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Thalamus-related anomalies as candidate mechanism-based biomarkers for psychosis

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ABSTRACT

Identification of reliable biomarkers of prognosis in subjects with high risk to psychosis is an essential step to improve care and treatment of this population of help-seekers. Longitudinal studies highlight some clinical criteria, cognitive deficits, patterns of gray matter alterations and profiles of blood metabolites that provide some levels of prediction regarding the conversion to psychosis. Further effort is warranted to validate these results and implement these types of approaches in clinical settings. Such biomarkers may however fall short in entangling the biological mechanisms underlying the disease progression, an essential step in the development of novel therapies. Circuit-based approaches, which map on well-identified cerebral functions, could meet these needs. Converging evidence indicates that thalamus abnormalities are central to schizophrenia pathophysiology, contributing to clinical symptoms, cognitive and sensory deficits. This review highlights the various thalamus-related anomalies reported in individuals with genetic risks and in the different phases of the disorder, from prodromal to chronic stages. Several anomalies are potent endophenotypes, while others exist in clinical high-risk subjects and worsen in those who convert to full psychosis. Aberrant functional coupling between thalamus and cortex, low glutamate content and readouts from resting EEG carry predictive values for transition to psychosis or functional outcome. In this context, thalamus-related anomalies represent a valuable entry point to tackle circuit-based alterations associated with the emergence of psychosis. This review also proposes that longitudinal surveys of neuroimaging, EEG readouts associated with circuits encompassing the mediodorsal, pulvinar in high-risk individuals could unveil biological mechanisms contributing to this psychiatric disorder.

1. Introduction

The onset of diagnosed psychosis is preceded by a prodromal phase that is characterized by the presence of basic symptoms and subthreshold positive symptoms. A set of criteria is used to identify individuals with potential prodromal symptoms. This includes 1) a genetic risk and a decline in functioning, 2) attenuated psychotic symptoms, and 3) brief limited intermittent psychotic episode (Fusar-Poli et al., 2013). Individuals with at least one of these criteria are considered as clinical high risk for psychosis. However, such a defined clinical high-risk group is not homogeneous. Many clinical high-risk subjects may never convert to full psychosis, but show other psychiatric outcome and retain relatively low levels of functioning. A meta-analysis indicates a mean of transition risk of about 20% after one-year follow-up (Fusar-Poli et al., 2012). Treatment and patient care during this prodromal phase may also reduce the risk to convert to full psychosis. Therefore, it is essential to develop diagnostic tools to improve the prediction of conversion to psychosis and other outcomes among this population. This includes the identification of reliable biomarkers of risk and prognosis. In this context, the "Attenuated Psychosis Syndrome" is proposed as a new diagnostic category that would better describe the prodromal phase and capture sub-threshold psychotic symptoms before they develop into a full psychotic disorder like schizophrenia. Many efforts have been engaged in identifying parameters that could discriminate individuals who convert to psychosis from those who do not. Thus, clinical variables (Ruhrmann et al., 2010), mild cognitive deficits (Seidman et al., 2016), reduced gray matter in prefrontal, cingulate, striatal, and cerebella regions (Koutsouleris et al., 2015), peripheral blood markers (Chan et al., 2015) carry predictive values. Advanced neuroimaging and machine-learning based analytical methods will further help refining the prediction of conversion risk and functional outcome (de Wit et al., 2017; Kambeitz-Ilankovic et al., 2018). These approaches may provide invaluable tools to clinicians. However, they may fall short in probing the biological mechanisms underlying the progression of the disorder, a necessary step for the development of novel therapies. In this context, a biology-driven approach based on defined brain circuits affected in the disorder and associated with well-identified functions, could meet these needs. Thalamus-related anomalies represent a valuable entry point to tackle circuit-based alterations associated with the

Abbreviations: TRN, thalamic reticular nucleus; CHR, clinical high-risk subjects.
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emergence of psychosis. Starting from several decades ago, a large body of evidence has revealed the involvement of the thalamus in the pathophysiology of schizophrenia (Andreasen, 1997; Byne et al., 2009; Clinton and Meador-Woodruff, 2004; McCarley et al., 1999). As part of multiple brain networks, the thalamus represents an essential hub for cognitive processes and an interface between sensory and motor systems. Therefore, thalamus dysfunction may potentially contribute to symptoms and deficits found in schizophrenia. This includes working memory and attention deficits, impairment of flexible-goal directed tasks, altered sensory perception, inability to properly recognize self-initiated motor outputs, sleep disruption (Behrendt, 2006; Cronenwett and Csernansky, 2010). The thalamus is mostly composed of excitatory neurons grouped into separate nuclei that have distinct patterns of connections with the cortex, subcortical brain structures, and sensory systems. This defines the function of each nucleus. Some nuclei relay sensory stimuli to primary sensory cortices. The lateral geniculate, medial geniculate, and ventral posterior nuclei constitute respectively the visual, auditory, and somatosensory thalamic nuclei. Other nuclei convey to the cortex more processed information coming from the cortex and/or a variety of subcortical structures. These nuclei can be classified as motor relays (ventral lateral, ventral anterior nuclei), associative (e.g. anterior and mediodorsal nucleus, pulvinar), or non-specific (midline, intralaminar nuclei). In addition, the thalamus is surrounded laterally by the thalamic reticular nucleus (TRN). This nucleus is composed of a dense layer of GABAergic neurons projecting into the different thalamic nuclei to inhibit thalamocortical neurons. Consequently, the TRN occupies a key position as gate-keeper to orchestrate thalamo-cortical and thalamo-striatal information flow. A comprehensive description of the thalamus anatomy and function is beyond the scope of this review (see Jones, 2007; Sherman and Guillery, 2013). However, Table 1 provides a brief description of the connections and functions of some nuclei discussed in the present review.

