Executive functions assessment in very preterm children at school age:

A pilot study about a clinical and experimental approach

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Abstract

While the survival rate of very preterm (VPT) infants has increased in the last decades, they are still at risk of developing long-term neurodevelopmental impairments, especially regarding self-regulatory abilities, and goal-directed behaviours. These skills rely on executive functions (EFs), an umbrella term encompassing the core capacities for inhibition, shifting, and working memory. Existing comprehensive tests are time-consuming and therefore not suitable for all paediatric neuropsychological assessments. The Flanker task is an experimental computer game having the advantage to last less than ten minutes while giving multiple EFs measures. Here, we tested the potency of this task in thirty-one VPT children aged 8-10 years during their clinical assessment. First, we found that VPT children performed in the norm for most clinical tests (i.e., WISC-V, BRIEF, and NEPSY) except for the CPT-3 where they were slower with more omission errors, which could indicate inattentiveness. Second, some Flanker task scores were correlated with standardized clinical testing without resisting to multiple comparisons correction. Finally, compared to full-term children, VPT children showed poorer performance in global EFs measure and lower accuracy in the Flanker task. These findings suggest that this child-friendly version of the Flanker task demonstrated a reasonable sensitivity in capturing EFs with good discrimination between VPT and term children despite VPT children’s mild difficulties. It may represent a promising tool for neuropsychological assessments and be suitable as a screening test, provided further validating larger studies. Moreover, while VPT schoolchildren globally display normal intelligence, subtle difficulties that seem to relate to EFs are observed.

Keywords: very preterm birth, executive functions, neuropsychological tests, cognitive development, flanker task

Introduction

In the past few years, preterm births represent 10% of the births worldwide, out of which 10% are very preterm births (i.e., birth occurring below 32 gestational weeks) (Blencowe et al., 2012; Chawanpaiboon et al., 2019). Although the survival rate has increased thanks to healthcare advances, very preterm children remain at risk of developing long-term neurodevelopmental impairments, especially cognitive deficits (Doyle et al., 2021; Joseph et al., 2016; Marlow et al., 2021). Difficulties in higher-order cognitive control, such as executive functions, are consistently reported. While the performance of preterm children in many different tasks evaluating executive functions and attention has been well studied (for reviews see Aarnoudse-Moens et al., 2009; Mulder et al., 2009; Taylor & Clark, 2016), assessment of executive functions in the clinical context is still time-consuming and generally depends on multiple tests or extensive batteries. In a population at greater risk of attentional deficits, such multiple time-consuming tests are not always appropriate. Indeed, with attentional difficulties, it can be complicated to complete long batteries of tests, and therefore the results could be the consequence of an attentional problem and do not necessarily show the ability being assessed. In addition, it is important to increase the attractivity of the tasks to improve children's involvement in the assessment (Lumsden et al., 2016). The clinical assessment would benefit from simpler, faster, and game-like tasks.

Executive Functions

Executive functions have been well studied and defined in many different ways (Baggetta & Alexander, 2016). Generally speaking, they are considered as higher-order cognitive processes (Lezak et al., 2004) largely supported by the frontal cortex (Miyake et al., 2000). These functions allow us to generate goal-directed behaviors (Baggetta & Alexander, 2016). There is a good agreement that there are three core functions –working memory, inhibition, and shifting. Working memory is the faculty to maintain information in the short memory to actively use it at the same time (Cowan, 2008). It embeds storage and processing by both organizing the information for an efficient memorization and using information for current tasks. This function also contributes to attribute sense by integrating things together as well as making plans (Diamond, 2013). Second, inhibition is the faculty to deliberately refrain from automatic responses (Miyake et al., 2000). It is a top-down process enabling an adequate response despite salient stimuli or instinctive responses (Diamond, 2013). Finally, shifting represents the ability to switch between two tasks (Monsell, 1996). It measures the cognitive flexibility namely the capacity to adapt ourselves to a changing situation (e.g., errors, an unforeseen event) dynamically (Diamond, 2013). This feature involves both working memory (i.e., the capacity to maintain both rules in memory) and inhibition (i.e., to inhibit the incongruent rule). Therefore, it is defined as the most complex executive function, becoming mature later than the other functions (Best & Miller, 2010)

Very preterm children likely display a global impairment in all these domains (Anderson et al., 2004). This is mainly due to specific brain injuries related to prematurity and immaturity. While severe insults are becoming less frequent, very preterm infants present more subtle brain injuries merged under the umbrella term “encephalopathy of prematurity” (Volpe, 2009). This encompasses diffuse periventricular leukomalacia, and neuronal and axonal injury, affecting both white matter and grey matter. Some of those damages are affecting areas related to executive functions, predicting general long-term difficulties (Peterson et al., 2000; Woodward et al., 2006).

At the behavioral level, all three core functions of executive abilities have been evaluated in preterm children. Regarding working memory, whereas Ritter et al. (2013) first found that preterm children perform worse on working memory tasks than term children at the age of eight, they meet the standard by the age of twelve (Ritter et al., 2014). In this study, they have then differentiated the cognitive aspect (i.e., performance in neuropsychological tests) and the more ecological behavioral aspect (i.e., parental questionnaire about the real-life functioning) of executive functions (Ritter et al., 2014). By making this differentiation, they have observed no differences between term and preterm children in terms of cognitive testing, however, these children have more working memory difficulties in their daily life. A second distinction being made is between spatial and non-spatial tasks. By doing so, Mulder et al., (2009) found only poorer working memory performance with spatial tasks in their review. Concerning inhibition, while mixed results have been reported (Mulder et al., 2009; Réveillon et al., 2018), it seems that preterm children present a deficit around six years of age which is then caught up in young adolescence. Finally, diverse studies have investigated shifting skills in very preterm children, highlighting that this is one of the most demanding functions. Indeed, eight to twelve years old preterm children were observed to perform worst on shifting cognitive tasks than full term children, whereas it is not the case with working memory and inhibition tasks (Aarnoudse-Moens et al., 2012; Ritter et al., 2014). A delay in shifting performance was observed in preterm children who performed worse than term children at eight years old, but who caught up by the age of twelve (Ritter et al., 2013). It should be noted that it exists a large number of different tasks and these performances depend closely on the experimental paradigm on which the task is based (Mulder et al., 2009). In conclusion, most of the studies suggest delayed development of core mechanisms of executive functions in preterm children but a recent meta-analysis conducted by van Houdt et al., (2019) did not show any improvement regarding their working memory, cognitive flexibility, or inhibition. Moreover, some difficulties may remain in adolescence and in adulthood (Nosarti et al., 2007). Very preterm adolescents show poorer executive function abilities, which could also explain lower academic skills (Burnett et al., 2013; Litt et al., 2012; Luu et al., 2011). Today's very premature adults are still at increased risk for impaired executive functions and lower social and emotional competencies as well as lower IQs and lower scholastic attainment (Eves et al., 2021; Johnson & Marlow, 2017; Ni et al., 2021). Thus, executive functions are commonly assessed, and it is critical to detect these difficulties at an early age to better support their development and provide adequate support at school.

