IMs (Figure 8) was 11 (6) in diary 1, 2 (4) in diary 2 and 2 (3) in diary 3. It significantly differed across the diaries, $\chi^2(2) = 26.548$, $p < .001$. Participants had fewer CB-IMs in diary 2 *vs.* diary 1, $Z = -3.500$, $p < .001$ (primary study outcome), and in diary 3 *vs.* diary 1, $Z = -3.600$, $p < .001$. Effect sizes were large, $r = -0.849$ [95%*CI*: -0.841, -0.851] and $r = -0.873$ [95%*CI*: -0.868, -0.875], respectively. The median (*IQR*) reduction of the number of CB-IMs in diary 1 *vs*. 2 was 81.89% (39.58), and 15 out of 18 participants reported a reduction of more than 50% of their number of CB-IMs. As expected, the number of CB-IMs did not differ in diary 2 *vs*. 3, $Z = -0.950$, $p = .342$.

In terms of CB-IMs sensory modality, the type of CB-IMs (with *vs.* without a visual component) did not moderate the reduction of the number of CB-IMs across the diaries, as the interaction terms (type of CB-IMs x diary) were not significant (diaries 1-2: $\beta = .370$, $SE = 0.404$, $p = .360$; diaries 1-3: $\beta = .914$, $SE = 0.516$, $p = .077$; diaries 2-3: $\beta = .544$, $SE = 0.592$ $p = .359$). CB-IMs

with a visual component respectively represented 71.31% (92/129 CB-IMs), 78.26% (36/46) and 86.11% (31/36) of CB-IMs in diaries 1, 2 and 3.

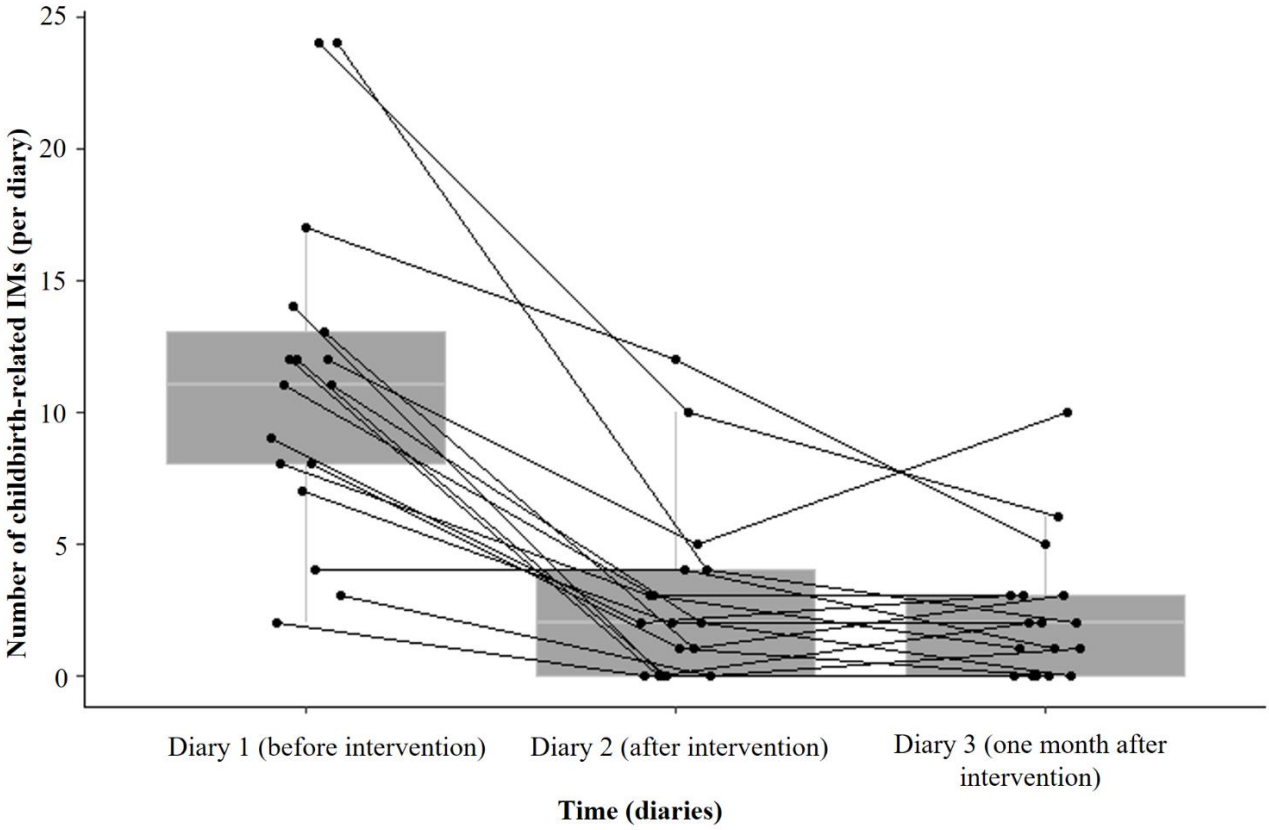

Figure 8. Number of childbirth-related intrusive memories (IMs) across the diaries (n = 17).

Note. Black lines correspond to individual trajectories (n = 17). Diary 1 covered the 14 days before the intervention, diary 2 covered the 14 days following the intervention, and diary 3 covered 14 days from one month post-intervention (i.e., the 5th and 6th post-intervention weeks). Box plots represent group medians and interquartile ranges.

Changes of CB-PTSD symptoms: Compared to before the intervention, the total CB-PTSD symptom severity (Figure 9) was reduced by 56.76% (SD = 28.87) at one month post-intervention ($t(16) = 6.190$, $p < .001$), with a large effect size, $g = 1.466$ [95%CI: 0.771, 2.140]. Similar results were observed for each of the symptom cluster scores ($p < .001$, large effect sizes) (Appendix I, Table 2). Ten out of 18 participants showed a reduction of at least 50% of their total CB-PTSD symptom severity. In terms of CB-PTSD diagnosis, significantly fewer participants met the criteria after (n = 0) compared to before the intervention (n = 8), $p = .013$.

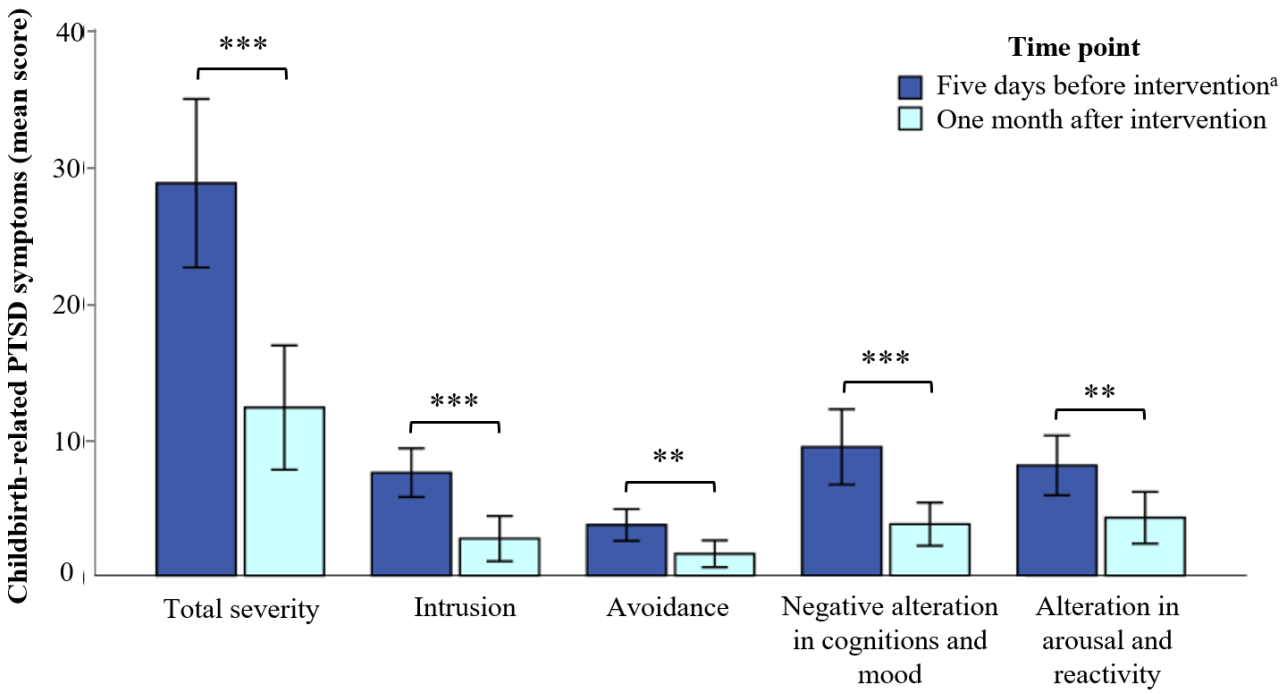

Figure 9. Mean scores of childbirth-related PTSD symptoms five days before and one month after the intervention (n = 17).

Note. Asterisks indicate statistical differences (* p < .05, ** p < .01, *** p < .001). Black bars represent 95% *CI*. [a] Childbirth-related PTSD symptoms were first measured five days before the intervention, i.e., close to the intervention day, but not on the same day, to avoid interference with the trauma-related memory processes.

With regard to their CB-PTSD symptoms, some participants reported other kinds of improvements, such a reduction of their fear of becoming pregnant: "*We wondered* [with my husband] *if I wasn't pregnant. And in fact I didn't experience this thinking "Oh my God, what a horror I'm going to have to go through this again" or anything like that. It was more like, I was more like, "if it's true, if I'm pregnant, well that's great and I welcome it and it's going to be great".*", "*Before it was not an option at all, to try,* [now] *we are trying to have a second child.*". Some also noticed feeling better in their daily lives: "*I am less tense, less stressed so, yes, it has helped me* […]. *Before I, I used to have mood swings, crazy outbursts, so I was, well, I was also verbally nasty or I would get carried away* […]. *I'm calmer now*", "*I'm a bit like I was before* [the childbirth], *I'm much happier and calmer again*", "*I feel really different, I feel the wound is less fresh, less open*". Finally, some felt that their couple relationship was also improved: "*My husband in any case saw the difference. He saw that I was less… Not aggressive, but less that I was less tense, less jaded*". Note that more quotations are available in Appendix J.

Intervention characteristics: During the memory reactivation phase, participants indicated that their narratives were extremely faithful to their childbirth experience (reminder cue specificity) (*Mdn* = 10/10, *IQR* = 1). Their median rating of their childbirth memory vividness was 80% (*IQR* = 15). The maternity ward strongly reminded them of their birth (context specificity) (*Mdn* = 9/10, *IQR* = 3).

Intervention acceptability: The intervention was rated as highly acceptable (*Mdn* = 9, *IQR* = 3), recommendable (*Mdn* = 10, *IQR* = 1), and 100% of participants would have been willing to do a second session.

4. Conclusion

This is the first time such a single-session RBI-VT was tested for CB-PTSD symptom reduction and, more generally, in a sample of participants having experienced a real-life single-event trauma, several months or years earlier. All the results were in accordance with the hypotheses. As indicated in Appendix J (Section 3), one participant showed a high, albeit temporary, increase of the number of her CB-IMs, thus suggesting the intervention could be further improved. While it has limitations inherent to its design, this study suggests that a single-session and low-cost RBI-VT may be suitable for CB-PTSD symptom treatment, thus warranting the launch of a RCT.

5. Personal contribution

I was highly involved in the design and conception of the study, as well as the establishment and refinement of all the procedures. I screened the 194 potentially eligible women and was responsible for carrying out the recruitment and interventions, as well as the data collection, preparation, and management. I was responsible for the ethics committee procedures and the supervision and training of research collaborators (interns, research psychologists, research assistant). I performed most of the analyses and significantly contributed to the data interpretation. Except for some paragraphs of the methods section, I drafted the manuscript. I am also responsible for the whole publication process.

III. Discussion

In addition to causing distress to the women who suffer from it, CB-PTSD has serious negative consequences for the whole family. Yet, evidence-based interventions to prevent or reduce CB-PTSD symptoms are lacking. Based on the framework of memory (re)consolidation, the overarching aim of this thesis was to translate fundamental research and laboratory findings into intervention proposals to address maternal symptoms of CB-PTSD throughout the perinatal period. In the next sections, the results of each study will be discussed in turn, along with their clinical, theoretical and research implications. Finally, the main strengths and limitations of this thesis will be presented.

A. Interpretation of findings

1. Insomnia symptoms and CB-PTSD symptom severity

In Study 1, in accordance with our hypotheses, insomnia symptoms at 32 weeks of pregnancy were associated with more severe CB-PTSD symptoms at eight weeks postpartum, and this association was fully mediated by negative SBE and postnatal insomnia symptoms. Importantly, all associations involving insomnia symptoms had small or very small effect sizes. The fact that prenatal insomnia symptoms were predictive of a negative SBE suggested that insomnia may reduce the psychological resources needed for coping with a difficult childbirth, for instance by disrupting emotional regulation (122) (see also Box 7, Section I.B.1), and thus foster maladaptive responses to it. As for the second mediation pathway, it may indicate that prenatal insomnia, by inducing a vulnerability to postnatal insomnia symptoms, which had already been identified as a maintaining factor of CB-PTSD (130), hinders postnatal recovery after a distressing birth experience. Indeed, sleep deprivation or wakefulness following a traumatic event would enhance the development of IMs and PTSD symptoms, notably by disrupting memory consolidation processes (131-133). Overall, despite the small effects sizes, these results tentatively suggested that prenatal insomnia may be a relevant target for the primary prevention of CB-PTSD symptoms.

Notably, the two mediations were additive and connected, as negative SBE was associated with postnatal insomnia symptoms. One possible explanation may be that a negative SBE, by causing ruminations, anxiety, infant-related worries, or even ASD (109), could trigger postnatal insomnia. Another interesting result of Study 1 was that postnatal insomnia symptoms fully or partially mediated the associations between prenatal psychological

symptoms (anxiety, PTSD and FOC, although not depression) and CB-PTSD symptoms, thus suggesting that postnatal insomnia may be one of the pathways through which prenatal difficulties put women at risk of developing CB-PTSD.

Apart from insomnia, the final model of Study 1 identified four additional predictors of CB-PTSD symptom severity: prenatal anxiety and depression symptoms, birth medical severity, and negative SBE. These results were in line with evidence in the literature (17, 125), whereas the fact that prenatal PTSD symptoms were not a direct predictor of CB-PTSD somewhat contrasted with previous research (17, 397) – however, a few prenatal PTSD symptoms did predict the absence of CB-PTSD symptoms in Study 2. With regard to FOC, several studies also found that its association with CB-PTSD symptoms was partially or fully mediated by SBE, as it is the case in our model (118, 125, 397). Overall, beyond insomnia symptoms, the final model, echoing the existing literature (e.g.,17), suggested several additional targets for CB-PTSD prevention, such as prenatal depression symptoms or FOC.

2. Obstetrical analgesics and CB-PTSD symptom prevention

In Study 2, N_2O intake during childbirth predicted reduced CB-PTSD symptom severity at eight weeks postpartum, with a small to medium effect size. This was not the case for morphine even if, in view of the low *p*-value and the very small number of participants who received morphine (n = 49/2,070), it is likely that we lacked power for this specific variable. Another element in favour of this assumption is that the literature is rather consistent regarding the association between early morphine administration and reduced subsequent PTSD symptoms (e.g., 250, 255, 256, 259, 260, 398). However, it should be remembered that morphine may have a dose-dependent effect on memory and PTSD (250, 251), and it cannot be ruled out that parturients receive lower doses than injured service members or patients admitted to EDs (i.e., typical populations studied so far), thus explaining the inconsistency. Importantly, in women reporting very severe pain during labour (≥ 9 out of 10, as illustrated in Appendix F, Figure 3), both morphine and N_2O were associated with more severe CB-PTSD symptoms. Finally, these results only applied to women reporting some CB-PTSD symptoms, as analgesics intake during childbirth did not predict the presence or absence of symptoms.

Despite the observational nature of the study, several elements may contribute to the debate on the mechanisms underlying the observed associations. As a reminder, morphine and N_2O

were initially expected to be associated with reduced CB-PTSD symptom severity due to their potential interference with memory consolidation ("memory consolidation interference assumption") and their pain relief action ("pain relief assumption").

One comment that immediately arises with regard to the **memory consolidation interference assumption** is that it cannot be guaranteed that analgesics were administered and active within the childbirth memory consolidation window. Indeed, it is important to point out that childbirth usually lasts many hours, with multiple occasions for traumatic experiences (e.g., the announcement of foetal distress requiring induction of labour, a painful gynaecological examination). Thus, some women may have received the drugs during the *post*-traumatic period (i.e., within the memory consolidation window), whilst others may have received them during the *pre*-traumatic period, before the trauma occurred (i.e., outside of the memory consolidation window). Admittedly, in the case of morphine, which has a half-life of approximately two to four hours (399), the analgesic may still be active in the post-traumatic period, even if it is administered before the actual traumatic experience. In RBIs, for instance, propranolol is sometimes administered *before* the trauma memory reactivation, so that it reaches its peak plasma concentration during the memory reconsolidation window (346). However, this hypothesis seems less likely for N_2O, which has a half-life of about three minutes (400). Furthermore, given that morphine and N_2O may sometimes have been administered during the pre-traumatic period, it cannot be excluded that, in addition to or instead of disrupting memory consolidation, analgesics affected the peritraumatic stress response to the birth. This may have occurred through regulation of the noradrenergic activity at the very moment of the traumatic event or reduction of anxiety[15] and modulation of threat appraisal. Overall, the lack of clarity regarding the timing of analgesic administration thus precludes firm conclusions regarding the fact that analgesics may be associated with reduced CB-PTSD symptom severity due to their interference with childbirth memory consolidation.

Concerning the **pain relief assumption**, N_2O predicted reduced CB-PTSD symptom severity, even when controlling for pain, and pain levels were not associated with subsequent CB-PTSD symptom severity. Moreover, as shown in Appendix F (Table 2), the pain levels of women who received N_2O or a combination of morphine and N_2O were significantly higher than those reported by the "no drug group" (i.e., neither morphine nor N_2O during birth), while women

[15] Indeed, both morphine and N_2O can also have anxiolytic effects (264, 401)

who received morphine only had a score comparable to that of the control group. It does not appear that those who received analgesics thereby had a less painful experience than the others, which is probably due to the fact that analgesics were given upon request – i.e., women who asked for analgesics were logically experiencing more pain than those who did not. Finally, additional mediation analyses (Appendix F, Section 3.2) did not suggest that pain levels mediated the association between N_2O and CB-PTSD symptom severity. Taken together, these results are not in favour of the pain relief assumption.

A third way of interpreting these data would be to consider not only the pharmacological action of morphine and N_2O, but also **women's experiences** of their intake. Firstly, the use of analgesics, which were given on demand, may enhance women's sense of control during the birth and thus protect against CB-PTSD symptoms (34, 402). This may be particularly true for N_2O, because its inhalation necessitates an active engagement of women, who control the pace and number of breaths. N_2O benefits could also be related to its mode of administration, as some parturients reported that its inhalation, which requires a focus on breathing, helped them to calm down or be distracted (403). For both analgesics, a protective effect could also be accentuated if the pain management is in line with the expectations formulated during pregnancy, just like the mode of delivery which, if it corresponds to the desired one, can be associated with less severe CB-PTSD symptoms (404). In addition to the feeling of control, it can be hypothesised that being offered pain relief treatment contributes to a sense of support from the medical staff, which is a key factor in CB-PTSD (17, 29, 405). Finally, all these non-pharmacological aspects could contribute to CB-PTSD symptom prevention through increased labour satisfaction (406) and improved overall birth experience (118). On the contrary, the impossibility of receiving pain relief despite requests may worsen the birth experience - it was associated with the development of PTSD symptoms in other populations (407). These factors may also explain why N_2O and morphine both predicted more severe CB-PTSD symptoms when combined with very severe labour pain. Indeed, experiencing severe pain despite analgesics intake could give women the feeling that their pain cannot be properly contained, despite the tools offered by the medical team. Thus, women may feel like they have run out of solutions to relieve their suffering and are no longer in control of the situation, thereby worsening their birth experience and putting them at risk of developing CB-PTSD symptoms (54, 408). Inefficient pain relief may give the impression that the staff is powerless, while perceiving the midwife as being in control of the situation is a protective factor for CB-PTSD (402). Conversely, in women with high pain scores who have not (yet) received pain

reliefs, the pain experience may be radically different, as parturients know that they can still ask for analgesia if needed. However, it is important to specify that these are only speculations since our study did not measure these variables. Moreover, most of them are specific to the obstetrical field and do not explain the protective associations found in other populations.

3. Treating CB-PTSD symptoms with a reconsolidation-based intervention involving a visuospatial task

In Study 4[16], compared to the two pre-intervention weeks, participants overall showed a large and stable reduction in their number of CB-IMs up to six weeks post-intervention. CB-PTSD symptom severity was also significantly reduced at one month post-intervention, compared to five days before, which applied to the total severity score as well as the four symptom cluster scores. Just as for the reduction of CB-IMs, all the effect sizes linked with CB-PTSD symptom reduction were large. Moreover, none of the eight participants who met the CB-PTSD diagnosis criteria before the intervention met them afterwards. In addition to the reduction of their CB-PTSD symptoms, as measured by the PCL-5, some participants spontaneously reported other types of changes, such as improvements in their everyday life (including their relationship with their partner), together with a reduction of their FOC. Overall, participants unanimously rated the intervention as very acceptable. Moreover, their rating of the reminder cue specificity, context specificity, and childbirth memory vividness suggested that the intervention procedure did facilitate the reactivation or, at least, the retrieval of their childbirth memory. At this preliminary stage, the tested RBI-VT thus appeared to have successfully reached all its objectives, namely a reduction of CB-PTSD symptoms and a positive evaluation of the intervention by the participants, despite high levels of depression before the intervention and a history of unsuccessful pharmaco- or psychotherapy for some of them.

To the best of my knowledge, Study 4 was the first study testing a RBI-VT in a sample of individuals traumatised by an old (i.e., which occurred more than a week ago) and single-event real-life trauma, as women had given birth seven months to seven years earlier. The data collected did not only include the number of CB-IMs but also their characteristics, in particular their sensory modality (see Appendix J, Section 1.1, for details). One puzzling result

[16] Study 3 is not discussed in this section, as the results are not yet available.

is that CB-IMs with a visual component (i.e., which contained images) did not decrease significantly more following the intervention than CB-IMs without a visual component. Yet, the modality specificity hypothesis would have predicted that a task taxing visuospatial resources, such as Tetris, would only interfere with the reconsolidation of the visual aspects of memory, and thus specifically reduce the number of intrusive *images* (see Section I.C.3.b). One participant, for example, had only tactile CB-IMs, which were all related to the sensation of the scalpel in her abdomen, during the caesarean section: none of these CB-ITMs included a visual component, yet she reported 14 CB-IMs in her diary 1 (pre-intervention), and none in diaries 2 and 3 (post-intervention), which suggests that the intervention was helpful for her. One may argue that participants may forget to report the visual component of their CB-IMs, but in her case, she actually did not *see* the scalpel, due to surgical drape hiding the obstetrician. While these results must be interpreted with caution given the small sample size and the fact that the study was not primarily designed to test the modality specificity hypothesis, they raise questions about the functioning of RBIs-VT. Note that our results cannot be properly compared with evidence from the literature because, as far as I know, such data has never been collected in prior clinical studies[17]. As for laboratory studies, an important limitation is that the TFP is, by definition, a visual trauma, thus participants' IMs do include images.

A unique feature of Study 4 was that the memory reactivation phase was highly immersive. As described in Appendix J (Section 2.1), participants indicated that returning to the maternity ward strongly reminded them of their birth, not only because they *saw* the place, but also because they *smelt* the hospital and heard the "*beeping of the blood pressure machines*" or infants crying. Thus, reminder cues were not comparable to still images, as used in RBIs-VT tested with the TFP (299), or even written narratives, as used in clinical studies (337). It may therefore be hypothesised that this crucial difference led to a multi-sensory reactivation of the memory. However, even if non-visual aspects of the memory were reactivated, the modality specificity hypothesis would have rather predicted that a visuospatial task interference would only affect visual CB-IMs. One hypothesis could be that, because the elements of the trauma memory are so strongly interconnected, reducing visual CB-IMs leads to a global reduction of CB-IMs or, alternatively, that Tetris engages other memory resources in addition to visuospatial ones (see also Box 13). Collecting more data on

[17] Kanstrup et al. (2021) (302) tried, but the measure was poorly understood by participants, and thus the data was not published.

the sensory modality of IMs before and after RBI-IMs could thus be important, although this type of data has previously been indicated to be difficult to report for participants of clinical studies (302).

Box 13. When images contained in CB-IMs fade away.

One participant reported an intriguing observation with regard to her CB-IMs: "*After* [the] *meeting, twice the flashbacks came back but the image was so blurred that it was absolutely not distinct.* […]. *It's like the flashes want to come but I can't tell what's their content. It's a flash but it's so blurry, bright and white, the image is so unclear that I can't see the content*". This is only one case and, of course, no conclusion can be drawn from this sole example. However, it is interesting that in her case not only the number of CB-IMs was reduced, but also the images themselves were changed: the traumatic scene, which she formally identified in these CB-IMs because she had the same bodily sensations as during the birth and as in previous CB-IMs, was blurred. This observation tentatively suggests that the RBI-VT did affect the reconsolidation of traumatic images.

The trajectory of the participant who was excluded from the group analyses due to non-compliance with the instructions, who will henceforth be referred as P18, also deserves a comment. As detailed in Appendix J (Section 3) and Appendix I (Section 2.6), this participant declared that she intentionally did not immerse herself in her childbirth memory, and that her narratives during the memory reactivation phase were not faithful to her actual experience because she kept a "*voluntary distance*" from them. Echoing her statement, she was the only extreme outlier for the reminder cue specificity question[18]. As for her data, she had a neat, albeit temporary, increase in her number of CB-IMs in diary 2, while their number did not differ between diary 1 and 3, and her CB-PTSD symptom severity was comparable before and after the intervention (see Appendix J, Section 3). There are certainly many scientific and clinical lessons to be learned from her participation, starting with the fact that the reminder cue specificity question was an efficient manipulation check to detect non-compliance to the intervention procedure. More importantly, if P18's trajectory is considered within the memory reconsolidation framework, it suggests that the memory reactivation phase is indeed a crucial component of the intervention, without which the visuospatial task is ineffective and that, in her case, the procedure failed to reactivate the memory. Beyond her own statements, this is suggested by her data, because if the intervention had, for some reason, reactivated the memory, the increase in her number of CB-IMs would have been expected to last (319, 349, 362) as the original childbirth memory would have been strengthened, which was not the case here. Other clinical observations, which are detailed in

[18] As indicated in Appendix J (Section 3), it should be mentioned that P18 was not outlier on any baseline measurements, nor on other intervention-related variables, such as emotional arousal. Despite her increase of CB-IMs, she rated the intervention as very acceptable.

Appendix J (Section 3), suggest alternative explanations. Notably, returning to the maternity ward while narrating her birth experience may have temporarily destabilised P18's avoidance strategies, thus leading to heightened perception of her CB-IMs. Otherwise, it may have weakened a potential inhibitory trace of the childbirth memory and induced a transient reinstatement of the fear response (167, 409), although all of these hypotheses are drawn from available evidence on memory processes as well as on the collected data, but could not be tested in the study.

B. Clinical implications

1. Prenatal preventive interventions

Clinically, the final model of Study 1 tentatively suggests that reducing prenatal insomnia symptoms may be a primary prevention pathway for CB-PTSD symptoms, as they may improve future SBE and prevent postnatal insomnia symptoms (see Box 14). However, the clinical benefits of such interventions remain to be tested in future studies, given that effect sizes of the associations involving insomnia were all small or very small. An advantage of intervening on prenatal insomnia symptoms is that it may have additional benefits, since insomnia and sleep deprivation affect a wide array of mental health (410), obstetrical (411) and child outcomes (170, 412, 413). Furthermore, evidence-based interventions to reduce insomnia are already available, as illustrated by CBT for insomnia (414), which is recommended in the general population (415) and shows good acceptability and effectiveness during the prenatal period (416, 417).

Box 14. Midwives' reactions to the results of Study 1.

The results of Study 1 were presented to different healthcare professionals, including a group of midwives in charge of a birth preparation class, and their reactions are worth mentioning because they are instructive from the point of view of clinical implications. Indeed, the midwives were almost all surprised that antenatal insomnia had so many associations with other pre- and postnatal psychological variables, as well as with SBE. Clinically, many of them indicated that they do not pay special attention to their patients' sleep complaints, and tend to tell them that sleep disturbances during pregnancy are simply normal. Although this was only a discussion with about 15 midwives, it suggests that **1.** Healthcare professionals following up women during the perinatal period would be interested in and benefit greatly from education regarding sleep disorders in this population, and **2.** It would be useful for them to have a screening tool, which could be used systematically, to more easily identify women whose sleep disorders require intervention. Indeed, the midwives indicated that they felt they had difficulty assessing the severity of insomnia during pregnancy, given its "*almost normative*" nature. One tool that may be suitable is the Sleep Condition Indicator, which is an eight-item self-report questionnaire having good psychometric properties (418, 419), including in pregnant women (420).

On a side note, the final model of Study 1, echoing Ayer's diathesis stress model (17), suggests that other prenatal psychological symptoms may also be relevant targets for CB-PTSD primary prevention, in particular depression, anxiety, and, more marginally, FOC. By reducing prenatal anxiety symptoms, it may also be possible to decrease both pre- and postnatal insomnia symptoms, as well as to improve SBE, which were all associated, directly or indirectly, with subsequent CB-PTSD symptom severity in the model.

2. Peripartum preventive interventions

Implementing new interventions on the labour ward can involve many practical difficulties, as many of the peripartum risk factors of CB-PTSD, such as mode of delivery or neonatal complications, cannot be modified. In this thesis, rather than adding new procedures during childbirth, the approach chosen was to consider those that already exist and that could be adapted. This is why morphine and N_2O were studied, in addition to their interesting properties from the point of view of memory consolidation. As an illustration, 60.7% of participants in Study 2 had received N_2O during labour (389). It would be very premature to conclude at this stage that these two analgesics can be used to prevent CB-PTSD, and it should be remembered that the effect sizes observed were small overall. However, this is a potentially promising direction - note that N_2O is also being studied for the treatment of depression (421) and established PTSD (422).

A crucial issue to be resolved concerns the observed interaction between analgesia and severe levels of pain during labour. If this is due, as hypothesised in Section III.A.2, to women's expectations of the pain relief effects of morphine and N_2O, more detailed information about the drugs may improve their experience and protect them in the case of analgesic failure. In this way, it may also allow more women to benefit from the potential protective effect of analgesia against CB-PTSD.

As with any intervention, especially pharmacological interventions, potential side effects must be considered. In this respect, N_2O seems more promising than morphine, beyond the fact that the effect observed in Study 2 with this analgesic was more important. Indeed, morphine has psychotropic and possibly addictive effects (423). It can also make both the mother and the infant drowsy, and induce a risk of breathing difficulties in the newborn (424). N_2O, on the other hand, has the advantage of having a short half-life, moderate side effects

(425), and is considered safe and minimally invasive (426). Moreover, laboratory data suggest that its inhalation leaves the declarative memory of traumatic events intact (75) – however, it should be noted that N_2O tended to increase the frequency of IMs in dissociated individuals (75).

Given that pain during childbirth tended to reduce or even negate the effectiveness of potential N_2O-based CBIs, an interesting avenue to explore would be to test this type of intervention in individuals at risk of experiencing a traumatic childbirth but not concerned by pain. This would specifically concern birth partners, 0.7-7.2% of whom develop symptoms of CB-PTSD in community samples (51, 427, 428), as well as professionals working on the labour ward: in Denmark, for example, a national study showed that 85% of obstetricians and midwives felt they had already experienced a traumatic birth. These experiences can lead to CB-PTSD, which may insidiously contribute to an increase of CB-PTSD in parents, as PTSD in healthcare professionals puts them at risk of burnout (429), itself associated with more patient safety incidents (430) and dehumanisation.

3. Postnatal preventive interventions

If its results are conclusive, START will lead to brief, single-session, and cost-effective CBI-VT to prevent CB-PTSD symptoms, without any known side effect. Such an intervention, available during the early postnatal period, would be a considerable advance for women who have experienced a traumatic birth, since no equivalent is available at present. In particular, it could prevent the development of CB-PTSD symptoms and thus limit the effects of these symptoms on the establishment of the first mother-infant bonds. In addition to being based on high-quality evidence, this CBI-VT seems promising from the point of view of implementation and accessibility, which are two major issues to ensure that the interventions developed bring a concrete benefit to women. Indeed, in START, the intervention is carried out by midwives and nurses (i.e., not highly trained mental health professionals), who are present anyway during the early postnatal period with the families. In addition, the intervention is fully compatible with routine postnatal care, can be performed whilst the infant is present, is potentially accessible to women who do not speak the local language, and does not involve having to recount the birth story. All these factors suggest that this CBI-VT can be made widely available, although its implementation will need to be carefully monitored (Box 15). An important issue that needs to be resolved is the criteria on which the

intervention should be offered. Indeed, it is unlikely to be useful to offer it to all women who have just given birth. In START, four brief screening questions concerning the SBE were used to determine whether or not women were eligible to receive the intervention, i.e., whether they experienced a sufficiently difficult birth (in line with criterion A1 of the DSM-5 (9)). These questions could also be used to identify women who would benefit most from the intervention, in the clinic.

Box 15. Is Tetris… too accessible?

Over the last years, this Tetris-based CBI-VT was presented countless times to professionals and the general public. Again, reactions were often instructive. One of the questions that almost systematically came up was: "*So, if I have a car accident or get hurt, can I play Tetris?*". This suggests the huge potential of this intervention, because people find it appealing, doable, and immediately consider applying it to their own everyday life context. Similarly, a father on the maternity ward, who had previously attended a conference during which our group had given a presentation on this CBI-VT, spontaneously decided to put a Nintendo in his wife's maternity suitcase, in case she had a difficult childbirth[1]. All these stories are encouraging, but they also raise a question: if these people "*play Tetris*" following a traumatic event, will it really be useful? In talking to some of them, who later said that they did have an occasion to "*play Tetris*" after a potentially traumatic event, it appeared that the conditions were not necessarily favourable: some played on their phones, occasionally checking their text messages, others only played for five minutes, or played more than six hours after the accident. Obviously, none of them received clear mental rotation instructions. Again, these are only anecdotes. However, they suggest that the implementation of Tetris-based CBIs, whether in the maternity ward or outside, should be accompanied and supervised; otherwise there seems to be a clear risk that the intervention will not be received under conditions that will provide clinical benefit.

[1] As it turned out, her childbirth went very well, and he was the one playing Tetris when I walked into their room.

Beyond the CBI-VT itself, START will likely provide valuable information on a wide array of psychological and physiological family outcomes. This will allow the assessment of clinical benefits of the intervention on other outcomes (e.g., the child development). By improving the understanding of variables, such as the partner's mental health, the couple relationship or the mother's sleep quality across the first six months postpartum, this study may also allow the identification of other protective or risk factors for CB-PTSD and thus be the starting point for new interventions for women but also partners, and, potentially, infants.

4. Postnatal therapeutic interventions

As far as I know, postnatal symptoms of insomnia had never been taken into account in studies investigating the association between prenatal insomnia and subsequent PTSD. Thus, the clinical conclusion of existing studies which, in the majority, found a direct association between these two variables (106, 107, 109) is that interventions targeting insomnia are

necessary before actual exposure to traumatic events. By adding post-traumatic insomnia symptoms in our model, we found in Study 1 that they play a significant role in the observed association, which thus questions the timing of insomnia interventions. Indeed, they may still be relevant in the post-traumatic period, either during the very first weeks, or even once CB-PTSD symptoms are settled, given that CBT addressing sleep disturbances has beneficial effects on PTSD (431).

With regard to Study 4, if future RCTs confirm the efficacy of the tested RBI-VT, it could be proposed as a new evidence-based treatment against CB-PTSD symptoms for women having regular CB-IMs. A major strength of this brief, single-session RBI-VT is that it appears to be cost-effective and does not need to be carried out by a highly trained mental health professional either - although it certainly requires more extensive training than the CBI-VT tested in START. Moreover, preliminary data collected in Study 4 suggest that it is a very acceptable intervention, as participants would unanimously recommend it to their friends, which is an encouraging signal. Finally, if the underlying mechanism of the intervention is indeed interference with memory reconsolidation, its effects on CB-PTSD symptoms should be long-lasting and robust over time, giving it considerable appeal over traditional therapies, such as exposure. Future studies will need to confirm whether the intervention is relevant to partners or healthcare professionals working on the labour ward but, from a theoretical point of view, there seems to be no reason why the intervention should not be offered to them too.

Before proposing this intervention, it would of course be important to see how it can be optimised. The case of P18, in particular, gives food for thought: even if the increase in her CB-IMs was only temporary, it would be important to study adjustments to the intervention that would make it possible to avoid this type of trajectory. Depending on the situation, several avenues could be envisaged. The first would be to improve the women's confidence in the procedure and the clinician beforehand. Indeed, P18 indicated that she would probably have tried to immerse herself more in her memory of the birth if she had previously known the assumed mechanisms of the intervention and thus understood the importance of the memory reactivation phase. The scientific reasoning behind the intervention was deliberately not explained to the participants in Study 4 until the end of the study, in order not to bias their expectations during participation; however, such explanations might be relevant in a clinical setting. To enhance the quality of the therapeutic relationship, and to therefore potentially promote the commitment of women to adhere to the procedure, it might also be useful to

extend the contact before the start of the intervention, either by allowing more time for discussion beforehand (while taking care not to evoke the memory of childbirth at this stage), or by offering a first contact appointment. Alternatively, it might be useful to adjust the duration of the narrative tasks, extending it if the women's response to the reminder cue specificity question suggests that they have not been able to fully reactivate the memory - although there is an increasing risk of inducing extinction. Finally, it might be preferable not to offer the intervention to women with high avoidance symptoms, even if it should be noted that P18 did not show high avoidance symptoms in her pre-intervention PCL-5 and that the fact that the appointment takes place at the hospital probably already dissuades most avoidant women to seek out such an intervention.

5. Overall clinical implications of the thesis findings

The main preoccupation of this thesis was to bring perspectives of concrete clinical benefits to women (at risk of) developing symptoms of CB-PTSD. I therefore hope to have contributed to the advancement of care for this disorder, which is largely understudied compared to other perinatal mental health disorders, such as anxiety or depression. Due to the multilevel consequences of CB-PTSD, the considered or tested clinical interventions should not only benefit women, but also their partners, and the children born or to come. It is because the stakes are so high for the whole family that all interventions, including those with seemingly small effect sizes, are worth exploring.

It may seem surprising that no study before Studies 1 and 2 had investigated the associations between prenatal insomnia, obstetric analgesia, and CB-PTSD. Indeed, sleep and analgesia during childbirth are issues that concern (almost) all women during the perinatal period. The results of Studies 1 and 2 thus suggest that, while there is a growing body of research on risk and protective factors for CB-PTSD, there are still many variables that can be considered for future interventions, and that focusing on research into modifiable factors is probably the approach that is the most likely to lead to clinical improvement. There are therefore many avenues for prevention and treatment of CB-PTSD, just as the studies in this thesis suggest that there are probably more intervention time points than we think. As CB-PTSD is a childbirth-triggered disorder, the focus is on the postnatal period, but ultimately it seems relevant to consider interventions that can be offered in the prenatal period.

Of course, even the interventions tested at a fairly advanced stage, such as in Studies 3 and 4, do not claim to be suitable for all women. Future research should allow us to specify for whom these interventions are the most relevant (e.g., high- vs. low-risk samples, women with or without associated depression, etc.). However, because they are quite different from traditional intervention approaches (their format is unique, they are single-sessions, and involve video games), there are strong reasons to believe that the interventions in Studies 3 and 4 may significantly enrich clinicians' tools for preventing and treating CB-PTSD symptoms. They provide an innovative and different response, which will certainly be appropriate for some of the women who have not previously found a suitable preventive or therapeutic approach. This also means that they will probably not be suitable for others, and this is why we must continue to look for new approaches, to explore other intervention pathways, and to optimise those that are already known.

One of the lessons of this thesis is also that the memory (re)consolidation hypothesis, although admittedly highly debated (313), is a framework that yields studies of clinical interest for the development of interventions for CB-PTSD symptoms. By guiding studies towards factors that might affect memory consolidation, such as sleep or analgesia, or by allowing the development of clinical interventions whose procedures are rigorously guided by evidence on memory (re)consolidation, this field of research seems to have clinical relevance and a real translational potential for combating CB-PTSD. It is very encouraging that research on these memory processes can have a real impact in an applied setting, especially if, as current hypotheses suggest, the benefits of CBIs and RBIs last considerably longer than other existing techniques. However, it is important to remember that just because the memory (re)consolidation framework has led to studies with interesting clinical prospects, this does not mean that the mechanisms involved in the studies in this thesis are indeed related to memory (re)consolidation. As we have seen in Study 2, a multitude of other explanations also need to be considered.

Another overall finding of this thesis is that targeted approaches, i.e., interventions focusing on a single process or symptom, may be relevant for addressing CB-PTSD symptoms. For example, the benefits of the RBI-VT tested in Study 4 on the overall severity of CB-PTSD symptoms while the intervention itself is supposed to specifically treat CB-IMs, is very encouraging. Echoing reflections on the transdiagnostic approach to mental health disorders (432), this type of result thus suggests that interventions specifically targeting CB-IMs may

have relevance for the reduction of intrusive memories and thoughts found in other disorders, such as obsessive-compulsive disorders, phobias, or substance use disorders (433, 434).