Most postmortem studies of schizophrenia patients have examined nuclei that do not process primary sensory stimuli (reviews: Byne et al., 2009; Dorph-Petersen and Lewis, 2017). Smaller volume and/or reduced number of neurons are robust findings for the pulvinar (Byne et al., 2002; Danos et al., 2003; Highley et al., 2003; Mileaf and Byne, 2012). Similar anomalies (including decreased number of glial cells) are reported in mediodorsal and anterior nuclei although with less consistency (Byne et al., 2002; Byne et al., 2006; Chana et al., 2008; Cullen et al., 2003; Dixon and Harper, 2004; Kreczmanski et al., 2007; Pakkenberg, 1990; Popken et al., 2000; Young et al., 2000). A trend towards reduced volume of the centromedian nucleus (part of the intralaminar nuclei) has been also reported (Byne et al., 2002), whereas no alterations in the lateral geniculate (Dorph-Petersen et al., 2009; Selemon and Begovic, 2007) and ventral posterior (Popken et al., 2000) nuclei have been found. Finally, the TRN of patients displays a reduced number and density of parvalbumin-immunoreactive neurons and altered extracellular matrix (Steullet et al., 2018). Altogether, postmortem studies pinpoint abnormalities mostly in several high-order nuclei and TRN. However, these do not clarify whether these are disease specific or caused by the interactions between illness, medication, and age. Furthermore, they do not inform about the temporal changes that occur along the different stages of the disorder. Understanding the ontogeny and nature of anomalies at the levels of individual thalamic nuclei and their associated circuits may lead to the identification of biologically relevant biomarkers. Recent preclinical studies have shed new light on the circuits-based mechanisms that support working memory, attention and memory consolidation. These involve thalamic nuclei known to be affected in schizophrenia (i.e. mediodorsal nucleus, pulvinar and TRN) (i.e. Barron et al., 2015; Bolkan et al., 2017; Fogel and Smith, 2011; Schmitt et al., 2017; Wimmer et al., 2015; Yu et al., 2018). In this context, impairments in attention, working memory, and declarative memory can be present during the premorbid phase, tend to

Table 1
Thalamic nuclei relevant to schizophrenia with their main connections and currently known functions.

Nucleus	Connectivity	Roles	References
Anterior complex (anterodorsal, anteromedial, anteroventral)	- Direct and indirect interconnections with hippocampus - Reciprocal connections with prefrontal, anterior cingulate and retrosplenial cortices	- Involved in mnesic functions and spatial navigation - Involved in propagation of EEG slow-waves during NREM sleep	(Gent et al., 2018; Jankowski et al., 2013)
Midline nuclei (i.e. reuniens)	- Interconnected with hippocampus and limbic cortical regions - Major source of thalamic inputs to the hippocampus	- Involved in tasks requiring interactions between hippocampus and prefrontal cortex - Modulate in concert with the hippocampus the activity of midbrain dopaminergic neurons	(Perez and Lodge, 2018; Saalmann, 2014; Vertes et al., 2015; Zimmerman and Grace, 2016)
Intralaminar nuclei (i.e. centromedian nucleus)	- Receive inputs from brainstem and subcortical regions, cerebellum - Project to dorsal striatum, amygdala and a wide range of cortical regions	- Probably involved in attention, arousal, and goal-oriented response to relevant stimuli - Involved in EEG slow-waves during NREM sleep	(Gent et al., 2018; Saalmann, 2014; Vertes et al., 2015)
Mediodorsal nucleus	- Reciprocal connections with prefrontal regions - Receives inputs from amygdala, limbic system, basal ganglia, midbrain and brainstem - Receives collateral inputs from cortical neurons projecting to subcortical motor regions	- Involved in goal-directed tasks relying on working memory, attention and behavioral flexibility - Relays information regarding motor instructions as efferent copies to other cortical regions	(Ouhaz et al., 2018; Parnaudeau et al., 2018; Schmitt et al., 2017; Sherman, 2016)
Pulvinar	- Receives inputs from superior colliculus - Reciprocally connected with prefrontal, temporal, parietal and occipital cortices	- Engaged in several domains of attention - Regulates synchronization between multiple cortical regions during attentional task - Participates in the suppression of distractors or stimuli to be ignored during selective attention via the modulation of cortical alpha oscillations	(Barron et al., 2015; Grieve et al., 2000; Ketz et al., 2015; Pessoa and Adolphs, 2010; Saalmann et al., 2012; Zhou et al., 2016)
Thalamic reticular nucleus (TRN)	- Constituted of inhibitory neurons that project into the thalamic nuclei - Receives strong collateral excitatory inputs from thalamic neurons projecting to the cortex and cortical layer VI pyramidal neurons projecting into the thalamic nuclei - Receives projections of a wide range of sources (basal ganglia, hypothalamus, amygdala, forebrain)	- Modulates and gates thalamo-cortical flow of information, influencing the states of cortical activity - Implicated in arousal, attention and sleep - Probably implicated in consolidation of procedural and declarative memories during sleep - Involved in generation of EEG spindles during NREM sleep	(Chen et al., 2015; Clemente-Perez et al., 2017; Crabtree, 2018; Herrera et al., 2016; Pinault, 2004)