During a standard clinical examination, executive functions are usually evaluated with several standardized tests (in the current study we report the routine clinical evaluation in the form of selective items of the Wechsler Intelligence Scale for Children (WISC-V), the Behaviour Rating Inventory of Executive Function (BRIEF), the NEPSY, and the Conners Continuous Performance Test (CPT3)). To carrying out the whole battery is time-consuming (~35 minutes) and is unsuitable for some assessment situations, especially with a population at risk of attention deficits such as preterm children. Moreover, complex tasks could lead to task impurity problems and might reflect other cognitive process (Miyake, Emerson, et al., 2000). Indeed, executive functions are intertwined with other cognitive functions and the completion of complex task requires also non-executive functions capacities (e.g., visual, number, spatial processing). Therefore, it would be helpful to have a simpler experimental tool to assess the diverse executive functions promptly, either to be used in case where the whole battery cannot be administered or to be applied as a screening test.

Flanker Task

The Flanker task, which is a selective attention task, was first designed for adults by Eriksen and Eriksen (1974). It consists of a target letter (i.e., the one appearing above the fixation cross) accompanied or not by distractive letters (i.e., identical as the target, same response as the target, different response as the target, with or without the same features as the target). (Cuevas & Bell, 2014; Garon et al., 2008; Klenberg et al., 2001). Even if the Flanker task does not produce a specific metric of attention, it has the advantage to require and rely on attentional skills particularly due to the different types of distractors. In this original version, the participants must press a right button if an H or a K was presented and a left one if it was an S or a C. Since then, various child-friendly versions of the task have been created (Diamond et al., 2007; McDermott et al., 2007; Rueda et al., 2004). Some of them have been used with preterm children. Using the arrows version (i.e., letters were replaced by arrows), Aarnoudse-Moens et al. (2012) found no differences in response time or omission and commission errors between preterm and term eight-year-olds. De Kieviet et al. (2014) also report similar results concerning performance (i.e., accuracy). However, they found that preterm children were more sensitive to interference from incongruent stimuli that impacted their response time. Réveillon et al., (2016, 2020) have recently used an emotional version of the task, where congruent and incongruent emotional faces were used. While they reported no impact of emotional characteristics on preterm and term children, preterm children responded faster to the go-signal presentations. This was interpreted as impulsivity. Moreover, they presented inhibition difficulties during the no-go trials and when they had a longer delay between stimuli.

While studies using a different version of the same paradigm have found various and contradictory results, none has related the Flanker task to standardized clinical evaluations. Consequently, there is no clinical Flanker task despite extensive research demonstrating its value.

Thus, here we choose to use a child-friendly version of the Flanker task created by Schonert-Reichl et al., (2015) where arrows were replaced by fishes. The choice of the fishes preserves the directional component while being more attractive to children. Fishes are the stimuli in the version of the Flanker subtest of the Attention Network Test (ANT) (Fan et al., 2002) and the NIH Toolbox Cognition Battery (Zelazo et al., 2013). But in their task, in addition of the standard version, Schonert-Reichl et al. (2015) added two conditions : the reverse flanker, and the mixed trials. Therefore, this task has the advantage to allows for a gradation of difficulty, with increasing demands on executive functions as the blocks progress. Moreover, despite these three blocks, the task lasts only 6 minutes with the advantage to be adapted for children from 4 years of age (Denervaud et al., 2019). By measuring the accuracy of individual blocks, inhibition and global executive functions can be assessed, and response times can be used to calculate the shifting (see the Method for exhaustive details).

Therefore, we 1) first aimed to describe the cognitive profile of our cohort of very preterm schoolchildren assessed with routine and extensive clinical tools (including the WISC-V, the BRIEF, the CPT3, and the NEPSY). Given their neonatal status, we expected to observe subtle impairments and below-standard performances. The 2) second purpose of our study was to test and compare a child version of the Flanker task with the standard clinical tests in very preterm schoolchildren. As there is no diagnosis of executive function deficit per se, neuropsychological tests assess some specific executive functions (i.e., *Working Memory Index* from the WISC-V, *Design Fluency* subtest of the NEPSY), as well as associated cognitive measures such as processing speed (i.e., *Processing Speed Index* from the WISC-V) (Mulder et al., 2011; Rose et al., 2011) and attention (i.e., CPT3) (Cuevas & Bell, 2014), for which correlations with the different executive functions scores of the Flanker task are expected. Indeed, many researchers have found that processing speed mediates executive functions and their development (Fry & Hale, 1996, 2000; Rose et al., 2011) by being accountable for the variance in working memory and inhibition (McAuley & White, 2011). Attentional capacities are known to be related with executive functions measures, especially with the working memory (Oberauer, 2019). Moreover, the CPT3 has been found to have small correlations with the Comprehensive Executive Functions Inventory Parent Form (Conners, 2014). In addition, given mixed results (Ritter et al., 2014; Toplak et al., 2013), we wanted to investigate its relationship with reported behavioral measures (i.e., BRIEF questionnaire). Moreover, 3) we tested the Flanker task's ability to discriminate between very preterm children with and without executive functions difficulties assessed through the clinical measures. Finally, 4) if the Flanker task was correlated with the clinical tests, we aimed to explore the comparison of executive functions in very preterm children with those of term schoolchildren through this simpler and shorter experimental task. Given their fragilities in executive functions, we expected that very preterm children scored lower than term children on the different measures. And, in addition, we addressed its ability to discriminate the very preterm and term children. Indeed, comparing and discriminating very preterm children from term children ensures that very preterm children show different executive functions patterns. Given that the Flanker task provides multiple executive function measures in only 6 minutes, the ultimate aim of the present study was to evaluate the possibility to integrate a child-version of the Flanker task in the clinical assessment.