One of the conclusions of this thesis is also that, in order to prevent and treat CB-PTSD, a multitude of simple interventions remain to be tested. Indeed, many of the interventions presented in the introduction may seem complex, as they imply repeated sessions and components, as well as highly trained clinicians – even for prevention, e.g., EFT. But the present studies show that, even if based on complex theoretical assumptions, interventions tackling CB-PTSD can also be very simple, from an adjustment of analgesia-related preferences to a brief visuospatial task. In the present case, "simple" does not only refer to content of the interventions, but also to their high accessibility by healthcare professionals and patients, and the small amounts of time and financial investment they require. Again, it cannot be claimed from the preliminary results of most of the studies of this thesis that the considered insomnia-, analgesia-, or (re)consolidation-based interventions are ready to be used in the clinic. However, if this turns out to be the case, the future perspectives are exciting because implementing these interventions seems feasible, precisely thanks to their simplicity.

Imagining the implementation of these interventions on maternity wards, especially those considered in Studies 2 and 3 since they would take place in hospital, suggests that routine care can be reconsidered at many different levels, in order to make it adjusted and sensitive to the issue of traumatic birth and CB-PTSD (as proposed by the model of trauma informed care (435)). This could even apply to the procedures that are *a priori* the most strictly oriented towards somatic care, such as analgesia. Looking at interventions in this way naturally invites us to look beyond the traditional separation of physical and mental healthcare where obstetricians, nurses, and midwives are in charge of the 'body', and mental health professionals are in charge of the 'mind'. Indeed, as illustrated by the present thesis, such a vision would necessarily deprive women of multiple interventions addressing CB-PTSD, and which should be in the hands of professionals working on the labour ward. Overall, I argue that it is necessary and possible to make "the hospital" (this term including here both the professionals and the general functioning of the institution) more sensitive to mental health issues. In a sense, CB-PTSD can be seen as a psychological complication of childbirth. Yet, it is not treated like other complications: nosocomial infections, for example, are subject to preventive measures, such as systematic disinfection of hands and equipment, which are perfectly accepted and integrated into routine procedures. The interventions envisaged in

this thesis suggest that it would be not only desirable but also feasible to integrate the issue of CB-PTSD into the routine procedures of the maternity ward.

Finally, there is reason to hope that the clinical implications of this thesis should also touch on unrelated-to-childbirth PTSD, and particularly concern individuals (at risk of) experiencing single-event traumas. Much of the research on which the four studies in this thesis were based focused on service members and ED patients. As noted in Section I.A.2 (Box 2), traumatic childbirths have the advantage of being relatively standardised compared to the traumas experienced by the above-mentioned populations. As a result, interventions tested in Studies 3 and 4 are likely to have significant clinical value beyond the perinatal context. As for Studies 1 and 2, they are the first to provide data on the prospective associations between pre-traumatic insomnia and PTSD in civilians[19], and on the association between early administration of N_2O and PTSD in a clinical setting. In the case of analgesia during childbirth, it seems that the question has strong clinical relevance for other populations, as N_2O and morphine are widely used in EDs and/or in intensive care units, and thus in patients at high risk of developing PTSD symptoms. By questioning their incidental role on the mental health of postpartum women, Study 2 also questioned clinical practices in other hospital departments. Moreover, the studies of this thesis may be of interest for professionals exposed to traumatic events, such as those working in the delivery room, but also firefighters, service members, or police officers. By proposing brief and simple interventions, Studies 3 and 4 could also benefit these high-risk populations: as an illustration, the prevalence of PTSD in healthcare professionals during the COVID-19 pandemic was 21.5% (436). Echoing this observation, RBIs-VT are currently being tested for healthcare professionals (370).

C. Theoretical and research implications

1. Comments about memory (re)consolidation

As discussed in Section I.D, memory reconsolidation processes are still debated, and impossible to measure. Thus, the fact that the results of Study 4 are in line with the memory reconsolidation hypothesis does not allow us to conclude that memory reconsolidation processes were the underlying mechanisms of the tested RBI-VT (but, if so, see Box 16 for

[19] This does not mean that pregnant women are representative of civilians. In their case, insomnia may have very specific causes (e.g., physical discomfort, childbirth-related ruminations) or be perceived as more normative and transient than in other populations.

ethical comments). This will also apply to memory consolidation processes in START. Admittedly, numerous additional mechanisms may explain the CB-PTSD symptom reduction in Study 4. For instance, narrating the childbirth experience, returning to the maternity ward, completing a CB-IM diary or simply asking for help and being followed-up by a study psychologist may, in itself, have had therapeutic effects.

Box 16. Ethical comments.

In addition to the fact that memory is central to identity and psychic life, preserving traumatic memories often involves legal issues (e.g., accuracy of testimony). Thus, the prospect of interfering with the (re)consolidation of a memory, or even "manipulating" or "editing" it (226, 437), legitimately raises ethical questions (see Elsey and Kindt (2016) (437) for a detailed discussion). The notion of "memory manipulation", for example, suggests that CBIs and RBIs could completely overwrite a memory or even accidentally delete non-targeted memories. It is important to confront these concerns with the data collected: laboratory studies consistently suggest that declarative memory is preserved in CBIs and RBIs, whether based on a drug (319) or a visuospatial task (277). The target of these interventions remains involuntary memories and maladaptive emotional responses triggered by the traumatic experience. However, it is true that tests evaluating the effect of CBIs and RBIs on declarative memory, typically in verbal recognition tests in TFP-based studies, can only be applied with difficulty in the clinical context.

One illustration of our limited understanding of memory (re)consolidation is that, in Study 1, postnatal insomnia was hypothesised to be a risk factor for CB-PTSD because it disrupts memory consolidation while, on the contrary, in Studies 2, 3 and 4, interfering with the trauma memory (re)consolidation was expected to be beneficial. This may look contradictory: how is it possible that the disruption of the same process can lead to either worse or reduced CB-PTSD symptoms? In fact, there are many potential responses to this question, starting with the fact that sleep has a multitude of effects, and thus that having symptoms of insomnia does not only disrupt memory consolidation but also prevents the emotional "depotentiation" of the traumatic memory (122, 131) or fear extinction (124), which are hypothesised to be protective against CB-PTSD. In this thesis, the example of insomnia illustrates the fact that associations between the variables of interest and CB-PTSD cannot be solely interpreted in the light of memory (re)consolidation; there are often numerous other pathways that can provide valuable explanations. Thus, the purpose of the present section is to reflect on memory (re)consolidation processes, but it is important to acknowledge, beforehand, that these interpretations remain tentative.

In fact, it was clear from the outset of the design of the studies of this thesis that they would provide little insight into the mechanisms involved, due to their clinical and/or observational nature. However, understanding how existing and future interventions work has been

identified by the Lancet Psychiatry Commission as one of the most critical areas of research for the advancement of psychological treatments (438). While clinical research cannot provide a clear answer regarding the involvement of the mechanisms of memory (re)consolidation in CBIs-VT and RBIs-VT, it can provide some elements that could contribute to the debate and in turn feed into laboratory research. The studies in this thesis are no exception.

A first comment can be made on the return to the trauma context in Study 4, i.e., the maternity ward where participants had given birth, which was assumed to facilitate memory reactivation, a necessary step before interfering with its reconsolidation. The fact that participants indicated that the maternity ward strongly reminded them of their birth (as indicated by the high score of context specificity) suggested that going back to the maternity ward was a judicious addition to the procedure. When asked to explain why this place reminded them or not of the birth, participants pointed out specific elements, such as the hospital elevators and smell, or the white coats (see Appendix J, Section 2.1.1). From the point of view of the memory reconsolidation hypothesis, these observations suggest that using the trauma context indeed facilitated the memory reactivation and labilisation, and may be relevant for other populations as well. However, it should be mentioned that CB-PTSD may be a rather specific case with regard to the trauma context. Indeed, on the one hand, the majority of women only come to the maternity hospital to give birth (in Study 4, most of the women had never returned since childbirth) and, on the other hand, the hospital environment includes a set of very singular stimuli, which women do not encounter elsewhere, such as the smell. Thus, it remains an open question whether returning to the trauma site for individuals who have experienced a traumatic event in a more ordinary context (e.g., car accident survivors) has similar effects.

As explained in Section I.D.2.a, certain conditions would foster memory reactivation, such as context specificity and reminder cue specificity. There is an additional condition, which was not mentioned in the introduction because it had no methodological implications for Study 4, but which could still help us to interpret the results from the point of view of memory reconsolidation: prediction error. Briefly, the idea of prediction error is that the reactivation-labilisation of a memory would be facilitated by the presentation of new and relevant elements during the memory reactivation phase, i.e., when the reminder cues contain elements discrepant with the expectations, thus justifying an updating of the memory (338,

439). Although still debated (168), a consistent body of research tends to substantiate the importance of prediction error in the success of memory reconsolidation-based manipulations (339, 439). In the laboratory, prediction error is typically induced by presenting a CS without the UCS, instead of presenting both together (440), as it is assumed to induce a mismatch between participants' or rodents' expectations and the actual outcome. In the clinic, a prediction error is hard to monitor and induce. One research group working on RBIs to treat phobias with propranolol, for instance, tried to induce prediction error by explaining to participants with spider phobia that they will be asked to touch a tarantula during the memory reactivation phase, without actually asking it once the spider was presented to participants (165). With these instructions, the tested RBI was found to be more efficient than when participants did not experience such discrepancy (i.e., preliminary instructions were in line with participant's actual instructions during the reactivation phase), even if this work remains at a very preliminary stage and the different settings were only tested in a series of pilot cases (165).

How prediction error may apply to RBIs for CB-PTSD and PTSD is unclear. However, even without being voluntarily induced in Study 4, it is possible that returning to the maternity ward did create a prediction error for participants. Indeed, some of them had given birth years ago, but over time the maternity ward inevitably evolved: the reception desk may have been moved, the signage changed, and, of course, so did the staff. When reflecting on the protocol of Study 4 from that point of view, it thus appears that the memory reactivation phase included many elements conducive to prediction error. This was also apparent in the spontaneous comments of some participants as they entered the maternity ward, e.g., "*Oh it has changed since last time*". In conclusion, it cannot be excluded that the prediction error, even if it was not deliberately integrated in the procedure of the intervention, did not contribute to the reactivation of the memory in Study 4.

2. Future laboratory studies

As noted in the introduction, laboratory studies played a crucial role in the development of interventions to prevent and treat PTSD, as well as in the understanding of memory (re)consolidation. While these laboratory studies have strongly inspired the clinical studies of this thesis, the results of the latter in turn suggest future directions for the laboratory

studies. Interventions tested in Studies 3 and 4, in particular, would greatly benefit from being taken back to the laboratory.

Firstly, if studying the effects of early administration of analgesics on subsequent PTSD symptoms is certainly difficult in clinical RCTs, for ethical and practical reasons, they could be assessed with TFP-based studies, as Ravi et al. (2016) (75) did for N_2O - although such studies do not model peritraumatic pain, which appeared as an important covariate in Study 2. In addition, several studies, in rodents as well as humans, suggested that the effects of morphine or N_2O on memory formation (267, 441), fear memory acquisition (251) or PTSD (250) are dose-dependent. Thus, TFP studies may allow a better understanding of the dose-response relationship for PTSD prevention with analgesics, which is a crucial parameter to assess the suitability of this type of intervention. Moreover, while many studies suggest that the timing of administration is determinant (250, 263, 442, 443) and is a key parameter for assessing the potential and applicability of preventive interventions, it has not, to our knowledge, been rigorously and systematically investigated in humans. This would typically be feasible in the laboratory.

The exact duration of the memory consolidation window in humans is not yet clearly defined. The most widely accepted duration is six hours, as discussed in the introduction, but this initially comes from rodent experiments. In the meantime, this is a major constraint for the CBI-VT tested in START, as women who just had an ECS may still be too tired, in pain, or too sedated to receive the intervention within the first six hours postpartum. Most likely, other research teams working on the development of CBIs face the same difficulty, typically for EDs patients who may be admitted several hours after their traumatic experience. By more systematically testing the duration of the time gap between the trauma film exposure and the visuospatial task, laboratory studies could help to clarify this grey zone and potentially make CBIs-VT more accessible.

The procedure of the RBI-VT tested in Study 4 could also be greatly optimised with the help of TFP studies. Firstly, such studies would be necessary to specify which elements of the trauma context are important during the memory reactivation phase. In the case of CB-PTSD, for example, returning to any maternity ward may be sufficient, which would make the intervention suitable for women who moved since their birth. More generally, returning to the trauma site can be impossible. Identifying which context-related elements are the most

decisive could make the intervention more accessible, by reproducing only those elements, for example via virtual reality. By reducing reminder cues to a minimum, the assumed memory reactivation phase may also become easier to handle for patients, and accessible to individuals with more severe avoidance symptoms. Secondly, testing this intervention in the laboratory could give insights into its mechanisms. For example, distinguishing between the memory reactivation components (including coming back to the place where the trauma film was initially watched) and the visuospatial task depending on the experimental condition would allow confirmation of whether, as hypothesised, it is only the combination of these tasks that is beneficial (319). Similarly, it would be helpful to test a condition in which participants engage in the visuospatial task 12 hours after the reactivation phase, i.e., supposedly outside of the memory reconsolidation window: if no reduction in ITMs was observed, it would reinforce the hypothesis that this intervention relies on interference with memory reconsolidation. Finally, with regard to the sensory modality hypothesis, future TFP-based studies testing RBIs should encourage participants to report all sensory modalities of the IMs, as some studies seem to have solely focused on image-based memories (300). It would also be interesting to test RBIs-VT on non-visual experimental trauma, for instance by replacing the trauma film with a trauma podcast, to test the intervention on IMs that do not include images.

3. Future clinical studies

As suggested by Study 1, future studies investigating the association between pre-traumatic or prenatal insomnia symptoms and PTSD symptom severity, whether in women during the perinatal period or in other samples, should more systematically include post-traumatic or postnatal insomnia symptoms as a covariate. Indeed, a question raised by Study 1 is whether other existing studies, which, to my knowledge, never included post-traumatic insomnia symptoms in their analyses (e.g., 106, 107, 109), would still find a direct association between pre-traumatic insomnia and PTSD if they controlled for this additional covariate - ideally measured before PTSD symptoms, rather than concurrently. (If yes, this may suggest that our results differed from the others due to some specificities of the perinatal context, and highlight the importance of studying more diverse populations). In order to better tailor potential future interventions, it would also be useful to assess other aspects of sleep than insomnia symptoms, such as sleep duration, sleep efficiency (the ratio of total sleep time divided by time spent in bed), or sleep quality.

Future clinical studies examining the association between early analgesics intake (in particular morphine and N_2O) and subsequent PTSD symptoms would also benefit from considering other drugs in the analyses, such as exogenous oxytocin used to induce labour (154). This is particularly true for anaesthetics: indeed, anaesthesia is another important gateway for drugs to enter the organism. It is therefore a variable that would need to be taken into account to better understand the effects of early analgesics administration on PTSD. In the obstetric context, for example, a large cross-sectional Spanish study found that an epidural during childbirth could be a protective factor (55, 444), although others have not found this association, either in women who had a caesarean section (445), or all types of delivery combined (446, 447). It would also be necessary to check whether the use of analgesics was satisfying for the patients, and whether it was in accordance with the birth plan, so as to rule out associations not directly related to the pharmacological action of the administered drug. Another variable that might be interesting to consider in future studies is the SBE. This would typically allow us to better understand whether, as hypothesised in Section III.A.2, women who had a very high level of pain during labour and who received morphine or N_2O had a more negative SBE compared to others. Another approach could be to explore women's expectations and experience of obstetrical analgesics with qualitative research.

In both Studies 1 and 2, but also in most CB-PTSD studies, a validated index to control for birth medical severity is still lacking and should be developed in future studies. In other populations at risk of developing PTSD, there is, for example, the Injury Severity Scale (448), which allows controlling for the severity of injuries. To the best of my knowledge, there is no brief equivalent validated for childbirth. Thus, the birth medical severity, which is an important risk factor for CB-PTSD, is taken into account in Studies 1 and 2 with proxies, such as operative birth, whose relevance is variable. Some authors developed their own index, for example by creating dichotomous variables for different obstetric complications and then calculating a total score in which each complication corresponds to one point (125). However, this type of calculation has limitations, as it gives the same weight to complications that may reflect a different level of medical severity of the birth. The development of a validated and standardised index to assess the latter would therefore be a major advance for CB-PTSD research, and could typically improve the quality of studies, such as Studies 1 and 2.

If the CBI tested in START proves to be effective in the prevention of CB-PTSD, its integration into routine care will require an implementation trial: this is a crucial issue, as the integration of a new intervention into practice is only successful in 50% of cases and would take about 17-20 years (449). Although START will already provide a lot of information regarding future implementation, as we have built up practical experience in our research group, e.g., on the training time needed for midwives and nurses in charge of the activity, the reception of the intervention by maternity staff, or the feasibility of the intervention in the context of postnatal care, it will be essential to conduct rigorous implementation work.

With regard to the proof-of-principle Study 4, the results justify, in our opinion, the launch of a RCT. By overcoming the design limitations (see Section III.D.2), this RCT could allow us to test the effectiveness of the RBI-VT on CB-IMs (but also CB-PTSD symptoms and diagnosis) more rigorously. Given the early stage of development of this intervention, as well as the fact that there is, to my knowledge, no comparable single-session intervention to reduce CB-IMs, a randomised waitlist-controlled trial might be the most appropriate next step. With a larger sample size than Study 4, such an RCT could provide valuable insights into how the intervention works, and how it could be improved. For example, it would allow examining the association between emotional arousal during the memory reactivation phase and the intervention effectiveness (as the level of arousal required to reactivate a memory is still unclear, see Appendix J, Section 2.1.2, for an overview of this debate). Still in the spirit of improving the intervention, it would be important to test whether the number of pre-intervention CB-IMs is a predictor of the effectiveness of the intervention: if not, this could suggest that this RBI-VT test is suitable for help-seeking women having CB-PTSD symptoms but rare CB-IMs, as was the case in 78 (40.2%) out of 194 of those screened for the study. Such a result would thus significantly increase the accessibility of the intervention. Another critical question is whether the reactivation phase should necessarily take place on the maternity ward where women gave birth. As previously discussed, maternity wards are very specific places, with many commonalities, such as the hospital smell. Thus, coming back to any maternity ward may be sufficient to trigger memory reactivation, and clarifying this question would be an important step to make the intervention accessible to a maximum of women.

Overall, most of the above-mentioned ideas for future clinical studies would also apply to studies on women's partners and healthcare professionals working on the labour ward, who can also be concerned by CB-PTSD (427, 450). The interventions tested in Studies 3 and 4, in

particular, may be particularly helpful to address CB-PTSD symptoms in these populations. A priori, there is no reason to expect that these interventions may be efficient for women but not their partners or healthcare professionals; and preventing or treating CB-PTSD symptoms in them may also indirectly benefit the women (451). Yet, it should be noted that the context specificity boundary condition, assumed to promote memory reactivation in Study 4, may be harder to meet for partners, who spend less time on the maternity ward than women, and even more for professionals, for whom the maternity ward is not only associated with traumatic childbirth experiences but also their everyday work life.

D. Strengths and limitations of the thesis

1. Strengths

Several of the strengths of this thesis deserve to be highlighted. First of all, the studies are, in many ways, innovative. As far as I know, the associations between prenatal insomnia symptoms or morphine and N_2O, on the one side, and CB-PTSD symptoms, on the other side, had never been investigated before Studies 1 and 2. Furthermore, for both studies, some selected covariates had rarely if ever been included in the literature on other populations. Yet, whether it is postnatal/post-traumatic insomnia or peripartum/peritraumatic pain, these have direct implications for the interpretation of the results and their clinical consequences, as illustrated by the studies' results. Studies 1 and 2 therefore made a significant contribution to the scientific literature by highlighting factors that had not previously been considered for CB-PTSD prevention and which could be the subject of future interventions. On the other hand, Studies 3 and 4 are among the first to look at (re)consolidation-based interventions involving a visuospatial task in a clinical setting. The RBI-VT tested in the proof-of-principle translational Study 4, in particular, appears to be the first of its kind developed for individuals with IMs related to old and single-event real-life trauma. The whole procedure was designed and adjusted to fit the needs and specificities of the perinatal context. In the end, both Studies 3 and 4 have the potential to lead relatively soon to brief, low-cost, and widely accessible interventions, whose unique profile could advantageously complement the existing arsenal of tools. It should also be noted that START combines psychological and physiological measures while integrating the whole family, and is thus expected to provide a unique insight into the consequences of CB-PTSD, by linking psychological and biological processes. Finally, this work has the merit of also drawing attention to the relevance of the prenatal and

peripartum period for the prevention of CB-PTSD, which had received little attention until now (97).

Another strength of this thesis is that its studies, which are motivated by the perspective of bringing concrete benefits to women (at risk of being) affected by CB-PTSD symptoms, are theory-driven. The key covariates in Studies 1 and 2, i.e., postnatal insomnia, SBE and pain, were all chosen according to mechanistic assumptions derived from the existing literature. While acknowledging the limitations of clinical studies in drawing conclusions about the mechanisms involved, the choice of covariates (e.g., postnatal insomnia, in Study 1), measures (e.g., sensory modalities of CB-IMs, in Study 4), and proposals for interpretation of the results were strongly based on mechanistic thinking. In doing so, the studies of this thesis actively participate in the dialogue between theory, the laboratory, and the clinic. With regards to the interventions proposed in Studies 3 and 4, which appear timely in view of the existing literature, each of the components was reflected upon and adapted according to the available evidence on memory (re)consolidation, as illustrated by the work conducted on the memory reactivation phase of the RBI-VT tested in Study 4, and the corresponding measures of boundary conditions – which proved to be relevant. While relying on memory (re)consolidation, the studies of this thesis also incorporated insights from other models, such as the single-session format of Study 4, inspired by the trauma memory network model of Foa and Rothbaum (1998) (87), or the choice of certain covariates in Studies 1, 2 and 3, which was based on Ayers' diathesis-stress model (2016) (17). In doing so, this thesis was integrative, it combined both general knowledge of memory and trauma with models and evidence specific to the perinatal context.

Finally, the studies of this thesis were conducted with as much methodological rigour as possible. Validated questionnaires were systematically used, with some notable exceptions, such as the SBE (Study 1) or the context specificity (Study 4), which had no validated equivalent. Additionally, Study 3 used a multimethod measurement for CB-PTSD and stress-related outcomes, by including objective and subjective measurements, clinical observations, as well as numerous physiological outcomes, which should reinforce the validity of the results. In Study 4, daily monitoring of CB-IMs and their characteristics over a six-week period allowed for a precise description of the evolution of CB-IMs over the weeks of study participation. Furthermore, important covariates were included in the analyses.

With regard to methodological rigour, all studies had a prospective design, which enhances the validity of results, and Studies 1 and 2 were based on a large population-based prospective cohort that adequately represented the Norwegian population in terms of obstetric complications (452). This design typically overcame some of the limitations found in the literature, as in Study 1, which was the first to prospectively look at the association between pre-traumatic insomnia symptoms and PTSD symptoms in a large population-based cohort of civilians. Additionally, for both Studies 1 and 2, the analyses, proposed and carried out by a statistician, were based on ambitious statistics and advanced models, such as the item response models (453), the piecewise SEM (381) or the Zero-inflated Tweedie compound Poisson model (390), thus maximising the quality of the conclusions drawn.

As for the two interventions tested (Studies 3 and 4), they were registered in Clinicalstrials.gov prior to data collection, the sample size was calculated *a priori* and, where applicable, adequate manipulation checks were performed (e.g., having an unblinded member of the research team verifying that participants carried out the activity during 15 minutes in Study 3, or measuring the context specificity in Study 4). Overall, the data quality appeared to be generally high: in Study 4, for example, none of the participants dropped out after receiving the intervention, no data were missing, and only ten (2.8%) out of the 360 diary entries were excluded from the analyses because they did not correspond to CB-IMs according to two independent and trained (psychologists) raters.

In addition, specific and appropriate research guidelines, ensuring the quality of the reporting, were followed: the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (454) for Studies 1 and 2, and the Consolidated Standards of Reporting Trials (CONSORT) guidelines (455) for Studies 3 and 4 (although adapted for Study 4, as CONSORT guidelines were not initially developed for pre-post studies).

2. Limitations

Nevertheless, some limitations must be noted and taken into account when interpreting the results of this thesis. The first concerns the samples of the studies, which lacked representativeness in some respects. For example, in the ABC study, from which Studies 1 and 2 were derived, women with prenatal depression symptoms were more likely to drop-out, although this was not the case for those with prenatal PTSD, anxiety, or insomnia symptoms

(127, 456, 457). As for START, women are not eligible, for ethical reasons, if their infant requires intensive care, whereas it is precisely a factor that puts them at higher risk of developing CB-PTSD (17). Moreover, in Study 4, having to come back the hospital where women had given birth certainly discouraged those with the most severe avoidance symptoms to participate. In addition, for all studies, participants had to be able to complete questionnaires in the local language (Norwegian for Studies 1 and 2, French for Studies 3 and 4), which thus automatically excluded a large proportion of (im)migrants, who are, during the perinatal period, at higher risk of PTSD symptoms than other women (458).

Several limitations of the studies of this thesis are also inherent to their designs. For example, Studies 1 and 2 were observational studies, thus allowing for the identification of associations but not causalities. While their prospective nature facilitated the interpretation of the data, it should be noted that some variables were measured at the same time: this is typically the case for postnatal insomnia symptoms and CB-PTSD symptom severity, measured at eight weeks postpartum in Study 2. In the latter case, statistical analyses can only confirm the association between the two variables, but not determine its direction. Thus, while postnatal insomnia was found to be a predictor of CB-PTSD up to two years postpartum in the same study sample (130), and this association was unidirectional in other populations (459), it may be bidirectional (460, 461), which would have implications for the interpretation of findings. Furthermore, the observational design of Study 2 meant that the groups, based on which analgesic was used, were largely unbalanced (n = 17 in the "morphine only" group *vs.* n = 1,225 in the "N_2O only" group). They also certainly had different characteristics, despite the fact that they did not differ in terms of prenatal PTSD symptoms, nor birth medical severity (Appendix F, Table 2).

Causal interpretation of the results of Study 4 is also impossible due to the chosen design: it is not possible to state with certainty that the observed improvements were due to the intervention. CB-IMs may have spontaneously declined over time, although this seems unlikely because participants still had them several years after their childbirth and some of them had already unsuccessfully engaged in previous pharmaco- or psychotherapy. Moreover, despite the shortcomings of the chosen design, it appeared appropriate for such a translational proof-of-principle study, as an RCT would not have been resource-efficient in the absence of preliminary data. Another point that should be highlighted concerning Study 4 is the absence of blinding: participants knew that they were receiving an intervention, which

may have biased their expectations and thus affected the study outcomes, all self-reported. Finally, all studies had a relatively short follow-up (from six weeks post-intervention in Study 4 to six months postpartum in Study 3), whereas examining the effects in the longer-term would have helped to gain a better understanding of their relevance and effectiveness.

The measures used also had several limitations. This is particularly true for Studies 1 and 2, as they were based on secondary analyses of the ABC study, which was not specifically designed to answer the research questions of these two studies. For example, in Study 2, there was no information available on the exact dose of analgesics received, on the extent to which they actually provided pain relief to the participants, or on the parallel administration of oxytocin and benzodiazepines. Additionally, most of the measures were based on self-report questionnaires, which could also lead to biases since, for instance, individuals with insomnia symptoms tend to underestimate their actual sleep duration (462). Although the BIS, which was used in Study 1, was validated against polysomnographic data (375), objective and subjective measurements of sleep, in particular sleep duration, generally do not fully correspond. This has notably been shown in pregnant women (463). Also, with regard to Studies 1 and 2, it should be noted that some measures, notably pain during labour and SBE, were retrospectively assessed at eight weeks postpartum - although both measures showed high correlations and intraclass correlations with the same questions, asked at 48 hours postpartum to a subsample of participants.

As aforementioned, operative birth was taken as a proxy for birth medical severity, as I am not aware of a brief validated index to assess it, as would do the Injury Severity Scale (448) for injuries. However, operative birth incompletely reflects the actual birth medical severity, and therefore may not have fully controlled for it. Another limitation related to the measures in Studies 1 and 2 was the use of the IES to assess CB-PTSD symptoms. Although widely used and well recognised, the IES is not based on DSM-5 (which was not published at the time the ABC was designed), and thus does not measure CB-PTSD symptoms in the same way as the PCL-5, which was used for Studies 3 and 4. The IES does not, for instance, measure hyperarousal symptoms, whereas these may have been particularly relevant for examining the association between insomnia symptoms and CB-PTSD symptoms in Study 2. However, please note that the Impact of Event Scale-Revised (464), which does contain items on hyperarousal symptoms, was not found to be superior to the original IES for measuring CB-PTSD symptoms (373). Overall, for all studies, the questionnaires used to measure CB-PTSD

were initially designed to measure any type of PTSD, even if the instructions were always adapted so that participants responded in relation to their childbirth experience. Now that there are questionnaires specifically validated for the measurement of CB-PTSD, such as the City Birth Trauma Scale (16), it would certainly be more appropriate to use them (20, 27).

With regard to measures, the reporting of CB-IMs by a daily diary in Studies 3 and 4 also has limitations. Indeed the unusual exercise of reporting CB-IMs daily in a diary may have made the participants more attentive to their CB-ITMs, and thus increased their perceived number. Furthermore, seeing the diary at home may have triggered additional CB-ITMs. Another limitation of daily CB-ITMs measurements is that they are sensitive to CB-ITMs-triggering life events. For example, after a reduction in CB-ITMs in diary 2, one participant almost returned in diary 3 to the number of CB-ITMs she had in diary 1, although all CB-ITMs noted in diary 3 occurred in the days before her traumatic childbirth anniversary, and disappeared again after that date. The daily measurement of CB-ITMs thus has several limitations and may not always correctly reflect the number of CB-ITMs on "normal" days, although I am not aware of any other method that is more reliable than diaries. Additionally, there is no reason to believe that CB-ITMs-triggering life events would affect the pre-intervention period more than the post-intervention period – or the control group more than the intervention group.

IV. Overall conclusion

The overarching aim of this thesis was to contribute to the development of clinical interventions to address maternal symptoms of CB-PTSD. To do this, it notably relied on research on memory (re)consolidation, with the aim of translating these mainly laboratory-based findings into applied proposals that would directly benefit women (at risk of) experiencing CB-PTSD symptoms. The four studies of this thesis allowed us to:

1. Identify factors, assumed to modulate the consolidation of the traumatic childbirth memory, which are associated with CB-PTSD symptoms and on which it would be possible to intervene to prevent CB-PTSD. Study 1 found that prenatal insomnia symptoms predicted subsequent CB-PTSD symptom severity through negative SBE and postnatal insomnia symptoms, while Study 2 found that N_2O (and, marginally, morphine) predicted reduced CB-PTSD symptom severity, except in women who

reported very severe pain levels during labour. Both studies were based on a large prospective cohort study.

2. Participate in the development and testing of the effectiveness of interventions hypothesised to interfere with the (re)consolidation of the traumatic childbirth memory, and thus likely to prevent or reduce CB-PTSD symptoms. On the one hand, Study 3 sought to confirm the effectiveness of CBI-VT in an ongoing multicentre double-blind RCT that should provide high quality evidence. On the other hand, a proof-of-principle single-group pre-post study (Study 4) provided preliminary evidence that a RBI-VT may be suitable to reduce CB-IMs and CB-PTSD symptoms.

If this thesis addressed some literature gaps, many questions remain unanswered and thus call for further studies, both in the clinic and the laboratory. Among other things, it would be necessary to confirm the results of Studies 1, 2 and 4, but also to better understand, with the help of the TFP, the mechanisms involved. If this yields conclusive results, the implementation of the CBI-VT tested in Study 3, will need to be carefully followed-up. As for Study 4, its results justify the launch of a RCT to test the effectiveness of the proposed RBI-VT. More generally, future studies should engage in the exploration of new risk factors for CB-PTSD, which could be the subject of interventions, but also in the extension of existing interventions to other populations at risk of developing CB-PTSD symptoms, such as partners and healthcare professionals working on the labour ward.

By testing its research hypotheses and developing interventions based on memory (re)consolidation, this thesis, which was intended to be innovative and rigorously informed by the existing evidence, contributes to the fight against CB-PTSD and, hopefully, against unrelated-to-childbirth PTSD as well. It suggests that, throughout the perinatal period, simple interventions can contribute to the prevention and treatment of CB-PTSD symptoms. Since this disorder may affect the entire family sphere, these interventions could benefit not only women but also the couple and their children, whether born or unborn. At the same time, this thesis has contributed to the dialogue between clinical and laboratory research and to the advancement of translational research based on memory (re)consolidation. Although the latter is still hotly debated, the studies presented here suggest that it may be a relevant framework for thinking about CB-PTSD interventions. Interference with the (re)consolidation of traumatic memories, which until recently was nothing more than science fiction (226), is likely to make significant advances in clinical practice in the near future.

V. Output and contribution to science

During the three years of my PhD, I had the chance to collaborate with researchers and clinicians from a wide range of fields: psychologists, obstetricians, midwives, nurses, statisticians, epidemiologists, paediatricians, and many others. This allowed me to learn a great deal about these respective fields, but also about research work in a clinical context, as I spent a large part of my PhD coordinating studies, particularly START, which involved two university hospitals. These responsibilities taught me, among other things, to be inventive in solving the scientific and practical problems that arose and to become even more thorough and methodical in my work. It also led me to develop training skills, as I co-supervised many students, research assistants and clinicians (Appendix K, Section 1). I was myself trained in the use of various tools, such as the Neonatal Behavioural Assessment Scale (465), CAPS-5 (392, 393), the Structured Play Interaction Scales (466, 467), and the Bayley Scales of Infant Development III (468) (Appendix K, Section 2). Following up the families participating in START from the very first hours postpartum, has undoubtedly allowed me to improve my clinical skills. However, the contact with the participants of Study 4 has probably taught me the most from this point of view, as the overtly therapeutic context of the study required a great deal of commitment on my part and a real work on the therapeutic alliance with the participants.

Over the years, I have also been involved in other research projects, including a rapid review on the mental health of healthcare professionals during pandemics (see the publication list in Appendix K, Section 3). Furthermore, I had multiple opportunities to communicate our work and knowledge on perinatal mental health outside the research group, for instance in national and international conferences (Appendix K, Section 4). I have made various public and scientific commitments (Appendix K, Section 5), as illustrated by the co-creation and coordination of the Early Career Researchers section of the Society for Reproductive and Infant Psychology. As for the general public, I was invited by PépiteMama to produce a podcast on traumatic childbirth for families. I participated in an Instagram live, organised by MotherStories.ch and the Lausanne University Hospital, on traumatic childbirth, postnatal depression and parental burnout. I also co-authored two articles in journals for Swiss and French perinatal professionals, aiming to inform them and raise awareness about CB-PTSD (Appendix K, Section 3). Additionally, I had the great pleasure of teaching student and graduate midwives on attachment and traumatic births, at the School of Health of the Canton de Vaud (Appendix K, Section 6). Finally, I co-supervised the work of a Master student, and I

will also, in the coming years, be involved in the co-supervision of the PhD thesis of the student who will coordinate the RCT testing the RBI-VT developed in Study 4 (Appendix K, Section 7).

VI. References

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VII. Appendices

A. The cognitive model of PTSD

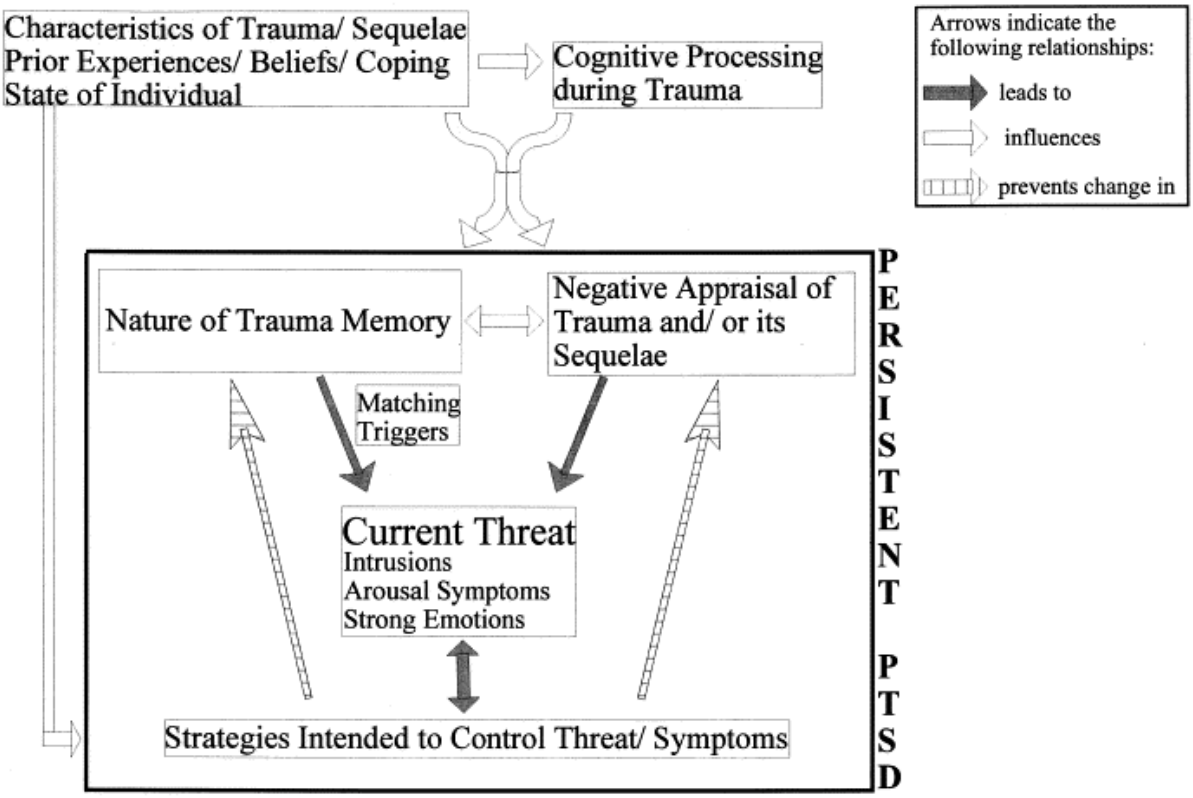

Figure 1. "*A cognitive model of PTSD*". Figure reprinted with permission from Ehlers and Clark (2000) (78, p. 321).

B. The fear network model

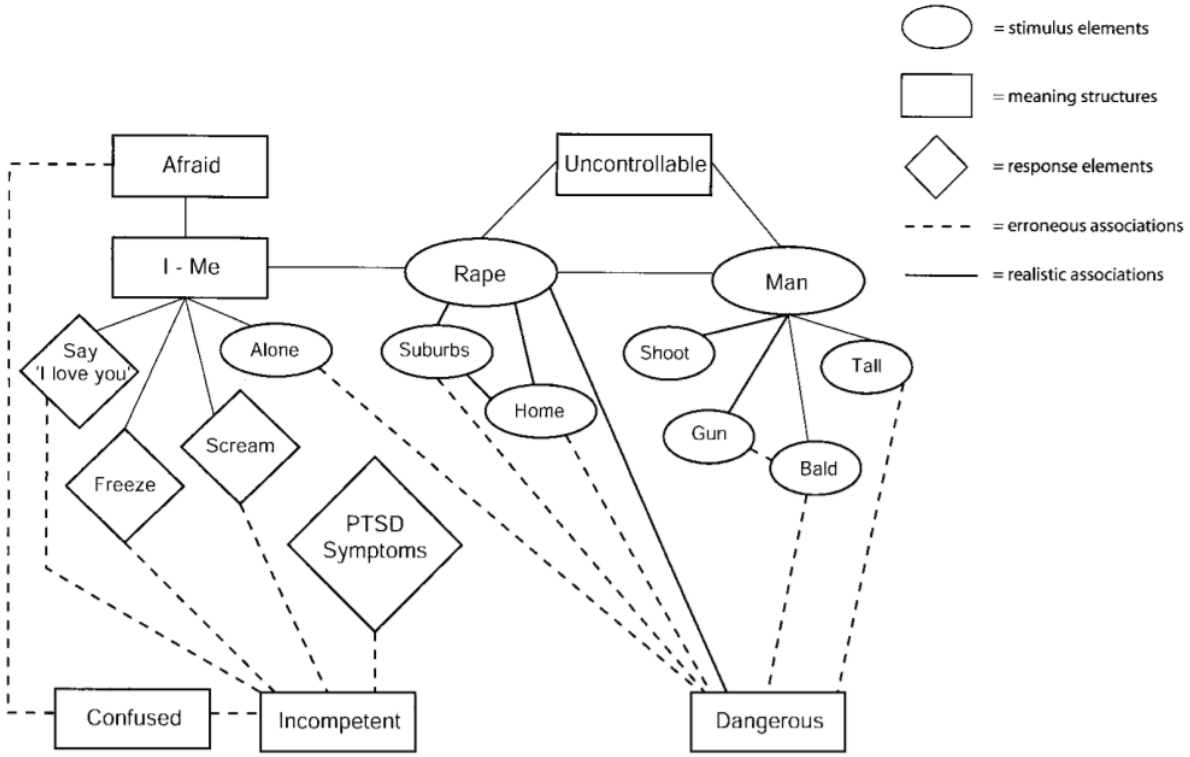

Figure 1. "*A schematic representation of a fear network following rape, from* Treating the Trauma of Rape: Cognitive Behavioral Therapy for PTSD *(p. 76), by E. B. Foa and B. O. Rothbaum, 1998, New York: Guilford Press. Copyright 1998 by The Guilford Press*". Figure reprinted with permission from Dalgleish (2004) (89, p. 237).

