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Development of visuospatial memory in preterm infants: a new paradigm to assess short-term and working memory

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Funding

This study was funded by Project Grants of SECRETARÍA DE ESTADO DE INVESTIGACIÓN, DESARROLLO E INNOVACIÓN Del Gobierno de España PSI2017-90806-REDT and PSI2017-83893-R and Programa "Severo Ochoa" de Ayudas Predoctorales de la CONSEJERÍA DE CULTURA Y DEPORTE del Principado de Asturias PA-17-PF-BP16090 to CF-B.

Disclosure statement

The authors report no conflict of interest.

Abstract

Preterm infants have a higher risk of showing visuospatial memory impairment, the function that allows to encode and remember visual and spatial information. It has been studied in late childhood in preterm children. Studies on visuospatial memory throughout the first 2 years of life are still scarce. Behavior, temperament, and overall cognition could be altered in preterm children affecting memory performance. Therefore, the main aim of this study was to evaluate short-term and visuospatial working memory performance in a preterm sample followed longitudinally at 12, 15, 18, and 22 months (N=15), and compare their performance with that of full-term children (N=65). The secondary aim was to analyze the course of mnesic development in preterm infants and relate their memory performance to other cognitive abilities and behavioral tendencies. Assessment included previously published tasks and an experimental paradigm. Results showed that preterm children scored lower than full-term children on visuospatial short-term and working memory at 12 and 22 months of age, although these results varied depending on the memory test used. Preterm children's memory results showed that these skills improve in this population between the first and second year of life. Finally, memory performance was directly associated with the level of cognitive development and the presence of proactive behaviors, while being inversely correlated with the presence of disruptive behaviors and a difficult temperamental style. These preliminary findings suggest that it is possible to detect visuospatial memory difficulties in the preterm population before the age of two.

Keywords: preterm; prematurity; visuospatial memory; cognition; temperament.

Introduction

Preterm births, those that occur before 37 weeks, are increasing in developed countries, with an estimated 8-11% of children being born before their due date (Beck et al., 2010). Infants born preterm present higher risk of adverse neurodevelopmental outcomes, including behavioral and cognitive problems, when compared to their full-term counter parts. Regarding behavior, some studies find that preterm children tend to show maladaptive behaviors. Thus, it has been found that premature infants present internalizing (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Cassiano, Gaspardo, Furini, Martinez, & Martins Linhares, 2016) and externalizing behaviors (Potijk et al., 2012). In addition, when examining temperamental style of preterm infants, behavioral style which determines how infants react to situations at early stages of development, studies report hyperactivity and inattention (Cassiano, Provenzi, Linhares, Gaspardo, & Montirosso, 2020), However, other studies disagree with these findings, showing that preterm children do not differ from children born at term in their temperamental style (Sajaniemi et al., 2001; Sun, Mohay, & Callaghan, 2009). Focusing on cognitive performance, findings have shown that preterm children often present difficulties in executive functioning and attention skills (Loe et al., 2015). However, memory is also an ability that may be altered in preterm children throughout childhood (Aanes et al., 2015; Omizzolo et al., 2014).

Memory function allows to store and retrieve information for a brief time (short-term memory) and manipulate it while it is held in mind (working memory) (Baddeley, 1997). This memory relies directly on the visual perception or the generation of a previously stored visual image, and it oversees the maintenance and visuospatial manipulation of these images. The first evidence of visuospatial short-term memory emerge around 6 months of age, when infants are able to detect changes in the position of previously presented items (Oakes et al., 2011) and anticipate the position of previously seen stimuli (Gilmore & Johnson, 1995; Reznick et al., 2004). Therefore, visuospatial memory, which encodes and retrieves visual and spatial information, shows development in the early years. Some studies evaluate visuospatial memory through tasks based on the classic A-not-B paradigm (Piaget, 1954), in which an object is hidden under a location A and the child is asked to look for it. Later, the same toy is hidden under a location B and the child must search in the new location. Based on the data obtained from typically developed children, A-not-B-type tasks should be successfully solved by 12 months of age (Diamond & Goldman-Rakic, 1989; Piaget, 1954). Therefore, from that age on, tasks based on a similar methodology seem appropriate to detect possible limitations in a child's memory development. However, other studies show that typically developed infants are able to solve more complex tasks than the A-not-B paradigms. Those include using up to four possible hiding locations (Garon, Smith, & Bryson, 2014; Pelphrey et al., 2004), not explicitly marking the toy's hiding place (Spencer, Smith, & Thelen, 2001) and including a delay period (Baillargeon et al., 1989).