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worsen during the prodromal stage, and are quite consistently associated with later conversion to psychosis (Dickson et al., 2012; Keshavan et al., 2010; Seidman et al., 2016). Progressive alterations within some thalamic could therefore contribute to the decline of cognitive capacities. Moreover, preclinical data support the hypothesis that thalamic dysfunction contribute to the dysregulation of the dopaminergic system leading to the emergence of positive symptoms (Lisman et al., 2010). Indeed, midline thalamic nuclei (reuniens and paraventricular nuclei) regulate, in concert with the hippocampus, the activity of dopaminergic neurons (Perez and Lodge, 2018; Zimmerman and Grace, 2016).

A large body of evidence from structural and functional magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and electroencephalography (EEG) indicates significant thalamic abnormalities in schizophrenia, from the early-course of the disorder to the chronic stages. The goal of the present article is to first provide, based on MRI (structural, functional, MRS) and EEG studies, an integrative overview on the thalamus-related abnormalities found respectively in patients suffering from chronic schizophrenia, first psychotic episode, and individuals at clinical and genetic high-risk. Based on the existing literature, the second part of the article will highlight potent endophenotypes and candidate predictive biomarkers for psychosis, and their potential clinical and translational relevance.

2. Thalamus-related abnormalities in chronic schizophrenia and first episode psychosis patients

2.1. MRI studies

Due to a lack of sufficient resolution and contrast, imaging the thalamus is a challenging task, particularly when aiming to investigate separately each of the functionally distinct nuclei. Therefore, a large majority of studies have investigated the thalamus as a whole. However, newly-developed analytical methods allow now to segment the thalamus into several subregions (Akram et al., 2018; Iglesias et al., 2018; Najdenovska et al., 2018). Thus, large nuclei, such as the pulvinar and mediodorsal nucleus, can be more reliably studied. But many other nuclei (i.e. the midline and intralaminar nuclei, TRN) remain currently inaccessible for proper analysis.

2.1.1. Thalamic structural alterations

A variety of MRI measurements has been used to assess structural integrity of the thalamus. This includes volume and shape of the thalamus, gray matter (GM) quantification, and water diffusion properties as revealed by diffusion-weighted MRI. Results from these investigations mostly corroborate postmortem data. Meta-analyses and consortium studies incorporating large cohorts reveal smaller volume of the thalamus in chronic (Adriano et al., 2010; Konick and Friedman, 2001; Okada et al., 2016; van Erp et al., 2016) and newly diagnosed patients (Adriano et al., 2010; Qiu et al., 2009), as compared to control subjects. Noteworthy, another meta-analysis indicates the presence of more pronounced effects in antipsychotic-naïve than in medicated patients (Haijma et al., 2013). This suggests that structural thalamic anomalies are present early-on during the course of the disease and are attenuated by antipsychotic treatments. Regarding the quantification of thalamic GM volume, a reduction in schizophrenia patients is supported by a meta-analysis (Glahn et al., 2008) and a recent study on two large cohorts (Maggioni et al., 2017). However, in first-episode psychosis, GM loss is less clear. Some studies found no significant GM volume alterations (Chan et al., 2011), while others reported reduced thalamic GM volume (Huang et al., 2015). The later report showed that GM was more affected in first-episode patients presenting auditory hallucination symptoms. In a large-scale longitudinal prospective study in which early psychotic patients were followed over many years, the rate of decrease of GM volume in the thalamus was most severe during the first years of the disorder (Andreasen et al., 2011). Mounting evidence also points to uneven structural alterations across nuclei. Thalamic surface shape deformation in chronic and first-episode patients suggests structural alterations in anterior, posterior, mediodorsal and ventrolateral regions of the thalamus (Coscia et al., 2009; Danivas et al., 2013; Harms et al., 2007; Qiu et al., 2009; Skatun et al., 2018; Smith et al., 2011). In a cohort of early-onset psychosis, the volume reduction of the thalamus was primary due to decreased volume in the anterior mediodorsal area and pulvinar (Janssen et al., 2012). Voxel-based morphometry (VBM) studies further support a focal reduction of GM, with GM loss most often centered on the mediodorsal and midline nuclei (Pergola et al., 2015). In chronic patients, microstructural alterations of the thalamus have also been observed by diffusion-weighted MRI (Agarwal et al., 2008; Li et al., 2016; Rose et al., 2006). Increased water diffusivity was particularly evident in the anterior and mediodorsal parts (Rose et al., 2006). Likewise, first-episode patients display diffusion-sensitive microstructural alterations in the mediodorsal and pulvinar regions connected to orbitofrontal and latero-temporal cortices (Cho et al., 2019b).