C. The working memory model

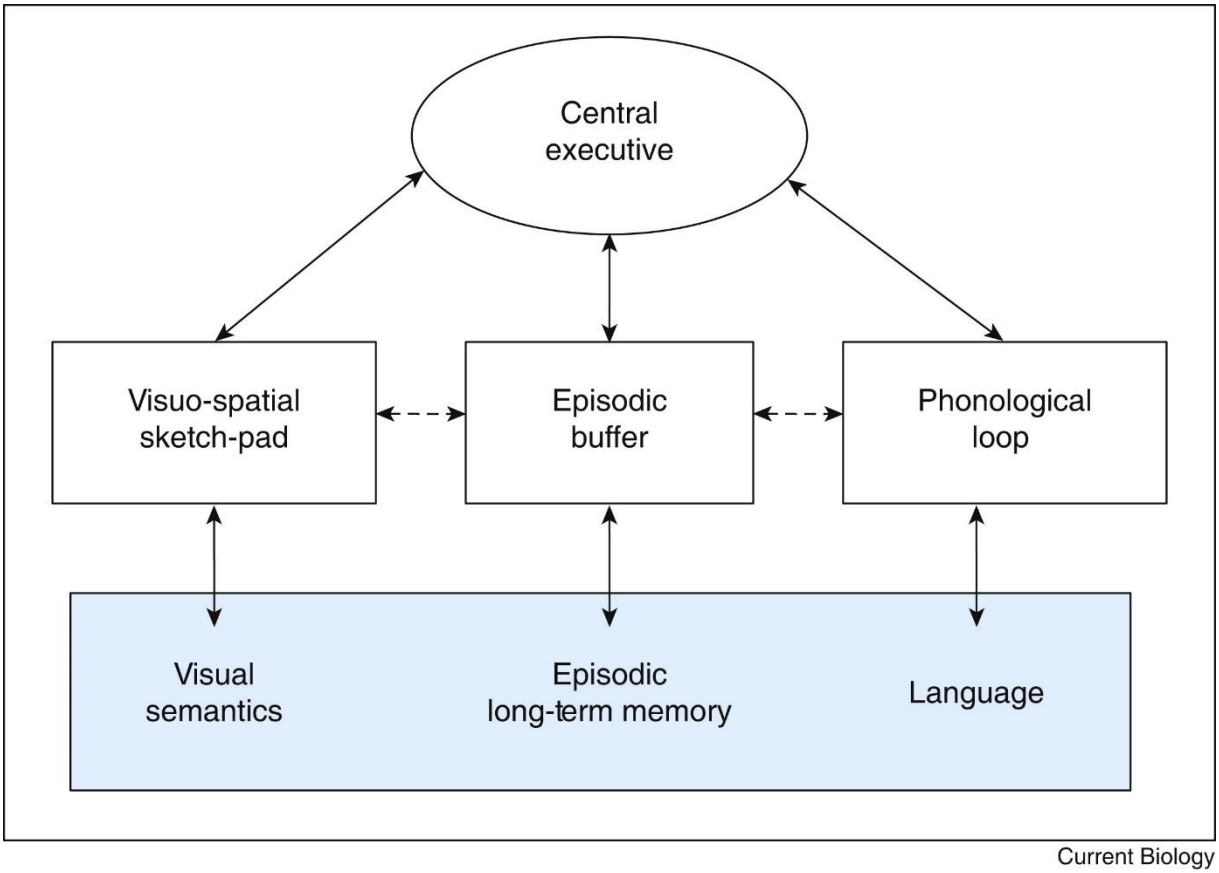

Figure 1. The working memory model. Figure reprinted with permission from Baddeley (2010) (273, p. 138).

D. Published manuscript of Study 1

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Title: Prenatal insomnia and childbirth-related PTSD symptoms: a prospective population-based cohort study

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Abstract:

Background. Certain populations are at high risk of experiencing a traumatic event and developing post-traumatic stress disorder (PTSD). Yet, primary preventive interventions against PTSD are lacking. It is therefore crucial to identify pre-traumatic risk factors, which could be targeted with such interventions. Insomnia may be a good candidate, but studies on

civilians are sparse. Furthermore, the mechanisms at stake in the relationship between pre-traumatic insomnia and PTSD symptoms are unclear.

Methods. This prospective population-based cohort study (*n* = 1,610) examined the relationship between insomnia symptoms at 32 weeks of pregnancy and childbirth-related PTSD (CB-PTSD) symptoms at eight weeks postpartum. Postnatal insomnia symptoms, prenatal psychological symptoms (depression, anxiety, PTSD, fear of childbirth), subjective birth experience (SBE) and birth medical severity were included as covariates in the analyses, which were based on a Piecewise Structural Equation Modelling approach.

Results. The relationship between prenatal insomnia and CB-PTSD symptoms was mediated by negative SBE and postnatal insomnia symptoms. All relationships involving insomnia symptoms had small or very small effect sizes.

Limitations. This study used self-report questionnaires. Postnatal insomnia and CB-PTSD symptoms were concurrently measured.

Conclusion. Prenatal insomnia symptoms may impair the ability to cope with a difficult birth experience and contribute to postnatal insomnia, a risk factor for CB-PTSD. Thus, prenatal insomnia symptoms may be a promising target for CB-PTSD primary preventive interventions, although other prenatal psychological symptoms could also be considered. Even beyond the perinatal context, future studies on pre-traumatic insomnia and PTSD should include post-traumatic insomnia as a covariate.

Keywords: Posttraumatic Stress Disorder; Prevention; Insomnia; Risk Factors; Pregnancy; Childbirth

Manuscript:

1. Introduction[1]

Triggered by a traumatic experience, post-traumatic stress disorder (PTSD) is a mental health disorder with a lifetime prevalence of 3.9% (Koenen et al., 2017). Its four symptoms clusters, which have to be present at least one month post-trauma, are: re-experiencing symptoms

[1] ABC = Akershus Birth Cohort; BIS = Bergen Insomnia Scale; CB-PTSD = Childbirth-related Post-Traumatic Stress Disorder; CES = Combat Exposure Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECS = Emergency caesarean section; EPDS = Edinburgh Postnatal Depression Scale; FOC = Fear Of Childbirth; GPCM = Generalised Partial Credit Model; IES = Impact of Event Scale; IES-R = Impact of Event Scale-Revised; IRM = Item Response Model; MINI = Mini International Neuropsychiatric Interview; MVC = Motor Vehicle Accident; PCA = Principal Component Analysis; RESI = Robust Effect Suze Index; SCL = Hopkins Symptom Checklist; SEM = Structural Equation Modelling; SBE = Subjective Birth Experience; VIF = Variance Inflation Factor; W-DEQ = Wijma Delivery Expectancy/ Experience Questionnaire.

(including distressing trauma-related dreams), avoidance of trauma-related stimuli, alterations in arousal (including sleep disturbances), and negative cognitions and mood (American Psychiatric Association, 2013). Certain populations, such as service members, are at increased risk of experiencing a traumatic event and developing PTSD (Stefanovics et al., 2020). This is also the case for women during the perinatal period, given that childbirth-related PTSD (CB-PTSD) affects 4% of mothers in community samples, and 18.5% in high-risk samples (Yildiz et al., 2017). Overall, these groups would benefit from primary preventive interventions for PTSD, but they are lacking (Howlett and Stein, 2016). To develop such evidence-based interventions, it is crucial to identify modifiable risk factors, at stake before trauma exposure.

In that respect, sleep disturbances could be a promising intervention target. It is well documented that they are associated with impaired mental health (Freeman et al., 2020) and disrupted physiological functioning (e.g., blunted diary cortisol trajectory, increased risk of hypertension, and higher body mass index) (Bei et al., 2017; Medic et al., 2017). Insomnia, in particular, which is characterised by difficulty falling or staying asleep and associated with distress or functional impairment (American Psychiatric Association, 2013), may contribute to PTSD development. As an illustration, pre-deployment insomnia predicted post-deployment PTSD in service members (Gehrman et al., 2013; Wang et al., 2019), although one study did not find such a relationship (van Liempt et al., 2013). In civilians, pre-traumatic insomnia symptoms also predicted PTSD(-like) symptoms following a traumatic injury (Bryant et al., 2010), an analogue trauma (Short et al., 2020), or a motor vehicle collision (MVC) (via, in the latter case, acute stress disorder) (Neylan et al., 2021). Importantly, the relationship between insomnia and PTSD seems to remain after controlling for other psychological symptoms, such as pre-traumatic depression, anxiety, and PTSD (e.g., Wang et al., 2019). This suggests that pre-traumatic insomnia may not only be a symptom of other psychopathologies: it could also be an independent predictor of PTSD symptom development (Cox et al., 2017; Kartal et al., 2021), albeit contradictory findings have been reported in service members (van Liempt et al., 2013),

One of the proposed mechanisms to explain this relationship is that insomnia fosters maladaptive responses to the trauma (Bryant et al., 2010; Cox et al., 2017) by disturbing emotional regulation (Tempesta et al., 2018), executive functions (Cox and Olatunji, 2016), and encoding (Cousins and Fernández, 2019; Krause et al., 2017), thus increasing the

stressor's psychological impact (Bryant et al., 2010). This could explain why combat-related stress severity partially moderated the relationship between pre-deployment sleep disturbances and subsequent PTSD – although, importantly, this was not found in the replication sample (Acheson et al., 2019). One study also reported that subjective peritraumatic distress mediated the relationship between prior insomnia and PTSD-like symptoms after exposure to an analogue trauma (Short et al., 2020), although, in another study, pre-traumatic insomnia did not appear to predict peritraumatic distress in MVC survivors (Neylan et al., 2021). Overall, these mixed results suggest that it is important to take into account both the stressor severity and the subjective response to it when investigating the potential link between pre-traumatic insomnia symptoms and PTSD.

Given the chronicity of insomnia, a second hypothesis could be that individuals with pre-traumatic insomnia also have *post*-traumatic insomnia, which has been shown to directly contribute to the aggravation or maintenance of PTSD symptoms (Biggs et al., 2020; Garthus-Niegel et al., 2015; Zeng et al., 2020). Post-traumatic insomnia involvement in PTSD pathogenesis may be linked with 1) the disruption of memory consolidation (Azza et al., 2020; Cousins and Fernández, 2019; Sopp et al., 2021), which corresponds to the stabilisation of the memory trace into long-term memory and is suspected to be impaired in PTSD (van Marle, 2015), and 2) the disruption of fear extinction or safety learning prevention (Colvonen et al., 2019; Seo et al., 2021), both allowing for a reduction of the fear response. Thus, post-traumatic insomnia emerges as a crucial factor, explaining by itself the relationship between pre-traumatic insomnia and PTSD. To our knowledge, however, post-traumatic insomnia has not been taken into account in previous studies. Clarifying its role therefore seems important to conclude on the relevance of treating pre-traumatic insomnia to prevent PTSD.

Furthermore, in civilians, pre-traumatic sleep and covariates are usually retrospectively measured, as it is difficult to recruit participants before trauma exposure (e.g., Bryant et al., 2010; Neylan et al., 2021). However, retrospective measurements, in particular following a traumatic event, may be subject to memory bias. Moreover, the literature on pre-traumatic insomnia and PTSD symptoms sometimes relies on sleep measurements reconstituted from different instruments or single-item questions (e.g., Gehrman et al., 2013; van Liempt et al., 2013), which reduces their validity. Finally, most studies focus on service members, yet the weight of PTSD risk factors varies across groups (Brewin et al., 2000), thus the evidence collected in this population may not be valid in other groups. In addition, the vast majority of

service members are men, whereas insomnia prevalence is higher in women (Suh et al., 2018; Zhang and Wing, 2006), and sex could affect the relationship between sleep and PTSD (Kobayashi et al., 2007; Kobayashi and Delahanty, 2013). To develop appropriate preventive interventions, it would therefore be crucial to conduct studies in new populations.

In this study, we examined the prospective relationship between prenatal insomnia symptoms and subsequent CB-PTSD symptoms. Beyond the fact that CB-PTSD is relatively common (Yildiz et al., 2017) and that women are underrepresented in the literature on pre-traumatic sleep and PTSD, pregnancy follow-up allows prospective measurement of pre-traumatic (i.e., pre-natal) insomnia symptoms and other covariates. Furthermore, traumatic childbirth represents a relatively standardised real-life trauma (homogenous population; mostly taking place in a care setting) and thus a good study model for PTSD. Hence, studying the relationship between insomnia and PTSD in the perinatal context may help to overcome the limitations identified in the current literature.

Previous research found that 39.7% of women suffer from insomnia during the third trimester of pregnancy (Sedov et al., 2021), and that it is also common postnatally (Dorheim et al., 2014; Sivertsen et al., 2015). Prenatal insomnia may, *inter alia*, be caused by pregnancy-related nocturnal ruminations (Swanson et al., 2020), potentially reflecting fear of childbirth (FOC). FOC has shown to be more intense in pregnant women with insomnia than in those without (Osnes et al., 2020), and is a risk factor for CB-PTSD (Ayers et al., 2016; Garthus-Niegel et al., 2014). Prenatal insomnia has also well documented links with prenatal anxiety and prenatal depression symptoms (Emamian et al., 2019; Osnes et al., 2020; Sedov and Tomfohr-Madsen, 2021). Its prospective relationship with CB-PTSD, however, has received little attention so far, although insomnia at eight weeks postpartum has been identified as a maintaining factor of CB-PTSD at two years postpartum (Garthus-Niegel et al., 2015).

In summary, pre-traumatic insomnia symptoms may be a risk factor for PTSD symptom development. If so, it could be a relevant target for PTSD primary preventive intervention. However, current evidence is mixed and most of the available studies concern male service members or suffered from significant limitations, which limits the results' generalisability. The objective of this prospective population-based cohort study was to examine the relationship between prenatal insomnia symptoms at 32 weeks of pregnancy and CB-PTSD symptoms at eight weeks postpartum, taking postnatal insomnia symptoms into account and

controlling for prenatal psychological symptoms (depression, anxiety, and PTSD symptoms as well as FOC) and childbirth-related factors (subjective birth experience (SBE), birth medical severity). We hypothesised that prenatal insomnia symptoms would predict CB-PTSD symptoms, but that this relationship would be mediated by postnatal insomnia symptoms and SBE.

2. Method

2.1. Design and study population

This study was derived from the Akershus Birth Cohort (ABC), a large population-based prospective cohort study. The ABC targeted all women planning to give birth between November 2008 and April 2010 at Akershus University Hospital (Norway), which serves around 350,000 inhabitants. Women were eligible to participate if they were able to complete questionnaires in Norwegian. They were recruited at 17 weeks of pregnancy, during their routine foetal ultrasound examination. Participation involved completing paper questionnaires at 17 weeks and 32 weeks of pregnancy, and at eight weeks and two years postpartum. Participants who delivered between May 2009 and September 2010 answered additional questions about SBE at 48 hours postpartum. Obstetrical information was retrieved from hospital birth records. The ABC was approved by the Regional Committee for Medical and Health Research Ethics (approval number S-08013a); all participants provided written informed consent.

In this study, we used data from the questionnaires at 17 weeks and 32 weeks of pregnancy, as well as the 8-week postpartum questionnaires and the hospital birth record. Of the eligible women, 80% (N = 3,752) agreed to participate and returned the 17-week questionnaires, of whom 131 were excluded from the cohort study due to new address or obstetrical complications (see Garthus-Niegel et al. (2018a) for detailed information on participants). Women were further excluded from the current study for the following reasons: having taken sleeping pills during the last ten weeks of pregnancy (because it could have biased the insomnia measures), missing hospital birth record (rendering birth medical severity assessment impossible) or missing data in the questionnaires of interest (rendering computation of total scores impossible). The final sample consisted of 1,610 participants (Figure 1).

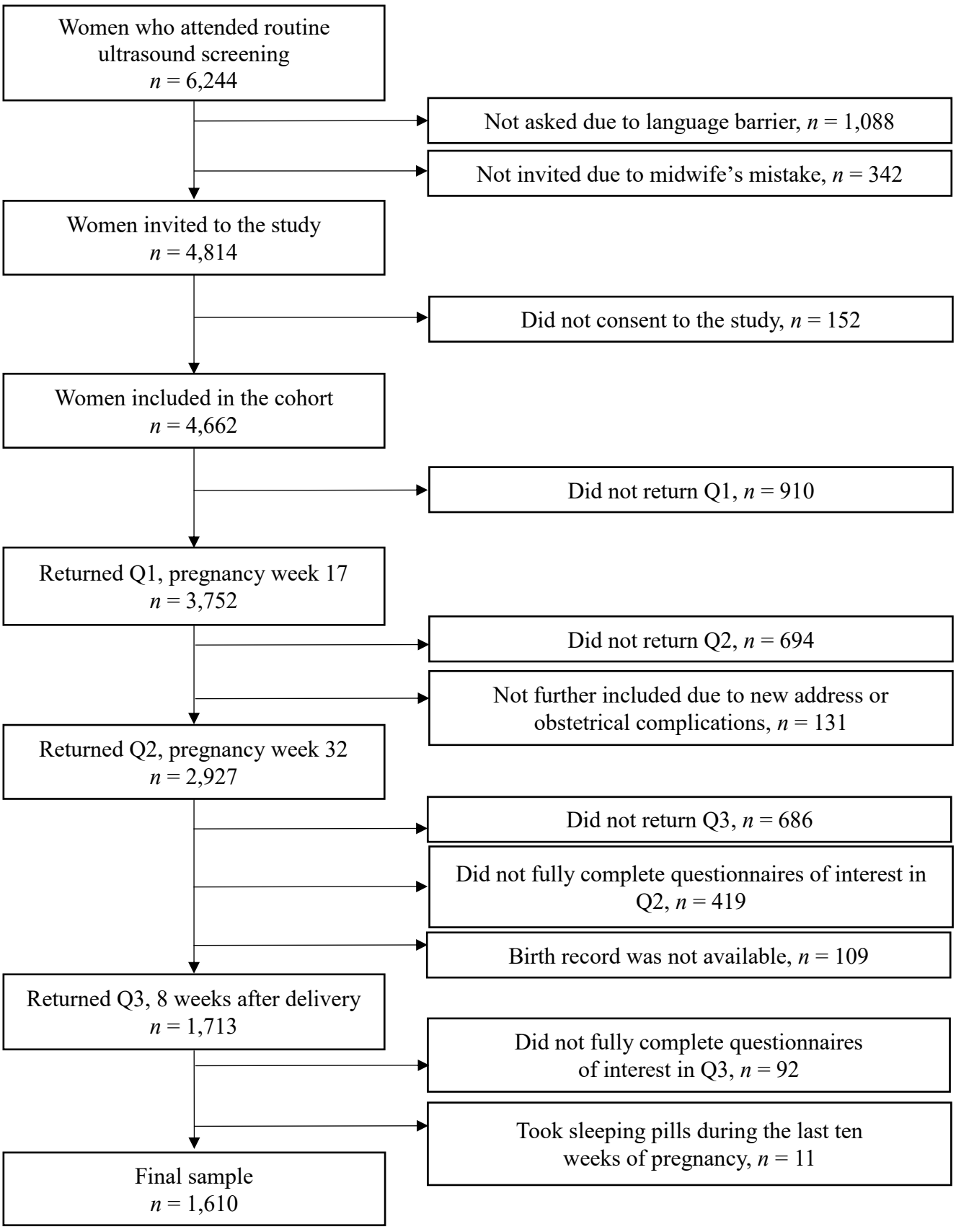

Figure 1. Responses to the study questionnaires.

2.2. Measures

Because a Structural Equation Modelling (SEM) approach was planned, and in order to obtain numeric scores, all questionnaires were statistically treated using item response models (IRM) or factor techniques.

Childbirth-related PTSD symptoms

CB-PTSD symptoms were measured at eight weeks postpartum, with the Impact of Event Scale (IES) (Horowitz et al., 1979). Participants were instructed to complete it in relation to their last childbirth. The IES is a 15-item self-rating questionnaire that has been validated in postpartum women (Olde et al., 2006). Each item has four response categories (usually recoded with the following weightings: 0 = "not at all", 1 = "rarely", 3 = "sometimes", and 5 = "often"). The sum score of the overall scale ranges from 0 to 75, with scores above 34 indicating probable PTSD (Neal et al., 1994). In this study, however, the ordinal nature of the response scale was taken into account by using a polytomous IRM (Hambleton et al., 1991) to compute a total IES score (see Supplementary material, section 1.1.).

Insomnia symptoms

Insomnia symptoms were self-reported at 32 weeks of pregnancy and eight weeks postpartum through the Bergen Insomnia Scale (BIS), a six-item self-rating scale which has been validated against polysomnographic data (Pallesen et al., 2008). Four items assess sleep impairment (which corresponds to criterion A for insomnia in DSM-IV-TR (American Psychiatric Association, 2000)), and two items respectively assess daytime impairment linked with sleepiness or sleep-related dissatisfaction (criterion B for insomnia in the DSM-IV-TR (American Psychiatric Association, 2000)). In the original scoring, items are scored from 0 to 7, reflecting the frequency of each symptom per week, over the past month. The BIS total score ranges from 0 to 42, with higher scores reflecting more severe insomnia symptoms. Because previous validation studies have retained one or two factor solutions depending on the calibration sample, a Principal Component Analysis (PCA) was run to check for dimensionality in the present data. A one-factor solution was finally retained (see Supplementary material, section 1.2.).

Prenatal depression symptoms

Prenatal depression symptoms over the past week were measured by the 10 item self-report Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987), at 32 weeks of pregnancy. The EPDS has been validated in pregnant women (Bergink et al., 2011; Bunevicius et al., 2009). Each item has four response categories, ranging from 0 to 3, yielding a total score from 0 to 30, with a higher score indicating more severe depression symptoms. In this study, given the categorical nature of responses, an IRM was adopted for score computation (see Supplementary material, section 1.3.).

Prenatal anxiety symptoms

Prenatal anxiety symptoms were reported at 32 weeks of pregnancy through the 10-item anxiety scale (SCL-A) of the Hopkins Symptom Checklist (SCL-25) (Derogatis et al., 1974). Each item assesses one anxiety symptom over the past week and has four response categories, from 1 = "not at all" to 4 = "extremely". The total score in the original scoring ranges from 10 to 40, higher scores reflecting more severe anxiety symptoms. Given the categorical nature of the data and previous successful item response modelling of the SCL (Kleppang and Hagquist, 2016), responses to the SCL-A were also analysed with an IRM (see Supplementary material, section 1.4.).

Prenatal PTSD symptoms

Prenatal PTSD symptoms were assessed at 17 weeks of pregnancy. Women reported whether and which of eight PTSD symptoms they experienced over the past month, in relation to a dramatic or terrifying event they potentially experienced. This PTSD symptom checklist was based on the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), see Garthus-Niegel et al. (2018a) for a full description of this scale. Symptoms were scored as 0 = "absent" or 1 = "present"; with the total score ranging from 0 to 8. The prenatal PTSD symptoms score was computed in this study with a dichotomous IRM (see Supplementary material, section 1.1.).

Fear of childbirth

FOC was assessed at 32 weeks of pregnancy, with the 33-item self-report Wijma Delivery Expectancy/Experience Questionnaire version A (W-DEQ) (Wijma et al., 1998). The W-DEQ evaluates women's cognitive appraisal of the forthcoming birth, with six response categories scored from 0 to 5, and a total score ranging from 0 to 165 in the original scoring. In this study,

scores were computed as a factor score on the first component of a standard PCA (see Supplementary material, section 1.5.), were higher values indicated more severe FOC.

Subjective birth experience

SBE was measured at eight weeks postpartum, with three items ("How frightened were you during the birth?"; "What was your overall experience of the birth?", and "To what degree did you feel taken care of during the birth?"). The first two were answered on a 10-point scale from 0 = "not frightened at all"/"very good", respectively to 10 = "extremely frightened"/"extremely bad", respectively. The last item was answered on a 4-point scale, from 1 = "very good" to 4 = "very bad". SBE has been shown to be a major risk factor for CB-PTSD (Ayers et al., 2016), notably when measured with these three items (Garthus-Niegel et al., 2013). In the present study, a PCA revealed a strong one-factor solution, with high scores reflecting a negative experience (see Supplementary material, section 1.6.).

Birth medical severity

Birth medical severity was expressed with a dichotomous variable, coded 1 if the birth involved vacuum, forceps, or an emergency caesarean section (ECS), or 0 if not. This information was retrieved from hospital birth records. The objective of the variable was to reflect birth-related stress exposure, comparable to the Combat Exposure Scale (CES) used in military populations to assess combat-related stress exposure (Cox et al., 2018). In the absence of a brief validated equivalent for childbirth, we chose operative birth as a surrogate. Indeed, although birth can be stressful in many respects, operative birth is an important indicator of the urgency of the birth and can be particularly stressful (Gamble and Creedy, 2005)

Parity

Based on participants' report at 17 weeks of pregnancy, parity was coded 0 = "nulliparous" and 1 = "parous".

Sociodemographic characteristics

Marital status (1 = "married/cohabiting" and 0 = "single"), education (0 = "elementary school", 1 = "high school", and 2 = "higher degree"), and maternal age at the time of birth were extracted from hospital birth records.

2.3. Data analysis

2.3.1. Sample description

Descriptive analyses were conducted with IBM SPSS 27. The difference between prenatal and postnatal insomnia scores was calculated with a Wilcoxon Signed-Ranks test, given that the data were skewed.

2.3.2. Piecewise Structural Equation modelling

Because several causal hypotheses involving a set of potentially mediating/moderating variables were to be tested in this study, a Structural Equation Modelling approach was adopted (Ullman and Bentler, 2003) using R version 4.0.4 (R Core Team, 2021). As many women reported no CB-PTSD symptoms, a particularity of the data was a strong bimodal zero-inflated distribution of the CB-PTSD variable (see Figure S1 in Supplementary material, section 2). This was taken into account by assuming a Tweedie distribution for this variable, which is appropriate for positive non-symmetric data, and can take a zero-inflated bimodal shape for some parameter values (Jorgensen, 1987). This particularity precluded a traditional SEM analysis of the variance-covariance matrix. Thus, a piecewise SEM approach (Shipley, 2000), using the piecewiseSEM R package (Lefcheck, 2016), was chosen as it can flexibly accommodate non-gaussian cases. Piecewise SEM allows connecting a set of generalised linear models within a network of hypothesised relationships. Apart from the Tweedie submodel on CB-PTSD symptoms, all other pieces in the model were standard gaussian linear models. The global fit of the piecewise SEM was examined through a Fisher's C statistic. Admissible but non-included relationships were tested through a set of directed separation tests (Shipley, 2013) for each model.

Three layers of variables were connectable in the model: prenatal variables, birth-related variables (birth medical severity, SBE), and postnatal variables. Because of this temporal structure, not all oriented connections were possible, which helped to define a maximal model including all admissible connections, with all variables from a given layer predicting all variables in subsequent layers.

A good predictive model of CB-PTSD symptoms was predefined as: 1) being inclusive: it includes, and potentially extends, a minimal set of relationships that are well-documented in

previous studies; 2) being parsimonious: it includes only the minimal set of relationships required to reach acceptable fit; 3) being strongly connected: it only includes statistically significant relationships, and does not include relationships for which conditional independence tests given the current model are non-significant; and 4) showing a good fit, in terms of Fisher's *C* statistic. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were also computed, as they allow for comparison between models that have the same numbers of parameters (e.g., models 11 and 13 in Table 2).

Seven theoretically expected relationships were taken as a starting point in the modelling sequence. The following causal influences were a priori assumed: 1) prenatal depression symptoms to prenatal insomnia symptoms (Dorheim et al., 2012; Sedov and Tomfohr-Madsen, 2021); 2) prenatal anxiety symptoms to prenatal insomnia symptoms (Osnes et al., 2020; Sedov and Tomfohr-Madsen, 2021); 3) FOC to prenatal insomnia symptoms (Swanson et al., 2020); 4) prenatal insomnia symptoms to CB-PTSD symptoms; 5) SBE to CB-PTSD symptoms (Garthus-Niegel et al., 2013); 6) birth medical severity to CB-PTSD symptoms (Ayers et al., 2016); and 7) birth medical severity to SBE (Garthus-Niegel et al., 2013). Because they are repeated measurements, it also appeared statistically meaningful to add 8) prenatal insomnia symptoms to postnatal insomnia symptoms. All eight relationships were gathered into a first basic structural model (M1, Table 2).

3. Results

3.1. Characteristics of the study sample

At birth, mean maternal age was 31.29 years (*SD* = 4.54) (Table 1). The majority of women had a higher education degree and were married/cohabiting. Half of them were nulliparous, and 20.3% of the deliveries involved forceps, vacuum, or ECS. At eight weeks postpartum, 1.9% of them had probable CB-PTSD according to the original IES scoring. Insomnia original scores at 32 weeks of pregnancy were significantly higher than at 8 weeks postpartum, $Z = -6.303$, $p < .001$ (Table 1).

Table 1. Characteristics of the study sample (*n* = 1,670).

Sample characteristics (*time point measured or range*)	Frequency (%)	Mean (*SD*)
Sociodemographic characteristics		
Age (*at birth*)		31.29 (4.54)
Education (*at birth*)		
Elementary	43 (2.7[a])	
High school	439 (27.3[a])	
Higher degree	1,072 (66.6[a])	
Marital status (*at birth*)		
Married or cohabiting	1,565 (97.2[a])	
Single	35 (2.2[a])	
Prenatal psychological symptoms		
Insomnia symptoms *(pregnancy week 32)*		
Score[b] (*0–42*)		17.45 (10.36)
PCA score[c] (*-1.58–2.67*)		0.19 (1.05)
Depression symptoms (*pregnancy week 32*)		
Score[b] *(0–24)*		4.90 (4.11)
IRM score[c] *(-0.69–0.37)*		0.01 (0.15)
Anxiety symptoms (*pregnancy week 32*)		
Score[b, d] (*10–32)*		12.80 (3.10)
IRM score[c] (-0.98–*2.81)*		-0.03 (0.83)
Prenatal PTSD symptoms (*pregnancy week 17*)		
Score[b] (*0–8*)		0.25 (0.77)
IRM score[c] (*-0.25–3.18*)		-0.04 (0.54)
Fear of childbirth (*pregnancy week 32*)		
Score[b] *(2–145)*		57.44 (19.64)
PCA score[c] *(-2.74–4.44)*		0.02 (0.98)
Birth-related variables		
Parity (*pregnancy week 17*)		
Nulliparous	812 (50.4)	
Parous	798 (49.6)	
Subjective birth experience (8 weeks postpartum)		
Score [b]		
“How frightened” (*0–10*)		2.96 (2.90)
“Overall experience” (*0–10*)		2.89 (2.69)
“Taken care of” (*1–4*)		1.37 (0.63)
PCA score[c] (*-1.14–3.81*)		0.00 (0.99)
Birth medical severity (forceps, vacuum, ECS)	327 (20.3)	
Postnatal psychological symptoms		

Insomnia symptoms *(8 weeks postpartum)*		
Score[b] (*0–42*)		15.57 (8.92)
PCA score[c] (*-1.58–2.67*)		-0.03 (0.91)
CB-PTSD symptoms (*8 weeks postpartum*)		
Score[b] (*0–52*)		7 (8)[d]
Score > 34, probable CB-PTSD[b]	30 (1.9)	
IRM score[c] (*0–3.94*)		1.31 (0.89)

Note. PCA = Principal Component Analysis; IRM = Item Response Model; CB-PTSD = Childbirth-related PTSD.

[a] Total of % does not equal 100 because of missing values (n = 1,554 for education; n = 1,600 for marital status).
[b] Scores derived from the original scoring. Reported for descriptive purpose only.
[c] Scores computed using a PCA or an IRM, used in the analyses.
[d] Computed on n = 1,601 because of missing items.

3.2. Prediction of CB-PTSD symptoms

The first basic model did not in itself show acceptable global fit (Fisher's C = 946.444, d.f. 36, p < .001) but all regression coefficients, in particular the prenatal insomnia symptoms – CB-PTSD symptoms relationship, were significant (p < .001). Examination of the d-separation tests suggested that several relationships ignored in the first model had a statistical significance, and could thus be included to improve the global fit. Prenatal insomnia symptoms ceased to directly predict CB-PTSD symptoms once anxiety symptoms were included as direct predictors of CB-PTSD. Sequentially including all relationships with a significant d-separation test (high criterion values first) resulted in an acceptable model fit (M12: Fisher's C = 20.458, d.f. 14, p = .116), once the prenatal insomnia – SBE relationship was added. Within M12, only the prenatal insomnia – CB-PTSD symptoms regression coefficient was non-significant (β = -0.0016, s.e. = 0.0160, d.f. 1603, t = -0.1021, p = .919). A reduction of deviance test, comparing M12 with a reduced model discarding this link, was non-significant ($\chi^2(2)$ = 0.397, p = .82). The final model (M13) met all four prior-mentioned quality criteria, in particular global fit (Fisher's C = 20.855, d.f. 16, p = .184) and strong connectivity (Table 3). In the final model, prenatal insomnia symptoms predicted CB-PTSD symptoms through SBE and postnatal insomnia symptoms (Table 4; Figure 2).

Table 2. Model construction and comparison.

Model	Links	AIC	BIC	Fisher C	Model d.f.	Model p value	Fisher C difference	D.f. diff.	*p* value
M1[a]	Basic model	976.444	1057.204	946.444	36	< .001			
M2	Fear of childbirth → Subjective birth experience	629.995	716.139	597.995	34	< .001	348.449	2	< .001
M3	Prenatal anxiety symptoms → CB-PTSD symptoms	405.227	496.755	371.227	32	< .001	226.768	2	< .001
M4	Prenatal anxiety symptoms → Postnatal insomnia symptoms	279.334	376.246	243.334	30	< .001	127.893	2	< .001
M5	Prenatal anxiety symptoms → Subjective Birth Experience	211.702	313.998	173.702	28	< .001	69.632	2	< .001
M6	Prenatal PTSD symptoms → Prenatal insomnia symptoms	185.038	292.718	145.038	26	< .001	28.664	2	< .001
M7	Fear of childbirth → Postnatal insomnia symptoms	152.329	265.393	110.329	24	< .001	34.709	2	< .001
M8	Subjective birth experience → Postnatal insomnia symptoms	129.439	247.887	85.439	22	< .001	24.89	2	< .001
M9	Prenatal PTSD symptoms → Postnatal insomnia symptoms	110.732	234.564	64.732	20	< .001	20.707	2	< .001
M10	Prenatal depression symptoms → CB-PTSD symptoms	91.309	220.525	43.309	18	.001	21.423	2	< .001
M11	Postnatal insomnia symptoms → CB-PTSD symptoms	80.206	214.806	30.206	16	.017	13.103	2	.001
M12	Prenatal insomnia symptoms → Subjective birth experience	72.458	212.442	20.458	14	.116	9.748	2	.008
M13[b]	Prenatal insomnia symptoms → CB-PTSD symptoms (removed)	70.855	205.455	20.855	16	.184	0.397	2	0.82

Note. CB-PTSD = Childbirth-related PTSD.

[a] M1 includes the eight basic links mentioned in the data analysis section.
[b] M13 is the last and best model. It removes the non-significant Prenatal insomnia symptoms → CB-PTSD symptoms relationship from the previous one, M1.

The robustness of M13 was tested by beginning the sequence from the full model including all admissible connections, and then removing, in turn, all non-significant terms. This backward procedure yielded the same final model as M13. Furthermore, removing any link in this model resulted in a non-acceptable fit of the modified model; a significant conditional dependence test on the removed term, and a significant relative increase in deviance (as measured by a reduction of deviance test). In order to ensure that the presence of two sleep disturbance-related items (one in the EPDS, one in the prenatal PTSD symptoms checklist) was not inflating the correlations of these questionnaires with insomnia measures (thus potentially affecting model fit and structure), the whole analysis was re-run without these two items. The very same structural model emerged, with almost identical parameter values and effect sizes. A choice was made to keep the model obtained from the original scales.

Table 3. *d*-separation tests of relationships not included in the final model.

Independence claim	D.f.	Criterion	*p* value
Fear of childbirth → CB-PTSD symptoms	1,603	0.7267	.468
Prenatal insomnia symptoms → CB-PTSD symptoms	1,601	-0.2624	.793
Prenatal PTSD symptoms → CB-PTSD symptoms	1,603	1.4421	.150
Prenatal depression symptoms → Subjective birth experience	1,604	1.6788	.093
Prenatal PTSD symptoms → Subjective birth experience	1,604	-0.8283	.408
Prenatal depression symptoms → Postnatal insomnia symptoms	1,603	1.3867	.166
Birth medical severity → Postnatal insomnia symptoms	1,603	1.0776	.281
Prenatal insomnia symptoms → Birth medical severity	1,604	-1.0346	.301

Note. CB-PTSD = Childbirth-related PTSD. The reported criterion values are conditional tests that a relationship is significant, given all links in the final model (M13).

Table 4. Coefficients of the final model.

Predictor	Explained variable	Estimate	Standard error	D.f.	Criterion	*p* value	Standard estimate	Effect size (S^2 / f^2)[a]	VIF
Prenatal anxiety symptoms	Prenatal insomnia symptoms	0.1448	0.0387	1,605	3.7444	< .001	0.1143	0.0132	1.8021
Prenatal depression symptoms	Prenatal insomnia symptoms	0.2785	0.0365	1,605	7.6334	< .001	0.2358	0.0589	1.8443
Fear of childbirth	Prenatal insomnia symptoms	0.0832	0.0267	1,605	3.1167	.002	0.0776	0.0061	1.1970
Prenatal PTSD symptoms	Prenatal insomnia symptoms	0.2383	0.0465	1,605	5.1273	< .001	0.1226	0.0153	1.1059
Birth medical severity	Subjective birth experience	0.4142	0.0516	1,605	8.0217	< .001	0.1832	0.0347	1.0141
Fear of childbirth	Subjective birth experience	0.2670	0.0246	1,605	10.8448	< .001	0.2651	0.0756	1.1618
Prenatal anxiety symptoms	Subjective birth experience	0.1541	0.0299	1,605	5.1600	< .001	0.1295	0.0171	1.2256
Prenatal insomnia symptoms	Subjective birth experience	0.0618	0.0227	1,605	2.7215	.007	0.0658	0.0043	1.1382
Prenatal insomnia symptoms	Postnatal insomnia symptoms	0.2875	0.0206	1,604	13.9843	< .001	0.3313	0.1233	1.1670
Prenatal anxiety symptoms	Postnatal insomnia symptoms	0.1032	0.0277	1,604	3.7286	< .001	0.0939	0.0089	1.3175
Fear of childbirth	Postnatal insomnia symptoms	0.0812	0.0228	1,604	3.5656	< .001	0.0872	0.0077	1.2443
Subjective birth experience	Postnatal insomnia symptoms	0.1012	0.0219	1,604	4.6258	< .001	0.1095	0.0121	1.1650
Prenatal PTSD symptoms	Postnatal insomnia symptoms	0.1479	0.0391	1,604	3.7835	< .001	0.0877	0.0078	1.1161
Subjective birth experience	CB-PTSD symptoms	0.2176	0.0140	1,604	15.5420	< .001	-	(*) 0.1789	1.1561
Birth medical severity	CB-PTSD symptoms	0.1111	0.0327	1,604	3.4014	< .001	-	(*) 0.0072	1.0515
Prenatal anxiety symptoms	CB-PTSD symptoms	0.1341	0.0229	1,604	5.8512	< .001	-	(*) 0.0217	1.7738
Prenatal depression symptoms	CB-PTSD symptoms	0.0781	0.0220	1,604	3.5543	< .001	-	(*) 0.0073	1.7757
Postnatal insomnia symptoms	CB-PTSD symptoms	0.0559	0.0167	1,604	3.3376	< .001	-	(*) 0.0068	1.1381

Note. CB-PTSD = Childbirth-related PTSD, VIF = Variance Inflation Factor.

[a] Cohen's (1988) f^2 indices were used to measure effect sizes, except for predictors of CB-PTSD (marked with an asterisk). As CB-PTSD symptoms is a Tweedie-distributed zero-inflated variable, squared Robust Effect Size Indices, readable on a Cohen's f^2 scale (small effect: 0.02, medium effect: 0.15, strong effect: 0.35), were computed (Vandekar et al., 2020).

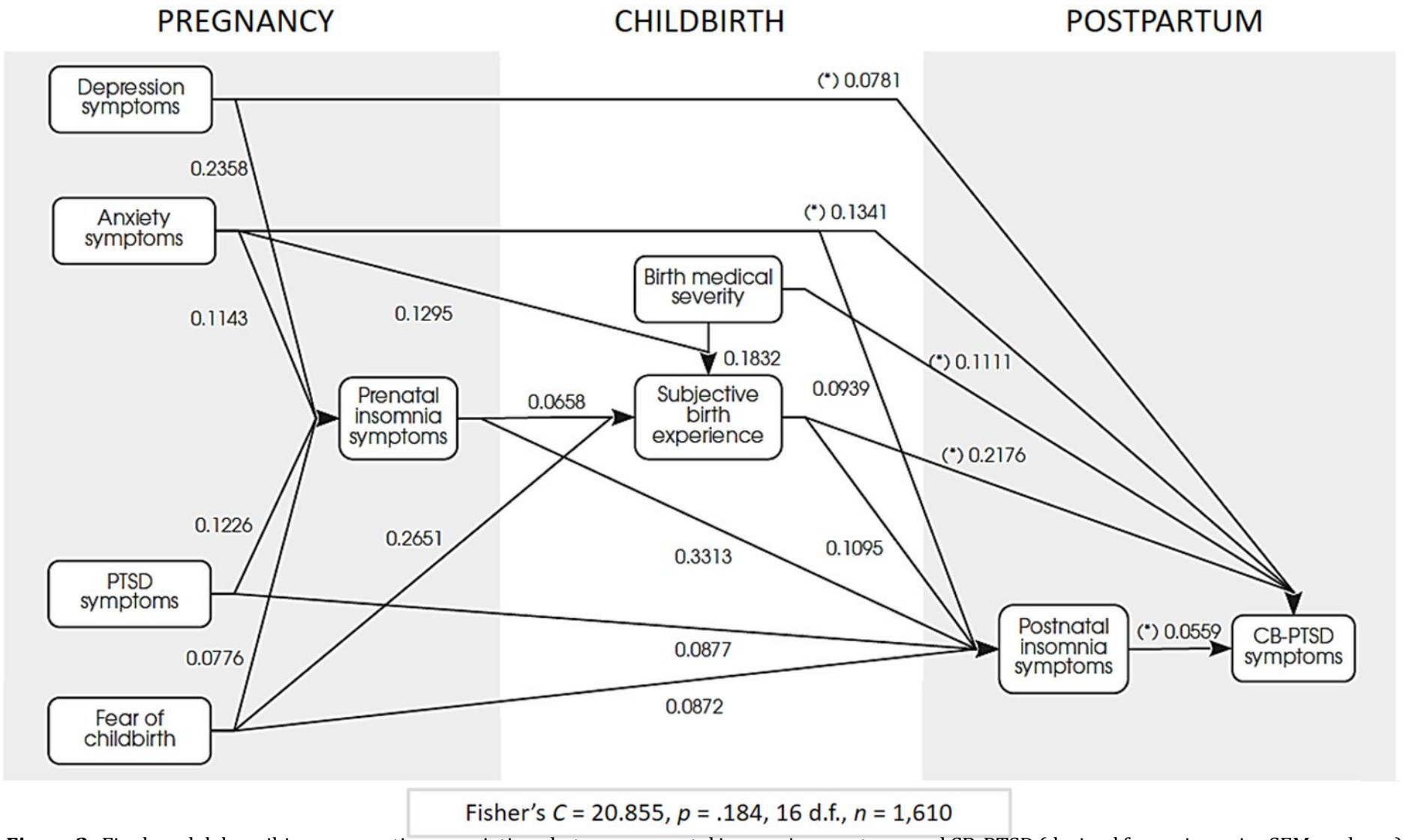

Figure 2. Final model describing prospective associations between prenatal insomnia symptoms and CB-PTSD (derived from piecewise SEM analyses). *Note.* CB-PTSD = Childbirth-related PTSD. Subjective birth experience is negatively oriented (higher scores reflect negative birth experience). Only the statistically significant pathways are shown. For all predictors of CB-PTSD symptoms, for which a log link function was used in the Tweedie model, only the unstandardised coefficients (marked with an asterisk (*)) are reported.