This visuospatial short-term and working memory function is found as impaired in most of the studies that assess preterm population in different stages of development: during childhood (Baron et al., 2010; Caravale et al., 2005; Clark & Woodward, 2010; Fitzpatrick et al., 2016), adolescence (Saavalainen et al., 2007) and adulthood (Aanes et al., 2015). However, the findings in younger preterm children are still controversial. Some authors have used A-not-B paradigms to assess memory in preterm children (Lowe, Maclean, Shaffer, & Watterberg, 2009; Matthews, Ellis, & Nelson, 1996; Sun et al., 2009; Wilcox, Nadel, & Rosser, 1996). Additionally, other experimental protocols have been proposed to assess spatial working memory in preterm infants (Woodward, Edgin, Thompson, & Inder, 2005). However, studies have revealed contradictory results. Some studies have found alterations in memory in preterm infants (Sun et al., 2009; Woodward et al., 2005), while others have shown normal (Wilcox et al., 1996) or superior (Matthews et al., 1996) memory in this population. These discrepancies among results could be due to methodological differences, which also involve age differences in their samples. The assessed ages range from 4 to 24 months. Considering typical developmental milestone in spatial memory, 1-year-old child should overcome A-not-B based tasks (Diamond & Goldman-Rakic, 1989; Piaget, 1954) but 2-years-old child should show difficulties when solving more complex tasks in which hidden places are not specifically marked (Spencer et al., 2001). For this reason, this age range, from the first to the second year of age, could be crucial for memory development in preterm children as well.

Early detection of cognitive impairment in preterm children seems a vital issue, due to the fact that such cognitive problems that are detected in early childhood, including visual memory and visuospatial abilities, could persist into later stages of development (Lind et al., 2019). These limitations have an impact on different aspects of their lives: academic (Aarnoudse-Moens et al., 2009; Twilhaar et al., 2017) and quality of life in general (Vieira & Linhares, 2016). For this reason, assessing memory in the preterm population at these early ages seems relevant in order to detect possible difficulties and initiate early intervention to minimize their impact on the child's life in the medium and long term. In addition, it seems crucial to consider other aspects that can influence children's memory performance. Although the literature is scarce, some studies suggest that reactivity and temperament regulation may influence cognitive performance in typically developed children. Specifically, reactive temperament negatively affects memory function (Bell, Kraybill, & Diaz, 2013). Considering the behavioral and temperamental characteristics of preterm children, it seems important to explore how these variables affect memory performance.

Thus, this preliminary study aimed to compare the performance of full-term and preterm infants from 12 to 22 months of age on their visuospatial short-term and working memory capabilities using two tasks, one previously employed to evaluate working memory in control populations and a new experimental protocol, which makes it possible to evaluate location memory through four possible positions, tolerance of delay, and the ability to update previously-learned information. The hypothesis was that control children would outperform preterm children on these visuospatial memory measures. The secondary aim was to trace the developmental course of visuospatial short-term and working memory in preterm children, and relate their performance on the different aspects of memory to other variables the literature has found to be potentially affected in this population, such as cognitive development, behavior, or temperament. The hypothesize was that an improvement will be seen between 12 and 22 months, and their performance on memory tasks will be directly related to their level of cognitive development, their behavior during the session, and their predominant temperament style.

Methods

Participants

The preterm sample consisted of 15 children (eight boys and seven girls) who were followed longitudinally at 12, 15, 18, and 22 months. Assessment took place between September 2018 and December 2019 in the Central University Hospital of Asturias (HUCA), Oviedo, Spain. Only children born before 37 weeks of gestation were included in the study. Death, lack of follow-up, and cases with a diagnosis of congenital malformations or syndromes leading to severe neurological disorders were ruled out. From an initial sample of 48 children who met the inclusion and exclusion criteria, 28 families did not respond or declined to participate. Thus, 20 children and their families began the study, although five of them did not complete the four follow-up measures. The control sample was composed of 65 infants (32 boys and 33 girls) measured transversally at 12, 15, 18, or 22 months of age. Evaluations were carried out between October 2017 and May 2019 in pre-schools in Oviedo, Spain. Absence of neurological illnesses or traumatic events, absence of visual or hearing impairments, and having been born after 37 weeks of gestation were established as inclusion criteria. Initially, 74 participants started the study, but nine infants were not included in the final sample due to lack of collaboration during the evaluation or not allowing us to apply all the tests included in the study.

Parents from both groups received information about the study aims, and they gave their written informed consent before the study began. The Local Research Ethics Committee approved this study, which was carried out according to the Helsinki Declaration for biomedical research involving humans.

Materials and measures

All the infants' visuospatial short-term and working memory and general cognitive development were measured while the parents completed some questionnaires. Preterm's medical risk factors were also included in the assessment.

For the memory assessment, two tasks were employed: one previously used, the Hide and Seek task (Garon et al., 2014), and another one designed for this study, Baby-Mnemo.

The Baby-mnemo (BM) task was designed to assess different aspects of visuospatial memory in infants and toddlers (Figure 1A). It consisted of a wooden mobile drawer with two main areas: one with six pushbuttons with light and the other with six platforms placed parallel to the pushbuttons that can be lifted vertically by the examiner with the levers located on the back of the device. Other elements on the back of the drawer were six switches that activated the light of the corresponding pushbutton. A blanket was used to cover the right side of the drawer (two pushbuttons and their two respective platforms) in order to minimize the attention span. Previous studies with children under two years of age have used as many as four hiding places on memory tasks (Garon et al., 2014; Pelphrey et al., 2004).

The Baby-mnemo task included three consecutive phases: Recall of Location, Tolerance to periods of Delay, and Updating of previously learned information (Appendixes 1, 2, and 3, respectively). However, the administration of the protocol started with object familiarization and training with the device.

First, the examiner showed and named four small toys and let the child play with them for roughly two minutes. The aim was to find out the child's preferred stimulus, in order to try to achieve higher motivation and attention levels during the tasks. The toy selected for the Baby-mnemo assessment was the one that was touched, pointed to, looked at, and/or named the most by the child.