2.1.2. Neurochemical profile alterations

Meta-analyses of MRS studies revealed a decrease of *N*-acetylaspartate (NAA) in the thalamus of schizophrenia (Kraguljac et al., 2012) and first-episode patients (Brugger et al., 2011; Wang et al., 2019). A recent study also reports a decrease in glutathione content in first-episode patients (Wang et al., 2019). By contrast, current data do not show very consistent alterations of glutamate and glutamine levels in first-episode and chronic patients (Merritt et al., 2016; Wang et al., 2019). However, this could be linked to the sparsity of studies.

2.1.3. Abnormal connectivity

By applying probabilistic tractography with either the thalamus or cortex as seed region, several groups have highlighted in chronic patients reduced structural connectivity between the thalamus and cortical prefrontal areas, but increased connectivity with somatomotor, somatosensory and occipital cortices (Giraldo-Chica et al., 2018; Marenco et al., 2012). Similar abnormal connectivity between thalamus and cortex is reported in first-episode psychosis (Cho et al., 2016). By correlating the static bold signals (averaged over several minutes) across brain regions during resting state fMRI, studies reveal also consistent disturbances in functional coupling between the thalamus and several brain regions (prefrontal and sensory-motor cortices, cerebellum, striatum and hippocampus). In chronic patients, they show a reduction in functional connectivity of the thalamus with prefrontal and cingulate cortices (Anticevic et al., 2014; Avram et al., 2018; Giraldo-Chica and Woodward, 2017; Penner et al., 2018; Skatun et al., 2018; Tu et al., 2013; Welsh et al., 2010; Woodward et al., 2012). By contrast, there is increased functional coupling between thalamus and sensorimotor cortices (Anticevic et al., 2014; Giraldo-Chica and Woodward, 2017; Klingner et al., 2014; Skatun et al., 2018; Skudlarski et al., 2010), which is correlated with the symptoms (Anticevic et al., 2014). Interestingly, glucose metabolism is reduced in the mediodorsal nucleus, but increased in the pulvinar (Hazlett et al., 2004). In addition, reduced and increased functional coupling with respectively the cerebellum and parahippocampus are reported in schizophrenia patients (Anticevic et al., 2014; Tu et al., 2013). A recent study demonstrated that thalamo-cortical hypo and hyper functional coupling extend to the basal ganglia (Avram et al., 2018). This indicates that disrupted cortico-thalamic networks are embedded into abnormal cortico-striato-thalamic loops. Similar aberrant functional coupling within thalamo-cortical circuits and reduced functional connectivity between thalamus and striatum are present in the early stages of psychosis (Martino et al., 2018; Woodward and Heckers, 2016).

Altogether, MRI data reveal structural anomalies in the thalamus of first-episode and chronic patients. These anomalies are found preferentially in anterior, mediodorsal and posterior parts. Moreover, aberrant functional connectivity between thalamus and other brain structures

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(cortex, striatum, cerebellum) exists during both early and later stages of schizophrenia.

2.2. EEG studies

As gateway to the cortex, the thalamus influences cortical neuronal activation and synchrony that can be captured by EEG. For instance, the pulvinar modulates cortical alpha oscillations (Liu et al., 2012; Lopes da Silva et al., 1980); delta oscillations are the consequence of low frequency recurrent activation within thalamo-cortical loops (Steriade, 2003); sleep spindles during NREM sleep rely on TRN neuron activity (Steriade, 2003). During NREM sleep, slow-waves are initiated in frontal areas and propagate to posterior cortical regions through trans-thalamic pathways (Gent et al., 2018). EEG-coupled fMRI methods reveal that the activity of thalamic nuclei during resting displays distinct patterns of correlations with individual EEG microstates associated with specific EEG oscillations (Schwab et al., 2015). Thus, the activity of the anterior nuclei is associated with cortical beta oscillations, while the activity of the medial nuclei is linked to both alpha and beta oscillations. Thus, some EEG features can provide indirect but relevant information on how different thalamic nuclei communicate with the cortex. Below, is a brief review of the main findings on EEG alterations reported in schizophrenia during resting and sleep.

The dynamic succession of EEG microstates during the resting state is altered in patients, with the microstate associated with the fronto-parietal attention network being decreased while that related to the saliency network being increased (Rieger et al., 2016). A meta-analysis highlights abnormal EEG spectral characteristics during resting (increased delta, theta, and high beta power; decreased alpha power, Boutros et al., 2008). Reduced alpha frequency is also reported in both chronic and first psychotic episode patients (Harris et al., 2006; Murphy and Ongur, 2019). Moreover, EEG features during NREM sleep (slow-waves and sleep spindles) are reduced in patients. Several research groups have reported sleep spindle deficits in chronic (Ferrarelli et al., 2007; Seeck-Hirschner et al., 2010; Wamsley et al., 2012), fist-episode and antipsychotic-naïve patients (Manoach et al., 2014; Schilling et al., 2017). A recent meta-analysis (Chan et al., 2017) indicates a lack of significant alteration of both slow-waves and sleep spindles. However, this might be due to methodological differences regarding sleep spindle quantification (manual versus automatic), and to the fact that slow-waves are not affected in stable chronic patients. By contrast, slow-waves are reduced during the acute and/or early phases of the disease and correlate with the symptom severity (Kaskie et al., 2019). Taken together, sleep and awake resting EEG reveal diverse abnormalities in brain activity that may relate to alterations within the thalamus and thalamo-cortical circuits.