Method

Ethics

This study was part of the project *Long-term impact of early nutritional and pain management in very preterm infants on brain health and function* and was embedded in a longitudinal study enrolling very preterm neonates at birth with long-term follow-up at eight to ten years of age. The study was approved by the local ethical committee (CER-VD, ID 2019-01056). Each parent gave their written informed consent for their child, and each child gave their oral consent.

Participants

Very Preterm Children

Fifty-one very preterm neonates born between February 2011 and May 2013 were recruited for the main project at their birth. For the current study, ten children were not included/recruited due to death (n=2), lost contact at a previous time point (n=2), unreachable parents (n=2), complicated social situations (n=2), or refusal to participate (n=2). In total, forty-one very preterm children took part in this study as part of their follow-up at the developmental unit of the University Hospital of Lausanne between July 2020 and October 2021. Data from ten children were excluded from the analyses due to incomplete data or technical issues during the task. The final sample consisted of thirty-one very preterm children (M_{age} = 8.87, SD = 0.453; age range = 8.25 years – 10.00 years, 16 girls) born before 32 gestational weeks including 19 being extremely preterm (birth occurring before 28 gestational weeks).

The initial inclusion criterion was to be born before 32 gestational weeks and exclusion criteria included major malformation or genetic syndrome, severe cardiorespiratory instability preventing MRI completion or intraventricular hemorrhage >II on early cerebral ultrasound. The current only exclusion criterion was parents' refusal to be informed of incidental findings on MRI and EEG, two tests that were part of the main project.

Full-term Children: Reference Group

Thirty-one term schoolchildren (M_{age} = 8.90, SD = 0.552; age range = 7.80 years – 10 years, 16 girls) from an existing database were selected based on age ($t(60)=0.268$, $p=.79$) and gender. They also performed the Flanker Task as part of a parallel study about neurodevelopment and school experience but have not done the clinical evaluation (i.e., WISC-V, the BRIEF, the CPT-3, and the NEPSY). They were recruited in the French-speaking side of Switzerland between 2018 and 2021 by one of the co-author (Denervaud et al., 2019).

Executive Functions Measures

Flanker Task Measures

This is an attentional computerized test providing different executive function measures. The fish version of the Flanker task from Schonert-Reichl et al., (2015) where the arrows are replaced by fishes was presented using Presentation® software (Version 23.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com) Children were asked to feed fishes. Fishes were presented in a line and children were instructed to feed the target fish by inhibiting distractors (for distractors conditions examples, see Figure 1) by pressing a key on the same side from which the fish was looking. Fishes were presented f or a maximum duration of 1500ms, during which the children could response. Once they had pressed a key, or after 1500ms, the next trial was presented directly. The task was composed of three blocks, the first two comprising 17 trials and the final one 65 trials. In the first block, blue fishes were presented, and the target was set in the middle. In the second block, the fishes were pink, and the children had to focus on the four other fishes flanking the central one. Both blocks were preceded by a training session that was repeated if they made too many errors. In the final block without training, both rules were mixed, children were instructed to feed the target fish according to their color.

Based on previous work in the field (Denervaud et al., 2019; Röthlisberger et al., 2012; Schonert-Reichl et al., 2015), we computed multiple scores:

- the general accuracy as the mean accuracy of the three blocks combined (i.e., the percentage of all correct responses)
- inhibition as the accuracy on the second block (i.e., the percentage of correct responses as the ability to inhibit the former rule)
- global executive functions as the accuracy on the third block (i.e., the percentage of correct responses as the ability to recruit the three core executive functions). The last block is the highest demanding of the three executive functions. Children had to recall both rules to use them adequately (i.e., working memory), they had

to inhibit previous rules and incongruent distractors (i.e., inhibition) and to flexibly apply the correct rule (i.e., shifting when needed).

- switch-cost as the flexibility measure (i.e., the mean of RTs differential between successive trials with a switch in the rules on the third block)
- the neutral trials' response time (i.e., the mean response time of trials with no-response distractors)
- the congruent trials' response time (i.e., the mean response time of trials with the same response distractors)
- the incongruent trials' response time (i.e., the mean response time of trials with other-response distractors)

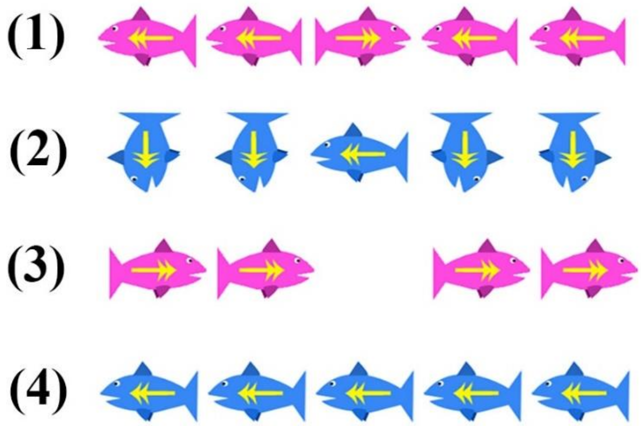

Figure 1. Examples of the different conditions; (1) other-response distractors, (2) no-response distractors, (3) no distractors, and (4) same-response distractors.