4. Discussion

In this population-based prospective cohort study, the direct relationship between prenatal insomnia symptoms at 32 weeks of pregnancy and CB-PTSD symptoms at eight weeks postpartum was initially significant, but disappeared when controlling for postnatal insomnia symptoms, prenatal psychological symptoms, and childbirth-related factors. More precisely, it was not significant anymore once the prenatal anxiety – CB-PTSD relationship was added to the model, suggesting that it was mostly the anxious component of prenatal insomnia that predicted CB-PTSD symptoms. Prenatal psychological symptoms (depression, anxiety, PTSD, and FOC) all predicted prenatal insomnia symptoms. Except for depression symptoms, they also predicted postnatal insomnia symptoms, thus confirming their relevance as covariates.

Pursuant to our hypothesis, both negative SBE and postnatal insomnia symptoms mediated the relationship between prenatal insomnia and CB-PTSD symptoms. In addition, postnatal insomnia partially or fully mediated the relationship between prenatal psychological symptoms (except depression) and CB-PTSD, thus suggesting that postnatal insomnia symptoms may be one of the pathways through which prenatal psychopathology renders women vulnerable to CB-PTSD. Importantly, all relationships involving insomnia symptoms had small or very small effect sizes. The four other predictors of CB-PTSD symptoms were birth medical severity, SBE, and prenatal anxiety and depression symptoms, which is in line with the existing evidence (Ayers et al., 2016; Garthus-Niegel et al., 2013). However, in contrast with previous research (Ayers et al., 2016; Grekin et al., 2021), neither prenatal PTSD symptoms nor FOC directly predicted CB-PTSD symptoms, although Grekin et al. (2021), Garthus-Niegel et al. (2013) and Garthus-Niegel et al. (2014) also found that SBE partially or fully mediated the relationship between FOC and CB-PTSD symptoms.

The fact that prenatal insomnia symptoms predicted CB-PTSD through a negative SBE suggests that they are likely to reduce psychological resources for coping with a difficult childbirth. Hence, they may be one of the vulnerability factors explaining why some women show a maladaptive stress response to a difficult childbirth and develop CB-PTSD symptoms. As for postnatal insomnia symptoms, they had already been identified as predictors and maintaining factors of CB-PTSD symptoms in the postpartum period (Garthus-Niegel et al., 2015). However, our results add an important element to the picture, as they show these symptoms also mediate the relationship between prenatal insomnia and CB-PTSD. Therefore,

prenatal insomnia symptoms could both reduce the resources for coping with a traumatic birth and hinder post-traumatic recovery by increasing the likelihood of experiencing postnatal insomnia. These two mediations were cumulative in our final model and appeared to connect, as negative SBE predicted postnatal insomnia symptoms. It is possible that this relationship results from ruminations, anxiety, infant-related worries, or even acute stress disorder (Neylan et al., 2021) caused by a negative SBE, which would trigger insomnia.

Clinically, our results tentatively suggest that targeting prenatal insomnia symptoms may, by improving SBE and reducing postnatal insomnia, be a primary prevention pathway for CB-PTSD. However, it should be remembered that the effect sizes observed were all small or very small, thus further studies are needed to clarify whether interventions focusing on prenatal insomnia do yield significant benefits for CB-PTSD prevention or not. Reducing prenatal insomnia symptoms may also have other benefits, as insomnia puts pregnant women at risk of adverse obstetrical outcomes (Palagini et al., 2014) and may affect long-term infant development (Adler et al., 2021; Monk et al., 2019). In that respect, cognitive behavioral therapy (CBT) for insomnia is recommended in the general population (Trauer et al., 2015) and shows good acceptability during pregnancy (Sedov et al., 2017). According to the final model, CB-PTSD prevention may also involve treating prenatal depression and anxiety symptoms. Reducing the latter could help to decrease pre- and postnatal insomnia, and to improve the SBE. Moreover, interventions targeting prenatal insomnia symptoms and FOC may help to prevent a negative SBE. As for CB-PTSD prevention or treatment *after* childbirth, targeting postnatal insomnia symptoms may be a beneficial strategy, echoing a recent meta-analysis indicating that CBT for sleep disturbances leads to PTSD symptom reduction (Ho et al., 2016). Overall, the final model, like the existing literature (e.g., Ayers et al., 2016), suggests that there are several potential targets for CB-PTSD prevention (e.g., depression symptoms or FOC), some of which may be more clinically relevant than pre-traumatic insomnia.

With regard to sleep, it is true that the perinatal population has some specificities: for instance, pregnant women report more nocturnal ruminations than non-pregnant women, and the hormonal changes and pregnancy-related physical discomfort are likely to affect their sleep (Swanson et al., 2020). Furthermore, prenatal insomnia may be perceived as more normative and transient than pre-traumatic insomnia in other groups. Despite these particularities, we believe the results of this study are of interest beyond the perinatal context.

The mediating role of SBE and prenatal insomnia, in particular, supports the hypotheses of reduced peritraumatic psychological resources and impaired post-traumatic recovery.

This study has important strengths. It is the first, to our knowledge, to prospectively look at the relationship between pre-traumatic insomnia symptoms and PTSD symptoms in a large population-based cohort of civilians. It is also the first to study this relationship while taking post-traumatic insomnia into account, and the first to consider these variables in the perinatal context. However, it has several limitations. Firstly, except for birth medical severity, all measures were self-reported. This may be problematic, as individuals with insomnia symptoms tend to underestimate their sleep duration (Bianchi et al., 2013). The BIS, however, has been validated against polysomnographic data (Pallesen et al., 2008) and thus represents the self-report questionnaire of choice. Secondly, operative delivery was used as a proxy for birth medical severity but only partially reflects the traumatic stressor intensity. It would have been preferable to use a validated scale but, to our knowledge, there is no brief scale available in obstetrics. Thirdly, it was impossible to exclude women who took sleeping pills after the delivery, as this information was not available. Given that only 11 women took sleeping pills during the last weeks of pregnancy, it seems unlikely, however, that this affected many participants. Fourthly, SBE was measured retrospectively, at eight weeks postpartum, although two out of the three SBE items were also completed at 48 hours postpartum and showed strong correlations with the 8-week ratings (see Supplementary material, section I.6.). Fifthly, a measure of exposure to trauma would have been helpful, given that it may be both associated with sleep disturbances (Brock et al., 2019) and an important risk factor for CB-PTSD (Andersen et al., 2012). Sixthly, the measurement of (CB-)PTSD symptoms could have been improved by 1) using the Impact of Event Scale-Revised (IES-R) (Weiss and Marmar, 1997), given that it contains items on hyperarousal symptoms, including on trauma-related sleep disturbances - however, one study found that the IES-R was not superior to the original IES to measure CB-PTSD (Olde et al., 2006); and 2) using the same instrument to measure prenatal and postnatal symptoms. Finally, the sample may lack representativeness. Indeed, in this cohort study, women having depressive symptoms at 17 weeks of pregnancy were more likely to drop out (Garthus-Niegel et al., 2017; Garthus-Niegel et al., 2018b). Importantly, at the same time point, neither anxiety nor PTSD symptoms predicted drop-out, and the sample was well representative of the Norwegian population in terms of obstetric complications (Storksen et al., 2013).

As for the model, while it allows to identify relationships between variables, the causal directions within a given time point are not determined statistically but according to existing scientific evidence. For example, although there are good reasons to postulate that prenatal anxiety and depression predict pre-natal insomnia, as reflected in the pregnancy layer of our model, the reverse relationship may exist. This particularly concerns the link between postnatal insomnia and CB-PTSD. Although postnatal insomnia was identified as a major predictor of CB-PTSD up to two years postpartum in the same study sample (Garthus-Niegel et al., 2015), and this relationship was reported as unidirectional in other populations (Wright et al., 2011), the relationship between postnatal insomnia and CB-PTSD symptoms may be bidirectional (Kartal et al., 2021; Richards et al., 2020).

Future studies should more systematically include post-traumatic insomnia symptoms as a covariate in the analyses: as our results illustrate, it seems to play a central role in the pre-traumatic sleep – PTSD relationship. One might wonder whether this direct relationship, which has been observed in other studies not controlling for post-traumatic insomnia (Gehrman et al., 2013; Neylan et al., 2021; Wang et al., 2019) but was not found in our sample, would persist when taking post-traumatic insomnia into account. Answering this question would help to determine whether the differences in results are due to the specificities of the perinatal context or the oversight of post-traumatic insomnia. If the former was true, this would reinforce the importance of studying more diverse samples. To better disentangle the effects of post-traumatic insomnia on the development of PTSD, it would also be necessary to measure insomnia symptoms before PTSD, rather than concurrently. Finally, complementing subjective measures of insomnia symptoms with objective measurements, such as polysomnography and actigraphy (e.g., smart watches), would help to consolidate the present findings.

5. Conclusion

Prenatal insomnia symptoms predicted CB-PTSD through SBE and postnatal insomnia symptoms, thus representing a vulnerability factor that may disrupt both maternal response during a traumatic childbirth and postpartum recovery. As a result, they may be a relevant target for CB-PTSD primary prevention, although it should be noted that effect sizes in our model were all small or very small. Finally, given that postnatal insomnia symptoms mediated the prospective relationship between prenatal insomnia and CB-PTSD symptoms, they should be more systematically included in future studies.

Declaration of interest. None.

Contributors. C. Deforges, S. Garthus-Niegel and A. Horsch conceptualised the study. Y. Noël performed all the analyses, in collaboration with C. Deforges. C. Deforges drafted the initial manuscript, with the contribution of Y. Noël for the statistics. M. Eberhard-Gran designed and coordinated the original cohort study. All authors approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work. A. Horsch is the PhD supervisor of C. Deforges.

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E. Published manuscript of Study 1 (Supplementary material)

1. Statistical analyses of the responses to each questionnaire

1.1. Childbirth-related PTSD symptoms and prenatal PTSD symptoms

For the total scores of the Impact of Event Scale (IES) and the prenatal PTSD symptom checklist, we used an item response model (IRM), which takes into account the ordinal nature of the response scale. IRM are a class of statistical models modelling categorical responses using probabilities (Hambleton et al., 1991). Thus, they do not a priori assume equidistant response categories but allow for proper quantification of response categories. Unlike factor techniques, IRM explicitly integrate person parameters (i.e., locations on some latent dimension) that directly model individual singularities in the response process. IRM mathematically express the relationship between a person location on some latent dimension (e.g., CB-PTSD severity) and the probability of reporting a specific response (e.g., "Not at all"… "Often", or "Yes"/"No") on a given item. Computing these probabilities allows computation of an expected rating curve, which is generally expected to be increasing (i.e., the higher the stress, the higher the expressed response).

Three unidimensional models of increasing flexibility were fitted to the data (using the binary or polytomous form, as appropriate): a fixed slope logistic model (Masters, 1982; Rasch, 1960), a varying slope logistic model (Birnbaum, 1968; Muraki, 1992), and a monotonic polynomial model (Falk and Cai, 2016). All analyses were conducted using the 'mirt' R package (Chalmers, 2012). Goodness of fit was considered at the item level, using the signed Chi-squared test (Orlando and Thissen, 2000). Analyses involving the IES score were carried out on the whole sub-sample for which full response patterns were present (n = 2,203). This also included participants who took part in the whole cohort study, but were not eligible for the present assessment study (e.g., due to intake of sleeping pills during the last ten weeks of pregnancy or unavailable birth record). Participants with missing data (n = 71 (3.2%)) were excluded from the analyses. The prenatal PTSD symptom score was created based on the set of all full response patterns (n = 3,555); there were no missing data.

Examination of item fit showed that all items of the prenatal PTSD symptom checklist were well accounted for by a two-parameter logistic model. A monotonic polynomial model was

necessary to correctly model 11 out of 15 items of the IES. However, person scores computed with or without the four IES misfitting items were highly correlated (r (2201) = .977, p < .001), showing that the scores resulting from the full scale analysis could be used for further analyses.

1.2. Insomnia symptoms

Because previous validation studies have retained one or two factor solutions depending on the calibration sample, a Principal Component Analysis (PCA) was run on the present data to check for dimensionality. For both prenatal and postnatal measurements, a one-factor solution was retained on the basis of eigenvalues (the second eigenvalue was below 1), explained variance (50% by the first component), and parallel analysis (Horn, 1965). To obtain comparable measurements across time points, a common factor was first extracted from the pooled correlation matrices, upon which pre- and postnatal response vectors were projected, to obtain factor scores that were used as final insomnia scores in the analysis.

1.3. Prenatal depression symptoms

A Generalised Partial Credit Model (GPCM, Muraki (1992)) was fitted using the mirt R package (Chalmers, 2012). Depression scores were taken as the participants' location parameter values within the fitted GPCM. The obtained scores were highly correlated with the standard Edinburgh Postnatal Depression Scale (EPDS) summed scores (R = 0.954, on n = 2,886 complete response patterns). An advantage of this approach is its ability, from item parameter estimates obtained on the full response patterns, to provide posterior participants' estimates for both complete and incomplete response patterns (marginal maximum likelihood estimation was used). The final GPCM scores were obtained for n = 2,934 participants (note that this included Akershus Birth Cohort participants who were not eligible for the present study).

1.4. Prenatal anxiety symptoms

Similarly, anxiety score were taken as the participants' parameter values within a fitted GPCM. The obtained scores were highly correlated with the standard SCL summed scores (R = 0.927, on n = 2,898 complete response patterns), with the advantage of being computable on incomplete response patterns (n = 2,932 final anxiety scores were obtained; which included Akershus Birth Cohort participants who were not eligible for the present study).

1.5. Fear of childbirth

Although validation studies have reported four to six-factor solutions (Garthus-Niegel et al., 2011; Wijma et al., 1998), recent analyses (Pallant et al., 2016) on separate subscales indicate that (reverted) positive expectancies are highly correlated to negative expectancies, suggesting that a negative-to-positive bipolar dimension could adequately subsume the corresponding subscales. A PCA performed on the present data showed that, although six eigenvalues were significantly higher than one, a strong first factor (30% of explained variance, over 33 items) was clearly opposing negative ("frightful", "afraid", "hopelessness", …) to positive ("glad", "happy", "fantastic"...) childbirth expectations, very much like what is traditionally observed in the analysis of affect items (Russell, 1980). Although the W-DEQ includes other types of items (in particular "personal control" and "confidence" items), a choice was made in the present study to take as a measurement of expectancy participants' factor scores on this first bipolar (valence) dimension. The benefit of this measure construction process is that negative and positive scores on this dimension straightforwardly correspond to negative vs. positive expectancies, which simplifies effect interpretation.

1.6. Subjective birth experience

Because the correlations between the three ratings ("How frightened were you during the birth?"; "What was your overall experience of the birth?", and "To what degree did you feel taken care of during the birth?") were reasonably high (0.53, 0.46, and 0.33), they were subsumed under a unique PCA score. As in the original items, the resulting score was negatively oriented, with high scores corresponding to a negative subjective birth experience. Note that the two first items ("How frightened were you during the birth?" and "What was your overall experience of the birth?") were completed at 48 hours postpartum by a subsample of 512 participants. The scores from both time points were strongly correlated (r = .78 for fear, r = .70 for the overall birth experience, both $p < .001$) and showed a good test-retest reliability (intraclass correlation = .87 for fear and .83 for the overall birth experience, both $p < .001$), thus suggesting the measure of SBE at 8-weeks postpartum was reliable.

2. Distribution of CB-PTSD scores

The distribution of IRM CB-PTSD scores is plotted on Figure S1. The zero inflation phenomenon is clearly apparent and needed to be addressed in the analyses (hence the use

of a Tweedie regression model). Note that the raw IES scores display exactly the same distribution shape, IRT scores being a monotonic transform of the raw scores.

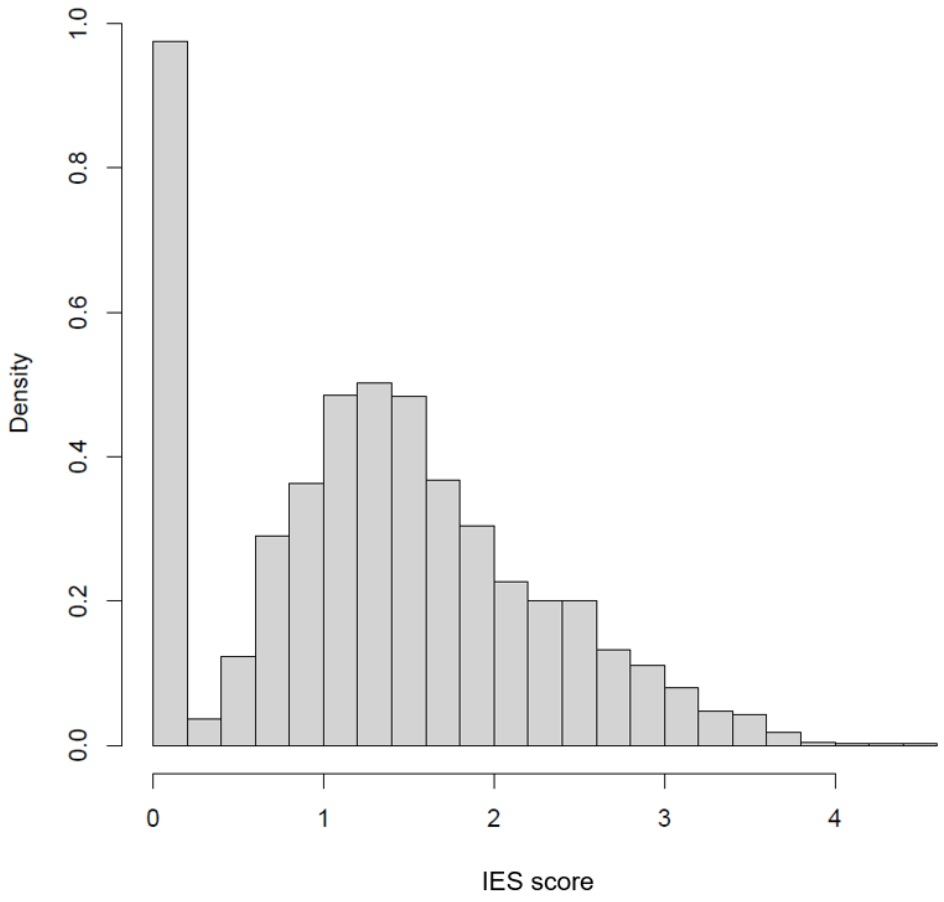

Figure S1. IES score distribution – computed with a polytomous IRM.

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F. Published manuscript of Study 2

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Title: The relationship between early administration of morphine or nitrous oxide gas and PTSD symptom development

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Abstract:

Background. Posttraumatic Stress Disorder (PTSD) is a debilitating mental disorder. Certain drugs, such as morphine and nitrous oxide gas (N_2O), are administered to individuals who just experienced a traumatic event (e.g., soldiers, injured civilians). It is therefore crucial to understand if they incidentally affect PTSD symptom development. Furthermore, such observations could pave the way for the development of pharmacological prevention strategies of PTSD.

Methods. In this prospective population-based cohort study (n = 2,070), we examined the relationship between morphine or N_2O administration during childbirth, and subsequent childbirth-related PTSD symptoms at eight weeks postpartum. Pain during labour, prior PTSD symptoms, and birth medical severity were included as covariates in the analyses.

Results. In women who developed PTSD symptoms, N_2O administration during childbirth predicted reduced PTSD symptom severity (p < .001). A similar tendency was observed for morphine, but was only marginally significant (p < .065). Both drugs predicted increased PTSD symptoms when combined with severe pain during labour.

Limitations. This study was observational, thus drug administration was not randomised. Additionally, C-PTSD symptoms were self-reported.

Conclusions. Peritraumatic N_2O administration may reduce subsequent PTSD symptom severity and thus be a potential avenue for PTSD secondary prevention. This might also be the case for morphine. However, the role of severe peritraumatic pain in context of drug administration deserves further investigation.

Keywords: Posttraumatic Stress Disorder ; Prevention ; Morphine ; Nitrous Oxide ; Pain ; Memory consolidation

Manuscript:

1. Introduction[1]

Posttraumatic stress disorder (PTSD) is a mental health disorder, which may occur after experiencing or witnessing a traumatic event (American Psychiatric Association, 2013), and

[1] ABC = Akershus Birth Cohort ; AIC = Akaike Information Criterion ; C-PTSD = Childbirth-related PTSD ; ECS = Emergency caesarean Section ; IES = Impact of Event Scale ; IRM = Item Response Model ; ISS = Injury Severity Score ; MINI = Mini-International Neuropsychiatric Interview ; N_2O = Nitrous oxide gas ; RESI = Robust Effect Size Index ; VIF = Variance Inflation Factor.

has a lifetime prevalence of 3.9% (Koenen et al., 2017). Symptoms include re-experiencing, avoidance of trauma-related reminders, alterations in arousal, and negative cognitions and mood (American Psychiatric Association, 2013). They are present at least one month after the traumatic event (American Psychiatric Association, 2013) and have a mean duration of six years (Kessler et al., 2017). PTSD is comorbid with depression, anxiety, and substance abuse disorders (Brady, Killeen, Brewerton, & Lucerini, 2012). Even at subclinical levels, PTSD symptoms are associated with substantial functional impairment (Brancu et al., 2016), distress and suicidal ideation (McLaughlin et al., 2015). While evidence-based treatments for PTSD exist (Lewis, Roberts, Andrew, Starling, & Bisson, 2020), preventive interventions are lacking (Qi, Gevonden, & Shalev, 2016). Yet, PTSD onset is linked to an identifiable and temporally defined causative event, making it an ideal candidate for secondary prevention approaches (Qi et al., 2016).

The evidence of successful drug treatments for PTSD is mixed (Hoskins et al., 2015). However, when administered during the early posttraumatic period, certain drugs are associated with reduced subsequent PTSD symptoms (Astill Wright et al., 2019). Preliminary evidence suggesting such a protective relationship has, for instance, been reported for morphine, a pain relief medication of the opiate family. Two retrospective studies found that military personnel had a reduced likelihood of developing PTSD if they received morphine within the first hours following their brain or limb injuries (Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010; Melcer et al., 2014). However, one did not find such a relationship (Mion, Le Masson, Granier, & Hoffmann, 2017). Amongst civilians, receiving opiates or elevated morphine dose within 48 hours following a traumatic injury was also associated with milder PTSD symptoms (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009; Mouthaan et al., 2015), although contradictory results were reported with opiate doses after lung injury (Bienvenu et al., 2013).

Another widely used pain relief is nitrous oxide gas (N_2O). Unlike morphine, the relationship between N_2O inhalation in the early posttraumatic period and PTSD development has received little attention. Yet, compared to medical air, N_2O inhalation after an analogue trauma significantly sped up the reduction of trauma-related intrusive memories (Das et al., 2016), a core symptom of PTSD. Importantly, results suggested that early inhalation of subanesthetic levels of N_2O may reduce PTSD symptoms while preserving voluntary memory.

However, this relationship has never been investigated in the context of real-life trauma, nor beyond the first posttraumatic week.

Morphine and N_2O are used in a variety of contexts, such as intensive care units, labour wards, and in military medicine. Hence, they are administered to populations at high risk of PTSD. It is thus critical to assess whether these drugs have unsuspected effects on PTSD symptom development when administered in the early posttraumatic period. Such observations could also be a first step towards secondary pharmacological prevention of PTSD (Astill Wright et al., 2019; Maccani, Delahanty, Nugent, & Berkowitz, 2012). On the contrary, they may reveal that morphine and N_2O cause iatrogenic harm (Fluegge, 2018). In any case, prospective studies on real-life traumas are lacking, especially for N_2O.

The underlying mechanisms of the association between early drug administration and PTSD symptom development are not well understood. One hypothesis is that morphine and N_2O impact memory consolidation, a time-dependent process of stabilisation of memories into long-term memory (McGaugh, 2000). During the consolidation window, lasting several hours after the event, memories are malleable and sensitive to interference (Nader, Schafe, & LeDoux, 2000). As PTSD is assumed to result from maladaptive memories and excessive fear learning (Pitman, 1989; van Marle, 2015), drugs disrupting the consolidation of trauma memories may prevent PTSD symptom development (Astill Wright et al., 2019). Morphine, for instance, impairs learning and reduces fear responses when administered after fear conditioning in rodents (e.g., McNally & Westbrook, 2003; Szczytkowski-Thomson, Lebonville, & Lysle, 2013). Similarly, N_2O inhalation can impair learning in both rodents (Rabat, Hardouin, & Courtiere, 2004) and humans (Dunlosky et al., 1998). N_2O is, inter alia, an antagonist of N-methyl D-aspartate receptors (Emmanouil & Quock, 2007), which are implicated in long-term potentiation (LTP) (Luscher & Malenka, 2012). As LTP is one of the hypothesised mechanisms of memory consolidation (Nader & Hardt, 2009), N_2O is likely to disrupt memory consolidation. In terms of memory processes, it is also possible that morphine and N_2O, if administered very early, interfere with encoding. In this case, they could contribute to memory disorganization, which is frequently found in patients with PTSD (Brewin, 2018), and thus potentially trigger or worsen PTSD symptomatology.

An alternative explanation of the relationship between early drug administration and PTSD symptoms is pain relief. Indeed, morphine and N_2O reduce peritraumatic pain, a well-known

risk factor for PTSD (Ayers, Bond, Bertullies, & Wijma, 2016). Given that the severity of the patients' medical situation may impact pain relief drug administration, peritraumatic pain may also reflect the severity of patients' medical situations. Both the severity of the patients' medical situation and peritraumatic pain are thus important to consider within this hypothesis. Importantly, the pain hypothesis is challenged by research on rodents, suggesting that morphine still reduces fear responses when administered after the end of the painful stimuli (e.g., RaiseAbdullahi, Vafaei, Ghanbari, Dadkhah, & Rashidy-Pour, 2019). So far, few clinical studies included pain in their analyses. Even if these tend to support the hypothesis of an independent action of morphine on PTSD development (Bryant et al., 2009), the lack of data from prospective studies precludes firm conclusions.

The relationship between early drug administration and PTSD symptom development has never been studied in the context of childbirth. Yet, childbirth seems an opportune context: firstly, childbirth-related PTSD (C-PTSD) affects four to six per cent of mothers in community samples, and 18.5% in high-risk samples (e.g., emergency caesarean sections (ECS)) (Yildiz, Ayers, & Phillips, 2017). Second, morphine and N_2O are routinely administered during birth. Third, childbirth is one of the most standardised real-life traumas, with a relatively homogeneous population and a similar peritraumatic environment (a care setting). Finally, since women have medical appointments during pregnancy, it is possible to obtain reliable measures of prior PTSD symptoms, a crucial risk factor for PTSD (Delahanty & Nugent, 2006).

To summarise, early morphine and N_2O administration might have an unexpected preventive effect on PTSD symptom development. However, there is a need for more prospective studies, taking the role of peritraumatic pain into account. This population-based cohort study firstly focused on the relationship between morphine or N_2O administration during childbirth and C-PTSD symptoms at eight weeks postpartum. In addition, we explored the role of pain during labour as a potential covariate, whilst controlling for prior PTSD symptoms and birth medical severity. We hypothesized that receiving morphine or N_2O during childbirth would predict reduced C- PTSD symptoms.

2. Method

2.1. Design and study population

Data were derived from a large population-based prospective cohort study: the Akershus Birth Cohort (ABC). Thus, the results of this study stem from secondary analyses.

The ABC targeted all women scheduled to give birth at Akershus University Hospital (Norway), which serves around 350,000 inhabitants. Recruitment took place between November 2008 and April 2010, during the 17-week routine examination. Women were eligible to participate if they could complete the questionnaires in Norwegian.

Participants completed questionnaires during pregnancy, at 17 weeks and 32 weeks of gestation, and at eight weeks and two years postpartum. Medical information relating to the birth was registered in the hospital birth record. Participants who gave birth between May 2009 and September 2010 completed an additional questionnaire on pain at 48 hours postpartum. The ABC obtained ethical approval from the Regional Committees for Medical and Health Research Ethics (approval number S-08013a), and all participants provided written informed consent. Of the eligible women, 80% (n = 3,752) agreed to participate and returned the first questionnaire. Detailed information on participants and drop out in the ABC can be found in Garthus-Niegel et al. (2018).

In this study, we used data from the 17-weeks of gestation questionnaires, the eight weeks postpartum questionnaires, and the hospital birth record. Out of the 3,752 women who returned the 17-week questionnaire, we excluded those for which the hospital birth record was not available (n = 189). We also excluded women who received pethidine, which is an opioid (n = 2), or general anaesthetics (n = 73) during childbirth, because these drugs might independently affect PTSD symptom development. Women who received opiates other than morphine (n = 8) were excluded, too: since data on the type of opiate and mode of administration were not available, their inclusion would have made interpretation of the results difficult. Finally, we excluded women who did not return the questionnaires of interest at eight weeks postpartum (n = 1,395), or did not fully complete them (n = 15). Our final sample consisted of 2,070 women (Figure 1).

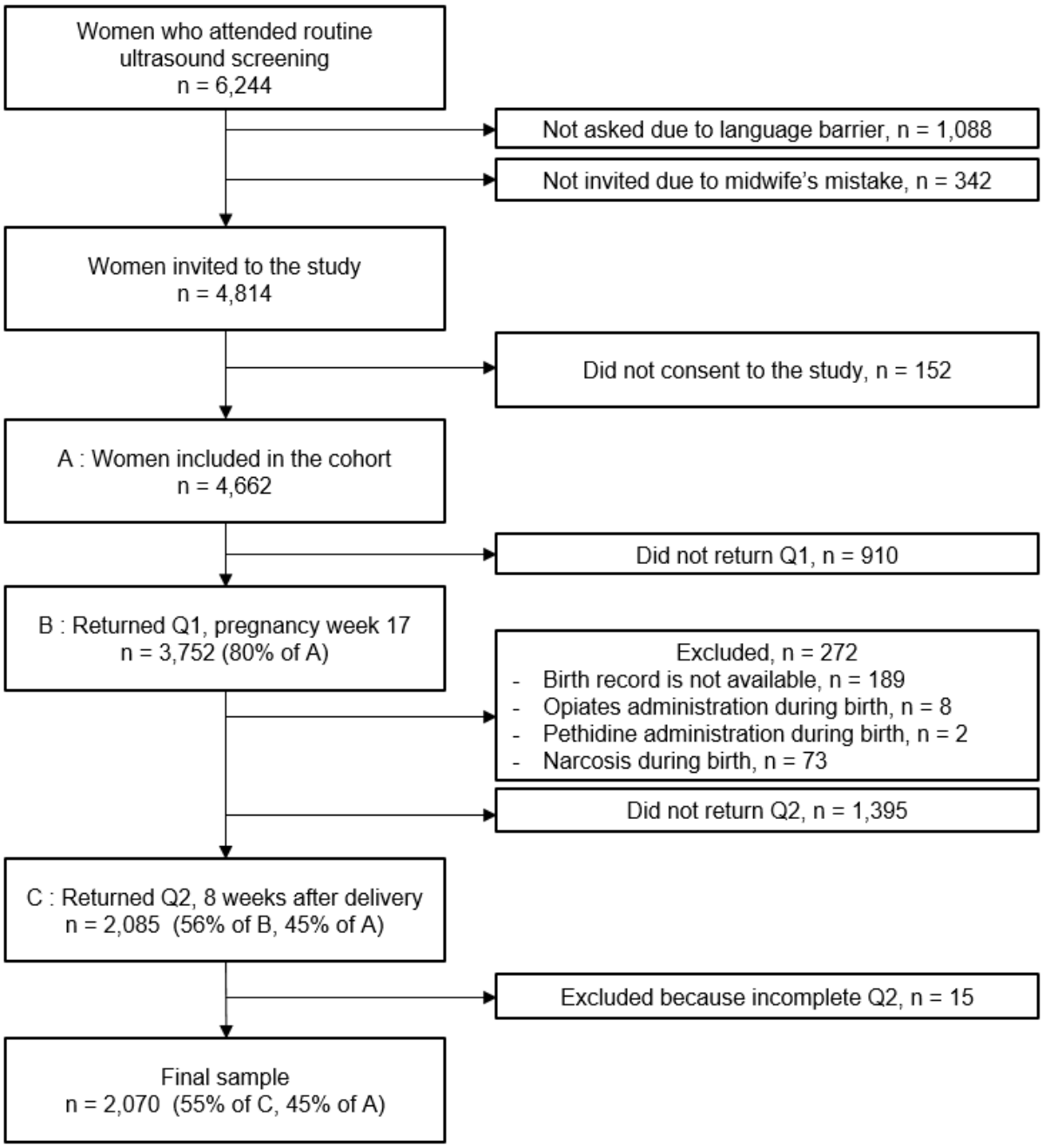

Figure 1. Response and participation rates of the study.

2.2. Measures

Childbirth-related PTSD symptoms

The 15-item self-rating Impact of Event Scale (IES) (Horowitz, Wilner, & Alvarez, 1979) was used to measure C-PTSD symptoms at eight weeks postpartum. The IES has been validated in postpartum women (Olde, Kleber, van der Hart, & Pop, 2006). Participants were instructed to complete the scale in relation to their childbirth. Each item concerns one symptom, with four response categories (usually recoded with the following weightings: 0 = not at all, 1 = rarely,

3 = sometimes, and 5 = often). Sum scores of the overall scale can be computed (range 0–75), and scores above 34 indicate probable PTSD (Neal et al., 1994). In this study, we took into account the ordinal nature of the response scale by using a polytomous Item Response Model (IRM) (Hambleton, Swaminathan, & Rogers, 1991), to estimate a global IES score.

Prior PTSD symptoms

Prior PTSD symptoms were reported at 17 weeks of pregnancy. Women indicated whether they suffered from eight PTSD symptoms over the past month, in relation to a dramatic or terrifying event they potentially experienced. This PTSD symptoms checklist was derived from the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Each item was scored 0 (symptom absent) or 1 (symptom present); the total scores ranged from 0 (no symptoms) to 8. See Garthus-Niegel et al. (2018) for a detailed description of this scale. In the present study, the prior PTSD symptoms score was computed with a dichotomous IRM (Hambleton et al., 1991).

Pain relief administered during childbirth

Data regarding morphine or N_2O administration during childbirth was extracted from the hospital birth record. Each drug was treated as a dichotomous variable, depending on whether it was used (1) or not (0). Both morphine and N_2O, if needed, were given during labour. Morphine was administered intramuscularly. N_2O was given through an inhalation mask. Participants were instructed to breathe in the mask as needed, and received 30 to 50% N_2O.

Pain during labour

Pain during labour was measured at 48 hours and eight weeks postpartum, with the following question: "How much pain did you feel during labour?". Participants replied using a numerical rating scale from 0 ("no pain at all") to 10 ("most intense imaginable pain"), which is a valid way of measuring pain intensity (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011). Not all participants completed the questionnaire at 48 hours, but the pain ratings from both time points were highly correlated (r = .76, p < .01) and indicated good test–retest reliability (intraclass correlation = .88, p < .001). Therefore, due to the larger sample size available at eight weeks (2,070 *vs.* 682 participants), we used the eight-weeks assessment.

Birth medical severity

Based on hospital birth records, a dichotomous variable was created, depending on whether the birth involved the use of forceps, vacuum, ended in an ECS (1) or not (0). ECS were considered as such if they were planned less than eight hours before delivery. This variable aimed to reflect birth medical severity, just as scores like the Injury Severity Score (ISS) reflect the severity of patients' medical situations in other populations (Holbrook et al., 2010). To our knowledge, a validated equivalent of the ISS does not exist in obstetrics. Thus, we used operative birth as a proxy for medical severity, as it indicates an urgency for the birth to occur quickly. Although they are operative, planned caesarean sections were coded "0", as they do not reflect medical emergency *during* birth. Besides, planned caesarean sections are not associated with as poor maternal adjustment outcomes as ECS (Alderdice et al., 2019), nor with comparable PTSD prevalence (Orovou et al., 2020).

Parity

Parity was reported by participants at 17 weeks of pregnancy, and recoded as 0 for nulliparous and as 1 for parous.

Sociodemographic characteristics

Education, marital status, and age at the time of birth were retrieved from the hospital birth record. Education had three categories, reflecting the highest achieved degree: elementary school (0), high school (1), and higher degree (2). Marital status was recoded into a dichotomous variable, distinguishing married/cohabiting women (1) versus singles (0).

2.3. Data analysis

Sample description

Descriptive analyses for the sociodemographic and obstetric variables, as well as PTSD-related scores were carried out for the total study sample. For C-PTSD symptoms, prior PTSD symptoms, pain during labour, and birth medical severity (the main study variables of interest), the sample was divided into four groups, based on drug administration during labour. Women either received no pain relief drug, morphine, N_2O, or a combination of morphine and N_2O. For all the analyses, we checked if the appropriate statistical assumptions were met and, if not, non-parametric tests were used. Group differences were investigated through chi-square analyses (categorical variables) or Kruskal-Wallis tests (continuous

variables). Post-hoc comparisons with a Bonferroni correction were used to assess group differences in pain during labour, across the four drug-administration groups.

Given that ageing may increase the risk of obstetrical complication (Schummers et al., 2018) and thus affect drug administration, a post-hoc one-way between-subjects ANOVA was carried out to evaluate if age differed across the drug-administration groups. Group comparisons with a Bonferroni correction were used to assess drug group differences in age. Similarly, an independent sample t-test was conducted to compare age depending on birth medical severity. IBM SPSS 24 was used for all analyses in relation with sample description (Tables 1 and 2).

Prior PTSD and C-PTSD scores

For the total scores of both the IES and MINI-based prior PTSD symptoms checklist, we took into account the ordinal nature of the response scale by using an Item Response Model (IRM). IRM are a class of statistical models designed to model categorical responses using probabilities (Hambleton et al., 1991). These models allow proper quantification of subject responses without a priori assuming equidistant response categories. By contrast with factor techniques, they explicitly incorporate person parameters (i.e., locations on some latent dimension) that directly model individual specificities in the response process, which is especially relevant for patient-reported outcomes (see Supplementary material, section I, "IRM and calculation of symptom scores" for details on scores computation).

Generalized linear regression models

A series of generalized linear regression models were fitted to explain IES scores at eight weeks from our main predictors: prior PTSD symptoms, pain during labour, birth medical severity, and morphine or N_2O administration. The latter were coded as present or absent because we wanted to quantify drug effects rather than group differences. An advantage of this coding is its ability to reveal more fine-grained interaction effects, in particular a potential interaction between both drugs, for women who received a combination of morphine and N_2O.

A zero-inflated Tweedie compound Poisson model (Zhang, 2013) was used, including two components: a logistic part discriminating between the zero and non-zero scores (absence vs. presence of symptoms), and a Tweedie compound Poisson model accounting for the non-null

score variance (i.e., modelling stress intensity) (see Supplementary material, section II, "Zero-inflated Tweedie compound Poisson model" for details on the reasoning behind this model choice). Note that two sets of regression coefficients result from this analysis, one for each part of the model. All analyses were performed using the 'cplm' R package (Zhang, 2013).

A model comparison approach, where models of varying complexity are considered in turn, was adopted. In our modelling strategy, for statistical but also interpretability reasons, no interaction effect was included without adding the corresponding main effects or lower order interactions. The four following structures have been fitted on both zero-inflated and Tweedie components: i) a full model including all variables and their interactions up to second order (third order interactions were not included to avoid zero counts cells); ii) a reduced model (reduced model 1) including all effects and first order interactions; iii) a reduced model (reduced model 2) including only main effects; iv) a restricted model where only significant predictors from the full model were included. Combining these hypothetical structures on both parts of the model resulted in a set of 16 models that were compared using the Akaike Information Criterion (AIC) (Akaike, 1973). Note that AIC model selection is relatively robust to collinearity, provided that the sample size is large enough (i.e. N ≥ 2000) (Brewer, Butler, & Cooksley, 2016). Robust Effect Size Indices (RESI) (Vandekar, Tao, & Blume, 2020) were calculated for each coefficient within the retained model.