To conclude, MRI and EEG studies provide compelling evidence for a diversity of anomalies related to the thalamus in both first psychotic episode and chronic schizophrenia patients (Table 2). These include reduced volume of the whole thalamus, reduced GM (mostly in anterior, mediodorsal, posterior regions), decreased levels of NAA (a metabolite involved in energy metabolism and potential marker of neuronal integrity), abnormal connectivity with cortex, basal ganglia, cerebellum, and hippocampus. Overall, these alterations are similar in the early and later stages of schizophrenia and do not evolve drastically with the chronicity of the disease. Of note, medicated patients appear to display less pronounced reduction of the thalamus volume than antipsychotic-naive patients, suggesting a partial normalization effect by pharmacological treatments. The next chapter will review the existing literature in genetic and clinical high-risk subjects.

3. Thalamus-related abnormalities in genetic and clinical high-risk individuals

Here, we consider as clinical high-risk individuals (CHR) those who meet the clinical criteria for high risk to psychosis (Fusar-Poli et al., 2013). Genetic or familial high-risk subjects refer to unaffected relatives/siblings who do not reach the criteria of clinical high-risk. This does not however exclude that some genetic high-risk individuals (particularly the youngest ones) in the reported studies would not develop schizophrenia or other psychiatric disorders later in life, well after the completion of the studies.

3.1. MRI studies

3.1.1. Thalamic structural alterations

Structural thalamic anomalies are already present in CHR and genetic high-risk subjects. Reduced thalamic volume has been observed in both CHR (Harrisberger et al., 2016; Lunsford-Avery et al., 2013) and subjects having affected relatives (Lawrie et al., 1999; Lawrie et al., 2001). Lawrie's data suggests that reduced thalamic size may be a genetically mediated risk factor. A meta-analysis of VBM studies also supports a reduction of thalamic GM volume in familial high-risk subjects (Cooper et al., 2014). One study shows that the thalamic GM volume in healthy siblings from patients suffering of schizophrenia is intermediate between that of their probands and control subjects (Staal et al., 1998). However, a meta-analysis of VBM studies did not reveal any significant loss of GM in the thalamus of CHR subjects (Dietsche et al., 2017; Fusar-Poli et al., 2011a). This suggests that GM loss within the thalamus is at best modest and confined in limited subregions prior to the emergence of psychosis. Indeed, one study has found a slight decreased GM volume in the anterior part of the thalamus in healthy siblings, as compared to control subjects (Pergola et al., 2017). Likewise, thalamic shape alteration due to an inward surface deformation of the anterior and posterior thalamus has been observed in genetic high-risk individuals and was intermediate between their schizophrenia siblings and healthy controls (Harms et al., 2007).

3.1.2. Neurochemical profile alterations

Reduced levels of NAA is found in the thalamus of CHR (Brugger et al., 2011), but also of genetic high-risk subjects (Legind et al., 2019; Tandon et al., 2013; Yoo et al., 2009). Lower glutamate level has been observed in the thalamus of CHR as compared to healthy controls (Fusar-Poli et al., 2011b) and associated with a poor functional outcome (Allen et al., 2015). By contrast in genetic high-risk subjects, studies show overall high levels of glutamate or glutamate + glutamine (Legind et al., 2019; Tandon et al., 2013; Yoo et al., 2009). It is therefore tempting to postulate that high glutamate levels in genetic high-risk may constitute a factor of resilience since low glutamate content appears to predict worse functional outcome in CHR.

3.1.3. Abnormal connectivity

Abnormal structural thalamo-cortical connections are reported during prodromal state but these appear more modest than during first-episode psychosis (Cho et al., 2016). CHR subjects also display aberrant functional coupling between the thalamus and cortex, striatum and cerebellum (Anticevic et al., 2015; Bernard et al., 2017; Cao et al., 2018; Dandash et al., 2014). The pattern of reduced functional thalamic connectivity with prefrontal cortex and cerebellum and hyperconnectivity with sensorimotor cortical areas are more pronounced in individuals who transit to psychosis (Anticevic et al., 2015). Bernard et al. (2017) have also found disturbed connectivity within cerebello-thalamo-cortical circuits that were associated with worsening of positive symptoms in CHR. Likewise, a recent study in CHR highlights abnormal functional coupling between several cerebral cortical regions, thalamus, and cerebellum (Cao et al., 2018). This aberrant connectivity was more pronounced in individuals who converted to psychosis. The authors have also observed a close to significant association between the functional connectivity and thalamic GM volume. This suggests a possible link between altered thalamus integrity and aberrant functional connectivity within circuits embedding the thalamus. Taken together, there is increasing evidence that abnormal connectivity within

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Table 2
Summary of currently described thalamus-related anomalies in genetic high-risk and clinical high-risk individuals, first-episode and early psychosis patients, and in subjects suffering from chronic schizophrenia. The table also shows anomalies that have been reported to be significantly stronger in prodromal subjects who converted into psychosis as compared with those who did not convert.