Clinical Measures

Wechsler Intelligence Scale for Children 5th Edition (WISC-V) (Wechsler, 2016)**.** This is a battery assessing the intelligence of children through different subtests. We first selected the *Working Memory Index* composed of the *Picture Span* and the *Digit Span* subtests. In the *Picture Span* subtest, children were asked to remember a sequence of pictures in the right order and select them from a larger picture array. Concerning the *Digit Span* subtest, children were instructed to remember a sequence of numbers in the correct, reverse, and ascending order. Secondly, we selected the *Processing Speed Index* composed of the *Code* and the *Symbol Search* subtests. In the *Code* subtest, children were given a digit-symbol code they had to transcribe using a specific key. In the *Symbol Search* subtest, children were presented with a line of symbols in which they had to detect whether the target is present or not. For both indexes, the scores were computed as the sum of the standard scores from the two subtests and then computed as a composite score.

Conners Continuous Performance Test 3rd Edition (CPT3) (Conners, 2014)**.** This computerized test evaluates different aspects of attention. Children were asked to press a key when they saw a letter except when the letter "X" was presented. It lasted 14 minutes and there were 360 trials. Seven scores were computed, transformed into T-scores, and retained for the analyses: detectability as the ability to differentiate non-targets from targets, the omission error as the failure rate to respond to the targets, commission error as the response rate given for the non-targets, perseveration as the rate of random, anticipatory or repeated responses, response time for correct responses, changes in response time during the task and vigilance as the performance depending on the variation of the inter-stimulus interval.

Nepsy – II (Korkman et al., 1997)**.** This is a battery evaluating the child's neuropsychological skills via various tests. We selected the subtest *Design Fluency* to measure specific executive functions including cognitive flexibility, working memory, and initiation capacity. Children were asked to draw as many unique designs as possible by connecting five dots in each time frame, one time with a structured positioning and a second time with a random positioning. The score was computed as the sum of the number of designs of the structured array subtest and the random array subtest and transcribed into a standard score.

Behaviour Rating Inventory of Executive Function (BRIEF) (Roy et al., 2013)**.** This validated questionnaire assesses the different executive functions in the family and school environment. For the present study, we retained the inhibition, working memory, and flexibility scores. Parents were asked to fill out this questionnaire by rating each 86 statements about their child's behaviour by whether it has rarely/never/often been a problem in the past 6 months. The scores were computed as the sum of each statement score for each category and then transcribed into T-scores.

Procedure

Very preterm children were tested separately at the University Hospital of Lausanne in a dedicated quiet room in the development follow-up unit. Testing was computer- and paper-based. As these tests are part of a larger clinical and research assessment, they were spread over two half-days. Generally, clinical evaluation (i.e., WISC-V, CPT-3, and parts of the NEPSY) was made on the first half-day and research assessment (i.e., two computer-based tests, MRI, and EEG) as well as a motor exam was performed on the second half-day. Not all participants completed the whole testing, and the order was sometimes changed.

Full term children were not assessed with the same tests. They performed the Flanker task alongside other experimental tasks and an MRI session either at the University Hospital of Lausanne or at their school.

Both groups were mostly tested by the same group of experimenters.

Data Analyses

Population Profile Description

We computed the descriptive statistics (i.e., the mean, and standard deviation of the T scores) of the clinical testing to describe the profile of our very preterm population according to the mean score of the general population.

Flanker Testing

Flanker data were pre-processed using Excel. Training trials were excluded and only correct trials with a valid response time (i.e., RT± 2*SD*) were included in the analyses. General accuracy, inhibition, and global executive function measures were calculated as the percentage of correct trials within the valid response time interval among all trials. Then, the statistical analyses were performed using R.3.6.3 (R Core Team, 2022) and, in part, Jamovi (Version 0.9) Computer Software.

Due to the non-normal distribution of several variables, Spearman's multiple correlations between measures of executive function from Flanker task measures (i.e., experimental measures) and clinical data were performed. As we expected positive correlations between the NEPSY, BRIEF and WISC-V subtests and the Flanker measures, positive one-sided correlations were conducted. Given negative correlations were expected between the three errors scores of the CPT-3 and the accuracy of the Flanker task and between the perseveration and commission errors of the CPT-3 and the inhibition of the Flanker task, negative one-sided correlations were conducted. For all other correlations, two-sided correlations were performed. The statistical significance level was set at $p \leq 0.05$, and the false discovery rate correction was applied for multiple comparisons. Then we computed receiver operating characteristic (ROC) curves for the global executive functions and general accuracy, as well as areas under curves (AUCs) to evaluate the discriminative power to differentiate executive functions difficulties among very preterm children. Very preterm children with executive functions difficulties were defined as having 3 or more scores with clinical significance in several neuropsychological tests (i.e., WISC-V, CPT-3, NEPSY) or very low scores in one test to represents either a general deficit or a severe impairment. Four children were removed from this specific analysis due to incomplete testing.

Finally, due to normality violations, Welch's t-tests were conducted between very preterm and term-born children on measures of the Flanker task. The statistical significance level was set at $p \leq 0.01$.ROC curves for the logistic model of the Flanker task and for each of its sub-measures individually, as well as AUCs were computed to discriminate very preterm and full-term children. As a rule of thumb, an AUC score between 0.6 and 0.7 is considered between poor and moderate, a score between 0.7 and 0.8 as a fair classification, a score between 0.8 and 0.9 as a good classification and a score >0.9 as excellent (Hond et al., 2022).

Results

Population Profile

Clinical Data

Neonatal Period. Concerning the neonatal characteristics, the gestational age of the participating children was between 25 and 31 weeks ($M_{gestationalage}$=27.10, *SD*=1.51), with a birth weight between 610 and 1590 grams ($M_{birthweight}$=948, *SD*=244). Eight very preterm infants out of the thirty-one were diagnosed with moderate or severe bronchopulmonary dysplasia, and two infants presented with an intraventricular haemorrhage more severe than grade II. No cystic periventricular leukomalacia was reported. Finally, only one child had retinopathy of prematurity that healed without treatment.