3. Results

3.1. Characteristics of the study sample

In our sample, mean maternal age at birth was 31.33 years (*SD* = 4.6) (Table 1). Most participants had obtained a higher educational degree. A majority of women received N_2O during birth, while a minority received morphine (Table 1). The mean number of PTSD symptoms before childbirth was low (*M* = 0.25 ; *SD* = 0.76). At eight weeks postpartum, according to the IES original weighted scoring, 1.9% of our sample had probable C-PTSD (Table 1).

Table 1. Characteristics of the study sample (*n* = 2,070).

Sample characteristics (*time point measured;range*)	Frequency (%)	Mean (*SD*)
Sociodemographic characteristics		
Age (*at time of childbirth;18–45*)		31.33 (4.6)
Education (*at time of childbirth*)		
Elementary	62 (3[a])	
High school	579 (28[a])	
Higher degree	1,362 (65.8[a])	
Marital status (*at time of childbirth*)		
Married or cohabiting	2,009 (97.1[a])	
Single	46 (2.2[a])	
Obstetrical factors		
Parity (*pregnancy week 17*)		
Nulliparous	1,009 (48.7)	
Parous	1,061 (51.3)	
Pain during labour (*8 weeks postpartum;0–10*)		7.73 (2.4)
Pain relief (*at time of childbirth*)	796 (38.5)	
No pain relief	17 (0.8)	
Morphine	1,225 (59.2)	
N_2O	32 (1.5)	
Morphine and N_2O	384 (18.6)	
Birth medical severity (forceps, vacuum, ECS)		
PTSD symptoms		
Prior PTSD symptoms (*pregnancy week 17*)		0.25 (0.76)
Raw score (*0–8*)		-0.04 (0.54)
IRM score[b] (*-0.25–3.19*)		
C-PTSD symptoms (*8 weeks postpartum*)		6.82 (8.11)
Score (*0–65*)	3 (1.9)	
Score>34, probable C-PTSD[c]		1.28 (.91)
IRM score[b] (*0–4.97*)		

Note. N_2O = Nitrous oxide gas; ECS = Emergency caesarean section; IRM = Item Response Model; C-PTSD = Childbirth-related PTSD

[a] Total of % does not equal 100 because of missing values (*n* = 2,003 for education and *n* = 2,055 for marital status).
[b] Scores computed using an IRM. It is these scores that are used in our analysis.
[c] Scores derived from the original weighted IES scoring. Reported for descriptive purposes only.

Table 2 reports each of the main study variables of interest, according to the drugs received by women during childbirth. Groups differed in terms of pain during labour ($H(3) = 137.08$, $p < .001$). A post-hoc pairwise comparison revealed that women receiving no pain relief reported significantly less pain than those who received N_2O ($p < .001$) or both morphine and N_2O ($p < .01$) (Table 2). Groups also significantly differed in terms of age ($F(3, 2066) = 3.124$, $p < .05$). A post-hoc pairwise comparison showed that the only difference was that women who received no pain relief ($M = 31.68$, $SD = 4.54$) were slightly older than those who received N_2O ($M = 31.09$, $SD = 4.6$) ($p < .05$). However, since the age difference was only seven months, it is unlikely to have led to a substantial increase of obstetrical complications. Women who received morphine ($M = 31.4$, $SD = 3.8$) or both morphine and N_2O ($M = 32.26$, $SD = 5.05$) did not differ from the others. Furthermore, women whose birth involved vacuum, forceps, or ECS ($M = 31.4$, $SD = 4.46$) were similar in age compared to the others ($M = 31.32$, $SD = 4.32$); $t(2068) = 0.302$, $p = .762$. Thus, age did not appear as a relevant variable and was not included in our model.

Table 2. Characteristics of the main study variables grouped by method of pain relief.

	No pain relief (n = 796)	Morphine (n = 17)	N_2O (n = 1,225)	Morphine and N_2O (n = 32)	P-value
Prior PTSD symptoms (*IRM score*[a]) (Mean(*SD*))	-0.01 (0.58)	0.10 (0.83)	-0.06 (0.51)	0.05 (0.6)	.22[b]
Pain during labour (Mean(*SD*))	6.73 (3.07)	8.18 (2.13)	8.35 (1.66)	8.66 (1.2)	<.001[b]***
Birth medical severity (forceps, vacuum, ECS) (Number(%))	134 (16.83)	3 (17.65)	239 (19.51)	8 (25)	.36[c]
C-PTSD symptoms (*IRM score*[a]) (Mean(*SD*))	1.25 (0.88)	1.27 (1.21)	1.29 (0.92)	1.6(0.8)	.09[b]

Note. N_2O = Nitrous oxide gas; IRM = Item Response Model; ECS = Emergency caesarean section; C-PTSD = Childbirth-related PTSD

[a] Scores computed using an IRM.
[b] Statistical significance was computed via Kruskal-Wallis test.
[c] Statistical significance was computed via Chi-square test.

* $p < .05$
** $p < .01$
*** $p < .001$

3.2. Associations with C-PTSD scores

The best model retained included only main effects on the zero inflation model, and main and first order interactions in the Tweedie regression model (see Supplementary material, section III, "Model comparison and selection" for the AIC of each model). Corresponding model coefficients are displayed in Table 3, along with RESI (Vandekar et al., 2020) and Variance Inflation Factors (VIF). Although a strong collinearity (VIF > 10) is apparent for six terms out of 20, the use of AIC model selection and the RESI allows to identify relevant predictors.

Table 3. Estimated coefficients on the Zero Inflated Tweedie Compound Poisson model of IES.

(a) Zero inflation logistic model

	Estimate[a]	Std. Error	z value	Pr(>|z|)	RESI[b]	VIF
(Intercept)	-0.6147	0.1692	-3.6326	0.0003***	0.0788	
Prior PTSD	-0.5374	0.1348	-3.9876	0.0001***	0.0833	1.0030
Pain	-0.1030	0.0229	-4.5054	0.0000***	0.0978	1.1175
Birth Medical Severity	-0.6798	0.1677	-4.0544	0.0001***	0.0861	1.0025
N_2O	0.1314	0.1219	1.0781	0.2810	0.0080	1.1165
Morphine	-0.2916	0.4175	-0.6984	0.4849	0.0000	1.0035

(b) Tweedie regression model

	Estimate[a]	Std. Error	z value	Pr(>|z|)	RESI[b]	VIF
(Intercept)	0.4168	0.0469	8.8948	0.0000***	0.2111	
Prior PTSD	0.0785	0.0521	1.5067	0.1319	0.0196	7.5925
Pain	-0.0004	0.0062	-0.0594	0.9527	0.0000	1.9691
Birth Medical Severity	0.0305	0.0917	0.3325	0.7395	0.0000	12.7208
N_2O	-0.4062	0.0841	-4.8291	0.0000***	0.1121	15.4729
Morphine	-0.8454	0.4568	-1.8507	0.0642	0.0290	41.0325
Prior PTSD x Pain	0.0072	0.0070	1.0286	0.3037	0.0000	8.8915
Prior PTSD x Birth medical severity	-0.0306	0.0451	-0.6776	0.4980	0.0000	1.2940

Prior PTSD x N_2O	-0.0402	0.0407	-0.9872	0.3236	0.0000	2.6150
Prior PTSD x Morphine	-0.0637	0.1210	-0.5260	0.5989	0.0000	1.2258
Pain x Birth medical severity	0.0217	0.0119	1.8258	0.0679	0.0373	15.2262
Pain x N_2O	0.0514	0.0101	5.0820	0.0000***	0.1179	17.5108
Pain x Morphine	0.0999	0.0508	1.9655	0.0494*	0.0326	39.9776
Birth medical severity x N_2O	-0.0580	0.0586	-0.9901	0.3221	0.0000	3.4923
Birth medical severity x Morphine	-0.0065	0.1575	-0.0411	0.9672	0.0000	1.3901
N_2O x Morphine	0.0390	0.1462	0.2668	0.7896	0.0000	3.2786
Dispersion parameter :	0.19617					
Index parameter :	1.8681					

Note. RESI = Robust Effect Size Index; VIF=Variance Inflation Factor; N_2O=Nitrous oxide gas.

[a] Estimates represent unstandardized β values.
[b] Interpretation of Robust Effect Sizes: [0;0.1]: None-Small,]0.10;0.25]: Small-Medium,]0.25;0.4]: Medium-Large (Vandekar et al., 2020). The RESI directly control for collinearity by using the parameter information matrix as its main metric (see Vandekar et al. (2020), formula 16): when covariances are high, parameter variances are high, and the RESI is low, such that effects with at least small-medium effect sizes (0.10 < S < 0.25) can be confidently interpreted.

* $p < .05$
** $p < .01$
*** $p < .001$

The zero inflation model (Table 3.a) showed that few prior PTSD symptoms, mild pain during labour, and low birth medical severity (neither vacuum nor forceps nor ECS) were all significant predictors of a zero response to IES, thus reinforcing the relevance of these covariates in our analyses. However, only pain was close to a noticeable effect size (S = 0.0978).

Coefficients in the Tweedie regression model (Table 3.b) showed that N_2O inhalation during childbirth decreased the IES score (β = -0.4062, $p < .001$), i.e., reduced C-PTSD symptom severity. The effect size was small to medium (S = 0.1121). A similar tendency was apparent for morphine, although the corresponding coefficient was not significant (β = -0.8454, p = .064) and the effect size was null to small (S = 0.0290) (Table 3.b). Significant first order interactions of both N_2O and morphine with pain during labour were found, with positive coefficients. The effects sizes were respectively small to medium (S = 0.1179) and null to small (S = 0.0326). This result suggests that women who received N_2O during birth were likely to develop more severe C-PTSD symptoms if the pain level was high, and log-proportionally to

pain level. The same pattern of opposite effects, with pain as a moderator, was observed for morphine, although the main protective effect of morphine did not reach significance (Table 3.b). Scatter plots of pain severity and IES scores in the four drug-administration groups can be found in Figure 2. As illustrated by Figure 3, the administration of morphine, N_2O or both was associated with more severe C-PTSD symptoms from a pain rating of about 9 out of 10. Note that morphine and N_2O administration did not statistically interact (p = .79).

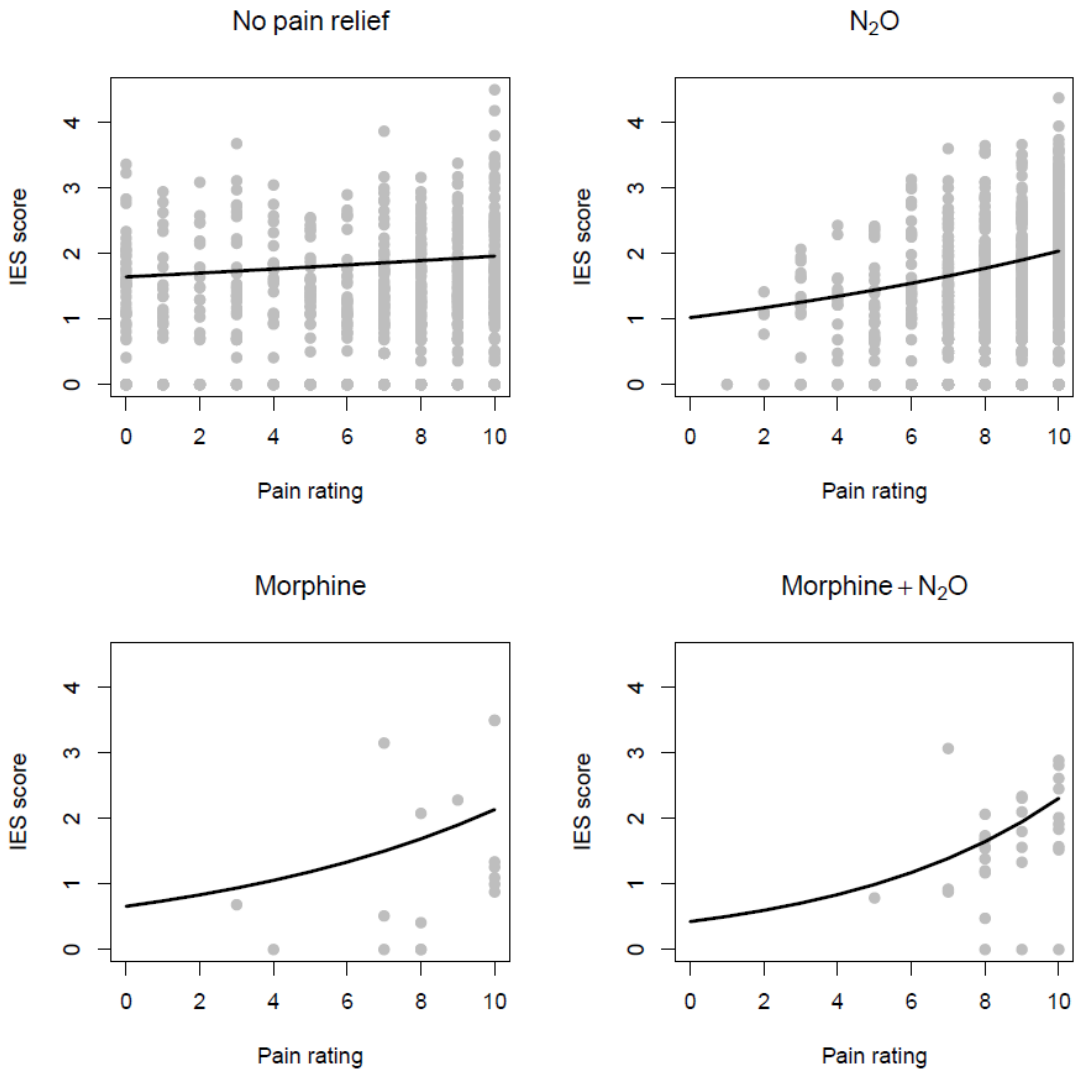

Figure 2. Marginal model curves of the relationship between pain rating and IES score in the four pain relief groups, based on the full Tweedie regression model.

Note. IES = Impact of Event Scale; N_2O = Nitrous oxide gas.

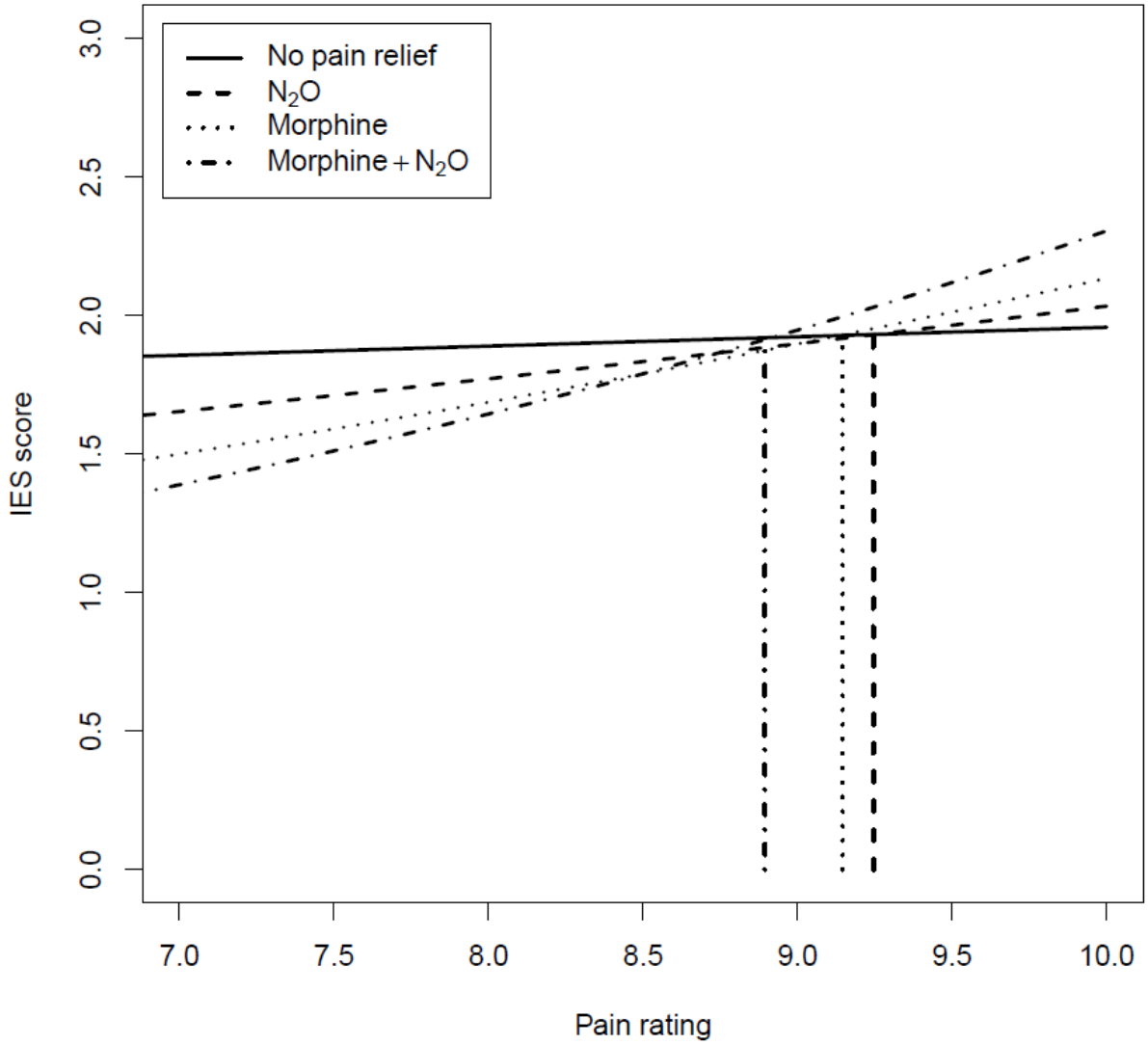

Figure 3. Relationship between pain and IES score for pain ratings above 7 (on a scale from 0-10), as predicted by the full Tweedie regression model for each pain relief group. Vertical lines correspond to thresholds for which drugs are associated with more severe C-PTSD symptoms.

Note. IES = Impact of Event Scale; N_2O = Nitrous oxide gas.

In view of the moderating role played by N_2O in the final model, its impact was further investigated by performing two mediation analyses on the Tweedie part of the model, using the mediation package in R (Tingley, Yamamoto, Hirose, Keele, & Imai, 2014). No significant mediating effect of N_2O in the pain/C-PTSD relationship, nor of pain in the N_2O/C-PTSD relationship, was found.

4. Discussion

In this large population-based cohort study, we examined the prospective relationship between morphine or N_2O administration during a real-life traumatic event, and PTSD

symptoms eight weeks later. Pursuant to our hypothesis, N_2O administration during childbirth predicted milder C-PTSD symptoms when controlling for birth medical severity, prior PTSD symptoms, and pain during labour. Although not statistically significant ($p < .065$), a similar association was observed with morphine. We believe this latter result warrants attention given the low p-value, the number of studies reporting a protective effect of morphine, and the small number of women who received morphine in our sample (n = 49/2,070).

The second aim of this study was to explore the role of peritraumatic pain as a covariate. The significant interaction between drugs and peritraumatic pain indicates that women who received analgesics and reported intense pain during labour (⩾9/10) had more severe C-PTSD symptoms, thus suggesting that pain does play a role. However, unlike N_2O, it should be noted that the effect size of the interaction between pain and morphine was null-small – which might be due to low power. Importantly, the above-mentioned results only apply to mothers reporting some C-PTSD symptoms, as neither morphine nor N_2O administration predicted the *absence* of C-PTSD symptoms.

4.1. Underlying mechanisms

Although our study remains observational, several elements could contribute to the debate on mechanisms underlying the relationship between early drug administration and PTSD.

Memory consolidation hypothesis

A priori, a drug can only disrupt memory consolidation if it is administered and active during the early *post*traumatic period, within the memory consolidation window. In our study, analgesics were administered *during* labour. Importantly, childbirth can be composed of several traumatic experiences (e.g., unexpected induction of labour, an ECS). Thus, some mothers may have received pain relief during the *post*traumatic period, whilst others may have received them during the *pre*traumatic period, i.e. outside of the memory consolidation window. This may explain why morphine was not significantly associated with milder C-PTSD symptoms although, since it has a half-life of a couple of hours (Berkowitz, 1976), the drug may still have been active in the posttraumatic period. This is less likely for N_2O, which has a half-life of three minutes (Hale, 1999). Finally, given that the drugs were sometimes given

during the pretraumatic period, they may have, in addition to disrupting memory consolidation, affected stress response (Mouthaan et al., 2015).

Pain hypothesis

In our study, N_2O predicted reduced C-PTSD symptoms, even when controlling for pain. Furthermore, pain did not predict C-PTSD symptom intensity, although low pain scores predicted their absence. Besides, the pain scores of women who received N_2O or a combination of morphine and N_2O were significantly higher than those of the control group, while women who received morphine had a score comparable to that of the control group. It does not appear that women who received analgesics thereby had a less painful experience than those who did not. This is probably explained by the fact that it was the pain intensity that led women to ask for pain relief. Besides, unless women reported highly intense pain, N_2O inhalation remained protective. Additionally, the mediation analysis did not show that the relationship between N_2O and C-PTSD symptoms severity was mediated by pain. Overall, these elements are not in favour of the pain hypothesis.

Non-pharmacological mechanisms

Aside from memory consolidation disruption or pain reduction, the observed association with PTSD symptoms could be due to indirect mechanisms. Firstly, the use of analgesics may enhance women's sense of control, or contribute to a sense of support from the staff, which both protect against C-PTSD (Ayers et al., 2016; Czarnocka & Slade, 2000). N_2O benefits could also come from its mode of administration, as focusing on breathing may help to relax (Richardson, Raymond, Baysinger, Kook, & Chestnut, 2019). Finally, all these non-pharmacological aspects could contribute to a reduction in PTSD symptoms through improved overall birth experience (Garthus-Niegel, Knoph, von Soest, Nielsen, & Eberhard-Gran, 2014). They may also explain why N_2O and morphine both predicted more severe C-PTSD symptoms when combined with intense labour pain: since perceiving the midwife as in control of the situation is a protective factor for C-PTSD (De Schepper et al., 2016), inefficient pain relief may give the impression that the staff is powerless.

4.2. Study limitations

Despite the prospective, population-based design, the large sample size and the inclusion of important confounding variables, this study has several limitations. The first, which is

inherent in observational clinical studies, is that drug administration was not randomised. While this is for obvious ethical and medical reasons, it may lead to biases. For that same reason, our sample included only a few women who received morphine, and thus we may have lacked statistical power for this drug.

Another limitation of our study concerns the type of measurement used. PTSD symptoms, whether pre-existing or childbirth-related, were self-reported. As for pain, it was measured at eight weeks postpartum, and thus may reflect pain memory, despite a strong correlation between pain at 48 hours and eight weeks postpartum. Additionally, since these analyses were not designed at the time of data collection, we do not have specific information on the intensity of pain relief provided by morphine and N_2O. Our measurement of pain thus remains a global indicator, which limits the mechanistic interpretations and notably the interpretation of the mediation analyses.

Furthermore, we acknowledge that using ECS, forceps, or vacuum as a proxy for birth medical severity is also a limitation. While it was necessary to take into account the severity of the obstetrical situation at the time of delivery, use of a validated index, had it been available, would have been preferable.

As shown by the VIF in Table 3, the important collinearity detected for several terms of the Tweedie regression may also limit the interpretation of results, although this collinearity is taken into account in the RESI computation.

Finally, despite our exclusion criteria, other drugs may have been given during childbirth and thus influenced PTSD symptom development. Oxytocin and benzodiazepines, for example, may affect PTSD development if administered following the traumatic event (Frijling, 2017; Guina, Rossetter, De, Nahhas, & Welton, 2015), although the evidence is mixed (Astill Wright et al., 2019; McGhee et al., 2009).

4.3. Implications and future directions

We believe that our results suggest that both N_2O and morphine merit further investigation about their use in the prevention of PTSD symptoms. However, while most of the published studies are naturalistic, research would benefit from randomised controlled trials. Even if

these are difficult to carry out in a clinical context, the trauma film paradigm seems to offer a good alternative for laboratory studies (James et al., 2016).

Future research should focus on the dose-response relationship between administered drugs and PTSD symptom development. Indeed, the effects of N_2O or morphine on memory (Good & Westbrook, 1995; Rabat et al., 2004) or PTSD (Bryant et al., 2009) may be dose-dependent. In our study, for instance, morphine dose may not have been sufficient to significantly affect PTSD symptoms. With a view to developing preventive interventions, greater clarity on this issue seems essential. In this respect, while morphine can be addictive and have psychotropic effects, N_2O has the advantage of having a short half-life, and moderate side effects (Likis et al., 2014). Besides, it seems to preserve the memory of the traumatic event (Das et al., 2016), which is a key aspect of the ethical debate on pharmacological prevention of PTSD (Jain, Nazarian, Weitlauf, & Lindley, 2011). Overall, its use is considered safe and minimally invasive (Zafirova, Sheehan, & Hosseinian, 2018). However, its toxicity is still debated (Fluegge, 2018), and it could increase intrusions frequency in dissociated individuals (Das et al., 2016). Furthermore, while many studies suggest that timing is key (e.g., Bryant et al., 2009; RaiseAbdullahi et al., 2019), it has not been systematically investigated.

Among injured or suffering populations, future studies should take into account the effects of anaesthesia provided during the peritraumatic period. Indeed, anaesthesia procedures may involve not only other drugs with singular effects on pain or memory, but also additional (locally administered) opioids and opiates. Thus, anaesthesia represents another gateway for drugs to enter the body, and its relationship with PTSD development remains unclear (Hernandez-Martinez et al., 2020; Lopez et al., 2017). Furthermore, the protective effect of N_2O in the absence of severe pain suggests that it would be relevant to examine the preventive potential of analgesics for uninjured victims of traumatic events such as witnesses of assaults. On the contrary, since morphine and N_2O are commonly used to relieve injured patients, it would be important to clarify whether their administration actually worsens the severity of subsequent PTSD symptoms in those in extreme pain.

5. Conclusion

In this study, N_2O was associated with reduced C-PTSD symptoms when inhaled during the peritraumatic period. Although not significant, a similar trend was observed for morphine.

Conversely, higher levels of pain predicted more severe C-PTSD symptoms in women who received morphine or N_2O. These results may be of interest to health professionals routinely using these two drugs in populations at risk of developing PTSD, by providing information on the associations between pain relief and mental health. Furthermore, they open up exciting prospects for research on N_2O as a potential pharmacological agent for PTSD prevention.

Declaration of interest. None.

Contributors. C. Deforges, S. Stuijfzand and A. Horsch conceptualized the study. Y. Noël and S. Garthus-Niegel performed all the analyses, in collaboration with C. Deforges, S. Stuijfzand, and A. Horsch. C. Deforges drafted the initial manuscript, with the contribution of S. Garthus-Niegel for the method section and Y. Noël for the statistics. M. Eberhard-Gran designed and coordinated the original cohort study. T. Breines Simonsen supervised the data collection and data extraction of the hospital birth record. M. Robertson contributed with her expertise in anaesthesiology and the interpretation of the data. All authors approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work. A. Horsch is the PhD supervisor of C. Deforges.

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G. Published manuscript of Study 2 (Supplementary material)

1. Item Response Models (IRM) and calculation of symptom scores

For the total scores of both the Impact of Event Scale (IES) and MINI-based prior PTSD symptoms checklist, we chose to explicitly take into account the ordinal nature of the response scale by using Item Response Models (IRM). All IRM share the property of expressing mathematically the relationship between a person location on some latent dimension (e.g., PTSD severity) and the probability of choosing a particular response category (e.g., *Not at all… Often*, or *Yes / No*) on a given item. Computing these probabilities helps computing an expected rating curve, which in most situations, is expected to be increasing (i.e., the higher the stress, the higher the expressed response).

Three unidimensional models of increasing flexibility were fitted to the data (using the binary or polytomous form as appropriate): a fixed slope logistic model (Masters, 1982; Rasch, 1960), a varying slope logistic model (Birnbaum, 1968; Muraki, 1992), and a monotonic polynomial model (Falk & Cai, 2016). All analyses were performed using the 'mirt' R package (Chalmers, 2012). Goodness of fit was examined at the item level, using the signed Chi-squared test (Orlando & Thissen, 2000). The analyses of the IES score were performed on the whole subset of the sample for which full response patterns were available (n = 2,120). Note that this included additional subjects that were part of the whole cohort study, but not eligible for the present assessment study of N_2O and morphine impact, due to general anaesthesia, other opiates, pethidine, or absence of the birth record. Subjects with missing responses (n = 71 (3.2%) participants) were discarded from the analyses. The MINI-based prior PTSD symptoms score was constructed from the set of all full response pattern (n = 3,555); there were no missing data to be accounted for.

Examination of item fit indicated that all 8 items from the MINI-based prior PTSD symptoms checklist were well accounted for by a two-parameter logistic model. A monotonic polynomial model was necessary to correctly model 11 out of 15 items of the IES. But person scores computed with and without the four IES misfitting items were highly correlated ($r(2118)$ = .976, $p < .0001$), indicating that the scores obtained from the full scale analysis could be used for further analyses.

2. Zero-inflated Tweedie compound Poisson model

A particularity of the IES score distribution in this sample is a strong proportion of zero scores (20%), leading to a bimodal marginal distribution where, besides a mass at zero, the positive scores displayed a Gamma-like skewed distribution (see Figure S1). This zero inflation phenomenon is common in clinical studies (see Hu, Pavlicova, and Nunes (2011) for some examples), and appears when a non-negligible portion of patients reports no symptoms at all, beyond what would be expected from a standard unimodal distribution. This deserves a specific statistical treatment, in the context of regression analyses. A zero-inflated Tweedie compound Poisson model (Zhang, 2013) was used in this paper. The model included two components: a logistic part discriminating between the zero and non-zero scores (absence vs. presence of symptoms), and a Tweedie compound Poisson model accounting for the non-null score variance (i.e., modelling stress intensity). A benefit of the Tweedie distribution hypothesis, on the second part of the model, is its ability to model skewed distributions with greater flexibility than alternative choices (Gamma, LogNormal), through the estimation of a shape (or index) parameter. Note that two sets of regression coefficients result from this analysis, one for each part of the model.

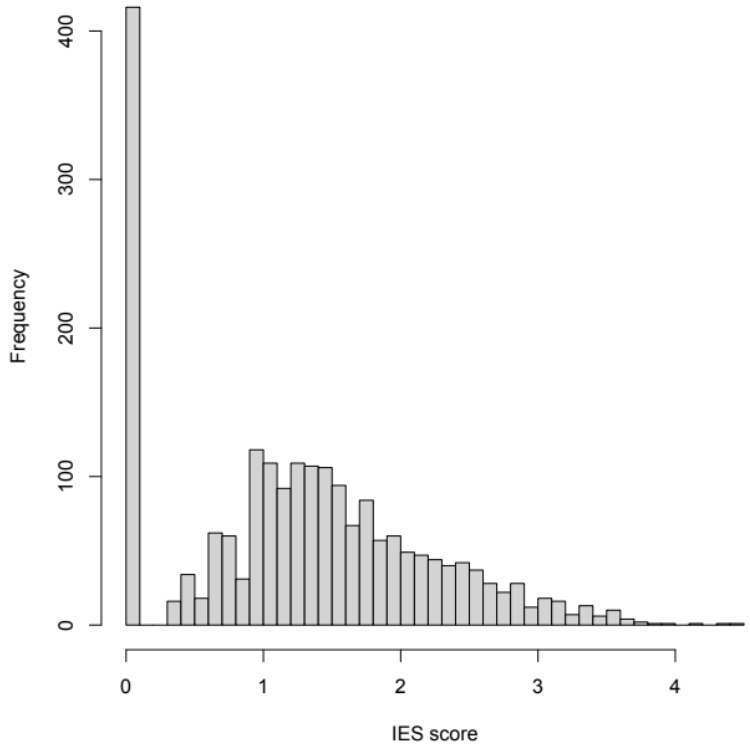

Figure S1. IES score distribution – computed with a polytomous IRM.

3. Model comparison and selection

Table S1. Akaike Information Criterion (AIC) of each of the models compared in the analyses.

		Zero inflation model			
		Full model[a]	Reduced model 1[b]	Reduced model 2[c]	Restricted model[d]
Tweedie compound poisson model	Full model[a]	5333.175	5332.749	5329.416	5351.094
	Reduced model 1[b]	5322.505	5318.746	5308.005*	5340.424
	Reduced model 2[c]	5335.479	5331.719	5320.978	5353.397
	Restricted model[d]	5380.45	5376.691	5365.95	5398.369

[a] This model includes main effects and first and second order interactions
[b] This model includes main effects and first order interactions
[c] This model includes main effects only
[d] This model includes only significant predictors from the full model

* Retained model

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H. Published manuscript of Study 3

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Abstract:

Introduction. Emergency caesarean section (ECS) qualifies as a psychological trauma, which may result in postnatal posttraumatic stress disorder (PTSD). Maternal PTSD may not only have a significant negative impact on mother-infant interactions, but also on long-term infant development. The partner's mental health may also affect infant development. Evidence-based early interventions to prevent the development of postpartum PTSD in mothers are lacking. Immediately after a traumatic event, memory formation is vulnerable to interference. There is accumulating evidence that a brief behavioural intervention including a visuospatial task may result in a reduction in intrusive memories of the trauma.

Methods and analysis. This study protocol describes a double-blind multi-centre randomised controlled phase III trial testing an early brief maternal intervention including the computer game "Tetris" on intrusive memories of the ECS trauma (1 week) and PTSD symptoms (6 weeks, primary outcome) of 144 women following an ECS. The intervention group will carry out a brief behavioural procedure including playing Tetris. The attention-placebo control group will complete a brief written activity log. Both simple cognitive tasks will be completed within the first 6 hours following traumatic childbirth. The intervention is delivered by midwives/nurses in the maternity unit. The primary outcome will be differences in the presence and severity of maternal PTSD symptoms between the intervention and the attention-placebo control group at 6 weeks postpartum. Secondary outcomes will be physiological stress and psychological vulnerability, mother-infant interaction, and infant developmental outcomes. Other outcomes will be psychological vulnerability and physiological regulation of the partner and their bonding with the infant, as well as the number of intrusive memories of the event.

Ethics and dissemination. Ethical approval was granted by the Human Research Ethics Committee of the Canton de Vaud (study number 2017-02142). Dissemination of results will occur via national and international conferences, in peer-reviewed journals, public conferences, and social media.

Trial registration number. *Clinicaltrials.gov* (NCT 03576586)

Keywords: Early intervention; PTSD; Maternal mental health; Infant development; HRV; Cortisol; Sleep; Bayley-III; Trauma; Mental imagery, Intrusive memories

Manuscript:

1. Introduction[1]

Childbirth and PTSD

Though childbirth is a common and often fulfilling event, one third of mothers rate their childbirth as traumatic (1). Childbirth can meet diagnostic criteria for a traumatic event, if women perceived their life and/or the life of their baby to be in danger (2). Posttraumatic stress disorder (PTSD) related to childbirth is diagnosable in around 3-4% of women (3, 4). PTSD consists of four symptom clusters (intrusions, avoidance, hyperarousal, and negative cognitions and mood) and can be diagnosed at least one month after the traumatic stressor occurred (2). Comparing different modes of childbirth, obstetric complications, such as emergency caesarean section (ECS) produce higher rates of postnatal PTSD (19-39%) (3). ECS is a relatively frequent event, and there is thus a need to better identify and support women who are vulnerable to developing PTSD following an ECS.

Postnatal PTSD can significantly influence the experience of subsequent pregnancies, with increased risk of maternal stress and its associated risks of intrauterine growth retardation, premature birth and low birth weight (5-7). It can lead to a fear of subsequent pregnancy and childbirth, sexual problems, and avoidance of medical care (8, 9). Postnatal PTSD can also have important negative consequences for breastfeeding, the attachment relationship with the baby and mother-infant interactions, with a subsequent detrimental impact on the development of the child, as well as for the couple relationship (7, 10-13). PTSD is also highly co-morbid with depression, for which there is substantial evidence of long-term negative effects on child development and behaviour (14-16). Estimated economic costs of perinatal mental health problems are about £8.1 billion for each one-year cohort of UK births, of which 72% relate to adverse impacts on the child rather than the mother (17). In Switzerland, 16.7% of women in the perinatal period used mental health services (18). New and innovative

[1] ANS = Autonomic Nervous System; ASD = Acute Stress Disorder; ASDS = Acute Stress Disorder Scale; BSID-III = Bayley Scales of Infant Development, 3rd Edition; CAPS = Clinician-Administered PTSD Scale for DSM-5; CAR = Cortisol Awakening Response ; CRIB = Clinical Risk Index for Babies; EAS = Emotional Availability Scales; ECG = Electrocardiography; ECS = Emergency Caesarean Section; EPDS = Edinburgh Postnatal Depression Scale; FFSF = Face-to-Face Still-Face paradigm; HADS = Hospital Anxiety and Depression Scale; HPA = Hypothalamic-Pituitary-Adrenal; HRV = Heart Rate Variability; IBIs = Interbeat Intervals; IBQ-R = Infant Behavior Questionnaire-Revised; MEQ = Morningness-Eveningness Questionnaire; MIBS = Mother-to-Infant Bonding Scale; MOS-8 = Modified Medical Outcomes Study Social Support Survey; NBAS = Neonatal Behavioural Assessment Scale; PCL-5 = PTSD Checklist for DSM-5; PDPSI = Post-delivery Perceived Stress Inventory; PPSI = Postnatal Perceived Stress Inventory; PSI-SF = Parenting Stress Index - Short Form; PSQI = Pittsburgh Sleep Quality Index; PSQI-A = Pittsburgh Sleep Quality Index Addendum; PTSD = Post-Traumatic Stress Disorder; RCT = Randomised Controlled Trial ; RDAS = Revised Dyadic Adjustment Scale; START = Swiss Traumatic Birth Trial.

evidence-based interventions are therefore needed to reduce those costs by preventing the development of postnatal PTSD (19).

To date, research investigating PTSD symptoms in partners following ECS is missing. Most studies on partners so far have focused on postnatal depression reporting that 1-8% experience depression symptoms in the first 6 weeks and 5-6% at 3-6 months following childbirth without complications (20-22), with increased risk following high risk situations (23). In one study, 5% of partners reported severe intrusions and avoidance symptoms at 9 weeks postpartum (24). Although the influence of partner mental health is understudied, it also seems to negatively impact child outcomes (25-27). Thus, partner mental health needs to be better understood not only in order to help the partner but also to support family and child outcomes.

Physiological stress responses associated with PTSD

Traumatic exposure activates the hypothalamic-pituitary-adrenal (HPA) axis, a cascade-like hormonal system resulting in the release of cortisol from adrenal cortex cells in body fluids. In parallel, the organism activates the more rapidly mobilizing autonomic nervous system (ANS) resulting in the release of norepinephrine from nerve terminals of the sympathetic nervous system as well as epinephrine and norepinephrine from the adrenal medulla (28). While the HPA axis shows the above stress-related reactivity, it also shows a basal activity with circadian variations in the respective hormones. For instance, cortisol peaks 30-45 minutes after awakening (the so-called CAR: cortisol awakening response) and gradually declines throughout the day with lowest levels early during sleep (29, 30).

Specific patterns of HPA axis functioning have been shown in PTSD (31) although this has so far not been studied after traumatic childbirth. While studies indicate that individuals with PTSD show different patterns of HPA axis functioning to those without PTSD, there is little consistency in the specificity of these patterns (32-38). A meta-analysis examining diurnal cortisol levels in adults with PTSD showed that low cortisol levels were not related to PTSD in general, but rather to trauma exposure and co-morbidities (39). Finally, a recent study in a postnatal population found a negative association between symptoms of re-experiencing and diurnal cortisol slopes in mothers of preterm children (40). Concerning cortisol reactivity to a subsequent stressor, again, results are discrepant (41, 42).

Although HPA axis reactivity following stress or trauma is thought to be adaptive, acute or chronic exposure to stress has been shown to have deleterious effects (43, 44). It may not only result in dysfunctions of HPA re-activity, but also in health-relevant changes in the basal activation of this system (45). Overall, these studies show the strong implication of the HPA axis dysregulation in the development and maintenance of PTSD, although studies in postnatal populations are scarce.

Reduced heart rate variability (HRV), an indicator of autonomic flexibility, has been found to be related to psychopathological processes (46). Individuals with PTSD show lower levels of HRV in comparison with trauma-exposed individuals without PTSD or healthy controls (47, 48). However, the relationship of PTSD and HRV has so far not been studied in a postnatal population.

Sleep in PTSD is also disrupted. Sleep disturbance (i.e., difficulty falling or staying asleep) and recurrent distressing dreams are both diagnostic criteria for PTSD(2), with 70-91% of patients with PTSD suffering from subjective sleep disturbances and 19-71% reporting nightmares(49). Findings from experimental research indicate that sleep on the first night after trauma may be important for the development of subsequent intrusive memories of the index trauma. One study found that totally sleep deprived participants reported *fewer* intrusive memories after a laboratory stressor compared to those who slept(50), though findings are mixed(51-53). Thus, it is important to assess sleep over time following a real world traumatic event, such as following an ECS. To date, no studies to our knowledge have examined sleep in postpartum PTSD.

Maternal PTSD and infant physiological stress responses

Maternal PTSD and its associated dysfunction of the HPA axis can also impact on the stress regulation of the offspring (54-63), such as the infant's HPA secretion patterns (64-66). A growing body of neuroendocrine research supports the notion that an altered maternal HPA axis functioning plays a role in the intergenerational transmission of stress-related psychopathology from parents (67, 68). Overall, findings suggest that PTSD symptoms and cortisol levels in mothers are important to assess, prevent and/or treat as they may affect the relationship with the infant (69-72) and impact the child's later regulative abilities (54). Some authors have suggested low maternal cortisol as a possible mechanism contributing to the

mother's difficulty in sensitively attuning to her infant's cues, which in turn impacts on the infant's reactivity to and recovery from a stressor (73-78).