	Genetic high-risk	Clinical high-risk	Converters versus non-converters	Early psychosis	Chronic schizophrenia
Total volume	Reduced (6)	Reduced (4,5)	N/A	Reduced (3)	Reduced (less than in antipsychotic naive and early psychotic patients) (1,2,3)
Gray matter (GM)					
Whole thalamus	Reduced (less than in patients) (7,8)	No significant reduction (9)	N/A	Inconsistency across studies. Probably progressive reduction (10)	Reduced (11)
Subregions	Reduced in anterior regions (12)	N/A	N/A	Reduced in anterior, mediodorsal and posterior regions (13,14)	Reduced in anterior, mediodorsal and posterior regions (12)
Shape deformation	Deformation in anterior and posterior regions (less than in patients) (16)	N/A	N/A	Deformation in anterior, medial, ventrolateral and posterior regions (14,15)	Deformation in anterior, medial, ventrolateral and posterior regions (16)
Diffusion-weighted imaging (microstructure)					
Whole thalamus	N/A	N/A	N/A	N/A	Alterations (17,19)
Subregions	N/A	N/A	N/A	Alterations in mediodorsal and posterior regions (20)	Alterations in anterior and mediodorsal regions (18)
Neurochemicals	Low NAA (22,24) High glutamate or glutamate + glutamine (23,24)	Low NAA (22) Low glutamate (25)	N/A Low glutamate associated with poor outcome (26)	Low NAA (22) Inconsistent alterations in glutamate (27)	Low NAA (21) Inconsistent alterations in glutamate (27)
Connectivity					
Structural	Reduced thalamus-PFC (31)	Reduced thalamus-PFC Increased thalamus-parietal Ctx (less than in first episode patients) (30)	N/A	Reduced thalamus-PFC Increased thalamus-parietal Ctx (30)	Reduced thalamus-PFC Increased thalamus-sensorimotor Ctx Increased thalamus-occipital Ctx (28,29)
Functional (resting)	Modest reduced thalamus-PFC during attentional task (40)	Reduced thalamus-PFC Reduced thalamus-cerebellum Increased thalamus-sensorimotor Ctx Reduced thalamus-basal ganglia (37,38,39)	Reduced thalamus-PFC Reduced thalamus-cerebellum Increased thalamus-sensorimotor Ctx Reduced thalamus-basal ganglia (37,38)	Reduced thalamus-PFC Reduced thalamus-cerebellum Increased thalamus-sensorimotor Ctx Reduced thalamus-basal ganglia (35,36)	Reduced thalamus-PFC Reduced thalamus-cerebellum Increased thalamus-sensorimotor Ctx Reduced thalamus-basal ganglia Increased thalamus-parahippocampus (32,33,34)
EEG					
Awake (resting)	Decreased alpha peak frequency (45)	Decreased alpha peak frequency in posterior areas Increased delta and theta power in frontal areas (44)	Decreased alpha peak frequency in posterior areas Increased delta and theta power in frontal areas (44)	Decreased alpha peak frequency (42,43)	Decreased alpha peak frequency and power Increased delta power Increased theta power Increased beta power (41,42)
Microstates	Altered (48)	Altered (47)	N/A	Altered (46)	Altered (46)
Sleep (NREM)	Reduced spindles (less than patients) (52,53)	N/A	N/A	Reduced spindles (52,53)	Reduced spindles (49,50,51)
	Reduced slow-waves (56)	N/A	N/A	Reduced slow-waves (55)	Not affected slow-waves (54)

N/A indicates readouts for which there is a lack of published data or may have been missed during the literature search.
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several brain circuits, in which the thalamus represents one of the nodes, is progressing during prodromal stage with the worsening of the functional outcome and emergence of psychosis. Currently, resting fMRI data in cohorts of genetic high-risk individuals are missing. However, there is report of reduced structural connectivity between thalamus and orbitofrontal cortex in unaffected relatives of schizophrenia patients (Cho et al., 2019a). Moreover during an attentional task, a modest alteration of the functional coupling between prefrontal cortex and thalamic regions encompassing the mediodorsal and intralaminar nuclei exists already in healthy siblings of patients (Antonucci et al., 2016). This suggests that a weakened connectivity between thalamus and prefrontal regions may represent a heritable trait and vulnerability factor.

3.2. EEG studies

The EEG microstate dynamic during resting is altered not only in first-episode and chronic patients (Rieger et al., 2016), but also in CHR (Andreou et al., 2014). Likewise, adolescents with the 22q11 deletion syndrome, who do not meet the diagnostic criteria for schizophrenia

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but present some positive symptoms, display similar abnormal microstate dynamic as schizophrenia patients (Tomescu et al., 2015). van Tricht et al. (2014) found increased frontal delta and theta oscillations during rest in CHR subjects who convert to psychosis but not in non-converters. This was accompanied by a decreased alpha peak frequency in posterior cortical areas in converters. In another study however, no difference in EEG parameters has been detected between converters and non-converters (Lavoie et al., 2012). In relatives of schizophrenia patients, there is report of decreased alpha peak frequency (Clementz et al., 1994). Current data also suggest EEG abnormalities during NREM sleep in genetic high-risk subjects, while such data during prodromal stage are still missing. Although less prominent than in schizophrenia patients (Schilling et al., 2017), sleep spindle deficits exist in first-degree relatives of schizophrenia patients (D'Agostino et al., 2018; Manoach et al., 2014; Schilling et al., 2017) and are correlated with magical ideation and with thalamic glutamine + glutamate levels (Lustenberger et al., 2015). Likewise, decreased slow-waves are reported in first-degree relatives of individuals with schizophrenia (D'Agostino et al., 2018).