School-age. Parental socio-economic status assessed with the Largo scale (Largo et al., 1989) ranged from 1 to 6 (M_{SES}=3.11, *SD*=1.45), 1 being the highest score and 6 the lowest. According to the parents, fourteen children presented learning difficulties at school: in French (i.e., writing and reading) (n=11), in Math (n=4), in other school topics (n=2), in motor skills and coordination (n=1), in global learning difficulties (n=2) and in memory (n=1). Out of them, seven needed educational support; provision of time or facilities to encourage attention (n=3), non-specific support (e.g., integration support) (n=3), specialized educational support (e.g., with an adapted program) (n=3). Fourteen children were having some attentional difficulties of varying severity, including hyperactivity treated with medication (n=1). Moreover, thirteen followed a therapy; speech therapy (n=10), occupational therapy (n=2), and psychomotor therapy (n=4).

Executive Functions

The different executive functions and related measures were assessed through diverse approved neuropsychological tests and compared to the mean score in the general population (see *Table 1* for exhaustive distribution details of their scores).

WISC-V. Very preterm children general mean was within the norm in working memory (*M*=103, *SD*=16.2; range 65-127) and processing speed (*M*=99, *SD*=15.9; range 69-135). This was the case for 62% of very preterm regarding the working memory and 69% regarding the processing speed.

CPT-3. They obtained a high average score (i.e., slightly below average performance) for detectability (*M*=56, *SD*=7.76; range 43-72) and omission errors (*M*=58.6, *SD*=14.4; range 42-90) indicating a slight clinical fragility. However, 65% of them performed within the norms for the detectability score, and 55% were within the norms regarding their omission errors. They scored on average for the commission errors (*M*=53, *SD*=7.60; range 38-71), for the perseveration errors (*M*=53, *SD*=10.2; range 43-84), this was the case for 70% of them. The group mean was also on average for the vigilance (*M*=48.9, *SD*=11.7; range 32-75), 47% of the children scored within average and 38% above the norms. Results were more mixed for their changes in reaction time over time, their general mean was average (*M*=53.9, *SD*=14;

range 38-82), but this represented only 38% of them, with 31% scoring above and 31% below the norms. They scored slightly below the norm, being generally a little slow (i.e., defined as a score between 55-59 (Conners, 2014)) in their hit reaction times (*M*=56.4, *SD*=9.78; range 42-85), 50% of the children reacted slower than the norm.

NEPSY. Group mean score for the executive functions measure were also within the norm (*M*=10, *SD*=2.89; range 5-16), indeed 70% of them scored within the norms.

BRIEF. Parents rated their children within the average on the inhibition subscale (*M*=51.1, *SD*=9.98; range 36-73), this was representative of 85% of them. They scored one standard deviation above the normative sample mean but their performance remained below the level of clinical significance (i.e., <65 (Gioia et al., 2000)), on flexibility (*M*=62.1, *SD*=12.3; range 41-91) and working memory subscales (*M*=60.3, *SD*=15.9; range 36-86) and respectively 62% and 70% of them scored within the norms.

		Number of very preterm children (%)		
		Below the norms	Between the norms	Above the norms
WISC-	Working Memory	5 (17%)	18 (62%)	6 (21%)
	Processing Speed	5 (17%)	20 (69%)	4 (14%)
CPT-3	Detectability	7 (27%)	17 (65%)	2 (8%)
	Omission Errors	8 (30%)	14 (55%)	4 (15%)
	Commission Errors	5 (19%)	18 (70%)	3 (11%)
	Perseveration Errors	4 (15%)	18 (70%)	4 (15%)
	Response Time	13 (50%)	13 (50%)	NA
	Response Time Changes	8 (31%)	10 (38%)	8 (31%)
	Vigilance	4 (15%)	12 (47%)	10 (38%)
NEPSY	Drawing Fluency	4 (14%)	21 (75%)	3 (11%)
BRIEF	Inhibition	4 (15%)	22 (85%)	NA
	Flexibility	10 (38%)	16 (62%)	NA
	Working Memory	8 (30%)	18 (70%)	NA

Table 1. Details of the distribution of the very preterm children scores at the various neuropsychological tests. *Note.* The BRIEF does not produce scores above the norms as well as the response time score of the CPT-3.

Flanker

Comparison With the Standardized Clinical Batteries for Very Preterm Children

Spearman correlations were performed between the executive functions scores from the experimental Flanker task and the scores from validated neuropsychological tests (Table 2).

Significant correlations were observed between the Flanker task and the WISC-V and the CPT-3 (see *Figure 2*).

Regarding the WISC-V, we found strong positive correlations between the inhibition score from the Flanker task and the working memory score ($r(27)=.372$, $p=.023$), and the processing speed score ($r(27)=.405$, $p=.015$) from the WISC-V. There were also positive correlations between the accuracy score from the Flanker task and the processing speed score ($r(27)=.443$, $p=.008$) from the WISC-V.

Concerning the CPT-3, negative correlations between the perseveration errors score from the CPT-3 and the inhibition score ($r(24)=-.356$, $p=.037$), and the accuracy score ($r(24)=-.354$, $p=.038$) from the Flanker task were found.

None of these correlations remained significant after applying the False Discovery Rate for correcting multiple comparisons.