During training with the Baby-mnemo drawer, the device was shown to the child for the very first time. The pushbuttons were accessible to the child, who was placed in front of the drawer, whereas the levers were next to the examiner, who was located behind it. The child was allowed to explore and touch the buttons. After that, the examiner turned on the corresponding light so that the child could observe that when a button was pressed, a light went on. During this familiarization phase, the examiner noted which button was employed the most, that is, the one looked at, pressed, pointed at, etc., the most by the child. Then, the examiner picked up the toy previously chosen and, while trying to keep the child's attention, lifted the lever associated with the most used pushbutton, placed the toy on the surface, and took it down. After that, the examiner touched the corresponding pushbutton, turned on its light, and raised the lever again. These three consecutive actions were called *Examiner examples,* and they were repeated three times. After these three *Examiner examples,* the evaluator pointed to the correct button and asked the child: "Where is the (name of the toy)?" If the child pressed the appropriate button, the examiner activated the light and lifted the lever with the toy, praising his/her performance. If the child pressed another button that was incorrect, the examiner said: "The (name of the toy) is not here. Where is the (name of the toy)? Try here", pointing again to the correct button. If the child did not answer or tried to retrieve the toy directly from the hole in the lever, the examiner pointed at the right button and told him/her: “Where is the (name of the toy)? Try here”. After this second chance, if the child touched the correct button, the examiner turned on the light, held up the toy, and verbally reinforced his/her performance. If s/he did not, which included touching another button, not answering, or trying to get the toy directly, three more Examiner examples were given, and the examiner asked for the toy again. These sequences (three examiner examples plus asking the child) could be repeated up to six times during the task in order to allow the child to learn how the device worked, but the number of sequences administered to each child depended on his/her performance. If the child gave two correct answers (s/he pressed the appropriate button two times consecutively), this familiarization ended, and the administration of Baby-mnemo started. If the child used up all six sequences without correctly answering two consecutive times, the Baby-Mnemo evaluation did not continue.

Baby-mnemo started with Recall of Location. If the child achieved two consecutive correct trials, the examiner asked for the toy four more times. However, in this phase, the examiner did not point to the correct button, and so the child had to remember it. The child scored one point for each correct response given. If s/he scored at least two points out of four (maximum score), the next phase of Baby-mnemo was administered. If s/he scored one or zero points out of four, the examiner went back to familiarization. That is, the examiner repeated the three Examiner Examples, asked the child to find the toy by pointing to the pushbutton (a new chance for familiarization), and then asked the child to find the toy again four more times without pointing to the pushbutton (a new chance for the Recall of Localization phase). Thus, familiarization with the protocol and Recall of Location alternated up to six times, as explained above, and the Baby-mnemo evaluation ended if the child did not manage to learn (2/4 points) on any Recall of Location trial. Because the child could give four correct answers in each of the six Recall of Location trials, the final score in this phase (BM Location) ranged between 0 and 12, where 0 meant no correct response made by the child, and 12 meant the child had all four correct answers on the first Recall of Location – and so the next Recall of Location phases were not administered, but their maximum score was assumed –.

In the next phase of Baby-mnemo, Delay, the child was not allowed to answer to retrieve the toy during an increasingly long delay. To do so, the examiner completely covered the drawer with the fabric for 2 seconds and uncovered it once the delay was over, then asking the child: “Where is the (name of the toy)?". If the child gave a correct answer, the next rehearsal increased by 2 seconds (4 seconds in this case). After a correct trial, the delay time was increased two seconds in each new trial (4", 6", 8", etc.), until reaching a maximum of 30 seconds. If the child gave an incorrect answer – pushed another button, did not respond, tried to retrieve the toy directly, etc. –, another trial with the same delay (2 seconds in this case) was performed. If the child succeeded this time, the delay increased by 2 seconds; if not, the Delay phase ended. Scores in this phase ranged between 0, where the child did not manage to tolerate any seconds of delay, and 30, where the child was able to tolerate 30 seconds of delay.

In the last phase, Update, the child had to retrieve the toy using the rest of the pushbuttons. Thus, the examiner took the toy and placed it on a different platform, one of those not previously used, chosen randomly. This procedure was done ensuring that the child had made eye contact with the toy and visually followed it until it was hidden on the new platform. Then, the examiner lowered the platform and asked the child to retrieve the toy ("Where is (name of the toy)?"). If the child pressed the new button, equivalent to the new platform, his/her performance was reinforced, and s/he received 3 points on this first trial. If the child did not answer correctly, his/her score was 0, and the examiner showed him/her how to retrieve the toy: she touched the new pushbutton and held up the toy. Then, the child was encouraged to try again. If s/he was accurate, s/he received 2 points on this second trial; if not, s/he scored 0 again, and the examiner performed 2 additional demonstrations. If, on this third attempt, the child managed to press the new button, s/he received 1 point; otherwise, s/he scored 0. Thus, using the same platform, the child could learn on the first trial (3 points), second trial (2 points), third trial (1 point), or not at all (0 points). This same methodology was followed in the next two blocks, where the toy was moved back to the two remaining platforms that had not previously been used. The range of total scores in this phase, BM Update, was between 0 and 9.