In contrast, studies assessing the role of ANS in the intergenerational transmission of stress in the postpartum period are so far scarce. Lifetime maternal psychopathology and maternal postnatal psychopathology have been found to be related with reduced HRV of their infants (79). Furthermore, mothers with anxiety symptoms during pregnancy and their infants showed lower HRV (80) and there was a higher sympathetic activation in children of mothers with abuse histories (81). However, to our knowledge none of the previous research has investigated the autonomic functioning in offspring of mothers with PTSD.

Developing an early intervention inspired by behavioural and cognitive neuroscience

To date, there is a lack of evidence-based early interventions for women following a traumatic childbirth (82). At the heart of PTSD are intrusive memories of the traumatic event, in which the person re-experiences aspects of the traumatic event, inflicting significant distress (2). They have also been indicated as a precursor to the disorder (83). Intrusive memories of trauma comprise sensory-perceptual images that are proposed to occur due to excessive perceptual (sensory) processing during a trauma (84).

The way in which individuals process a traumatic event influences their later intrusive memories of the trauma. Evidence from lab-based experiments have demonstrated that a brief behavioural intervention including a reminder cue, mental rotation and a visuospatial task (Tetris) can significantly reduce the frequency of intrusive images following exposure to traumatic film material(85, 86). One study showed that individuals who were instructed to engage in conceptually-driven processing, relative to those engaged in sensory-based, data-driven processing, reported more intrusive memories to a traumatic film (87). It has been hypothesised that tasks which interfere with data-driven processing, such as sensory-perceptual, visuospatial tasks, may reduce the occurrence of intrusive memories of an index event (85, 86). Visuospatial cognitive tasks, such as the computer game Tetris, are thought to compete for resources with visuospatial images (88). Studies of memory consolidation have shown that human memories are likely to still be malleable within 10 min to 6 hours, at which point the memory is thought to stabilise consolidation, making it more resistant to interference from a competing memory (89-91). This indicates that such a working memory

task may be most beneficial if delivered within approximately the first 6 hours following a traumatic event (see (92) for a review).

Two recent translational studies presented preliminary evidence for the efficacy of a brief intervention (including Tetris) in reducing the number of traumatic intrusive memories (over 1 week post-trauma) in patients arriving at an accident and emergency department (vs. attention placebo) (93) or in women in the first hours following ECS, the latter when compared with a treatment-as-usual control group (4). In the latter study, per protocol analyses also showed significantly lower re-experiencing symptoms at 1 week and lower rates of PTSD diagnosis at 1 month following ECS (secondary outcomes) (4).

Aims of the present study

The objectives of the present study are to investigate the effects of an early brief, behavioural intervention (including the computer game Tetris) delivered in the hospital context within 6 hours of the trauma, on maternal mental health and infant development after a traumatic event (ECS). The primary outcome measure will be the presence and the severity of maternal PTSD symptoms at 6 weeks. Secondary objectives will be to measure the impact of this intervention on intrusive memories of the trauma, on stress exposure and perception, on other indicators of maternal psychological vulnerability (including acute stress disorder (ASD), PTSD, anxiety, depression, and sleep), on physiological stress reactivity, on physiological regulation, on mother-infant interactions, and on infant development. The START study also aims to investigate additional maternal and partner psychological vulnerability, partner physiological regulation, partner-infant bonding, and measures related to the acceptability and expectancy of the intervention.

2. Methods

Study Design

We will conduct a multi-centre double-blind randomised controlled trial (RCT) with minimal risk testing the effect of an early brief behavioural intervention including computer game play for women at risk of PTSD in the hospital soon following an ECS and their infant, compared with an attention-placebo control task.

Study population, recruitment, group allocation, and blinding

All women who have an ECS ≥ 34 weeks gestation, give birth to a live baby, and give written consent are eligible to participate. In addition, they have to answer with a score of ≥ 2 separately for at least two out of four screening questions regarding perceived threat (94). All screening questions are answered on a 7-point Likert scale (*1 = not at all, 7 = extremely*): Did you think that your life was in danger? Did you think that your baby's life was in danger? Did you feel frightened during the birth? Did you feel helpless during the birth?

Exclusion criteria include: established intellectual disability or psychotic illness, insufficient French-speaking level to participate in assessments, severe illness of mother or infant (e.g., cancer, cardiovascular disease, severe neurodevelopmental difficulties, malformations) or if the infant requires intensive care, and alcohol abuse and/or illegal drug use during pregnancy.

Following an ECS and once the mother has sufficiently recovered, the mother's midwife/nurse will assess eligibility and if eligible, will inform the mother about the study. After providing written and informed consent to be screened, participants will be screened immediately for perceived threat of the mother and/or child with four screening questions. If participants score ≥2 separately for at least two out of the four questions, they will be randomly assigned to either the intervention or attention-placebo control group. We aim to recruit 144 women and their infants (see sample size calculation).

If the woman agrees, then the partner will also be informed about the study. Inclusion criteria for the partners are that they were present at the childbirth and give written consent. Partners are excluded if they do not speak French sufficiently well to participate in assessments. All participants will be reimbursed for their time and effort.

The allocation ratio of randomisation is 1:1. The randomization sequence will be generated using a computer-generated block randomisation (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX) using blocks of sizes 2, 4 and 6 over 144 participants per stratum (stratified by research centre). Opaque envelopes will be prepared in advance, numbered sequentially by alternating between stratums by block. After conducting the baseline assessment, the clinical midwife/nurse will open the envelope and announce the cognitive task to be carried out (i.e., the cognitive visuospatial task or the attention-placebo control task) to the participant (95). All members of the research group as well as participants

are blind to group allocation. All participant data will be coded to ensure confidentiality. After completing the 15-minute cognitive tasks, both women of the control and intervention group will complete the same assessments, as shown in Table 1; see Figure 1 for an overview of the study variables.

Intervention group

Mothers in the intervention group will be instructed to engage in a cognitive visuospatial task, the computer game Tetris, for 15 minutes continuously, on a handheld gaming device (Nintendo DS) (see (4)). They are given a 3-min training in how to play the game and how to actively use mental rotation as they play the game. The intervention is delivered in the same context as that in which the trauma occurred (e.g,, wake-up room) so additional memory reminder cue to the trauma is not used.

The intervention will take place within the first six hours after ECS whilst participants are still in their hospital bed. Procedures are managed not to interfere with important routine care procedures. An unblinded independent researcher will check during the days following the intervention that the intervention protocol was followed correctly via a 4-item survey completed by the participant. Study information and materials refer to 'simple tasks' in both conditions for credibility.

Attention-placebo control group

Mothers assigned to the control group will be asked to engage in a written activity log for 15 minutes (based on previous research (93)). They are instructed to write down very briefly nature and duration of the activities (e.g., "*being with baby for 10 min*", "*phone call for 5 min"*) and they are instructed not to sleep. The activity log was selected to control for nonspecific confounding factors, while minimizing the potential for harmful effects, as to date, no preventive treatment in the immediate aftermath of trauma exists that could be used as a control condition (96-99). This control condition was matched with the intervention condition for nonspecific factors including length of the task, contact with the midwife/nurse, location of treatment procedure and engagement in a structured task (93). The attention-placebo control task will take place within the six hours after ECS, whilst participants are still in their hospital bed and will not interfere with important routine care procedures. An unblinded independent researcher will check during the days following childbirth that the attention-placebo control task protocol was followed correctly via a 2-item survey completed

by the participant. Study information and materials refer to 'simple tasks' in both conditions for credibility.

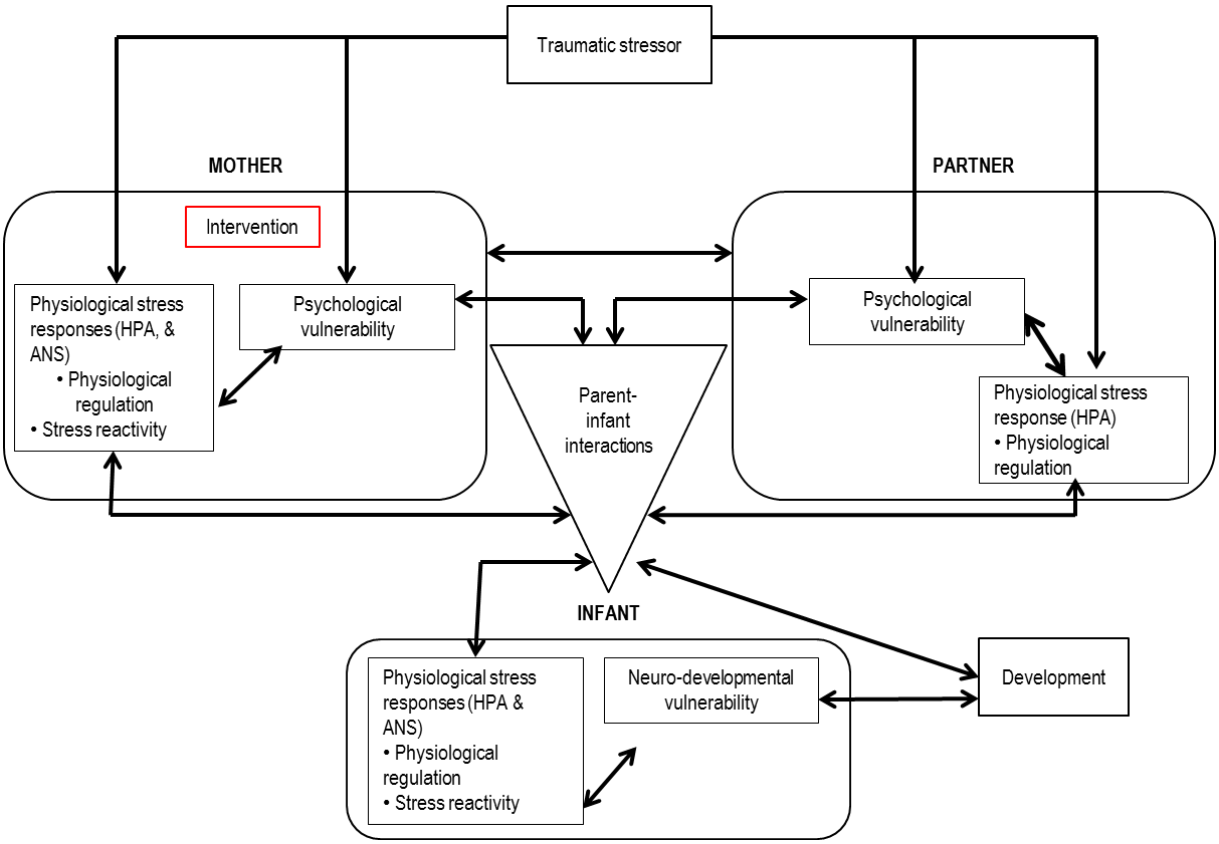

Figure 1. Study variables: processes in mothers, partners, infants and their interactions following traumatic childbirth.

Note. ANS = autonomic nervous system; HPA = hypothalamic–pituitary–adrenal.

Primary outcome

The primary outcomes are differences in the presence and severity of maternal PTSD symptoms between the intervention and the attention-placebo control group at 6 weeks postpartum measured with the Clinician-administered PTSD Scale (100) and the PTSD Checklist (101).

Secondary outcomes

The following outcomes will be assessed via validated assessments at different time-points (i.e., ≥ 6 hours following ECS, ≤ 1 and 6 weeks, and 6 months follow-up).

- *Maternal outcomes*

The maternal mental health outcomes will be compared between the two groups at all time-points, including number of intrusive memories of the index trauma (at ≤ 1 week follow-up) and indicators of maternal psychological vulnerability namely: symptoms of ASD, PTSD, anxiety, depression, sleep and physical activity (at ≥ 6 hours following ECS, ≤ 1 and 6 weeks, and 6 months follow-up) (see Table 1). Additional physiological outcomes will be collected in reactivity to stress and as regulation indicators (at 6 weeks and 6 months follow-up). Finally, maternal bonding and sensitivity in mother-infant interaction will also be measured (at ≤ 1 and 6 weeks, and 6 months follow-up).

- *Child secondary outcomes*

As shown in Table 1, infant development will be assessed at 6 months postpartum. Additionally, physiological outcomes will be assessed in response to stress and as regulation indicators (at 6 weeks and 6 months follow-up).

Other outcomes

Additional measures of maternal and partner psychological vulnerability (at ≤ 1 and 6 weeks, and 6 months follow-up), partner infant interaction (at ≤ 1 and 6 weeks, and 6 months follow-up), infant neurodevelopmental vulnerability (at ≤ 1 week), medical outcomes (at ≤ 1 and 6 weeks, and 6 months follow-up), and measures related to the acceptability and expectancy of the intervention (at ≥ 6 hours following ECS) are described in Table 2.

Data collection and visits

Figure 2 summarises study procedures and Table 1 indicates the measures collected at each time point.

Measures

Measures of the primary and secondary outcomes can be found below, measures relating to the 'other outcomes' in the study can be found in Table 2. The time points of when all measures are taken can be seen in Table 1.

- *Psychological vulnerability*

Clinician-administered PTSD Scale (CAPS-5) (100). The CAPS-5 assesses presence and severity of PTSD symptoms and diagnosis. This gold standard instrument contains 20 items referring to the four symptom clusters, as well as 10 items referring to symptoms duration,

distress or impairment, global ratings, and dissociative subtype. Each diagnostic criterion is rated from *0 = absent* to *4 = extreme/incapacity* in function of symptoms intensity and frequency with a diagnostic cut-off equal to 2. The CAPS-5 has demonstrated good psychometric proprieties (100). In the absence of a French version at the time when the study was designed, a forward-back method was executed to realise a translation and cultural adaptation (102).

The PTSD Checklist (PCL-5) (101). This 20-item self-report questionnaire measures symptoms of PTSD over the past month and is used to assess frequency of PTSD symptoms. The PCL-5 refers to the four symptoms clusters of PTSD and scales on a 5-point scale with *0 = not at all* and *4 = extremely*. Scores are summed to create a total symptom severity score (103). The French version of the PCL-5 demonstrated strong reliability and validity (104).

Trauma-related intrusive memories diary (4). Intrusive memories of birth-related trauma experienced during the seven days following ECS are reported in a daily diary, adapted from previous work (4), to assess the frequency of intrusive memories of the trauma. For each intrusion, the time, content and type (intrusive memory, nightmare or other) are recorded, as well as the level of distress on a 5-point scale with ratings of *0 = not at all* to *5 = extremely.*

Acute Stress Disorder Scale (ASDS) (105). This self-assessment instrument measures frequency of ASD symptoms over the last week and is based on DSM 5 (106). Each of the 19 items is scored using a scale from *1 = not at all* to *5 = extremely*, with a higher score indicating higher ASD symptoms. Good sensitivity and specificity has been reported (105). The forward-back method was executed to realise a French version translation and cultural adaptation(102).

Anxiety subscale of Hospital Anxiety and Depression Scale (HADS) (107). This self-report questionnaire measures severity of anxiety symptoms during the last week. The anxiety subscale consists of 7 items scored on a 4-point scale (*0 = never*, *3 = most of the time*). Higher scores indicate higher distress. Good psychometric properties have been reported for the French version (108).

Edinburgh Postnatal Depression Scale (EPDS) (109). This self-assessment examines postnatal depression symptoms over the previous week (109). The 10 items are scored on a 4-point scale and scores range from 0 to 30. Higher scores indicate higher distress. The French version has demonstrated good psychometric proprieties (110). A clinical cut-off score of 10.5 has been reported for the use of the French validated version (110).

Physical and sleep activity. Frequency and duration of maternal sleep and physical activity of the 5 days following childbirth is measured using an accelerometer watch GENEActiv® (111).

Sleep diary. Mothers record their hours of sleep during the week following ECS in a daily sleep diary.

Pittsburgh Sleep Quality Index (PSQI) (112). This 19-item questionnaire measuring sleep during the past month is composed of seven sleep quality-related subscales. The overall score assessing sleep quality is scored by summing the subscales; scores range from 0 to 21. Higher results indicate poor sleep quality while a score of > 5 distinguishes good and poor sleepers. The validated French version of the PSQI has shown good psychometrics proprieties (113).

We also included the 10 items of the PSQI-A (114) to assess PTSD-specific sleep disturbances over the past month, answered on a four-point Likert scale (0 = *not during the past month*; 3 = *three or more times a week*), that assess the frequency of different kinds of trauma-related sleep disturbance. The items are summed to create the total score, where the higher the score the more disturbed the sleep. The validated French version of the PSQI-A has shown good psychometrics (114).

- *Maternal and infant physiological stress responses.*

Physiological regulation. Resting heart rate of the mother and infant are assessed using resting HRV measured by Firstbeat Bodyguard 2 devices providing a continuous measure of cardiac activity. Resting heart rate will be assessed during the 15 minutes resting period before the stress paradigms (see *Physiological stress reactivity* for stress paradigms) at ≤1 week and 6 months. Baseline salivary cortisol and cortisol daily profile will be established for the mother in the two days after leaving the maternity ward (usually the 6th and 7th day postpartum) and for her and her baby for two days at 6 months through salivary sample; 5 saliva samples are taken per day, including CAR. Maternal salivary cortisol will be collected using Salivettes© Sarstedt (item number: 51.1534.500) and SalivaBio Infant's Swab (Salimetrics, item number: 5001.08 50) for infants.

Physiological stress reactivity. Maternal and infant stress reactivity will be assessed via salivary cortisol and HRV using Firstbeat Bodyguard 2 devices during the stress phases of their respective stress paradigms at 6 months for the mother and at ≤ 1 week and at 6 months for the infant. The stress paradigm for the mothers is the Trier Social Stress Test (TSST) (115) at 6 months. Maternal salivary cortisol will be measured 7 times before, during, and after the stress paradigms and heart rate throughout the stress paradigm. Stress paradigms for the infants involve the Neonatal Behavioural Assessment Scale (NBAS) (116) at ≤1 week and the double-exposure Face-to-Face Still-Face paradigm (FFSF) (117-120) at 6 months. Salivary

cortisol will be measured 3 times, once before and twice after the stressor, and HRV will be measured throughout the stress paradigms. Maternal cortisol will also be collected during the FFSF. Maternal salivary cortisol will be collected using Salivettes© Sarstedt and SalivaBio Infant's Swab (Salimetrics) for infants. Participation in maternal stress reactivity assessments at ≤1 week is optional (involving an additional consent obtained before hospital discharge).

- *Mother-infant interaction*

Mother-to-Infant Bonding Scale (MIBS) (121). This 8-item questionnaire assesses the mothers' feelings towards her new baby in the first few weeks after birth. Eight adjectives are rated on a scale from *0 = very much* to *5 = not at all*. Scores are summed to create a total score, with a higher score indicating worse mother-to infant bonding. The MIBS has shown good initial psychometrics[121], and has been validated in French (122).

Emotional Availability Scale (EAS) (123, 124). Maternal sensitivity and responsiveness will be investigated during a free-play session of mothers with their six-months old. Interactions are coded on six dimensions: sensitivity, structuration, intrusion, hostility toward the infant, reactivity to the mother, and maternal involvement (123, 124). Higher scores on each scale indicate better performance. Two trained psychologists blind to the condition will rate each interaction and inter-observer reliability will be calculated. The EAS shows good psychometric properties (123, 124).

- *Infant developmental outcomes*

Infant Behaviour Questionnaire – Revised (IBQ-R) Very Short Form (125). This is a parent-report questionnaire consisting of 36 items answered on a 7-point Likert-scale (*1 = never* to *7 = always*). The items assess the frequency of infants' behaviours during the previous two weeks to measure child temperament. The very short form has shown good psychometric properties (125). There was no available validation French translation. Therefore, the forward-back method was completed to realise a French version translation and cultural adaptation (102).

Bayley Scales of Infant Development (Bayley-lll) (126). The cognitive, language and motor subscales of the Bayley Scales of Infant Development assess the developmental functioning of the infant. The scales are administered by a trained psychologist or paediatrician through a standard set of play tasks following a standardized protocol. The composite scores for the subscales are age-standardized with a mean score of 100 (127).

- *Sociodemographic, obstetric and neonatal characteristics*

Mothers will report demographic information, including marital status, nationality, profession, level of education (128), and previous and current psychiatric disease as well as any trauma history via a self-report questionnaire. Mothers will also report their height, weight (before pregnancy and current), menstrual cycle, smoking behaviours, and alcohol/drug use. Obstetric data will be extracted from the hospital medical record, such as pregnancy-, labour- and birth-related information, gravidity, parity, mode of previous childbirths, history of miscarriage, stillbirth, and prematurity, pain, medication, birth control, sexual activity, and psychological support. Neonatal characteristics will be collected from the medical record on severity of morbidity (gestational age and weight at birth, Apgar score, neonatal complications), as well as the Clinical Risk Index for Babies (CRIB II) (129), which represents neonatal morbidity severity.

Table 1. Overview of primary, secondary and other outcomes, measures, and time points

	Domain	Variables	Instruments	Timing			
				6h after ECS (T1)	**≤ 1 week (T2)**	**6 weeks (T3)**	**6 months (T4)**
Mother	Sociodemographic and medical data	Sociodemographic variables	Demographic questionnaire		**X**	**X**	**X**
		Medical data	Obstetric data and pregnancy outcomes from medical records		**X**		**X**
			Menstrual cycle (if applicable)				**X**
			Breastfeeding diary/questions		**X**	**X**	**X**
	Acceptability and expectancy of the intervention	Satisfaction and expectancy	Feedback questionnaire	**X**			
	Maternal psychological vulnerability	Intrusive trauma-related memories	Trauma-related intrusive memories diary (4)		**X**		
		Stress exposure and perception	Post-delivery Perceived Stress Inventory (PDPSI) (134)		**X**		
			Major life events (135, 136)		**X**		**X**
			Postnatal Perceived Stress Inventory (PPSI) (137)				**X**

	Parenting Stress Index – Short Form (PSI-SF) (138, 139)				**X**
PTSD	Clinician-administered PTSD scale (CAPS) (102)			**X**	**X**
	PTSD Checklist (PCL-5) (101)			**X**	**X**
ASD	Acute Stress Disorder Scale (ASDS) (105)	**X**	**X**		
Anxiety	Hospital Anxiety and Depression Scale: anxiety subscale (HADS) (107)	**X**	**X**	**X**	**X**
Depression	Edinburgh Postnatal Depression Scale (EPDS) (109)	**X**	**X**	**X**	**X**
Social support	Modified Medical Outcomes Study Social Support Survey (MOS-8) (140)		**X**	**X**	**X**
	Revised Dyadic Adjustment Scale (RDAS) (141, 142)		**X**	**X**	**X**
Sleep	Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) (114)			**X**	**X**
	Morningness-Eveningness questionnaire (MEQ) (143)		**X**		

			Pittsburgh Sleep Quality Index (PSQI) (112)	**X**	**X**	**X**
			Sleep diary	**X**		
			Overnight accelerometer assessments (GENEActiv®) (144)	**X**		**X**
	Maternal physiological stress responses	Physiological regulation	Baseline cortisol and cortisol daily profile (saliva)	**X**		**X**
			Resting heart rate and heart rate variability (Firstbeat Bodyguard 2)			**X**
		Physiological stress reactivity	Cortisol (saliva)			**X**
			Heart rate variability (Firstbeat Bodyguard 2)			**X**
Partner	Sociodemographic data	Sociodemographic variables	Demographic questionnaire	**X**	**X**	**X**
	Paternal psychological vulnerability	Intrusive traumatic memories	Traumatic intrusions diary (4)	**X**		
			Major life events (135, 136)	**X**		**X**

Stress exposure and perception	Parenting Stress Index – Short Form (PSI-SF) (138, 139)			**X**
PTSD	Clinician-administered PTSD scale (CAPS) (102)		**X**	**X**
	PTSD Checklist (PCL-5) (101)		**X**	**X**
ASD	Acute Stress Disorder Scale (ASDS) (105)	**X**		
Anxiety	Hospital Anxiety and Depression Scale: anxiety subscale (HADS) (107)	**X**	**X**	**X**
Depression	Edinburgh Postnatal Depression Scale (EPDS) (109)	**X**	**X**	**X**
Social support	Modified Medical Outcomes Study Social Support Survey (MOS-8) (140)	**X**	**X**	**X**
	Revised Dyadic Adjustment Scale (RDAS) (142, 141)	**X**	**X**	**X**
Perception of ECS-related trauma	Screening questions of the Posttraumatic Diagnostic Scale (94)	**X**		
Sleep	Pittsburgh Sleep Quality Index (PSQI) (112)	**X**	**X**	**X**

			Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) (114)		**X**	**X**
			Morningness-Eveningness questionnaire (MEQ) (143)	**X**		
	Partner physiological responses	Physiological regulation	Cortisol daily profile (saliva)	**X**		**X**
Infant	Sociodemographic and medical data	Sociodemographic variables	Demographic questionnaire (completed by mother)	**X**	**X**	**X**
		Medical data	Neonatal outcomes from medical records	**X**		
	Infant neurodevelopmental vulnerability	Infant irritability	Dubowitz neurologic examination (146)	**X**		
	Infant physiological stress responses	Physiological regulation	Baseline cortisol and cortisol daily profile (saliva)			**X**
			Resting heart rate and heart rate variability by (Firstbeat Bodyguard 2)	**X**		**X**
		Physiological stress reactivity	Cortisol (saliva)	**X**		**X**

			Heart rate variability (Firstbeat Bodyguard 2)	**X**		**X**
	Developmental outcomes	Neonatal behaviour	Neonatal Behavioural Assessment Scale (NBAS) (116)	**X**		
		Infant development	Infant Behaviour Questionnaire-revised (IBQ-R) (125)			**X***
			Bayley Scales of Infant Development (Bayley-III; clinician-rated) (126)			**X**
Parent-infant interaction	Mother-infant interaction	Maternal sensitivity	Emotional Availability Scale (EAS, clinician-rated) (123, 124)			**X**
		Bonding	Mother-to-Infant-Bonding Scale (MIBS) (121)	**X**	**X**	**X**
	Partner-infant interaction	Bonding	Mother-Infant-Bonding Scale (MIBS) (121)	**X**	**X**	**X**

Note: * = completed by mothers and partners. ECS = Emergency Caesarean Section; PTSD = Post-Traumatic Stress Disorder.

Table 2. Other Outcomes and a brief description of the measures used for each outcome.

Domain	Instruments	Description
Maternal and paternal psychological vulnerability	Morningness-Eveningness Questionnaire (MEQ) (143) (at ≤1 week follow-up)	19 multiple-choice questions self-assessment questionnaire investigating the **mother and partner**'s circadian rhythm. Scores are summed to create a total and a higher score indicates a more 'morning' person.
	Modified Medical Outcomes Study Social Support Survey (MOS-8) (122, 140) (≤1 and 6 weeks, and 6 months follow-up)	8-item self-report questionnaire assessing **mother and partner** social support across four functional support scales: emotional/ informative, tangible, affectionate, and positive social interaction. Items are answered on a 6 point scale (0 = *Never*, 5 = *Always*).
	Revised Dyadic Adjustment Scale (RDAS) (141, 142) (at ≤1 and 6 weeks, and 6 months follow-up)	14-item self-report questionnaire measuring the **mother and the partner** relationship satisfaction. Three categories are evaluated: consensus, satisfaction and cohesion.

Parenting Stress Index - Short Form (PSI-SF) (138, 139) (6 months follow-up)	Self-report questionnaire measuring the **mother and partner** parenting stress. It consists of three subscales: parental distress, parent-child dysfunctional interactions, and child difficulties. 36 items are answered on a 1-point Likert scale *(1 = Strongly agree, 5 = Strongly disagree).*
The Post-delivery Perceived Stress Inventory (PDPSI) (134) (at ≤1 week follow-up)	16-item self-report questionnaire assessing **mother's** perceived stress linked to delivery. Each item is a potential stressor the mother may have experienced during or after delivery. Mothers are asked whether they found the items more or less stressful using a 5-point Likert scale *(1 = Never, 5 = Very often).*
Postnatal Perceived Stress Inventory (PPSI) (137) (at 6 weeks, and 6 months follow-up)	19-item self-report questionnaire assessing **maternal** postpartum perceived stress. Each item relates to a potential stressor they may encounter within the postnatal period. Mothers are asked to indicate whether they were more or less stressed on a 5

	point scale (1 = *Not at all*, 5 = *Extremely*).
Life Events Questionnaire (135, 136) (at ≤1 week and 6 months follow-up)	15-item self-report scale where **mother and partners** are asked to indicate if they have experienced different major life events and how stressful they found these events. One item allows participants to identify an event not mentioned and one asks if a major life event occurred within the first trimester of pregnancy.
Trauma-related intrusive memories diary (4) (at ≤1 week follow-up)	Completed by **partners**; see Measures section for more details.
Clinician-administered PTSD scale (CAPS) (100) (at 6 weeks and 6 months follow-up)	Completed by **partners**; see Measures section for more details.
PTSD Checklist (PCL-5) (101) (at 6 weeks and 6 months follow-up)	Completed by **partners**; see Measures section for more details.
Acute Stress Disorder Scale (ASDS) (105) (at ≤1 week follow-up)	Completed by **partners**; see Measures section for more details.
Edinburgh Postnatal Depression Scale (EPDS) (109) (at ≤1 and 6 weeks, and 6 months follow-up)	Completed by **partners**; see Measures section for more details.

	Anxiety subscale of Hospital Anxiety and Depression Scale (HADS) (107) (at ≤1 and 6 weeks, and 6 months follow-up)	Completed by **partners**; see Measures section for more details.
	Pittsburgh Sleep Quality Index (PSQI) (112) (at ≤1 and 6 weeks, and 6 months follow-up)	Completed by **partners; s**ee Measures section for more details.
	Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) (114) (at 6 weeks and 6 months follow-up)	Completed by **partners**; see Measures section for more details.
	Perception of ECS-related trauma (at ≤1 week follow-up)	**Partners** complete the 4 screening questions of the Posttraumatic Diagnostic Scale [94]
Partner physiological regulation	Cortisol daily profile (at ≤1 and 6 months follow-up)	Completed by **partners**; see Measures section for more details.
Partner-infant interaction	Mother-to-Infant-Bonding Scale (MIBS) (121) (at ≤1 and 6 weeks, and 6 months follow-up)	Adapted for partners, **s**ee Measures section for more details
Demographic Information	Partner demographics (at ≤1 and 6 weeks, and 6 months follow-up)	Adapted for partners, **s**ee Measures section for more details
	Infant demographics (at ≤1 and 6 weeks, and 6 months follow-up)	**Mothers** report on their child's weight and height.
Medical data	Breastfeeding diary and questions (at ≤1 and 6 weeks, and 6 months follow-up)	**Mothers** report on breastfeeding in a 2-day daily diary including breastfeeding length and type (exclusive or mixed).

Acceptability and expectancy of the intervention	Self-report questionnaire of satisfaction and acceptability of the intervention (at ≥6 hours following ECS)	On completing the intervention activity, **mothers** complete 7 items to assess intervention fidelity, satisfaction and acceptability of the intervention.
Infant neurodevelopmental vulnerability	Dubowitz neurologic examination (146) (at ≤1 week follow-up)	Examination of the **infant** on 34 items subdivided into 6 categories (tone, tone patterns, reflexes, movements, abnormal signs, and behavior). Full examination by a pediatrician follows standardised instructions and takes 10-15 minutes.

Note. Participant groups for whom the outcome is relevant are highlighted in bold.

Sample size calculation

Based on a previous proof-of-principle RCT (4), a sample size of n = 120 participants is necessary to have 80% power (α = 0.05) to detect a between-group difference of d = 0.30 of the primary outcome (PTSD symptoms at 6 weeks). Furthermore, we calculated the sample sizes necessary to obtain significant group differences with 80% power (α = 0.05) based on small effect sizes (d < 0.30) for maternal secondary outcomes (PTSD diagnosis, ASD symptoms and physiological stress reactivity) and infant secondary outcomes (physiological stress reactivity) based on small effect sizes (d < 0.30) with 80% power (α = 0.05), which range between a total of n = 56 and n = 84. Predicting a 20% drop-out rate, we aim to recruit 144 women.

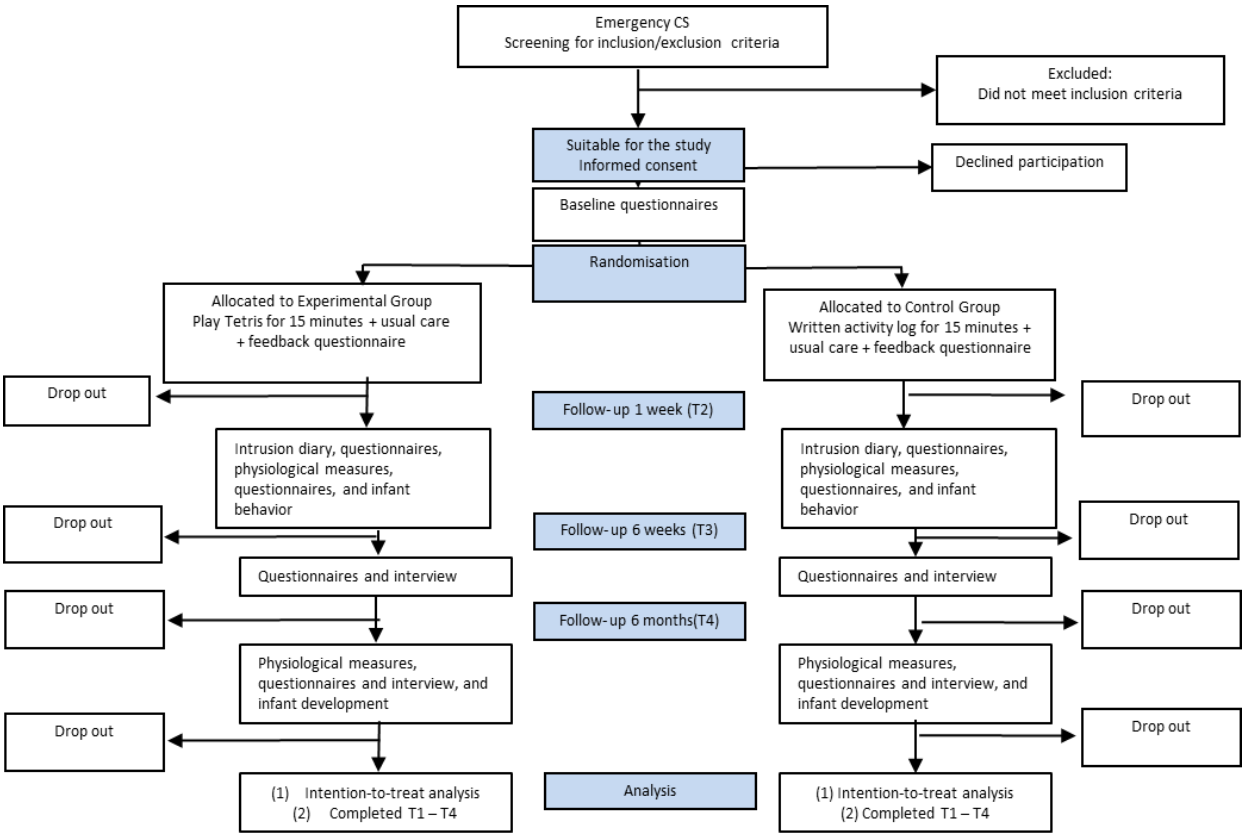

Figure 2. Flowchart of study procedure. ECS, emergency caesarean section.

3. Patient and public involvement

The acceptability of the intervention was assessed by participants during the previous proof-of-principle RCT (4). A questionnaire of satisfaction and acceptability examined the burden of the intervention. An individual feedback and debriefing session will be offered to each participant. Results will be disseminated in written form to the participants and distributed to the public via social media and public events. They will also be discussed with clinical professionals involved in this project.

4. Data management and statistical analyses

All study data will be entered by research staff. Study data will be managed using REDCap electronic data capture tools hosted at Lausanne University Hospital (130, 131). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Double data entry will be done for the primary outcomes. For the rest of the data, a random 5% will be double-checked. Access to the full final trial dataset will be restricted to the principal investigator.

For the primary analyses, group differences regarding the mean subscale and total scores of the PCL-5 and CAPS-5 at 6 weeks will be analysed using separate linear regression analyses. Analyses will be adjusted for recruitment centre and the respective baseline values. Associations between primary outcomes and potential confounders, such as maternal and gestational age, will first be assessed applying univariate tests. Subsequent analyses will be adjusted for significant covariates. For secondary aims, the analyses will be performed for differences in changes between groups and differences between groups at different time points in maternal and infant outcomes. Proportion of participants meeting the diagnostic criteria for PTSD at 6 weeks and 6 months between the two groups will also be compared using logistic regression analyses. The same procedure for identifying significant covariates described above will be applied here. Furthermore, post-hoc exploratory analyses will be conducted but described as such in publications. All regression analyses regarding cortisol data will be adjusted for potential covariates, such as co-sleeping, breastfeeding, menstrual cycle, and infant and maternal medication. For HRV analyses interbeat intervals (IBIs) from baseline, stress task and recovery will be analysed by the extraction from ECG recordings. Statistical parameters of HRV (132) will be calculated using Kubios HRV Analysis 2.2 software (133). Time domain measures and spectral frequency measures will be used for calculations. Multiple imputation methods will be used to manage missing data, if appropriate.

5. Ethical approval

This study protocol was approved by the Human Research Ethics Committee of the Canton de Vaud (Switzerland, study number 2017-02142, protocol version 5 of September 13rd 2019) and is registered in *clinicaltrials.gov* (NCT03576586). Substantial amendments will only be implemented after approval of the ethics committee, and all non-substantial amendments are communicated to the ethics committee within the Annual Safety Report. Participating mothers and, where included, partners will provide their written informed consent before their enrolment in the study by the clinical and research staff. The written informed consent contains an optional part on the re-use of data in ancillary studies. Participation will not interfere with typical care provided to patients after an ECS. The scientific conduct of the study is overseen by an interdisciplinary steering committee of national and international experts. Confidentiality will be ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

Competing interests. None declared.

Author contributions. AH designed the study with input from all co-authors and members of the consortium. VS, ME, YV, NS, NMB, UE, MBG, MMH, KP, DS, SA and EH participated in the design of the study. AH, VS, CD and SS drafted the manuscript. VS, CD, ME, NMB, MBG, SS, EH and AH significantly contributed to the establishment and refinement of study procedures. All authors critically revised the manuscript and approved the final version of the manuscript.

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I. Submitted manuscript of Study 4

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Title: Reducing childbirth-related intrusive memories and PTSD symptoms via a single-session behavioural intervention including a visuospatial task: A proof-of-principle study

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Abstract:

Background. Intrusive memories (IMs) of traumatic events are a key symptom of posttraumatic stress disorder (PTSD), and contribute to its maintenance. This translational proof-of-principle study tested whether a single-session behavioural intervention reduced the number of childbirth-related IMs (CB-IMs) and childbirth-related PTSD (CB-PTSD) symptoms, in women traumatised by childbirth. The intervention was assumed to disrupt trauma memory reconsolidation.

Methods. In this pre-post study, 18 participants, whose traumatic childbirth had occurred two years before, received an intervention combining childbirth-related reminder cues (including the return to maternity unit) with a visuospatial task. They recorded their daily CB-IMs in the two weeks pre-intervention (diary 1), the two weeks post-intervention (diary 2; primary outcome), and in week 5 and 6 post-intervention (diary 3). CB-PTSD symptom severity was assessed five days pre-intervention and one month post-intervention.

Results. Compared to diary 1, 15/18 participants had ≥ 50% fewer CB-IMs in diary 2. The median (*IQR*) reduction of the number of CB-IMs was 81.89% (39.58%) in diary 2, and

persisted in diary 3 (*n* = 17). At one month post-intervention, CB-PTSD symptom severity was reduced by ≥ 50% in 10/18 participants. Of the 8 participants with a CB-PTSD diagnosis pre-intervention, none met diagnostic criteria post-intervention. The intervention was rated as highly acceptable.

Limitations. The design limits the causal interpretation of observed improvements.

Conclusion. This is the first time such a single-session behavioural intervention was tested for old and real-life single-event trauma. The promising results justify a randomized controlled trial, and may be a first step toward an innovative CB-PTSD treatment.

Keywords: Posttraumatic stress disorder; Intervention; Intrusive memories; Memory reconsolidation; Childbirth; Behavior therapy.

Manuscript:

1. Introduction

Intrusive memories (IMs) are repeated, involuntary and distressing sensory-perceptual fragments of a trauma memory (American Psychiatric Association, 2013; Ehlers et al., 2002). They are a core symptom of posttraumatic stress disorder (PTSD) (Iyadurai et al., 2019), a mental health disorder having four main symptom clusters: intrusion (including IMs), avoidance of trauma-related reminders, negative alterations in cognitions and mood, and alteration in arousal and reactivity (American Psychiatric Association, 2013). It is hypothesized that IMs drive other PTSD symptoms (Solberg et al., 2016) and prevent the normative decay of trauma memories (Herz et al., 2020). Thus, targeting them could be a relevant strategy to tackle PTSD symptoms (Iyadurai et al., 2019; Singh et al., 2020).

A leading evidence-based PTSD treatment are trauma-focused cognitive behavioural therapies (National Institute for Health and Care Excellence, 2018), including exposure therapy. Based on extinction learning, exposure therapy does not prevent the return of the trauma-linked fear response (Monfils and Holmes, 2018). Indeed, extinction would produce a new memory trace inhibiting the original fear memory, which still exists and can thus resurface (Bouton, 2004). Therefore, innovative treatments directly targeting the original maladaptive memories would be advantageous.