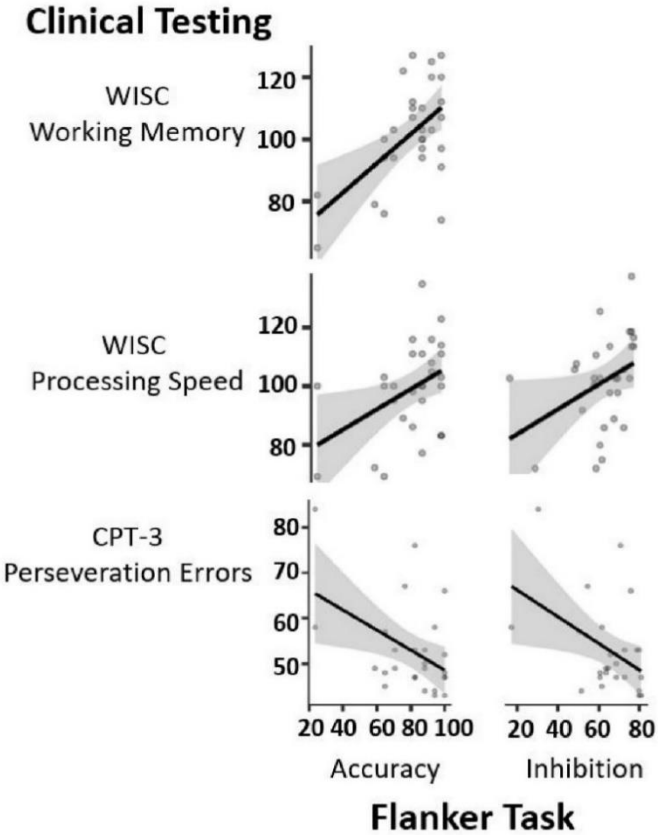

Figure 2. Significant Spearman correlations showing the relation between the accuracy and the inhibition of the Flanker and the working memory and the processing speed of the WISC-V and the perseveration errors score of the CPT-3.

There were no significant correlations with the NEPSY and the BRIEF results (for details, see *Table 2*).

		Flanker Task Measures			
		Accuracy	Inhibition	Executive Functions	Switch Cost
WISC-V	Working Memory	0.28	0.37*	0.14	0.16
	Processing Speed	0.44**	0.41*	0.30	0.18
CPT-3	Detectability	-0.15	-0.11	-0.20	0.27
	Omission Errors	-0.25	-0.13	-0.15	0.02
	Commission Errors	-0.07	-0.14	-0.13	0.33
	Perseveration Errors	-0.35*	-0.36*	-0.32	0.24
	Response Time	-0.35	-0.31	-0.18	-0.20
	Response Time Changes	-0.03	-0.14	0.02	-0.14

	Vigilance	0.09	0.07	-0.04	0.10
NEPSY	Drawing Fluency	-0.10	0.11	-0.12	0.21
BRIEF	Inhibition	-0.261	-0.28	-0.17	-0.19
	Flexibility	-0.04	0.04	0.05	-0.27
	Working Memory	-0.16	-0.02	-0.15	0.06

Table 2. Correlations between Flanker task measures and Clinical Data. Note. * p <.05, ** p <.01, *** p < .001. Missing Data: WISC-V (n = 1), CPT-3 (n = 4), NEPSY (n = 2), BRIEF (n = 4).

Discrimination of Executive Function Difficulties in Very Preterm Children

All measures of the Flanker task were only able to discriminate moderately or poorly very-preterm children with executive functions difficulties from those with small or without difficulties (for details, see *Table 3*).

	AUC	95%CI	Children with EFs difficulties correctly classified	Children without EFs difficulties correctly classified
General Accuracy	0.63	0.40-0.85	8 (100%)	7 (41%)
Inhibition	0.68	0.42-0.95	5 (63%)	14 (82%)
Global Executive Functions	0.59	0.35-0.82	8 (100%)	6 (35%)
Switch Cost	0.68	0.34-0.87	7 (88%)	8 (47%)
Congruent RT	0.51	0.22-0.81	4 (50%)	13 (76%)
Incongruent RT	0.62	0.30-0.93	2 (25%)	17 (100%)
Neutral RT	0.54	0.25-0.84	2 (25%)	16 (94%)

Table 3. AUC coefficients of the ROC analysis discriminating very-preterm children with executive functions difficulties from very-preterm children without executive functions difficulties

Very Preterm vs Term Children's Comparison

Very preterm children (*M*=65.49, *SD*=14.3) compared to term children (*M*=76.15, *SD*=7.98) significantly had a lower accuracy in the Flanker task, $t(47.1) = 3.62$, $p<.001$. Moreover, very preterm children (*M*=57.42, *SD*=15.2) compared to term children (*M*=70.37, *SD*=9.03) also obtained lower global executive functions scores, $t(48.9) = 4.08$, $p = <.001$.

Despite very preterm children having a lower switch cost ability score than term children, the difference was not significant. Moreover, regarding their response time, even if very preterm children were faster than term children in all conditions, there was no significant difference either. The rest of the comparisons were not significant either (for more details, see *Table 4*).

	Group				
	Very Preterm Children	Term Children	*Welch's t*	*p* value	ε
Neutral Response Time	841.8(135.82)	879.3(147.10)	1.04	0.301	0.26
Congruent Response Time	785.93(116.3)	822.09(131.56)	1.15	0.256	0.29
Incongruent Response Time	818.08(140.7)	857.60(125.18)	1.17	0.247	0.30
Accuracy	**65.49(14.3)**	**76.15(7.98)**	**3.63**	**<.001*** **	**0.92**
Inhibition	80.65(20.00)	81.78(17.47)	0.24	0.812	0.06
Executive Functions	**57.42(15.2)**	**70.37(9.03)**	**4.08**	**<.001*** **	**1.04**
Switch Cost	-5.00(71.4)	-1.32(65.09)	0.212	0.833	0.05

Table 4. Flanker task results from the comparison between very preterm and term children. Note. Results are expressed as means and standard deviations, Cohen's d was used as effect size

Very Preterm vs Term Children's Discrimination

The general model with all sub-measures of the Flanker task performed an AUC of 0.827 (95% confidence interval (CI) = 0.609–1) for differentiating between very preterm and term children, 27 (87%) full term children and 25 (81%) very preterm children were correctly classified. Regarding the two sub-measures for which significant differences between very preterm and term children were found, the accuracy differentiated the two populations with an AUC of 0.759 (95% CI = 0.636-0.881; 28 (90%) full term children and 18 (58%) very preterm children were correctly discriminated), and the executive functions showed an AUC of 0.771 (95% CI = 0.653-0.889; 29 (94%) full term children and 16 (52%) very preterm children were correctly discriminated). The sub-measures for which no significant differences between very preterm and term children were discovered, were only able to discriminate moderately or poorly, or were unable to discriminate the two populations (for more details, see *Figure 3*).