In the original study, the Hide and Seek (HS) task was proposed for working memory assessment in children between 1.5 and 5 years old (Garon et al., 2014). This task used two large boxes with lids that contain small boxes with lids. One of the two large boxes only had one small box inside it that was used for the training phase. The other large box, which was employed for the assessment phase, had four small boxes, each one located in each corner of the bigger box. During training, the child's preferred toy, as described in Baby-mnemo, was selected and moved in front of the child to catch his/her attention. Then, the examiner hid the toy in the small box, closed the lid of the small box and then the large box, and after a brief delay of 4 seconds for 12-month-olds, 6 seconds for 15-month-olds, and 10 seconds for 18- and 22-month-olds encouraged the child to retrieve it. Delay period used in this study is based on the original study performed in infants over 18 months (Garon et al., 2014) and normative data obtained assessing typically developed children aged 12 and 15 months (pilot study, unpublished data). After this procedure had been performed twice, the assessment started with the larger box. Once again, the toy was hidden in one of the four small boxes, and the child was asked to find it after the delay (Figure 1B). This procedure was performed four times, one for each small box. From this task, several measurements were obtained: the HS Retention (score on the first two trials, from 0 to 8), the HS Update (score on the last two trials, from 0 to 8), and HS Correct Answers (score for total right answers, from 0 to 16).

For general cognitive assessment, the cognitive battery from the Merrill-Palmer Revised Scales of Development (MP-R) was employed, which included variables such as Cognition, Fine Motor Skills, Receptive Language, Visuomotor coordination, and a General Cognitive Index (Roid & Sampers, 2011). Two questionnaires from these MP-R scales were also used. On the first, Behavior during evaluation, the examiner scored different types of behavior the child displayed during the evaluation, and several measurements were obtained: for children aged 12 and 15 months: Irritability, Attention, and Fear and caution (MP-R B Irritability, MP-R B Attention, and MP-R C Fearful, respectively); and for children aged 18 and 22 months: Organization and cooperation, Activity and diligence, and Anger and poor collaboration (MP-R B Organized, MP-R B Active, and MP-R B Angry, respectively). The second questionnaire was the Temperamental

Style, where parents scored the child's emotional reactions and behaviors in regular contexts, providing the measures of Easy and Difficult Temperament for children 12 and 15 months old, and Easy, Difficult and Fearful for children 18 and 22 months old (MP-R T Easy, MP-R T Fearful, and MP-R T Difficult) (Roid & Sampers, 2011).

Procedure

Parents received information about the aims of the study by letter and/or telephone, and they signed the informed consent before the evaluation began. Then, the assessment was performed in a single session that lasted approximately one hour. Evaluation sessions were carried out in their own pre-schools, in the case of control children, and in the local hospital in the case of preterm children. Two examiners, both trained psychologist with experience in neuropsychological assessment, participated in each session: one examiner was in charge of administering the tests, while the other provided assistance and materials. The protocol started with the Hide and Seek task, followed by Baby-mnemo and, lastly, the Merrill-Palmer Scales. The size of the sample did not allow a counterbalanced design in the order of administration of the tasks. At the end of the assessment, both the examiner and the parents completed the questionnaires. Neonatal variables for the preterm children, such as gestational age, birth weight, and the presence of perinatal risk factors, were obtained from medical records.

Statistical analysis

Analyses were performed with SPSS Version 24. Neonatal measures from the preterm children and sociodemographic data from both groups were analyzed descriptively, in terms of means, standard deviations, and percentages. Shapiro-Wilk was used to test normality, and Levene was employed to check homogeneity. The Mann-Whitney test was employed to compare the two groups on Baby-mnemo, Hide and Seek, behavior and temperamental style. Non-parametric comparisons were performed, as groups differed in their cognitive ability. Friedman's statistic was used to analyze the longitudinal measurements obtained from the preterm sample on Baby-mnemo and Hide and Seek, employing Wilcoxon corrected by Bonferroni in post-hoc comparisons. Spearman correlations were used to relate the Baby-mnemo performance with the other cognitive and behavioral measurements, as well as gestational age and birth weight, in preterm children.

Results

Sociodemographic data

The main sociodemographic data for the preterm and control samples are shown in Table 1. Regarding sociodemographic variables, significant differences were obtained between the control and preterm group in regard to the father's educational level (χ^2_3=11,459; p=0,009). The fathers of control children had achieved a higher educational level compared to fathers of preterm children. The neonatal measures of the preterm children can be found in Table 2. In addition, the level of cognitive development of the children in the sample was analyzed descriptively as a percentage. In the control sample, although all the children achieved a generalized developmental index within normative values, four children obtained values below average (<1SD) on the Fine Motor Skills measure (6.15%), and two children on the Cognitive measure (3.07%). In preterm children, six children scored below average (<1SD) on the General Cognitive Index (10%), and three obtained lower scores than average on the Cognitive scale (5%) and Fine Motor Skills (5%). Means and standard deviations for both groups on the Merrill-Palmer-R subscales are shown in Table 3.

Comparison between control and preterm infants

First, the Baby-mnemo measures (BM Location, BM Delay, BM Update) in the control and preterm groups were compared according to their age using Mann-Whitney's U. We found significant differences between controls and preterm children at 22 months on BM Location (U=74; p=0.048, r=0.360) and BM Update (U=55; p=0.014, r=0.450). In both cases, controls obtained better results (Figure 2A). However, we did not find significant differences between controls and preterm children in the remaining age groups (p>0.05).