Memory reconsolidation processes could be the starting point for such treatments. After memory reactivation (MR), triggered by memory reminder cues, memories may enter a transient state of malleability (Agren, 2014; Visser et al., 2018). During this time-dependent window of "memory lability" (Lee et al., 2017), opening within minutes following MR (Agren et al., 2012), memories can reconsolidate unchanged, strengthened, or weakened (Schwabe et al., 2014; Visser et al., 2018), depending on what happens when they were labile. This process has been termed reconsolidation. Although debated (Besnard et al., 2012), the memory reconsolidation hypothesis opens up exciting therapeutic perspectives. Assuming that PTSD results from maladaptive memories and excessive fear learning, reconsolidation-based interventions targeting and weakening the trauma memory could reduce its impact (Elsey and Kindt, 2017). However, translating memory theory and emerging laboratory findings into clinical interventions poses challenges concerning 1) the trauma MR and memory labilisation (ML), and 2) the memory reconsolidation disruption (MRD).

First, MR depends on "boundary conditions" that are assumed to determine whether the memory is only recalled or reactivated-labilised (Treanor et al., 2017). Given that memories of trauma may be harder to labilise (Elsey and Kindt, 2018), boundary conditions such as the reminder cue and context specificity are critical in the clinical context. *Reminder cue specificity* means that the cues used for MR must be close to the original memory, to avoid creating a new memory trace (Debiec et al., 2006). In PTSD, personal narratives provide idiosyncratic and specific reminder cues. *Context specificity*, i.e., being in a context similar to that of the initial trauma environment, could also facilitate MR (Hupbach et al., 2008). However, its translation is challenging: context cues can trigger intense emotions and re-visiting the trauma site may be impossible.

After MR, MRD could be achieved by engaging in a competing visuospatial task, resulting in fewer IMs (James et al., 2015). Indeed, IMs are thought to result from excessive sensory processing during the traumatic event (Brewin and Holmes, 2003), and are predominantly visual (Ehlers et al., 2002), i.e., mental imagery-based (Singh et al., 2020). After trauma ML, engaging in a visuospatial task may take up the visuospatial information processing capacities necessary for memory reconsolidation, particularly of its visual aspects (Andrade et al., 1997; Baddeley and Andrade, 2000; Holmes et al., 2009). Thus, a visuospatial task such as the game Tetris may create a sensory modality-specific interference with the trauma memory reconsolidation, and reduce the number of IMs (Holmes et al., 2009; Holmes et al., 2010). As

an illustration, two randomized controlled trials (RCT) showed that a behavioural intervention including Tetris carried out within *the six first posttraumatic hours*, during the initial memory consolidation, reduced the number of subsequent IMs (Horsch et al., 2017; Iyadurai et al., 2018). Given that intervening in the aftermath of a traumatic event is often impossible, adapting such interventions to propose them years later would be a significant clinical advance.

Encouragingly, three laboratory studies showed that playing Tetris after reactivating the memory of a 24 to 72-hours-old experimental trauma reduced IMs in healthy volunteers (Hagenaars et al., 2017; James et al., 2016; Kessler et al., 2020).On the clinical side, a single case series of patients with complex PTSD tested a multiple-session intervention consisting of describing the content of a specific IM (one per session) and playing Tetris for 25 minutes (Kessler et al., 2018): from pre- to post-intervention, the targeted IM frequency diminished by 64%. Similar improvements were reported in smaller studies (Iyadurai et al., 2020; Kanstrup et al., 2021).

Beyond these preliminary results, many questions remain. First, such interventions have never been tested on memories of single-event real-life traumas that occurred years previously, such as a traumatic childbirth. Yet, single-event traumas have their own memory specificities: rather than targeting IMs in turn, it might be possible to aim for a global MR, drawing on the strong relationship between the different elements of the single trauma memory network (Brewin and Holmes, 2003; Scully et al., 2017). Second, the benefits of this type of intervention on PTSD symptoms other than IMs are unclear. After several sessions, Kessler et al. (2018) reported a 50% PTSD score reduction in half of the participants; however, they had received other trauma-care in parallel. Third, we have little information on the effects of these interventions on the qualitative characteristics of IMs, including their associated distress, nowness (Michael et al., 2005), and sensory modality.

This translational proof-of-principle study tested whether a single-session behavioural intervention can reduce the number of childbirth-related IMs (CB-IMs) and childbirth-related PTSD (CB-PTSD) symptom severity. Indeed, CB-PTSD concerns up to 18.5% of mothers in high-risk samples (Yildiz et al., 2017). The intervention combined brief memory reminder cues of the traumatic childbirth, on the maternity ward where participants had given birth (hypothesised to allow MR), a 10-minute time gap (hypothesised to allow ML) and a Tetris

gameplay procedure (hypothesised to allow MRD). The primary objective of this single-group pre-post study was to assess CB-PTSD symptom changes: compared to pre-intervention, it was expected that 1) the number of CB-IMs would be lower during the first two post-intervention weeks (primary outcome), and that this reduction would persist up to six weeks post-intervention, 2) CB-PTSD symptom severity would be lower at one month post-intervention. The secondary objective concerned intervention acceptability, which was expected to be high. Changes in CB-IMs characteristics between pre- and post-intervention measures, as well as participants' experience and compliance to the procedure, were also described.

2. Methods

2.1. Design and study population

A single group pre-post design was chosen for this proof-of-principle study. At the time of inclusion, participants had given birth to a live baby at the XXXX Hospital more than six weeks ago. They reported having had at least four CB-IMs over the past two weeks, which corresponds to « severe » IMs in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Blake et al., 1995). CB-IMs had to be linked to labour, delivery, or the stay on the maternity ward. Women experiencing unrelated-to-childbirth IMs had to be able to distinguish them from CB-IMs. Exclusion criteria were: maternal or child severe illness, insufficient French-speaking level, established intellectual disability or psychiatric history (e.g., psychotic illness), alcohol abuse, or illegal drug use. Women who had ongoing childbirth-related psychological treatment were not eligible either. To avoid a floor effect, participants who reported less than two CB-IMs in their pre-intervention diary were excluded. The study was approved by the ethics committee for research in humans of the Canton of Vaud (approval number: 2019-01435), and registered on ClinicalTrials.gov before recruitment began (trial number: NCT04286724). All participants provided written informed consent.

2.2. Sample size calculation

Given our experience with the study population (Horsch et al., 2017; Sandoz et al., 2019), we expected women to report approximately 5 (SD = 3) CB-IMs in the pre-intervention diary. Despite the large effect sizes reported in lab studies (James et al., 2015; Kessler et al., 2020),

the sample size calculation was conservative due to the study's exploratory nature. A sample size of *n* = 18 was considered as sufficient to detect a 35% reduction of the number of CB-IMs between diary 1 (pre-intervention) and diary 2 (post-intervention) (80% power; $\alpha = 0.05$) (primary outcome). Expecting a 20% drop-out and 20% exclusion due to less than two CB-IMs in the pre-intervention diary, we intended to recruit 25 participants. Recruitment took place between July 2020 and February 2021, data collection ended in April 2021. Of the *n* = 194 screened women, *n* = 18 received the intervention (Figure 1, next page).

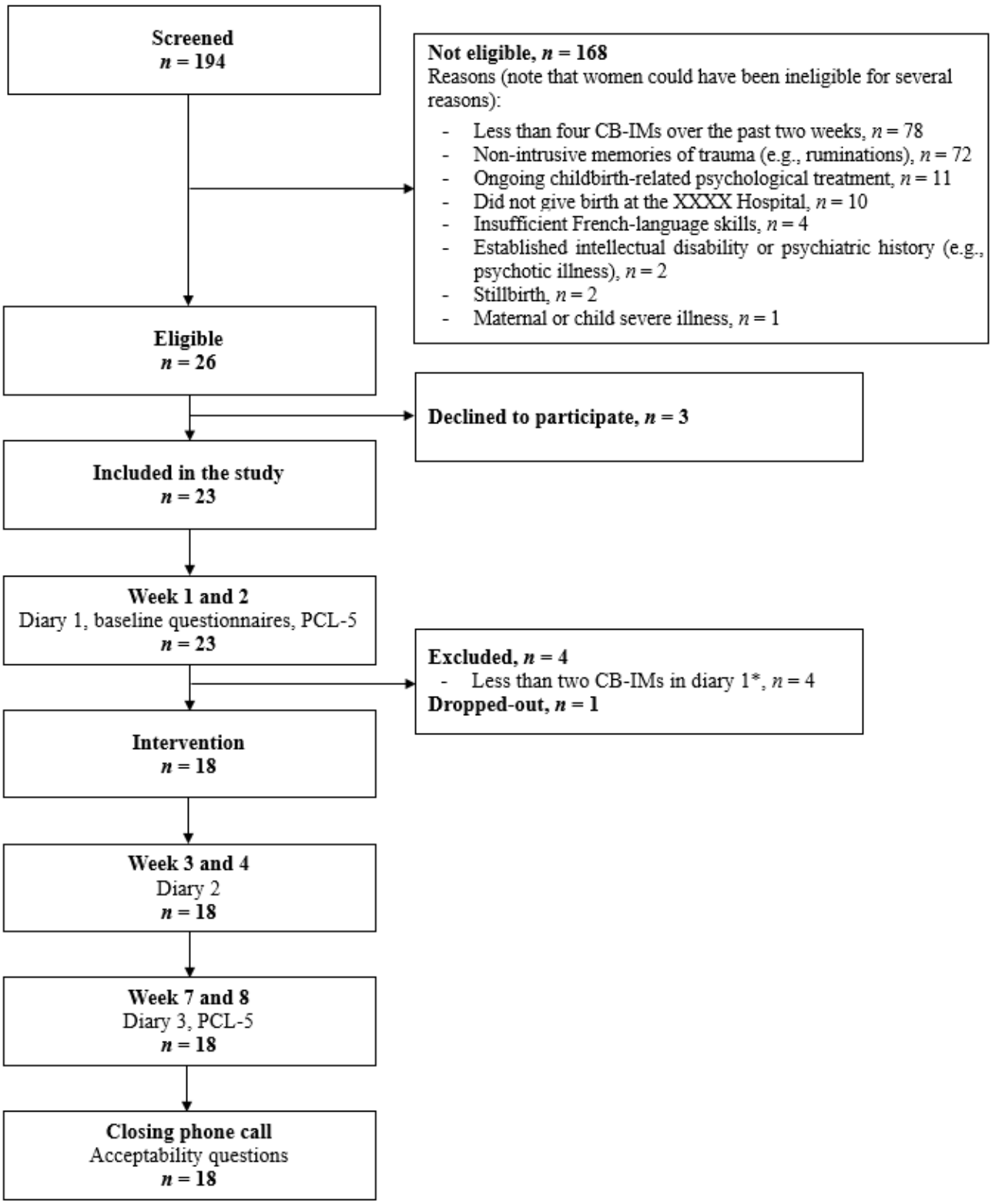

Figure 1. Study flowchart.

Note. CB-IMs = Childbirth-related intrusive memories; PCL-5 = PTSD Checklist for DSM-5.
* If interested, these participants were still offered the intervention. Their data were not analysed.

2.3. Measures

Childbirth-related intrusive memories were daily self-reported in 14-day diaries, spanning the two pre-intervention weeks (diary 1), the first and second post-intervention weeks (diary 2), and the fifth and sixth post-intervention weeks (diary 3). Participants were instructed to briefly describe the content of each CB-IM, defined to them as "*involuntary memories in relation to the labor and birth of your child, that pop into your mind without warning*" (see Horsch et al. (2017) for the full instructions). Participants ticked a "no memory" box on days when they had not had any CB-IM. Each diary ended with a diary compliance question ("*To what extent were you able to report your intrusions in the diary?"*), which was answered on a 10-point scale from 1 (*not capable at all*), to 10 (*extremely capable*). For each CB-IM, participants also reported its associated distress, nowness, and sensory modalities (Supplementary Material, section 1).

Childbirth-related PTSD symptoms were self-reported in the PTSD Checklist for DSM-5 (PCL-5) (Blevins et al., 2015), which contains 20 items assessing PTSD symptoms over the past month, on a five-point scale from 0 (*not at all*) to 4 (*extremely*). Items rated ≥ 2 reflect present symptoms. The PCL-5 allows to calculate a total severity score (range 0–80) and the four symptom cluster scores; higher scores indicate more severe symptoms. Participants were instructed to complete it in relation to the childbirth. The PCL-5 French version has good psychometric properties (Ashbaugh et al., 2016). For this study, Cronbach's α were .865 pre-intervention and .856 post-intervention.

Participants' experience during the intervention. Ten times during the intervention (Figure 2), participants orally reported their emotional arousal using a 10-point visual analogue scale (VAS) ranging from 1 (*not stressed and/or anxious at all*) to 10 (*extremely stressed and/or anxious*). At the end of the putative MR phase, participants rated their childbirth memory vividness from 0% (*not at all vivid/intense memory*) to 100% (*extremely vivid/intense memory*) and the reminder cue specificity (boundary condition 1) (*"To what extent did you narrate your childbirth in a way that is faithful to your actual childbirth experience? (In other words, is what you have told similar to your experience, or is it very different?)"* on a 10-point scale from 1 (*not faithful at all/does not correspond at all*) to 10 (*extremely faithful/completely corresponds*)). After playing Tetris, they rated Tetris difficulty on 10-point scale from 1 (*very easy*) to 10 (*very difficult*). At the end of diary 2, participants answered a context specificity question (boundary condition 2) *("How much did the maternity ward remind you of your*

childbirth?") on a 10-point scale from 1 (*not at all*) to 10 (*very strongly*). They were also invited to explain their ratings regarding the two boundary condition questions. Participants completed this questionnaire 14 days post-intervention to avoid interference with the memory reactivation-reconsolidation processes. Finally, during the last study phone call, participants indicated to what extend they expected their number of CB-IMs to change following the intervention, on a 21-point scale from -10 (*extremely decrease*) to 10 (*extremely increase*).

Intervention acceptability was assessed on a 10-point scale from 1 (*not at all acceptable*) to 10 (*extremely acceptable*). Participants were also asked whether they would be willing to participate in a second session if the intervention was scientifically proven to be useful; and to what extend they would recommend it to a friend, on a 10-point scale from 1 (*no, not at all*) to 10 (*yes, absolutely*).

Depression symptoms were self-reported on the 10-item Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). EPDS items are scored on a four-point scale, from 0 to 3, higher total scores (range 0−30) reflect more severe symptoms. The clinical cut-off of the French version, which has good psychometric properties, is 10.5 (Guedeney and Fermanian, 1998). In this study, the Cronbach 's α was .838.

Sociodemographic characteristics. Participants' age, nationality, marital status, and education were self-reported.

Mental health history. Participants reported whether they had already received any psychological treatment linked with their traumatic childbirth experience and, if yes, of which type. They also indicated if they had ever experienced a traumatic event.

Obstetric and neonatal characteristics, including parity, information concerning the childbirth (date, mode of delivery, pregnancy type) and the neonate (Apgar scores, birth weight, gestational age) were retrieved from hospital birth records.

2.4. Recruitment and screening

Flyers advertising the study were displayed in places eligible women could frequent (e.g., nurseries). The study psychologist (CD) also contacted participants of completed observational studies of our research group, who had consented to be contacted concerning other studies.

Eligibility was screened by telephone by the study psychologist. The number of CB-IMs was assessed the CAPS-5 (item B1) (Blake et al., 1995). Alcohol abuse was screened using the T-ACE questionnaire (Sokol et al., 1989), the other criteria were assessed with single-items. Women knew that the intervention would take place at the XXXX Hospital and comprise a childbirth evocation followed by a "*computerized task*". Non-eligible/non-interested women received a list of organisations who could support them concerning their childbirth experience. Their screening data were destroyed.

2.5. Study procedure

2.5.1. Pre-intervention

To situate the sample, participants completed the online baseline questionnaires (EPDS, sociodemographic, and mental health history questionnaires) on day 1 of diary 1. CB-PTSD symptoms were measured online five days pre-intervention (i.e., close to the intervention day, but not on the same day, to avoid interference with the trauma-related memory processes). In the meantime, participants completed diary 1 during the 14 pre-intervention days.

2.5.2. Intervention

On the 15th day, participants individually met the study psychologist in a neutral office of an administrative building, at the hospital (Figure 2). They brought diary 1.

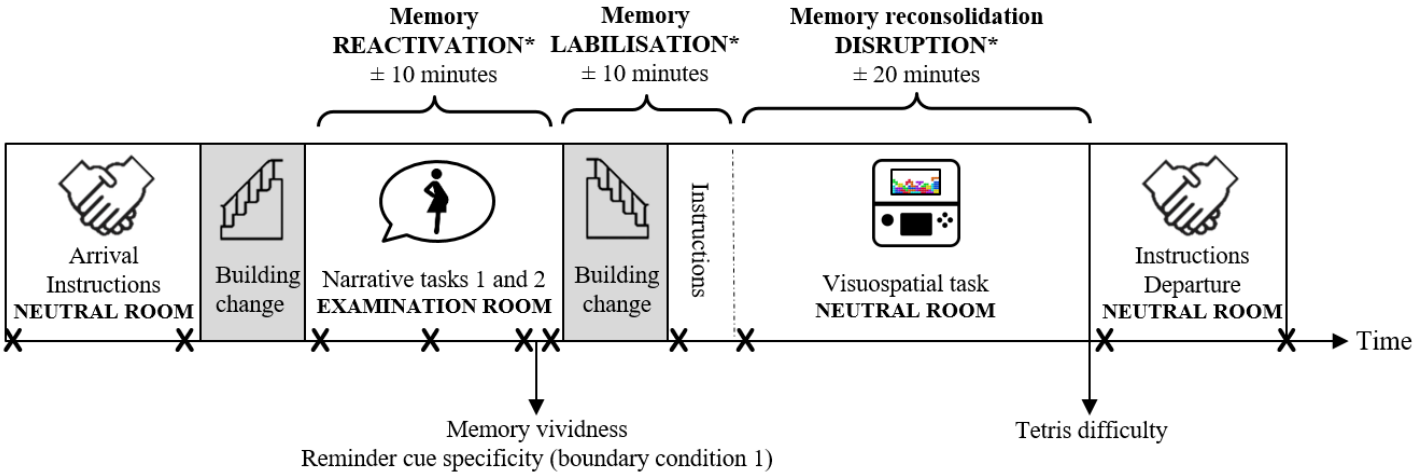

Figure 2. Schematic overview of the intervention procedure.

Note. Black crosses indicate an oral measure of emotional arousal with a 10-point visual analogue scale (VAS) ranging from 1 (*not stressed and/or anxious at all*) to 10 (*extremely stressed and/or anxious*). Details of each emotional arousal rating throughout the intervention is available in Supplementary Material, section 2.1.2.

* Memory processes supposedly involved.

Assumed MR phase: After receiving detailed intervention-related information, participants went, with the psychologist, to a gynecological examination room of the maternity ward, which was in a separate building. Reaching this room implied to walk past the delivery suite, and to cross the postpartum unit where they had been hospitalized. In the examination room, participants were asked to orally narrate their childbirth in 5-7 minutes, in chronological order, focusing on its unfolding rather than going into details (narrative task 1). The psychologist only intervened to ensure that participants recounted their entire childbirth within the allocated time (e.g., "*What happened next?*"). Following the same procedure, participants then narrated, during 3-5 minutes, the moment corresponding to the most frequent CB-IM of diary 1 in more detail (narrative task 2). After that, the childbirth was no longer discussed. Participants rated memory vividness and reminder cue specificity and returned, with the psychologist, to the neutral office.

Assumed ML phase: Because of the distance between the two buildings, ten minutes elapsed between the end of the narrative tasks and the beginning of Tetris, thus supposedly allowing for ML.

Assumed MRD phase: Participants were instructed to play Tetris ("Marathon" mode, sound and 3D switched off) according to the instructions detailed in Horsch et al. (2017). After a three-minute practice run, they played for 20 minutes. Before leaving, participants rated Tetris difficulty and were instructed not to play Tetris or seek information about its use in a healthcare context.

2.5.3. Post-intervention

Participants completed diary 2 during the first 14 post-interventions days. At one month post-intervention, participants reported their CB-PTSD symptoms online again, and started completing diary 3 for the next 14 days. The study ended with an audio-recorded phone call. At first, a neutral research assistant asked participants the acceptability questions and checked that they had not received another childbirth-related psychological treatment, played Tetris since the intervention, or researched its therapeutic use. Finally, the study psychologist provided explanations regarding the study and discussed the participants' CB-PTSD symptom changes. Participants received a contact list in case they needed further professional help.

2.6. Data analysis

Two-tailed tests and an alpha level of .05 were used for statistical tests. The choice of parametric or non-parametric tests depended on whether the appropriate statistical assumptions were met or not. Descriptive statistics of continuous data are mean and standard deviation, or median and interquartile range (*IQR*) if the data were not normally distributed according to a Shapiro-Wilk test. Analyses were carried out with IBM SPSS version 27; except for the Wilcoxon signed-rank tests, the McNemar test, and Figure 3, which were generated with R version 4.0.5 (R Core Team, 2021). Data are available from the open access repository Zenodo [Link will become live after acceptance].

Differences in the number of CB-IMs across the three diaries were investigated with a Friedman test. Wilcoxon signed-rank tests with a Bonferroni correction were used for *post-hoc* pairwise comparisons, including between diary 1 and 2 (primary study outcome). Effect sizes were computed using the following formula: $r = Z/\sqrt{N}$ (N = total number of pairs) (Kassambara, 2021) (r interpretation: -0.1 = small; -0.3 = moderate; -0.5 = large effect size)

(Fritz et al., 2012). Confidence intervals were calculated using bootstrapping on 1,000 samples. The same approach was used to inspect differences in diary compliance. Changes in CB-IMs characteristics are reported in Supplementary Material, section 1.

Differences between pre- and post-intervention CB-PTSD symptoms (total severity and each symptom cluster score) were analysed with paired *t*-tests. Effect sizes were estimated with Hedges' *g* (interpretation: 0.2 = small; 0.5 = moderate; 0.8 = large effect size) (Lakens, 2013). The evolution of the number of participants meeting the CB-PTSD diagnostic criteria was examined *post-hoc*, with a McNemar's test with continuity correction.

The number of participants showing more than a 50% reduction of their CB-IMs or total CB-PTSD symptom severity between pre- and post-intervention measurement was reported, as this conservative criterion is one way to quantify the proportion of participants responding to an intervention (Kessler et al., 2018). To illustrate the results, some participants' quotes are reported in Supplementary Material, section 2.

A research assistant uninvolved in data collection checked 100% of the data for accuracy for the primary analysis of CB-IMs, and a randomly selected 50% of data for all other analyses. There was no missing data. Participants reported 360 diary entries. Two trained psychologists, who were uninvolved in data collection and blind to diary time points, independently checked the content of all entries to detect non-compliance with diary instructions. They reached a 100% agreement. Ten diary entries were excluded from the analyses for one of the following reasons: 1) unrelated to the childbirth (three entries, $n = 3$), 2) not IM (e.g., unequivocally a verbal rumination) (two entries, $n = 2$), 3) provoked by a new traumatic experience involving a life threat to oneself or the child (five entries, $n = 1$). Analyses were thus carried out on 350 CB-IMs (e.g., *"when he was born, not breathing"* (P14), *"the team arrives in a hurry. I am losing a lot of blood and I don't understand anything"* (P08)).

One participant, who will henceforth be referred to as "P18", did not comply with the intervention instructions. She stated that she intentionally did not immerse herself in her childbirth memory and that her narratives were not faithful to her actual experience (5 out 10 on the reminder cue specificity question). She was the only participant whose response to this question was an extreme outlier, defined as being more than three *IQR* above quartile 3 (*Group Mdn* = 9.50; *IQR* = 1). She wrote that, during the narrative tasks, she "*developed the*

same avoidance strategies as with the flashbacks" and thus that what she narrated *"was only very mildly faithful to* [her] *real experience*". Because the procedure was not correctly followed, P18 was excluded from the analyses. Except for the sample description (Table 1), her data are reported and discussed separately (Supplementary Material, section 3).

3. Results

3.1. Characteristics of the study sample

At the time of the intervention, the childbirth had occurred between seven months and 6.9 years earlier (*Mdn* = 2.01 years, *IQR* = 2.23). Participants were Swiss or from another European country, and mostly in a relationship (Table 1). Eight participants met the diagnostic criteria for CB-PTSD; the mean depression score was above the clinical cut-off. Four participants had received a psychological treatment addressing their traumatic childbirth experience. Three had received psychotherapy (one of whom received Eye Movement Desensitization and Reprocessing), one had received both pharmaco- and psychotherapy.

Table 1. Sociodemographic, obstetrical, neonatal, and mental health characteristics of the study sample (*n* = 18).

Sample characteristics	**Frequency (%)**	**Median (*IQR*) or Mean (*SD*)[a]**
Sociodemographic characteristics at the time of the intervention		
Age (years)		33.55 (6.35)△
Time since traumatic childbirth (years)		2.01 (2.23)
Nationality		
Swiss	12 (66.67)	
Other European	6 (33.33)	
Education		
Secondary/high school	1 (5.56)	
Apprenticeship	7 (38.89)	
University	10 (55.55)	
Marital status		
Married or cohabiting	17 (94.44)	
Single	1 (5.56)	
Obstetrical variables		
Parity		
Nulliparous	13 (72.22)	
Parous	5 (27.78)	
Mode of delivery		
Non instrumental vaginal delivery	6 (33.33)	
Vacuum or forceps-assisted delivery	4 (22.22)	
Planned caesarean section	1 (5.56)	
Emergency caesarean section	7 (38.89)	
Gestational age (weeks)		39.42 (2.46)
Pregnancy type		
Single	16 (88.89)	
Multiple	2 (11.11)	
Neonatal variables[b]		
Apgar score		
Apgar score 1 minutes		9 (3)
Apgar score 5 minutes		9 (1)
Birth weight (grams)		3,125 (858)
Mental health variables before intervention		
Prior psychological trauma	8 (44.4)	
Depression symptoms (EPDS score)		10.67 (4.63)△
Probable depression[c]	8 (44.44)	
CB-PTSD symptom severity (PCL-5 score)		27.89 (12.14)△
CB-PTSD diagnostic criteria[d]	8 (44.44)	
Previously received a psychological treatment addressing their traumatic childbirth experience	4 (22.22)	

Note. EPDS = Edinburgh Postnatal Depression Scale (range 0–30); CB-PTSD = Childbirth-related posttraumatic stress disorder; PCL-5 = PTSD Checklist for DSM-5 (range 0–80).

[a] Median and interquartile ranges are reported if the data did not follow a normal distribution according to a Shapiro-Wilk test.
△ Reported values are a mean and standard deviation.
[b] In case of multiple pregnancy, data of the firstborn child was used.
[c] EPDS score > 10.5.
[d] At least one intrusion, one avoidance, two negative alteration in cognitions and mood, and two alterations in arousal and reactivity symptoms reported on PCL-5.

3.2. Intervention characteristics and participants' compliance to instructions

The median duration of the assumed MR and MRD phases were 10 and 20 minutes, respectively (Supplementary Material, Table S1). Participants' median (*IQR*) emotional arousal rating was 5.75/10 (2.38) during the assumed MR phase (VAS3 to 6, Figure 2), and 2/10 (1) at the beginning and the end of the appointment. Participants' median rating of their childbirth memory vividness was 80% (15). They reported that their narratives were extremely faithful to their actual childbirth experience (*Mdn* = 10/10, *IQR* = 1) (reminder cue specificity, boundary condition 1), and that the maternity ward strongly reminded them of their childbirth (*Mdn* = 9/10, *IQR* = 3) (context specificity, boundary condition 2). This was reflected in their comments (Supplementary Material, section 2.1). The median rating of Tetris difficulty was 2/10 (2). Participants did not expect their number of CB-IMs to change following the intervention (*M* = -0.29, *SD* = 4.71).

3.3. Number of CB-IMs

Diary compliance was high and stable across diaries, $\chi^2(2) = 1.064$, $p = .587$. The median (*IQR*) was 8/10 (3) in diary 1, 9/10 (4) in diary 2 and 9/10 (4) in diary 3. The median number of CB-IMs was 11 (6) in diary 1, 2 (4) in diary 2 and 2 (3) in diary 3 (Figure 3). It significantly differed between the diaries, $\chi^2(2) = 26.548$, $p < .001$. Participants reported fewer IMs in diary 2 *vs.* diary 1, $Z = -3.500$, $p < .001$, and in diary 3 *vs.* diary 1, $Z = -3.600$, $p < .001$. Effect sizes were large, $r = -0.849$ [95%*CI*: -0.841, -0.851] and $r = -0.873$ [95%*CI*: -0.868, -0.875], respectively. There was no difference between diary 2 and 3, $Z = -0.950$, $p = .342$.

The median (*IQR*) reduction of the number of CB-IMs was 81.89% (39.58) in diary 2 *vs*. diary 1, and 76.92% (28.99) in diary 3 *vs*. diary 1. Overall, 15/17 participants reported a reduction

of more than 50% in their number of CB-IMs between diary 1 and 2, and 16 between diary 1 and 3 (see Supplementary Material section 2 for participants' comments and their day-to-day CB-IMs).

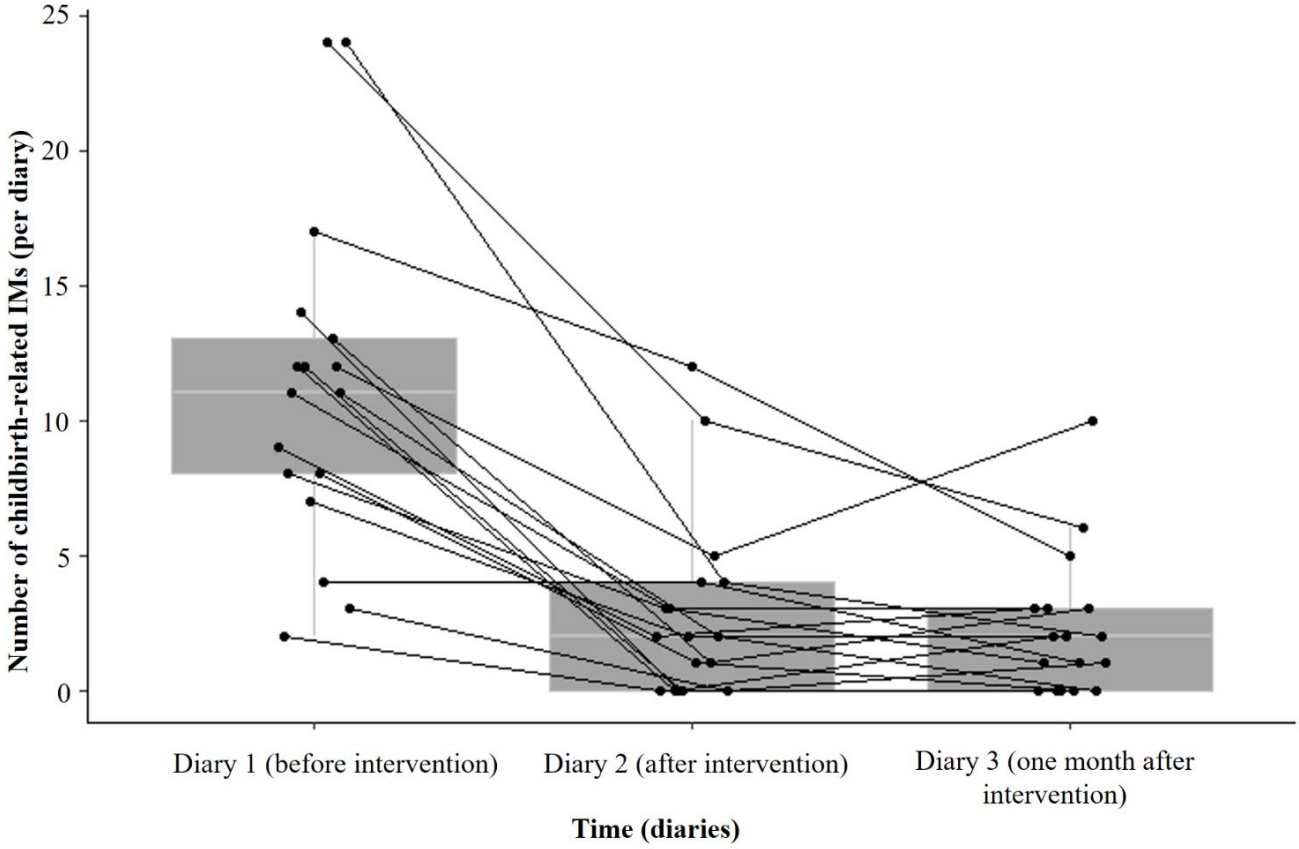

Figure 3. Number of childbirth-related intrusive memories (IMs) across the diaries (n = 17).

Note. Black lines correspond to individual trajectories (n = 17). Diary 1 covered the 14 days before the intervention, diary 2 covered the 14 days following the intervention, and diary 3 covered 14 days from one month post-intervention (i.e., the 5th and 6th post-intervention weeks). Box plots represent group medians and interquartile ranges.

3.4. CB-PTSD symptoms

Total CB-PTSD symptom severity was, on average, reduced by 56.76% (SD = 28.97) (p < .001; Table 2, Figure 4) between five days pre-intervention and one month post-intervention, and the four symptom cluster scores also decreased. All effect sizes were large (Hedge's g > .8). A 50% reduction of CB-PTSD total symptom severity was observed in 10/17 participants. Significantly fewer participants met CB-PTSD diagnostic criteria after the intervention (n = 0 (0%)), than before (n = 8 (47.06%)), p = .013 (see Table 1 for details about CB-PTSD diagnostic

criteria with the PCL-5). Some reported that they were no longer afraid to become pregnant again, or that their everyday life had improved (Supplementary Material, section 2.3).

Table 2. Comparisons between childbirth-related PTSD symptoms five days before and one month after the intervention (n = 17).

	Before intervention Mean (*SD*)	**After intervention Mean (*SD*)**	***t*(16)**	***g***	**95% *CI* for *g***	***p***
Total severity score	28.71 (12)	12.29 (8.84)	6.190***	1.466	0.771, 2.140	< .001
Intrusion symptom cluster score[a]	7.53 (3.47)	2.71 (3.22)	5.705***	1.351	0.684, 1.997	< .001
Avoidance symptom cluster score[b]	3.71 (2.26)	1.59 (1.91)	3.960**	0.938	0.363, 1.493	.001
Negative alteration in cognitions and mood symptom cluster score[c]	9.41 (5.36)	3.76 (3.07)	5.159***	1.222	0.585, 1.837	< .001
Alteration in arousal and reactivity symptom cluster score[d]	8.06 (4.26)	4.24 (3.68)	3.378**	.800	0.251, 1.330	.004

Note. Symptoms were measured with the PTSD Checklist for DSM-5 (adapted for childbirth) (PCL-5) (range 0–80).

[a] PCL-5 intrusion subscale (5 items; range 0–20).
[b] PCL-5 avoidance subscale (2 items; range 0–8).
[c] PCL-5 negative alteration in cognitions and mood subscale (7 items; range 0–28).
[d] PCL-5 alteration in arousal and reactivity subscale (6 items; range 0–24).

* $p < .05$
** $p < .01$
*** $p < .001$

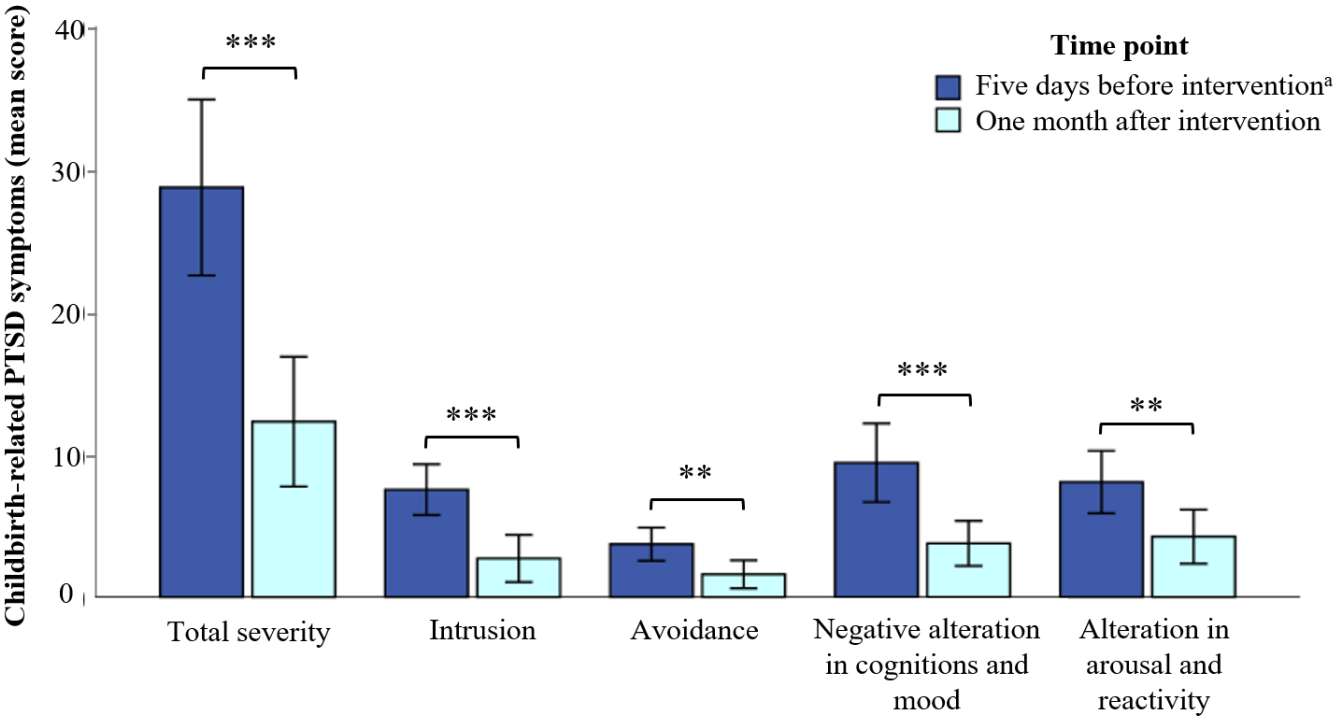

Figure 4. Mean scores of childbirth-related PTSD symptoms five days before and one month after the intervention (n = 17).

Note. Asterisks indicate statistical differences (* p < .05, ** p < .01, *** p < .001). Black bars represent 95% *CI*.

[a] Childbirth-related PTSD symptoms were firstly measured five days before the intervention, i.e., close to the intervention day, but not on the same day, to avoid interference with the trauma-related memory processes.

3.5. Intervention acceptability

The median rating of intervention acceptability was 9/10 (3). If scientifically proven to be useful, participants would recommend the intervention to a friend at 10/10 (*IQR* = 1), and 100% of them would have been willing to participate in a second session.

4. Discussion

In this translational single-group pre-post study, participants traumatised by childbirth received a brief, single-session behavioural intervention, which combined real-life memory reminders with a visuospatial task. Compared to the two weeks pre-intervention, 15/18 participants had at least 50% fewer CB-IMs during the first two post-intervention weeks, and this large reduction persisted up to six weeks post-intervention. Furthermore, compared to

baseline levels, the total CB-PTSD symptom severity and each of the four symptom clusters were largely reduced at one month post-intervention. Thus, the intervention appeared to successfully reduce CB-PTSD symptoms in participants, despite high depression symptoms at baseline and a history of unsuccessful pharmaco- or psychotherapy for some of them. The intervention was unanimously rated as very acceptable, and participants would strongly recommend it. In light of these results, this study could be a promising step toward a brief, simple and low-cost evidence-based clinical intervention for CB-PTSD symptom reduction.

A unique feature of this intervention was the participants' *in vivo* return to the trauma context during the putative MR phase. Unlike still images (Hagenaars et al., 2017) or written narratives (Kessler et al., 2018), the reminder cues were multi-sensory (e.g., hospital smell, newborn crying) and highly immersive (Supplementary Material, section 2.1). Combined with the brief recount of the whole birth, this return likely facilitated a global reactivation of the childbirth memory (Debiec et al., 2013), rather than of a particular memory hotspot, like in Kessler et al. (2018). Participants' ratings suggested that both the context specificity and the reminder cue specificity boundary conditions were met. Importantly, the reminder cue specificity question allowed to identify the participant who did not follow the instructions.

Some findings were unexpected. For example, CB-IMs with a visual component did not appear to reduce more than non-visual CB-IMs after the intervention (Supplementary Material, section 1.1). Yet, assuming that a visuospatial task would specifically interfere with the reconsolidation of visual aspects of memory, one would expect this to be the case. Thus, Tetris may induce a more global engagement of memory resources - not just visual ones. The momentary increase of P18's CB-IMs also deserves comment. The data suggested that her trauma MR failed due to non-compliance with the instructions. Further discussion and suggestions to avoid this outcome are available in Supplementary Material, section 3. Future studies should consider measures that would allow all participants to follow the instructions.

Importantly, the reduction of CB-PTSD symptoms, in line with our hypotheses, is insufficient to confirm that memory reactivation-reconsolidation processes actually took place during the intervention. Indeed, the latter are not measurable in such clinical interventions (Visser et al., 2018). It is therefore possible that separate or additional mechanisms have led to the observed improvements. For instance, even though participants did not anticipate a CB-IMs reduction, the intervention benefits may have been accentuated by positive expectations

linked to help-seeking. Narrating the childbirth, returning to the trauma context, or monitoring the CB-IMs may in itself have had therapeutic properties. While it was not the current study's objective, studying the underlying mechanisms would be necessary to improve the intervention.

4.1. Strengths and limitations

To our knowledge, this is the first reconsolidation-based intervention involving a visuospatial task to target IMs linked with an old and single-event real-life event. It includes innovative and theory-driven adaptations, such as the single-session format and the use of trauma context. Daily measurement of CB-IMs for six weeks allowed for a detailed assessment of the trajectory of participants' symptomatology over the weeks. Furthermore, the study was conducted rigorously, as indicated by the study registration prior to recruitment, no post-intervention drop-out, and no missing data.

However, this study has several limitations, the first of which is inherent in its design: the comparison of pre- and post-intervention measures does not allow to affirm that the observed improvements were caused by the intervention. CB-IMs may have spontaneously declined over time, although this seems unlikely, given that participants had given birth several years earlier (see Soderquist et al., 2006) and that some of them had unsuccessfully engaged in prior pharmaco- or psychotherapy. Despite the design's shortcomings, it seemed the most appropriate for this proof-of-principle study: in the absence of preliminary data, an RCT design would not have been resource-efficient.