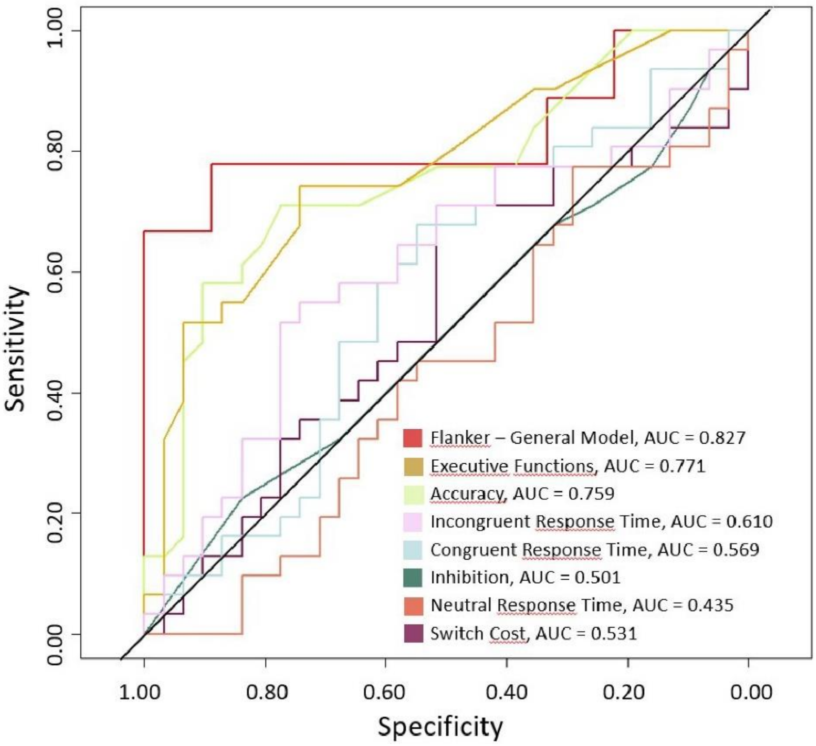

Figure 3. ROC curves of the General Model of the Flanker task and of each sub-measures conducted to test the discrimination of very preterm and term children. The General Model is based on the generalized linear regression including all sub-measures.

Discussion

In clinical practice, assessing the various executive functions is time-consuming. Therefore, simpler and shorter tasks are needed, especially for a population likely to have attentional and concentration difficulties, as a screening tool for executive functions when they are known to be frequently impaired such as in very preterm children. The Flanker task would represent a quick and easy-to-administer measure of executive functions problems in these at-risk populations.

In the present study, while half of the very preterm children showed scholastic difficulties or received therapies, mostly speech therapies, most executive function mean scores were within the norm. The present cohort was healthier than reported in the literature, it may be a selection bias inherent to the experimental design of our study (i.e., children well enough to participate in all tasks). It might also be inherent to their better health at birth and especially to their fewer brain lesions related to prematurity, contrary to what is reported in the literature (Back & Miller, 2014; O'Reilly et al., 2020; Réveillon et al., 2016). However, average scores of these children demonstrated slow reaction times, slightly more omission errors, and less detectability (i.e., the capacity to differentiate non-targets from targets) which could indicate inattentiveness. But despite these averages, apart from 50% of these children who showed slower reaction times, only 15-30% very preterm children showed scores indicating attentional difficulties. Moreover, slightly elevated average BRIEF scores suggested the possibility of a certain vulnerability, but it should be kept in mind that this represented only between 15% and 38% of children. Past findings report signs of impulsivity in very preterm children (Réveillon et al., 2016) associated with inattention and hyperactivity. While in our cohort several children presented attention deficit, and one had a hyperactivity disorder, we interpret our results to rather express the slower processing speed often found in preterm children (Anderson, 2014; de Kieviet et al., 2012; Mulder et al., 2011). Therefore, depending on the tests, between 15% and 50% of the very preterm children of our study showed some attentional and executive functions difficulties in at least one subtest. However, it should be noted that the present cohort is not fully representative of the general population of very preterm children and prevents, at least partially, generalization of the results.

Regarding the Flanker task, and corroborating some of our hypotheses, the resulting scores correlated moderately with some of the clinical scores, however they did not resist to the multiple comparison correction. First, we observed a positive correlation between both WISC-V sub-scores (i.e., working memory and processing speed) and the Flanker task's accuracy and inhibition scores. It is known that working memory processes share certain neural circuits with inhibitory processes and that they seem to be dependent on each other (Castellanos & Tannock, 2002; Conway & Engle, 1994; Jonides et al., 1998; Kane & Engle, 2003). Surprisingly, their working memory assessed with the WISC-V was not correlated with the accuracy of the Flanker task. The WISC-V working memory index relies upon memory of pictures and number and their manipulation, whereas in the Flanker task, it is only the rules that need to be remembered. Therefore, the accuracy seems to be based on different cognitive processes. However, the greater their inhibition capacity, the higher their processing speed was. That seems legitimate as if they could easily inhibit previous rules, they would be faster. From the other perspective, if they are faster in integrating and identifying the stimuli and have a good attentional capacity, their accuracy should be better as they are more prepared to respond correctly in the short time available, which is the case with the Flanker task.

Second, concerning the CPT-3, we reported negative correlations between perseveration errors and both accuracy and inhibition scores from the Flanker task. The more mistakes made at the CPT-3, the more difficult it was for them to inhibit past rules at the Flanker task, and the lower the accuracy. Curiously, accuracy at the Flanker task was not related to omission or commission errors at the CPT-3. It may be that accuracy at the Flanker task relies more on the inhibition and the constant selection of the rules and the type of response that are actively maintained in the working memory, than inattention and impulsivity. Future studies should investigate error-monitoring abilities more in detail in preterm children, as it may be specifically affected.