Differences between groups on the Hide and Seek task (Retention, Update, Correct answers) were also examined using Mann-Whitney's U. Thus, at 12 months, we found statistically significant differences in Correct answers (U=89.5; p=0.023; r=0.388), where controls made fewer errors and had a greater number of right answers compared to preterm children (Figure 2B). However, no differences were found on the Retention and Update measures; nor did we observe differences in any of the variables in the comparison of the older groups (p>0.05).

Course of memory development in preterm

We compared memory performance in the preterm group across the different ages using Friedman's statistic. Starting with Baby-mnemo, we found significant differences between ages on BM Location (χ^2_3=8.289; p=0.040) and BM Delay (χ^2_3=12.475; p=0.006), but not on BM Update (p=0.277). In the two-to-two comparisons using the Wilcoxon statistic, corrected by Bonferroni (considered significant when p<0.008), we only found significant differences between 12 and 22 months (p=0.004; r=0.531) and between 15 and 22 months (p=0.003; r=0.545) on BM Delay, whereas the differences in BM Location did not remain significant (p>0.008) (Figure 3A). In both comparisons, preterm infants were able to tolerate significantly longer delays at 22 months, compared to 12 and 15 months. Regarding Hide and Seek, using Friedman's statistic, we found significant differences in HS Retention (χ^2_3=13.455; p=0.004), HS Update (χ^2_3 =10.488; p=0.015), and HS Correct answers (χ^2_3=20.056; p<0.001). In the post-hoc analyses using Wilcoxon corrected by Bonferroni (considered significant when p<0.008), we found that these differences were observed on Retention at 12 and 22 months (p=0.006; r=0.353), Update at 12 and 18 months (p=0.007; r=0.345) and 12 and 22 months (p=0.003; r=0.382), and Correct answers at 12 and 18 months (p=0.005; r=0.360) and 12 and 22 months (p=0.001; r=0.410) (Figure 3B). In all these cases, preterm children performed better with age.

Relationship between visuospatial memory and cognitive development, behavior and temperament, and gestational age and birth weight in preterm children

First, we set out to analyze the possible relationships between the Baby-Mneno sub-tasks and the Merrill-Palmer R scale (Table 4). On the one hand, we found that BM Total Location was significantly related to the General Index (r=0.357; p=0.003), Cognition (r=0.341; p=0.005), Fine Motor Skills (r=0.370; p=0.002), and Visuomotor Coordination (r=0.316; p=0.010). On the other hand, BM Delay was significantly associated with the General Index (r=0.485; p<0.001), Cognition (r=0.399; p=0.001), Fine Motor Skills (r=0.478; p<0.001), Receptive Language (r=0.446; p=0.001), and Visuomotor Coordination (r=0.396; p=0.001). Finally, BM Update was significantly related to the General Index (r=0.373; p=0.002), Cognition (r=0.313; p=0.011), Fine Motor (r=0.338; p=0.006), Receptive Language (r=0.304; p=0.030), and Visuomotor Coordination (r=0.280; p=0.023). Analyzing the associations between Hide and Seek and the Merrill-Palmer R scale, we found that HS Retention was significantly correlated with General Index (r=0.585; p<0.001), Cognition (r=0.518; p<0.001), Fine Motor Skills (r=0.526; p<0.001), Receptive Language (r=0.323; p=0.021) and Visuomotor Coordination (r=0.570; p<0.001). In addition, all MP-R indexes were significantly associated with HS Update General Index (r=0.362; p=0.003), Cognition (r=0.332; p=0.006), Fine Motor Skills (r=0.381; p=0.002), Receptive Language (r=0.300; p=0.032) and Visuomotor Coordination (r=0.381; p=0.002), as well as with HS Correct answers (General Index (r=0.571; p<0.001), Cognition (r=0.485; p<0.001), Fine Motor Skills (r=0.556; p<0.001), Receptive Language (r=0.431; p=0.002) and Visuomotor Coordination (r=0.587; p<0.001)).

Next, the behavioral measures during the session were correlated with memory tasks. In this case, we considered each age measure separately because this scale offers different measures for each age. At 12 and 15 months, no significant associations were found between the behavior shown by the child and their scores on Baby-mnemo. However, at 18 months, Angry behavior was significantly associated with lower scores on BM Location (r=-0.652; p=0.011) and BM Delay (r=-0.592; p=0.026), whereas Organized behavior was significantly related to BM Update (r=-0.534; p=0.049). At 22 months, we found that Angry behavior was significantly related to poor performance on BM Location (p=-0.637; p=0.011), BM Delay (r=-0.696; p=0.004), and BM Update (r=-0.780; p=0.001), and Organized behavior (r=0.554; p=0.032) and Active behavior (r=0.629; p=0.012) were significantly associated with higher scores on BM Delay. Regarding Hide and Seek, significant correlations were found between Fearful behavior at 12 months (r=-0.459; p=0.042), Irritable behavior at 15 (r=-0.642; p=0.005) and Active behavior at 22 (r=0.567; p=0.028) with HS Correct responses scores.