4. Thalamus-related anomalies as biomarkers

4.1. Potent endophenotypes

The reviewed literature reveals that several thalamus-related anomalies are present in unaffected relatives/siblings who do not meet the criteria for clinical high-risk (Table 2) and are potent endophenotypes. These include 1) reduced thalamus volume (Lawrie et al., 2001), 2) reduced GM particularly in the anterior region (Cooper et al., 2014; Harms et al., 2007; Pergola et al., 2017), 3) decreased NAA content (Legind et al., 2019; Tandon et al., 2013), 4) reduced structural and functional connectivity between thalamus and prefrontal cortex (Antonucci et al., 2016; Cho et al., 2019a), 5) decreased alpha peak frequency during resting EEG (Clementz et al., 1994), 6) reduced spindles and slow-waves during NREM sleep (D'Agostino et al., 2018; Manoach et al., 2014; Schilling et al., 2017). These strongly support that the integrity and function of several thalamic nuclei (i.e. anterior complex and TRN) and brain networks in which these nuclei are embedded (i.e. thalamo-prefrontal circuits) are affected by a vulnerable genetic background. Thus, sleep spindle deficits and possibly altered dynamic of EEG microstates could be the result of aberrant function of the TRN. Slow-waves decrease could be also associated with anomalies within TRN-thalamocortical networks (Crunelli et al., 2015) including the intralaminar and anterodorsal nuclei which contribute to these brain-wide synchrony (Gent et al., 2018). Some of these thalamus-related anomalies might be causal to cognitive deficits in children of individuals suffering from schizophrenia, most affected domains being memory and processing speed (Hemager et al., 2018). Thus, sleep spindle activity correlates with many cognitive domains and are particularly linked to consolidation of procedural and declarative memories during sleep (Clemens et al., 2005; Fogel and Smith, 2011; Manoach et al., 2014; Nishida and Walker, 2007; van der Helm et al., 2011). Of note, alpha peak frequency during resting EEG have been associated with cognitive and memory performance (i.e. working memory, speed processing) (Klimesch, 1999; Richard Clark et al., 2004). The genetic liability for thalamus anomalies in relation to psychosis is supported by preclinical studies. Several genes (i.e. GRM3, ERBB4, CACNA1I, DISC1) linked to schizophrenia (Andrade et al., 2016; Ma et al., 2018; Mei and Nave, 2014; Ripke et al., 2014; Saini et al., 2017) are highly expressed in the TRN and thalamus, encode proteins which influence thalamo-cortical circuits (Ahrens et al., 2015; Astori et al., 2011; Dawson et al., 2015; Gu et al., 2008; Richard et al., 2017; Turner and Salt, 2003; Wang et al., 2015). Genetic deletion of NMDA receptors in midline thalamic nuclei also produces schizophrenia-like phenotypes in mice (Yasuda et al., 2017). Noteworthy, in mice susceptible to oxidative stress, alterations of parvalbumin-expressing neurons in the TRN are present already during early postnatal development and precede impairments of parvalbumin interneurons in other subcortical (e.g. amygdala, globus pallidus, hippocampus) and cortical regions (e.g. anterior cingulate cortex) (Cabungcal et al., 2019). Early perturbation in thalamus integrity and function could therefore impact the developmental trajectories of other brain regions. Abnormal thalamic inputs into the cortex can affect normal maturation and refinement of cortical circuits (Anton-Bolanos et al., 2018). Proper development and maturation of the reciprocal connections between the thalamus and cortex require finely tuned interplay between the two regions (Anton-Bolanos et al., 2018; Lopez-Bendito, 2018). Defaults in the thalamus could potentially lead to alterations in the maturation of cortico-thalamic circuits. Data from EEG and fMRI suggest disruption of normal development of thalamo-cortical connectivity during adolescence in individual suffering from schizophrenia. Thus during rest, delta, theta, beta and alpha oscillations in patients resembles those observed in adolescent healthy individuals (Uhlhaas and Singer, 2011). Likewise, weak functional coupling between thalamus and prefrontal cortex in schizophrenia could result from a failure of increased coupling between prefrontal cortex and dorso-anterior parts of the thalamus (Fair et al., 2010). It is also tempting to propose that genetic-based thalamic alterations may render multiple brain circuits susceptible to environmental stresses leading to the emergence of psychosis and schizophrenia.