Finally, no correlation was found between the BRIEF's scores and the Flanker task's scores, partially corroborating previous research. In their review, Toplak et al., (2013) reported that only 19% of the correlations between the BRIEF and diverse neuropsychological tests were significant. Regarding the executive functions assessment in very preterm, Ritter et al. (2014) also found some differences between cognitive (i.e., neuropsychological tests) and behavioral (i.e., BRIEF) measures. While performance measures assess specific domains of cognitive functions (i.e., 'cool' executive functions), the BRIEF might reflect a more global measure. Indeed, the BRIEF is showing how these "cold" aspects are implemented in everyday life with multiple and simultaneous demands, while also capturing emotion-related self-regulatory aspects (i.e., 'hot' executive functions).

These correlations between the Flanker task scores of inhibition and accuracy and the clinical tests show that the experimental task is partially associated with different clinical measures from different neuropsychological tests. However, it should be noted that the global executive functions and switch cost scores were not correlated with any clinical scores. These scores might be based on other executive abilities and measure distinct executive functions. Moreover, it should be noted that none of the correlations survived the False Discovery Rate correction. It is therefore important that future studies replicate this research, in particular with testing batteries examining exactly the same concepts. In addition, the Flanker task measures only discriminated moderately and poorly the very-preterm children with executive functions difficulties and those without in the present cohort. Yet, it should be noted that the very-preterm children's classification based on the neuropsychological tests could not be done precisely. The categorization had to be set arbitrarily, as there is no existent cut-off based on the neuropsychological tests used in the present study. In addition, most of the children were classified without executive functions difficulties (17 vs 8 very-preterm children). These two factors may have limited this analysis and further studies should investigate this discrimination power more precisely.

When comparing the Flanker task's scores of executive functions of very preterm children with those of term children, we reported global lower executive abilities and lower accuracy. This last result contradicts the earlier findings of de Kieviet et al., (2014), but in their study they used a version of the Flanker task without the two blocks with the rule change. It may therefore seem simpler and significant difficulties often arise in the most complex tasks (Wehrle et al., 2016). While our findings are consistent with most previous studies (Aarnoudse-Moens et al., 2012; Baron et al., 2012; O'Meagher et al., 2020; Ritter et al., 2013), the fact that no other scores differed could be explained by the children of our cohort having only minor difficulties. In addition, as mentioned above, these very preterm children did not show signs of impulsivity and hyperactivity, reducing the likelihood of inhibition impairments. However, even within a clinical population without major developmental difficulties, some specific Flanker task sub-scores (i.e., accuracy and executive functions scores) discriminated accurately the very preterm children from the term children highlighting quickly and efficiently their subtle difficulties.

Some limitations need to be stated. First, the very preterm children from our cohort were generally healthy, presented minor developmental impairments, and were able to achieve the Flanker task. More impaired children may not succeed in doing the task. Future work should increase the sample size, and, hopefully, include a less homogenous population of preterm children. However, it is important to state that thanks to medical advances, very preterm children in Western societies have less severe and overt brain injuries and more subtle deficits that manifest themselves notably in the brain connectivity (Back & Miller, 2014; Schneider et al., 2014.; Smyser et al., 2019), and scholastic difficulties. It would be interesting to also test other at-risk populations of children with clearer executive functions difficulties, such as attention deficit hyperactivity disorder, traumatic brain injury or autism. Regarding the comparison between preterm and term children, we have to admit that the testing context was not the same. The hospital context and the presence of parents could be more stressful for the preterm child than it was for the term children evaluated in school contexts. In addition, term children were not assessed with the WISC-V, and a global functioning measure is not available for this control group. It would be beneficial for future studies to have this type of measure to ensure that differences at the Flanker task are not due to a general ability difference. Also, we compared the Flanker task scores with the different clinical score from our routine assessment. Future work should extend these preliminary findings using standardized tests assessing purely and specifically executive functions. This is the case in the FÉE battery (Roy et al., 2020), a battery used in research and in a clinical setting that measures executive functions (i.e., planning, inhibition, flexibility, and working memory). It consists of 12 tests and lasts 90 minutes. From the age of eight years, there is also the Delis-Kaplan Executive Function System (Delis et al., 2001) which is composed of 9 subtests evaluating different executive functions. Assessing the whole battery also takes 90 minutes. Therefore, it would be interesting to compare their comprehensive results with each of the Flanker task scores. In addition, specific standardized scores would permit the classification of children according to the presence of an executive functions deficit which is not possible in the present study which is based solely on clinical measures. The finality is to improve patient care, notably by replacing 90 minutes of testing by a 6-minute playful task when appropriate. Finally, in this study, we wanted to focus on the three core executive functions measures according to the model of Miyake et al., (2000). Some other aspects of executive functions were not evaluated, such as planning. This ability is not measured with the Flanker task, and it should be kept in mind that for a detailed comprehensive evaluation, additional tests would be needed. Moreover, due to the task impurity problem (Miyake, Emerson, et al., 2000), it is more reliable to have several tests with different paradigms for an extensive perspective.

Furthermore, the Flanker task is an experimental task, the final steps would be to standardize the task and to calibrate the test. In this way, we would have norms established for a healthy population and for different age groups. This would allow the use of the Flanker task in a clinical setting for individualized executive function results.

To conclude, this version of the Flanker task, a simple and rapid task adapted for school age children with the advantage to be language independent, presents a reasonable sensitivity in capturing executive functions with good discrimination between very preterm and term children despite only mild difficulties of the very preterm children. These initial results, combined with the few correlations with clinical tests, seem to suggest that this Flanker task could be a good candidate as a clinical tool assessing executive functions. Therefore, this pilot study paves the way to further studies confirming and justifying the integration of this experimental task into a clinical setting, especially as a screening tool. This latter would give a global executive functions evaluation with also specific measures of inhibition and shifting, to identify if further extensive investigations are needed or not, bearing in mind that several tests are needed to get the comprehensive picture. However, it should be noted that children born very preterm could have mostly normal cognitive development, showing normal IQ scores, and present only minor difficulties at school age, possibly also thanks to appropriate treatment and follow-up.

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Statements and Declarations

Disclosure Statement

The authors have no competing interests to declare that are relevant to the content of this article.

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