Temperamental styles were correlated with memory tasks. Although we did not find a significant association between temperament and Baby-mnemo performance at 12 months nor at 22 months, we observed that Difficult temperament was significantly associated with scores on BM Location at 15 months (r=-0.557; p=0.020) and 18 months (r=-0.627; p=0.016). In the Hide and Seek task, only Difficult temperament was significantly correlated with HS Update (r=-0.621; p=0.018) and HS Correct responses (r=-0.592; p=0.026) at 18 months.

Finally, the possible associations between gestational age and birth weight and the Baby-mnemo and the Hide and Seek variables were analyzed. No statistically significant differences were found between these measurements.

Discussion

The main purpose of this preliminary research was to evaluate different aspects of visuospatial memory (location memory, tolerance of delay and update of previously learned information) before the age of 2 in preterm children. The predictions were that children born at term would outperform children born preterm in all the measures of visuospatial memory, hypothesizing that preterm children would improve their performance in visuospatial memory between the ages of 12 and 22 months, as well as that their achievements would be directly associated to their level of cognitive development, their behavior during the assessment session, and their temperamental style. The main findings of the present study have shown that preterm children obtained lower scores in their visuospatial memory compared to their at term peers and this ability is affected at early ages. However, preterm performance seemed to progress across ages, specifically, in their tolerance of delay at 22 months of age compared to 12 and 15 months in Baby-mnemo, and in their short-term and working visuospatial memory at 18 and 22 months compared to 12 months in Hide and Seek. In addition, preterm memory performance appeared to be positively related to several aspects of their cognitive development, such us cognition, fine motor skills, receptive language, or visuomotor coordination, and to certain behaviors shown during the assessment session, such us organized and active behaviors. In contrast, it also seemed to be negatively related to some disruptive behaviors and to a difficult temperamental style. Finally, gestational age or birth weight of preterm children may not be associated with their visuospatial memory achievements at these ages.

Comparison between control and preterm infants in visuospatial memory performance

The analysis of the differences in visuospatial short-term and working memory in the Baby-mnemo task revealed that preterm infants performed worse than full term infants on visuospatial memory at the age of 22 months. Specifically, this group presented poor ability to remember one location out of four (Location) and manipulate and update that information once it had been learned (Update). The results of the current study could be comparable to some previous studies. In relation to location learning, previous researchers have found that children born very prematurely required a greater amount of time and trials to remember a location at the age of 24 months (Woodward et al., 2005), and also 3 years (Baron et al., 2010). Regarding the ability to update previously learned information, previous studies have found similar results in both younger and older preterm infants and toddlers (Espy et al., 2002; Sun et al., 2009; Woodward et al., 2005). However, this worse performance of the preterm population was not confirmed in all published literature (Lowe et al., 2009; Matthews et al., 1996; Wilcox et al., 1996). The great variability of the sample included in these studies could account of these discrepancies. The studies not only differ in terms of the number of children evaluated or their ages, but also their neonatal variables, such as gestational age, birth weight, head circumference, and other perinatal risk factors. The studies also used different methods, which vary in the number of possible locations where the stimulus is hidden, delay periods and degree of accessibility of the stimulus. Hence, a larger number of studies performed using equivalent methodologies would be necessary to draw a definitive conclusion about preterm visuospatial working memory under the age of 2.

Results found in the present study showed that preterm and control infants were able to tolerate approximately the same period of delay. However, previous findings showed contradictory results: some of the studies pointed out that preterm children performed worse in memory tasks when there is a delay between learning and retrieval (Sun et al., 2009; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004), while other studies did not found any effect of the delay on memory performance (Matthews et al., 1996; Wilcox et al., 1996). Nevertheless, it is important to take into account that these studies used delays which range from 0 to 30 seconds, and only a few included the delay as a variable in their analyses. Therefore, further research is needed in order to elucidate if preterm infants shows difficulties in retaining visuospatial information.

Preterm children performed worse than full term at 12 months in the Hide and Seek task. However, performance of both groups was similar at later ages. Despite both tasks, Baby-mnemo and Hide and Seek, assessed the same psychological process, preterm children differed in their performance on the two tasks. The different types of methodologies of both tasks might account of these results. In the Hide and Seek task, the toy is hidden in one location and the motor act of accessing that location allowed the child to retrieve the object, but in our Baby-mnemo task, the toy's location and the location where the child had to give a motor response did not coincide, requiring the child to make an association such as that the memorized location (button) leads the child to access the object's hiding place (platform). In terms of the development of spatial cognition, the Hide and Seek task employed coincident cues, in which the objective stimulus is directly associated with the particular characteristics of its location or hiding place, whereas the experimental Baby-mnemo task employed non-coincident cues, in which the objective stimulus must be found following relative positions related to the target place. Typical development suggests that the use of coincident cues emerges before the use of non-coincident ones (Fernandez-Baizan, Arias, & Mendez, 2019). Therefore, the procedure of Baby-mnemo is closely related to other tasks, such as the MultiSearch MultiLocation (MSML) (Woodward et al., 2005), where the object cannot be directly retrieved, while the methodology of Hide and Seek task is similar to the A-not-B paradigms. Baby-mnemo's procedure adds an extra component of complexity, which may explain why Hide and Seek task has revealed better performance of children born at term compared to those born prematurely at 12 months of age, while groups differences in Baby-Mnemo have not emerge until 22 months. The order of administration of the tasks (first Hide and Seek) could also account of these differences in the results. Nevertheless, if fatigue had been more present in Baby-Mnemo than in Hide and Seek task, it might have affected to children of all ages. However, none of the tasks, neither Baby-mnemo nor Hide and Seek, showed differences at 15 and 18 months. Future research should counterbalance the administration of these tests to examine the effect of the order of administration. Within the limits of the present study, it can be concluded that Hide and Seek task, which involves a simple procedure, might be able to detect visuospatial short-term and working memory alterations at early ages; meanwhile, difficult procedures, such as Baby-mnemo or MSML tasks, would be useful in the analysis of these disturbances at later ages.