4.2. Candidate predictive biomarkers for functional outcome and psychosis

Current data strongly support that several thalamus-related anomalies appear or worsen as the disorder progresses into psychosis and schizophrenia (Table 2), suggesting they may be stage-specific biomarkers. Some are directly linked to the thalamus integrity. These include 1) progressive decrease in GM (assessed in the whole thalamus) from familial high-risk subjects to psychotic patients (Staal et al., 1998), 2) progressive GM reduction in the mediodorsal and posterior parts of the thalamus with the emergence of psychosis (Pergola et al., 2017), 3) low level of glutamate during the prodromal stage (Allen et al., 2015; Fusar-Poli et al., 2011b). Other potential biomarkers are more circuit-based anomalies. They include 1) progressive aberrant functional coupling between thalamus and several brain regions such prefrontal and sensory-motor cortices, basal ganglia, and cerebellum (Anticevic et al., 2015; Bernard et al., 2017; Cao et al., 2018), 2) progressive increase in delta and theta power and decrease in alpha peak frequency in resting EEG (van Tricht et al., 2014). Several of these anomalies deserve attention as potential predictive biomarkers for functional outcome and transition to psychosis. However, most published studies are cross-sectional and do not inform about the predictive value of the reported alterations in terms of future outcome. To date, the most promising candidates as predictive biomarkers for the conversion to psychosis are the abnormal functional coupling between thalamus, prefrontal cortex, sensorimotor areas, basal ganglia and cerebellum. Several prospective studies have shown that such aberrant functional connectivity is associated with worsening of positive symptoms and is more pronounced in individuals who convert to psychosis within the following 1–2 years (Anticevic et al., 2015; Bernard et al., 2017; Cao et al., 2018). These support that the transition into psychosis involves an imbalance between several large-scale networks encompassing the thalamus. Likewise, glutamate within the thalamus represents another candidate biomarker, as low glutamate level has been associated with poor functional outcome (Allen et al., 2015). The predicting value of resting EEG has also been examined. One study reports that increased frontal delta and theta power and decreased occipito-parietal alpha peak frequency contribute to short-term prediction of a first psychotic episode (van Tricht et al., 2014). By contrast, Zimmermann et al. (2010) found that the power in delta, theta, beta1, and beta2 bands in frontal-central electrodes carry a predictive value for transition only when combined with clinical scores. In both cases, the authors suggest that EEG parameters could also be helpful to stratify prodromal subjects

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into biologically or clinically relevant subgroups. Meanwhile, machine-learning algorithms could predict psychosis from specific pattern of beta and gamma oscillations (Ramyead et al., 2016). Another study has however failed to predict psychosis in CHR when using the power of frontal delta and alpha and occipital-parietal beta1 oscillations (Clark et al., 2016). The lack of consistency across studies may lie in part on differences in the EEG readouts selected for the prediction assessment. Nevertheless, longitudinal prospective investigations on resting EEG during prodromal stage is of high interest and may eventually lead to the identification of validated EEG parameters as predictive biomarkers. Thus, resting EEG and functional fMRI coupling between thalamus and cortical and subcortical regions may become useful readouts to refine the assessment of risk to develop schizophrenia in clinical high-risk populations.

Current literature supports that the thalamus constitutes a node within multiple large-scale brain circuits that are altered early on during the course of the disorder. But due to the limitations of imaging techniques in terms of resolution, contrast and analytical methods, most studies have considered the thalamus as a whole despite the fact that each individual nucleus belongs to distinct networks. Overall, the anterior, mediodorsal, and posterior regions appear most affected. Progress in imaging techniques and analytical approaches open new avenues to investigate thalamic subregions associated with specific circuits (Akram et al., 2018; Najdenovska et al., 2018). The mediodorsal nucleus and pulvinar, both of which are affected in early psychosis and chronic patients, are now more accessible to longitudinal prospective investigations of gray matter density, diffusion parameters (extracted from diffusion-weighted MRI data). Characterization of the dynamic alterations within mediodorsal and pulvinar and their respective connected regions (see for connectivity: Ouhaz et al., 2018; Pessoa and Adolphs, 2010) during the prodromal and first psychotic episode stages will be helpful to determine the contribution of these regions and their associated circuits to the emergence of psychosis, worsening of cognitive functions, and overall functional outcome. In this respect, parallel assessment of cognitive domains known to depend on circuits encompassing these nuclei (i.e. working memory and cognitive flexibility for the mediodorsal nucleus, spatial visual attentional tasks for the pulvinar) is of particular interest. A better understanding of the temporal changes occurring at thalamic nucleus level will be helpful for scrutinizing, via translational studies, the biological mechanisms involved in the progression of the deficits and symptoms associated with schizophrenia.

5. Conclusion

Thalamus abnormalities appear a central core of schizophrenia pathology. The review presents solid evidence for multiple thalamus-related anomalies throughout the different stages of schizophrenia, including in genetic and clinical high-risk subjects. This review also highlights the need to perform further specific investigations on several readouts that are still missing in either clinical or genetic high-risk individuals (see Table 2). Several alterations are potent endophenotypes and may constitute vulnerability factors for psychotic disorders (i.e. reduced thalamic volume, low NAA level, decreased alpha peak frequency in resting EEG, reduced spindles and slow-waves during NREM sleep). Other anomalies carry a predictive value for transition to psychosis as they are present during the prodromal stage and more prominent in CHR with poor outcome (i.e. low glutamate level, altered connectivity within cortico-striato-thalamic loops). The primary dysfunctions could originate within the thalamus itself but may also stem from alterations in other brain structures belonging to brain networks encompassing the thalamus. The thalamus constitutes an entry point to investigate the emergence and progression of circuit-based anomalies associated with specific cognitive domains and/or symptoms. In this respect, mediodorsal nucleus and pulvinar are particularly affected. Longitudinal prospective assessment of the integrity and function of these two large nuclei and their associated circuits during the prodromal stage is therefore warranted. Together with the use of modern optogenetic and chemogenetic approaches to probe the organization and function of these circuits (Schmitt and Halassa, 2017) in relevant animal models, this may unveil biological mechanisms that contribute to the emergence of this psychiatric disorder.

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