Furthermore, given that the sample size was calculated to assess the reduction in the number of CB-IMs, it was insufficient for complementary analyses that could have provided some insights into the intervention mechanisms and potential improvement (e.g., the relationship between high emotional arousal during the narrative tasks and CB-PTSD symptom reduction). The daily reporting of CB-IMs also has limitations because participants may have been more attentive than usual to their CB-IMs, thus increasing their perceived number. Moreover, seeing the diary at home may have triggered additional CB-IMs.

4.2. Perspectives and future studies

The results of this study warrant a RCT, which would incorporate a clinical interview in addition to self-report questionnaires for CB-PTSD symptom assessment. Such an RCT could also examine if the number of pre-intervention CB-IMs is a predictor of overall CB-PTSD symptom reduction. If not, the intervention might be suitable to help-seeking parents suffering from CB-PTSD symptoms but having rare CB-IMs (as it was the case of 78 women screened for this study). Beyond the perinatal context, this intervention may apply to other trauma types, such as healthcare professionals (Singh et al., 2021), whose PTSD prevalence is 21.5% during the COVID-19 pandemic (Marvaldi et al., 2021).

Another critical step would be to identify which elements of the trauma context, including potential mismatches with the remembered place (Fernandez et al., 2016), are important to trigger MR. In the case of CB-PTSD, for example, returning to any maternity ward may be sufficient, which would make the intervention more widely accessible. Identifying the most decisive context-related cues could help to make the intervention available when the trauma context cannot be visited, by reproducing only these particular elements (e.g., with virtual reality). By reducing reminder cues to a minimum, the procedure may also become easier to handle for patients.

5. Conclusion

This translational proof-of-principle intervention study provides preliminary evidence that a brief behavioural intervention can reduce CB-PTSD symptoms following a traumatic childbirth. It is a first step toward the development of a single-session and low-cost evidence-based intervention, enabling durable treatment of (CB-)PTSD symptoms. Future studies are necessary to follow up on these promising results, using more sophisticated designs and larger sample sizes.

Declaration of interest. None.

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approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work. A. Horsch is the PhD supervisor of C. Deforges.

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J. Submitted manuscript of Study 4 (Supplementary material)

1. Changes in the characteristics of childbirth-related intrusive memories (CB-IMs) across the diaries

For each CB-IM, participants reported its associated distress and nowness (Hackmann et al., 2004), as well as its sensory modalities. Changes in CB-IMs characteristics across the diaries were inspected on an exploratory basis. Because several participants had no further CB-IM after the intervention, it should be noted that CB-IMs characteristics were examined on a subsample of the 10 participants who had CB-IMs in both diary 2 and 3.

1.1. CB-IMs sensory modality

Rationale: The reason why a task such as Tetris would reduce the number of IMs is still debated. It has been suggested that this visuospatial task specifically taxes the visuospatial working memory (Lau-Zhu et al., 2017) and therefore interferes with the (re)consolidation of the visual aspects of memories. Thus, it would be suitable for targeting IMs (Holmes et al., 2009), since they are primarily visual (Ehlers et al., 2002). Whether tested during the consolidation or reconsolidation window, some laboratory studies showed that a visuospatial task was indeed more efficient than a verbal or narrative task (Deeprose et al., 2012; Kessler et al., 2020), and even that verbal tasks could increase subsequent IMs (Bourne et al., 2010; Holmes et al., 2010). However, the fact that verbal tasks can also be effective (Hagenaars et al., 2017; Krans et al., 2009) challenges this hypothesis. Overall, there is mixed evidence and the question of the mechanisms of Tetris is still unresolved (Meyer et al., 2020). If the underlying mechanisms of Tetris are sensory modality-specific, one would expect IMs with a visual component to respond more to the intervention than non-visual ones.

Method and analysis: For each CB-IM, participants reported its sensorial modalities (visual, auditory, gustatory, olfactive, proprioceptive, tactile, nociceptive). CB-IMs were then recoded as 1 if they had a visual component (i.e., at least one of the sensory modality was visual) and 0 if not. This analysis was conducted on 211 CB-IMs, corresponding to the total number of CB-IMs reported by the 10 participants who had CB-IMs in diary 2 and 3. Poisson generalized

linear mixed-effects models, taking participants as the random effect, were used to examine the moderation effect of the type of CB-IMs (with *vs.* without a visual component) on the change of the number of CB-IMs over the diaries.

Results: The type of CB-IMs did not moderate the reduction of the number of CB-IMs across the diaries, as the interaction terms (type of CB-IMs x diary) were not significant (diaries 1-2: β = .370, *SE* = 0.404, *p* = .360; diaries 1-3: β = .914, *SE* = 0.516, *p* = .077; diaries 2-3: β = .544, *SE* = 0.592 *p* = .359). This means that, following the intervention, CB-IMs with a visual component did not decrease significantly more than CB-IMs without a visual component. There were 71.31% (92/129 CB-IMs) of CB-IMs with a visual component in diary 1, 78.26% (36/46) in diary 2 and 86.11% (31/36) in diary 3. For comparison, participants who reported no CB-IMs in at least one of the post-intervention diaries (*n* = 7) had 59.68% (37/62) of CB-IMs with a visual component in diary 1.

Comment: Although they should be interpreted with caution due to the small sample size, these results are not in line with the sensory modality specificity hypothesis. In this respect, two specificities of the study are worth noting. First, as detailed in the discussion, the putative memory reactivation (MR) phase is *in vivo*, i.e. multi-sensory and highly immersive due to the return to the maternity ward. Second, childbirth is a multi-sensory event, involving numerous bodily sensations, as reflected in the CB-IMs, e.g., « *Sensation of the blade in the lower abdomen, during the cesarean* » (P05), « *I am suffocating in the oxygen mask* » (P12), « *Feeling cold when lying on the table* » (P05). Nevertheless, even if non-visual hotspots are reactivated, the sensory modality specificity hypothesis would have predicted that their reconsolidation would be insensitive to the disruption caused by a visuospatial task.

Comparison with the results obtained in the above-mentioned studies is difficult, as most of them were laboratory studies, and the initial trauma and reminder cues were images or scenes displayed on a screen. The evolution of the sensory modalities of the IMs after (re)consolidation-based interventions should therefore also be explored in larger clinical studies, following real-life traumatic events. Note that this measurement may be difficult to carry out, because it can be laborious and distressing to report all the sensory modalities of an IM. As an illustration, (Kanstrup et al., 2021) were not able collect such data, because the measure was poorly understood by participants, which calls for a cautious interpretation of our own data.

In the laboratory, it would be helpful to encourage participants to report all sensory modalities of the IMs, as some studies seem to have solely focused on *image*-based memories (Kessler et al., 2020). Furthermore, it would be interesting to test the sensory modality specificity hypothesis by testing such visuospatial tasks-based interventions on non-visual experimental trauma, for instance by replacing the trauma film with a trauma podcast.

1.2. IMs-related distress

Rationale: IMs are defined as distressing in the Diagnostic and Statistical Manual of Mental Disorders DSM-5 (American Psychiatric Association, 2013). IMs-related distress has been found to predict concurrent and subsequent PTSD symptom severity (Michael et al., 2005). However, to our knowledge, reconsolidation-based interventions involving a visuospatial task mainly focused on the number of IMs, and did not examine the evolution of IMs-related distress.

Method: For each CB-IM, participants rated its associated distress on a 10-point scale from 1 (*not distressing at all*) to 10 (*extremely distressing*). When CB-IM-related distress was rated one, the study psychologist checked during the closing study phone call whether the CB-IM was not a positive memory – this was never the case. As only 10 participants had CB-IMs in their post-intervention diaries, no statistical analysis was carried out but descriptive scores are reported.

Results: Mean CB-IM-related distress ratings for these 10 participants were 4.80 (*SD* = 1.34) in diary 1, 4.16 (*SD* = 1.79) in diary 2, and 4.59 (*SD* = 2.09) in diary 3. For comparison, the mean CB-IM-related distress rating in participants who reported no CB-IMs in at least one of the two post-intervention diaries (*n* = 7) was 3.73 (*SD* = 1.95) in diary 1.

Comment: Distress ratings do not appear to decrease between pre- and post-intervention, but this cannot be confirmed due to the small sample size, which does not allow for statistical comparison. Future studies may hopefully complete our observation. If no IM-related distress reduction was found in other samples, it would suggest that the intervention affects the quantity rather than the quality of IMs, despite the fact that some participants reported that their CB-IMs were less emotionally difficult to manage (see section 2.2 below).

1.3. IMs-related nowness

Rationale: IMs are often associated with a sense of "nowness" (e.g., Hackmann et al. (2004)), which corresponds to the impression that the sensations experienced during the traumatic event are happening "here and now", in the present. Michael et al. (2005) found that IMs-related nowness were a unique predictor of both concurrent and subsequent PTSD symptom severity (but see also Kleim et al., 2013). Therefore, it is important to determine whether the intervention presented in this work can also decrease the feeling of nowness associated with IMs.

Method: For each CB-IM, participants reported to what extend they had the "*impression that the memory was happening here and now*" on a 10-point scale ranging from 1 *(not at all*) to 10 (*extremely*). Since only 10 participants had CB-IMs in their post-intervention diaries, statistical analyses were not carried out. Only mean scores and standard deviation are reported.

Results: In the subsample of 10 participants, mean CB-IM-related nowness ratings were 3.73 (*SD* = 1.67) in diary 1, 3.46 (*SD* = 1.99) in diary 2 and 4.88 (*SD* = 3.13) in diary 3. For comparison, the mean CB-IM-related nowness rating in the remaining participants (*n* = 7) was 2.96 (*SD* = 1.43) in diary 1.

Comment: The comments in section 1.2 apply here. However, from a purely observational point of view, nowness ratings seemed to increase in diary 3. This would be necessary to explore in future studies. Given that the number of CB-IMs decreased following the intervention, a potential increase of CB-IM-related nowness may be due to the fact that CB-IMs with the highest levels of nowness are more resistant to the intervention. Such a result would be very helpful for intervention development.

2. Complementary results and participants' remarks

The following quotes were retrieved from the last study phone call or from the questionnaires. They are reported to illustrate and enrich the results. Subsections follow the same order as results in the article, and contain the relevant additional figures and tables.

2.1. Intervention characteristics and participants' perception of the intervention (corresponding to section 2.2 of the article)

2.1.1. Intervention characteristics

Table S1. Intervention characteristics (*n* = 17).

Intervention characteristics	**Median (*IQR*) or Mean (*SD*)[a]**
Intervention timing	
[Assumed memory reactivation] Narrative task 1 duration (minutes)	6 (2.5)
[Assumed memory reactivation] Narrative task 2 duration (minutes)	4 (1)
[Assumed memory labilisation] Labilisation phase duration (minutes)[b]	12 (1)
[Assumed memory reconsolidation disruption] Tetris duration (minutes)	20 (0)
Participants' experience	
Memory vividness at the end of the assumed reactivation phase (%)	80 (15)
Reminder cue specificity[c]	10 (1)
Context specificity[d]	9 (3)
Tetris difficulty	2 (2)
Expected changes in CB-IMs following the intervention[e]	-0.29 (4.71)△

[a] Median and interquartile ranges are reported if the data did not follow a normal distribution according to a Shapiro-Wilk test.
△ Reported values are a mean and standard deviation.
[b] From leaving the examination room to the start of Tetris training.
[c] To what extend the participants' narratives were faithful to their actual childbirth experience (1 = *not faithful at all/does not correspond at all*; 10 = *extremely faithful/completely corresponds*).
[d] To what extend the maternity ward reminded participants of their traumatic childbirth (0 = *not at all*; 10 = *extremely*).
[e] On a 21-point scale ranging from -10 (= participant expected CB-IMs to extremely decrease following the intervention) to +10 (= participant expected CB-IMs to extremely increase).

Participants mentioned different elements of the maternity ward that reminded them of their childbirth: "*The corridors, the elevators, the paediatrician's room*" (P01), "*Buildings, corridors, white coats, crying babies, signs*" (P17), "*To hear the beeping of the blood pressure machines, the light from the ceilings and the clothing of the medical staff*" (P05) or simply "*Seeing that place again*" (P15), "*Being there was sufficient to recall*" (P16). Three participants also mentioned the hospital smell.

Overall, participants seemed sceptical about the intervention: "*To be honest when I played Tetris I didn't really believe in it*" (P03), "*I was surprised to play Tetris, I told myself that it's not a game that will make me forget what I went through. In fact, I didn't find... for me it wasn't very logical* [laughs] […]. *When I finished the meeting I was like "hum what have I been doing here, exactly?*" (P04), but also amused "*It was funny* [laughs], *wow I just played Tetris for therapy* [laughs] […] *I thought it was really nice*" (P10).

2.1.2. Emotional arousal

Rationale: A certain level of emotional arousal would be required to allow for MR and memory labilisation, although the exact level of arousal needed is still unclear (Kindt and van Emmerik, 2016; Treanor et al., 2017). Triggering a level of arousal that is too high is not ethically acceptable, and may compromise participants' ability to engage in intervention-related tasks. On the contrary, low emotional arousal could indicate that they did not immerse themselves in the memory, and thus that the MR may have failed. Interestingly, a sharp decrease of arousal between the putative MR phase and the end of Tetris gameplay would tend to predict a response to the intervention in Kessler et al. (2018). In our study, emotional arousal was measured to ensure that it remained at acceptable levels throughout the intervention, and to collect information on the emotional response to the procedure. Emotional arousal was expected to be high during the narrative tasks, to decrease once leaving the examination room, and to be low after Tetris gameplay.

Method: Participants orally reported their level of emotional arousal using a 10-point visual analogue scale (VAS) ranging from 1 (*not stressed and/or anxious at all*) to 10 (*extremely stressed and/or anxious*). In total, they reported their emotional arousal ten times throughout the intervention (Figure 2 of the article).

Results: During the intervention, participants had the highest emotional arousal rating at the end of the narrative task 2 (Figure S1). Emotional arousal decreased after leaving the examination room and remained low from the moment they received Tetris instruction to the end of the intervention.

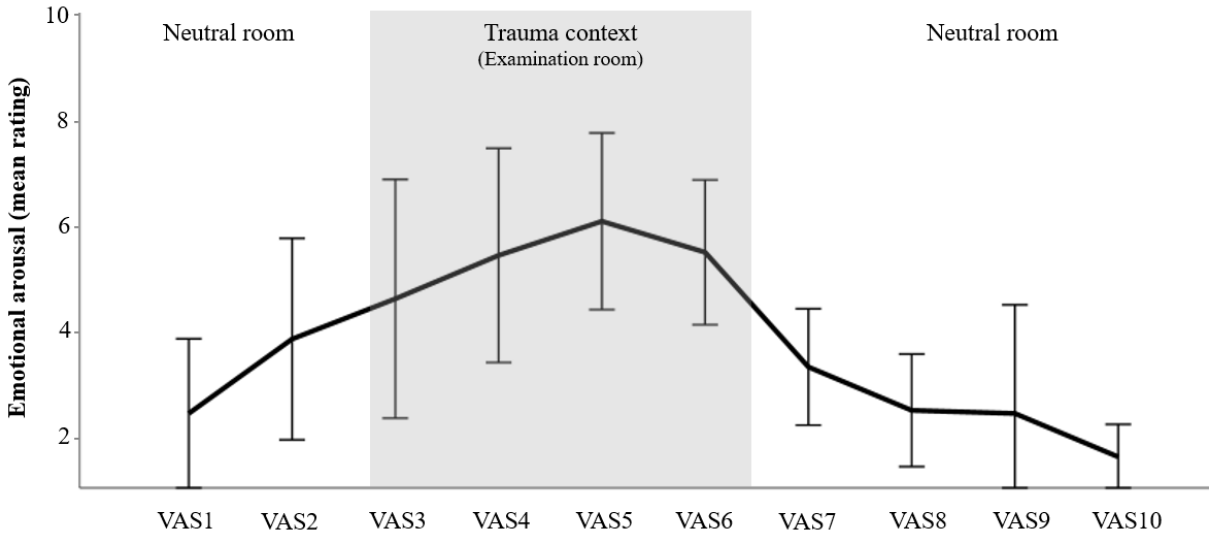

Figure S1. Mean emotional arousal rating throughout the intervention (*n* = 17).

Note. VAS = Visual analogue scale, oral 10-point scale measuring emotional arousal from 1 (*not stressed and/or anxious at all*) to 10 (*extremely stressed and/or anxious*). Black bars represent ±1 SD. See Figure 2 in the article for details on the timing of each VAS measurement.

Comment: Emotional arousal levels throughout the intervention were in line with our expectations. Participants did show a response to the reminder cues, although an increase was already observable once they received detailed explanations about the intervention (VAS2), which probably reflects anticipation of the maternity ward visit. Importantly, emotional arousal at the end of the intervention was back to the same level as at arrival.

Several participants indicated that going back to the maternity was surprisingly emotionally intense and challenging "*The stress rose suddenly when I recognised the place and I wanted to run away*" (P13), "*I didn't think it would upset me*" (P06), "*I found the feeling I had… surprising. When we went into the room, well, everything came out* […]. *I thought things were settled on my side* […]. *It's more this surprise that I had, in the sense that it was as if it had jumped into my face"* (P11).

2.2. Perceived changes of CB-IMs following the intervention (corresponding to section 2.3 of the article)

Participants not only reported a reduction of the number CB-IMs, but also changes in the nature of their CB-IMs: "*After our meeting, twice the flashbacks came back but the image was so blurred that it was absolutely not distinct.* […]. *It's like the flashes want to come but I can't*

tell what's their content. It's a flash but it's so blurry, bright and white, the image is so unclear that I can't see the content" (P12), "*I feel like when all of a sudden my brain is trying to bring something up it is, it is like all of a sudden like blocked*" (P06), "*I have few flashbacks and when I do, they are less intense than before*" (P14) "*I had few intrusions, and the feeling of having been able to handle them, emotionally speaking*" (P02). Some participants also indicated CB-IMs were less easily triggered: "*Overall, less avoidance attempts and not always problems (e.g., seeing a pregnant friend didn't bring back any flashbacks at all)*" (P10), "*It's* [the CB-IMs] *less spontaneous or um, at least less random*" (P10).

2.3. The day-to-day trajectories of CB-IMs

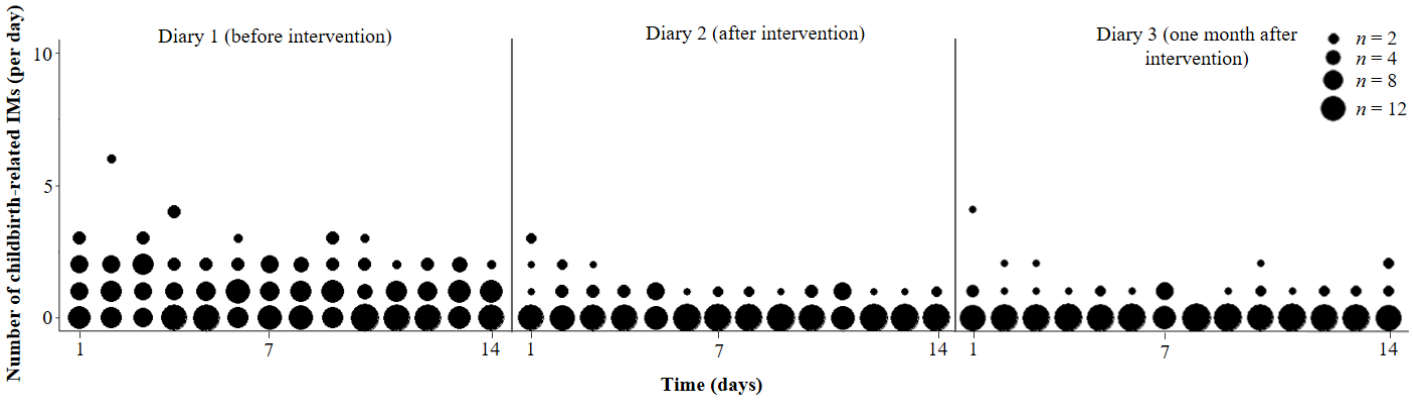

Figure S2. Frequency scatter graphs showing the daily number of CB-IMs recorded in the diaries (n = 17).

Note. Diary 1 covered the 14 days before the intervention, diary 2 covered the 14 days following the intervention and diary 3 covered 14 days from one month post-intervention (i.e., the 5th and 6th post-intervention weeks). The size of the circles represents the number of participants who reported the indicated number of CB-IMs on that particular day.

2.4. CB-PTSD symptoms (corresponding to section 2.4 of the article)

Participants' comments reflected the CB-PTSD symptom reduction. For instance, four participants spontaneously mentioned they were no longer afraid of becoming pregnant, which is a typical avoidance symptom in CB-PTSD: "*We wondered* [with my husband] *if I wasn't pregnant. And in fact I didn't experience this thinking "oh my God, what a horror I'm going to have to go through this again" or anything like that. It was more like, I was more like, "if it's true, if I'm pregnant, well that's great and I welcome it and it's going to be great"*." said P06, echoing P07 : "*Before it was not an option at all, to try,* [now] *we are trying to have a second child*.". Other participants also reported an improvement of their everyday life: "*I am*

less tense, less stressed so, yes, it has helped me […]. *Before I, I used to have mood swings, crazy outbursts, so I was, well, I was also verbally nasty or I would get carried away* […]. *I'm calmer now*" (P09), "*I'm a bit like I was before* [the childbirth], *I'm much happier and calmer again*" (P03), "*I feel really different, I feel the wound is less fresh, less open*" (P08). Some of them also indicated their relationship with their partners was improved: "*My husband in any case saw the difference. He saw that I was less… Not aggressive, but less that I was less tense, less jaded*" (P04).

3. Participant 18

P18 was excluded from the analyses, as explained in section 2.6 of the article. Given that her response to the intervention is of scientific and clinical interest, her data are reported and discussed in the following section.

Participant's data: Despite being the only extreme outlier (more than three IRQ above quartile 3 or below quartile 1) with regard to her score to the reminder cue specificity question, it should be noted that P18 was not an outlier on any baseline measurements (depression, CB-PTSD), nor intervention-related variables (e.g., phases duration, emotional arousal, Tetris difficulty).

1. **CB-IMs**: P18 reported 11 CB-IMs in diary 1, 48 in diary 2, and 12 in diary 3. Her pattern of CB-IMs was really distinct from other participants', as noticed by the two psychologists blind to the time point who rated the diary entries. Indeed, her CB-IMs were very close to each other's, e.g., most CB-IMs of the day occurred within the same half-hour, sometimes within two minutes of each other.
2. **CB-PTSD symptoms**: Her total CB-PTSD severity score before the intervention was 14 (intrusion: 8, avoidance: 3, negative alteration in cognitions and mood: 2, and alteration in arousal and reactivity: 1) and 13 one month later (intrusion: 6, avoidance: 1, negative alteration in cognitions and mood: 3, and alteration in arousal and reactivity: 3).

   Acceptability: P18 rated the intervention as highly acceptable (10/10), would recommend it to a friend (10/10) and would have accepted to do a second session if it was scientifically proven to be useful.

Participant's experience of the intervention: P18 explained that she intentionally did not immerse herself into her childbirth memory and used the same avoidance strategies during the narrative tasks as she used with her everyday CB-IMs, which consisted of "*putting voluntary distance*" with the narratives. She explained having engaged in these strategies because of a fear of confronting herself to the memory, which was too painful. Interestingly, she had been working on the maternity ward of the XXXX Hospital when she gave birth. She said that, therefore, the place where the reactivation took place did not only remind her of her childbirth but also of her work. However, she reported that the maternity ward reminded her of her childbirth at 6 out of 10 (context specificity question), which did not make her an outlier on that question. It should also be noted that she had not experienced anything stressful or memorable in the hours following the intervention. At the time of the appointment, she did not know, like all the other participants, what the rationale and assumed mechanisms of the intervention were. She indicated that, being a very analytical person, she might have been willing to immerse herself in her memories if she had had prior knowledge of how the intervention worked.

Participant's experience of the temporary CB-IMs increase: When contacted by the study psychologist (CD), P18 said she did not notice the increase of her number of CB-IMs in diary 2, and that these CB-IMs did not impact her everyday functioning, although she found them irritating. For information, given the sharp increase of CB-IMs P18 had reported in diary 2, the study psychologist and the study investigator (AH) met her in person at the end of the study, instead of the usual closing phone call. This allowed to have a face-to-face conversation, which seemed more appropriate, although P18's CB-IMs were back to their baseline level at the time of the meeting. The participant received a list of professionals and associations that could support her with regard to her traumatic childbirth experience.

Comment: Assuming that the tested intervention reactivates the traumatic childbirth memory and disrupts its reconsolidation, several elements suggest that P18's childbirth memory was not reactivated. Firstly, her response to the reminder cue specificity question as well as her comments indicate that she voluntarily and consciously did not immerse herself in her memory. Secondly, and importantly, CB-IMs increased during diary 2 but were back to their pre-intervention level in diary 3, and CB-PTSD symptoms did not increase. If the intervention had strengthen the memory of trauma following its reactivation, the memory reconsolidation hypothesis would have predicted that the change would have been stable and lasting

(Bjorkstrand et al., 2015; Elsey et al., 2018), not temporary. Furthermore, neither her emotional arousal ratings, nor her comments suggested that she was more distressed than the other participants during the intervention or in the hours afterwards, during the assumed reconsolidation window. These different observations suggest that it was not a memory reconsolidation-related mechanism that was at play with this participant.

An alternative hypothesis could be that coming to the maternity ward and narrating the childbirth temporarily weakened P18's avoidance strategies, which would then have led to heightened perception of her CB-IMs, thus leading to an increase in their report. This hypothesis is reinforced by the fact that, clinically, this participant seems to have developed strong avoidance strategies, which she mentioned orally, and that allowed her to avoid engaging in the narrative tasks. Furthermore, it seems paradoxical that she barely noticed the increase in her CB-IMs after the intervention, given its magnitude. Conversely, this unusual situation may have reduced a potential inhibitory trace of the memory of trauma, leading to a transient reinstatement of the fear response (Bouton, 2002, 2004). Again, these are assumptions drawn from the collected data and the current knowledge of memory processes, but they are impossible to prove.

To avoid a similar situation from occurring again, several avenues can be envisaged, depending on the context and participant's profile. 1) Explain more to the participant (or patient) the importance of the narratives, and the importance of not pushing back the trauma memory, even if it is difficult. For instance, P18 stated that it would have been helpful to understand better the assumed mechanisms of the intervention to engage in the task, which was deliberately not done at the time of the intervention in order to avoid biasing participant's expectancies. 2) Extend, to a certain limit, the assumed MR phase for participants with a low rating of their narrative faithfulness, until it increases. 3) Make a first appointment solely dedicated to the meeting between the clinician and the participant, in order to strengthen the therapeutic relationship, the trust, and thus the participants' commitment to the procedure. These three proposals are all aimed at helping participants to follow the instructions, however it could also be considered appropriate to 4) not offer the intervention to participants with significant avoidance symptoms (although this was not the case for P18). In any case, it seems important to be particularly careful with the follow-up of participants who do not engage with the procedure.

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Disruption of Memory Reconsolidation and Its Applications. Perspect Psychol Sci 12, 290-305.

K. Publication list, scientific outreach, supervision and training

1. Team co-supervision

Table 1. Team co-supervision.

Status	Duration	Work percentage
Graduated psychologist	6 months	40%
Graduated psychologist	6 months	80%
Graduated psychologist	6 months	50%
Psychology student	10 months	50%
Psychology student	9 months	50%
Psychology student	1 year	50%
Psychology student	1 year	50%
Psychology student	6 months	50%
Psychology student	1 year	50%
Psychology student	1 year	50%
Psychology student	6 months	50%
Psychology student	1 year	45%
Psychology student	1 year	35%
Psychology student	6 months	30%
Psychology student	6 months	20%
Psychology student	3 months	100%
Psychology student	2 months	50%
Psychology student	1 year	50%
Psychology student	1 year	50%
Nursing student	1 year	50%

Note. The co-supervisions are or were jointly carried out with Ms Vania Sandor and/or Prof. Antje Horsch. Note that this list does not include clinicians trained and/or supervised for Study 3.

2. Training

Table 2. Participation in training courses during the PhD.

Tool	Date	Institution and place
Structure Play Interaction Scales	April 2020–Present (ongoing)	University of Liverpool. Liverpool (Online), UK.
Interpersonal psychotherapy, level A	26-27th June 2021	Association pour la Recherche et l'(In)formation en Périnatalité. Avignon (Online), France.
Neonatal Behavioural Assessment Scale	January to November 2019	Centre d'Ouverture Psychologique et Sociale (COPES). Paris, France.
CBT psychotherapy for PTSD	10-11th May 2019	Formation des Associations Romandes et Tessinoises des Psychologues (FARP). Lausanne, Switzerland.
Humanitarian psychology and resilience	23th February 2019	Formation des Associations Romandes et Tessinoises des Psychologues (FARP). Geneva, Switzerland.
Bayley Scales of Infant Development III	December 2018-February 2019	Internal training. Lausanne, Switzerland.
Clinician-Administered PTSD Scale for DSM-5	October-November 2018	Internal training. Lausanne, Switzerland.

Note. This list is not exhaustive and does not include courses taken as part of the doctoral program.

3. Publication list

a. Articles published in peer reviewed journals

1. **Thesis study 1: Deforges C**, Noel Y, Eberhard-Gran M, Garthus-Niegel S, Horsch A. Prenatal insomnia and childbirth-related PTSD symptoms: A prospective population-based cohort study. J Affect Disord. 2021;295:305-15.
2. Sandoz V, Stuijfzand S, Lacroix A, **Deforges C**, Quillet Diop M, Ehlert U, et al. The Lausanne Infant Crying Stress Paradigm: Validation of an Early Postpartum Stress Paradigm with Women at Low vs. High Risk of Childbirth-Related Posttraumatic Stress Disorder. J Pers Med. 2021;11(6).
3. **Thesis study 2: Deforges C**, Stuijfzand S, Noël Y, Robertson M, Breines Simonsen T, Eberhard-Gran M, et al. The relationship between early administration of morphine or nitrous oxide gas and PTSD symptom development. J Affect Disorders. 2021;281:557-66.
4. Stuijfzand S, **Deforges C**, Sandoz V, Sajin CT, Jaques C, Elmers J, et al. Psychological impact of an epidemic/pandemic on the mental health of healthcare professionals: a rapid review. BMC Public Health. 2020;20(1):1230.
5. **Thesis study 3:** Sandoz V, **Deforges C**, Stuijfzand S, Epiney M, Vial Y, Sekarski N, et al. Improving mental health and physiological stress responses in mothers following traumatic childbirth and in their infants: study protocol for the Swiss TrAumatic biRth Trial (START). BMJ Open. 2019;9(12):e032469.

b. Submitted manuscript under review in a peer-reviewed journal

1. **Thesis study 4:** Deforges C, Fort D, Stuijfzand S, Holmes EA, Horsch A. Reducing childbirth-related intrusive memories and PTSD symptoms via a single-session behavioural intervention including a visuospatial task: A proof-of-principle study. J Affect Disord. Under Review.

c. Articles published in non-peer reviewed journals

1. Sandoz V, **Deforges C**, Avignon V, Horsch A. Le vécu traumatique de la naissance : quelles en sont les conséquences pour les familles ? Obstetrica (In press). 2021.

2. **Deforges C**, Sandoz V, Horsch A. Le trouble de stress post-traumatique lié à l'accouchement. Revue de Médecine Périnatale. 2020.

4. Presentations at national and international conferences

Table 3. Oral or poster presentations at national and international conferences during the PhD.

Authors, title, date, conference and location	Type of presentation
Deforges C, Stuijfzand S, Noël Y, Robertson M, Breines Simonsen T, Eberhard-Gran M. et al. Does Obstetrical Analgesia have Unexpected Effects on Childbirth-Related PostTraumatic Stress Disorder? (2021). Research day of the Woman-Mother-Child Department of the Lausanne University Hospital. Lausanne, Switzerland.	Oral
Stuijfzand S, **Deforges C**, Sandoz V, Sajin CT, Elmers J, Horsch A. Robertson M, Breines Simonsen T, Eberhard-Gran M. et al. Psychological impact of an epidemic/pandemic on the mental health of healthcare professionals: a rapid review. (2021). Research day of the Woman-Mother-Child Department of the Lausanne University Hospital. Lausanne, Switzerland.	Poster
Sandoz V, Messerli-Bürgy N, **Deforges C**, Stuijfzand, S, Rubi, MS, Ehlert U, et al. The Lausanne Infant Crying Stress Paradigm: Development and validation of an Early Postpartum Stress Paradigm within birth-related traumatised vs. nontraumatised women. (2021). Research day of the Woman-Mother-Child Department of the Lausanne University Hospital. Lausanne, Switzerland.	Oral
Deforges C, Fort D, Stuijfzand S, Holmes EA, Horsch A. Treating posttraumatic stress disorder symptoms with a single-session behavioral intervention. (2021). 41st Annual conference of the Society of Reproductive and Infant Psychology. Online	Oral
Deforges C, Noël Y, Eberhard-Gran M, Garthus-Niegel S, & Horsch A. The relationship between maternal perinatal insomnia and childbirth-related posttraumatic stress disorder symptoms: A prospective population-based cohort study. (2021). 41st Annual conference of the Society of Reproductive and Infant Psychology. Online.	Oral
Sandoz V, Stuijfzand S, Messerli-Bürgy N, Deforges C, Quillet Diop M, Ehlert U, et al. Psychophysiological stress reactivity in response to the Lausanne Infant Crying Stress Paradigm of women at low- vs. high-risk of childbirth-related posttraumatic stress disorder: a	Oral

cross-sectional experimental study. (2021). 41st Annual conference of the Society of Reproductive and Infant Psychology. Online.	
Deforges C, Stuijfzand, S, Noël Y, Robertson M, Breines Simonsen T, Eberhard-Gran M, et al. Effects of obstetrical analgesia on childbirth-related posttraumatic stress disorder symptoms. (2021). 41st Annual conference of the Society of Reproductive and Infant Psychology. Online.	Oral
Sandoz V, Stuijfzand S, Messerli-Bürgy N, **Deforges C**, Quillet Diop M, Ehlert U, et al. The Lausanne Infant Crying Stress Paradigm: Development and validation of an Early Postpartum Stress Paradigm within birth-related traumatised vs. nontraumatised women. (2020). 2nd Annual meeting of the Swiss Society for Early Childhood Research. Online	Oral
Deforges C, Stuijfzand S, Noël Y, Robertson M, Breines Simonsen T, Eberhard-Gran M, et al. Use of Pain Relief Medication during Childbirth Impacts Birth-related Posttraumatic Stress Disorder Symptoms. (2020). 2nd Annual meeting of the Swiss Society for Early Childhood Research. Online.	Poster
Sandoz V, Messerli-Bürgy N, **Deforges C**, Stuijfzand S, Sekarski N, Ehlert U, et al. Development and validation of the Lausanne Infant Crying Stress Paradigm: A stress paradigm for the early postpartum period. (2019). 1st Annual meeting of the Swiss Society for Early Childhood Research. Lausanne, Switzerland.	Oral
Stuijfzand S, Sandoz V, **Deforges C**, Morisod Harari M, Horsch A. START Project: The effect of postpartum PTSD on mother-child interaction. (2019). 1st Annual meeting of the Swiss Society for Early Childhood Research. Lausanne, Switzerland.	Poster
Deforges C, Sandoz V, Stuijfzand S, Porcheret K, Horsch, A. Impact of sleep after a traumatic childbirth on posttraumatic symptom development: a prospective study. (2019). 1st Annual meeting of the Swiss Society for Early Childhood Research. Lausanne, Switzerland.	Oral
Sandoz V, **Deforges C**, Stuijfzand S, Epiney M, Vial Y, Sekarski N, et al. Improving mental health and physiological stress responses in mothers following traumatic childbirth and in their infants: a randomized controlled trial. (2019). 39th Annual Conference of the Society for Reproductive and Infant Psychology. London, UK.	Oral
Sandoz V, Messerli-Bürgy N, **Deforges C**, Stuijfzand S, Sekarski N, Ehlert U, et al. The Lausanne Infant Crying Stress Paradigm: Development and validation of an early postpartum stress paradigm within birth-related traumatised vs non-traumatised women. (2019). 39th Annual Conference of the Society for Reproductive and Infant Psychology. London, UK.	Oral

Deforges C, Sandoz V. Stuijfzand S, Porcheret, Horsch A. Impact of sleep after a traumatic childbirth on posttraumatic symptom development : a prospective study. (2019). 39th Annual conference of the Society of Reproductive and Infant Psychology. London, UK.	Oral
Sandoz V, Messerli-Bürgy N, **Deforges C,** Stuijfzand S, Sekarski N, Ehlert U, et al. The Lausanne Infant Crying Stress Paradigm: Development and validation of an early postpartum stress paradigm within birth-related traumatised vs non-traumatised women. (2019). Doctoral Day of the Faculty of Biology and Medicine of the University of Lausanne. Lausanne, Switzerland.	Poster
Deforges C, Sandoz V, Stuijfzand S, Procheret K, Horsch A. Impact of sleep after a traumatic childbirth on posttraumatic symptom development: a prospective study. (2019). Swiss Perinatal Research Day. Lausanne, Switzerland.	Poster
Sandoz V, Messerli-Burgi N, **Deforges C**, Stuijfzand S, Sekarski-Hunkele N, Ehlert U. The Lausanne Infant Crying Stress Paradigm: Development and validation of an early postpartum stress paradigm within birth-related traumatised vs non-traumatised women. (2019). Swiss Perinatal Research Day. Lausanne, Switzerland.	Poster
Sandoz V, Messerli-Bürgy N, Sekarski N, Ehlert U, **Deforges C**, Stuijfzand S. Maternal and Infant Stress Physiology in the Early Postpartum Period. (2019). 2nd Annual meeting of the Swiss Stress Network. Basel, Switzerland.	Poster
Stuijfzand S, Sandoz V, **Deforges C**, Harari Morisod, M, Horsch A. START Project: the effect of postpartum PTSD on mother-child interaction. (2019). 2nd Annual meeting of the Swiss Stress Network. Basel, Switzerland.	Poster
Stuijfzand S, Sandoz V, **Deforges C**, Morisod-Harari M, Horsch A. START Project: The effect of postpartum PTSD on mother-child interaction. Swiss Perinatal Research Day. (2019). Lausanne, Switzerland.	Poster
Deforges C, Sandoz V, Stuijfzand S, Porcheret K, Horsch A. Impact of sleep after a traumatic childbirth on posttraumatic symptom development: a prospective study. Swiss Perinatal Research Day. (2019). Lausanne, Switzerland	Poster

Note. If not the first author, the name of the presenter is underlined.

5. Public and scientific engagements

Table 4. Public and scientific engagements during the PhD.

Event or outcome and date	Description
Online intervention on parental mental health (2021)	Intervention live on Instagram with Dr. Morisod Harari on traumatic childbirth, postnatal depression and parental burnout. Hosted by MotherStories.ch and the Lausanne University Hospital.
Podcast on traumatic childbirth (2021)	In this 40-minute podcast, I try to inform, sensitise, and relieve parents of their guilt about traumatic birth experiences and their consequences. I also indicate where to turn to for support. I was invited by PépiteMama.
Early Career Researcher (ECR) section of the Society for Reproductive and Infant Psychology (2019-Present)	Conjointly with other early career researchers, I am actively involved in organising online workshops and meetings for junior researchers. We also coordinate a conference day for them, which usually take place before the start of the official Society for Reproductive and Infant Psychology conferences.
Swiss Perinatal Research day (2019)	Volunteering.
World Prematurity Day (2018)	Organisation of activities to raise awareness among families and professionals about mental health issues in preterm birth.
Scientific afternoon (2018-2021)	Organisation and coordination of the scientific afternoons of the Lausanne Perinatal Research Group. These events are held approximately every six weeks and provide an opportunity to present and discuss ongoing research in the group, including with scientists and clinicians from outside the group.
Journal club (2018-2021)	Organisation of the journal clubs of the Lausanne Perinatal Research Group.

6. Teaching activity

Table 5. Teaching.

Course title and date	Students	Institution and place
Attachment theory and attachment styles (19th March 2021)	Midwifery students	School of Health Vaud, Lausanne, Switzerland. (Online).
Perinatal mental health: clinical implications and research perspectives (3rd March 2021)	Graduated midwifes	School of Health Vaud, Lausanne, Switzerland. (Online).
Attachment theory and attachment styles (12th March 2019)	Midwifery students	School of Health Vaud, Lausanne, Switzerland.

7. Master and PhD thesis co-supervision

Table 6. Master and PhD thesis co-supervision.

Name of the student	Thesis topic, years of supervision	Targeted degree
Myriam Dos Santos Pêgo (Nursing sciences student)	Title: Transition to parenthood and migration: childbirth-related acute stress disorder and post-traumatic stress disorder according to parental migration status (2021).	Msc
Déborah Fort (Life sciences student)	Ms. Fort will coordinate the randomised waitlist-controlled trial launched to confirm the effectiveness of the RBI-VT tested in Study 4. Her work will focus on parental mental health after traumatic childbirth (2021-?)	PhD

Note. The co-supervisions are or were jointly carried out with Prof. Antje Horsch.

8. Awards and scientific visits

1. **SRIP bursary award** for attendance at the 41st annual meeting of the Society for Reproductive and Infant Psychology. 8-10th September 2020. Online.
2. **Scientific visit** at the Institute and Outpatient Clinics of Psychotherapy and Psychosomatic Medicine : activities related to the collaboration necessary to realise study 1, e.g., discussion and data base preparation. 3-6th December 2019. Technische Universität Dresden, Dresden, Germany.
3. **SRIP bursary award** for attendance at the 39st annual meeting of the Society for Reproductive and Infant Psychology. 5-6th September 2019. London, United Kingdom.