The alterations in visuospatial memory found in preterm infants could be due to abnormal maturation of prefrontal and temporal brain regions. Precisely, in infants, the lateral portion of the prefrontal cortex is intensely activated when detecting novel stimuli or holding information in mind during memory tasks (Grossmann, 2013). Differences in these neocortical areas have been found in older preterm children during visuospatial working memory tasks performance. Preterm involved fewer prefrontal areas compared to term-born children (Tokariev et al., 2019). Besides, it was demonstrated that the higher the activation of prefrontal cortex, the better working memory in preterm children (Mürner-Lavanchy et al., 2014). However, memory impairment in preterm children could be related to disturbances in the maturation of other brain regions, such as the temporal lobes or the hippocampus (Aanes et al., 2019; Beauchamp et al., 2008).

Visuospatial memory improvements in preterm children across ages-months

A longitudinal analysis was carried out in order to understand how visuospatial memory skills developed within the preterm population across different ages. Performance of preterm infants in Baby-mnemo across the different ages remained relatively stable in terms of remembering the location of the object and updating its position, but not in tolerance of delay. Preterm infants at 22 months were able to maintain a longer delay than when they were 12 and 15 months old. Previous longitudinal studies, which included ages from 28- to 60-weeks, revealed that the older the child, the longer the delay tolerated (Matthews et al., 1996). Regarding Hide and Seek task, the results of the present study showed that preterm children performed better at 18 and 22 months of age than at 12 months. Thus, the results presented in this research showed that preterm performance improved slightly at 15 months and more noticeably at 18 and 22 months. These results are hardly comparable to those obtained on the Baby-Mnemo task. As mentioned above, the two tasks use very different methodologies. However, these results allow to conclude that the Hide and Seek test could be more useful for the longitudinal assessment of short-term and working memory development in the preterm population, despite its procedure does not allow delay tolerance to be measured, being the Baby-mnemo task more appropriate for this purpose.

Association between visuospatial memory achievements and cognitive development in preterm infants

In the present study, we aimed to investigate whether preterm infants performance on memory tasks, Baby-mnemo and Hide and Seek, is associated with other cognitive and behavioral measures. The results of the present study revealed that almost all the memory subtasks from both Baby-mnemo and Hide and Seek were related to the Merrill-Palmer R subscales in preterm children. The Cognitive and Fine Motor skills subscales generally showed the largest effect sizes in their association with the Baby-mnemo and Hide and Seek measurements, followed by Visuomotor Coordination and, finally, Receptive Language. This last subscale was the only one that did not correlate with all the Baby-Mnemo measures, showing correlations with Delay and Update. This association between memory tasks and scores on the developmental cognitive scales was found in this population in previous literature (Lowe et al., 2009). Motor behaviors were needed to solve both the Baby-mnemo and Hide and Seek tasks. Previous studies showed that preterm children tend to have lower levels of motor or psychomotor development than controls (Sun et al., 2009; Woodward et al., 2005). However, these studies also found that when the motor development level was controlled, preterm children continued to present visuospatial working memory difficulties (Sun et al., 2009), and that they performed equally on both visual and manipulative versions of the memory tasks (Matthews et al., 1996). Therefore, the influence of motor development on memory tasks seems rather limited. Associations with the Visuomotor coordination subscale could point out that preterm children who present better hand-eye coordination could obtain better scores in memory tasks. Other studies revealed that preterm children could show lower visuomotor skills (Flamand, Nadeau, & Schneider, 2012), which could potentially affect any task that requires a synchronization of hand-eye fine motor movements. Regarding language, the associations found in the present research may seem surprising, considering that both tasks were focused on visuospatial, but not verbal memory. It should be noted that verbal instructions were given, accompanied with gestures and movements which showed the child how to perform the task. The possible association between language development and verbal, but not visuospatial, working memory was previously explored in typically developed older children (Newbury, Klee, Stokes, & Moran, 2016), and in healthy adult subjects, suggesting that spatial working memory could be related to reading comprehension (Pazzaglia & Cornoldi, 1999). Therefore, it is possible that this association between spatial working memory and oral language comprehension found in the current study could start at such early developmental stages. However, a specific language evaluation at these ages would be necessary in order to establish this association. Finally, the General Index was one of the most interrelated scales with Baby-mnemo and Hide and Seek, which seems logical considering that such index consisted of the sum of the different subscales, which were also associated with both memory sub-indexes, as it was previously discussed.

Association between visuospatial memory achievements and behavior and temperament in preterm infants

Analyzing the relationship between Baby-mnemo and Hide and Seek with the behavior shown during the evaluation, as well as the predominant temperament of the child, it was observed a trend in which collaborative and proactive behaviors were associated with better mnesic performance, especially in the oldest ages measured, whereas more disruptive behaviors and difficult temperamental styles were related to worse performance at almost all ages. These behavioral findings are consistent with previous studies, which found that on A-not-B tasks, greater emotional regulation in extremely preterm children aged 18-22 months was associated with better test performance (Lowe et al., 2009). Although previous literature suggested that older preterm children may present a higher prevalence of disruptive behaviors (Aarnoudse-Moens et al., 2009; Cassiano, Gaspardo, & Linhares, 2016; Potijk et al., 2012), we must consider that the behavioral measure used in these studies is static; that is, it did not assess the usual behavior of the children in their daily contexts and, therefore, may not be representative of their overall behavior. In the present study, considering temperament as a general style of the child's behavior, the temperamental measure could provide us with relevant data on the child's day-to-day behavior. Thus, the results presented in this work pointed out that the presence of a difficult temperament could be related with a worse memory performance. Although not many previous studies linked temperament to cognition, it did seem that a more reactive temperament may worsen cognitive performance later on in childhood (Chong et al., 2019; Suor, Stuge-Apple, Davies, & Cicchetti, 2017). In relation to a possible impact on later neurodevelopment, it seems more important to consider behavior than temperament, as previous literature found that behavior measured at 2 years, compared to the temperamental style, were more associated with language development at 4 years in a preterm sample, being low resistance and poor cooperation behaviors the best predictors of later language disorders

(Sajaniemi et al., 2001). Nevertheless, the results of the presented study clearly highlight the relevance of considering behavioral and temperamental aspects in the neuropsychological assessment of preterm infants.

Association between visuospatial memory achievements and gestational age and birth weight in preterm infants

The results of the present study did not reveal significant correlations between neonatal factors, such us gestational age and birth weight, and memory performance in preterm children, contrary to what was expected based on previous literature on cognitive performance (Fan, Portuguez, & Nunes, 2013; Lemola et al., 2017; Urben et al., 2015). In the specific case of mnesic abilities in older preterm children, previous studies have reported that either gestational age or birth weight was related to lower visuospatial memory (Baron et al., 2010; Fitzpatrick et al., 2016; Saavalainen et al., 2007), whereas other works have not found such associations (Aanes et al., 2015; Vicari et al., 2004). Focusing on ages closer to those included in the present research, many authors chose to focus on a particular category according to gestational age, birth weight, or both, as an inclusion criterion (Lowe et al., 2009; Woodward et al., 2005), while others included an extremely variable preterm sample (Matthews et al., 1996; Sun et al., 2009; Wilcox et al., 1996). In general, studies that considered gestational age or birth weight as variables for analysis found that high-risk preterm infants performed worse on memory tasks than their full-term peers (Sun et al., 2009). The preterm participants of the current study are considered moderately preterm, with a birth weight labeled in the low-birth-weight category, and without very prevalent perinatal risk factors. Hence, in the present study we can conclude that even low-risk preterm infants may present visuospatial memory problems.

The present study showed several limitations. Due to the size of the sample, non-parametric statistics were applied. For this reason, it was not possible to control influential variables, neither to perform construct validity analysis, issues that may be addressed in later studies. The different data collection should also be considered, being longitudinal in the preterm group and cross-sectional in controls. In addition, this latter group was evaluated at their pre-school, an environment where distractions may potentially affect performance. It should also be noted that the control group presented borderline scores on some cognitive scales, especially in the older age groups. This could indicate that the assessment battery may not be entirely suitable for the evaluation of those ages.

In conclusion, the findings presented in the current study showed that some mnesic limitations typically found in older preterm children may already be detected before two years of age. However, these memory difficulties were found at different developmental stages on different tasks. Thus, simpler memory tasks, such as Hide and Seek, detected difficulties in preterm children at 12 months of age, and more complex tasks, such as Baby-mnemo, at 22 months. Nevertheless, preterm children were able to improve these skills, especially as they approached two years of age. Furthermore, these mnesic functions seemed to be associated with the development of different cognitive skills, as well as with the presence of proactive or disruptive behaviors and a difficult temperamental style. These findings may have implications for health and education professionals who were involved in caring for the premature. Not only should these professionals be aware of the child's general cognitive development, but also of specific domains, such as memory, that may be altered at these early ages. In this sense, the early detection of memory problems would make an earlier intervention possible.

References

Aanes, S., Bjuland, K. J., Skranes, J., & Løhaugen, G. C. C. (2015). Memory function and hippocampal volumes in preterm born very-low-birth-weight (VLBW) young adults. *NeuroImage*, *105*, 76–83. https://doi.org/10.1016/j.neuroimage.2014.10.023

Aanes, S., Bjuland, K. J., Sripada, K., Sølsnes, A. E., Grunewaldt, K. H., Håberg, A., Løhaugen, G. C., & Skranes, J. (2019). Reduced hippocampal subfield volumes and memory function in school-aged children born preterm with very low birthweight (VLBW). *NeuroImage: Clinical*, *23*(May), 101857. https://doi.org/10.1016/j.nicl.2019.101857

Aarnoudse-Moens, C. S. H., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-Analysis of Neurobehavioral Outcomes in Very Preterm and/or Very Low Birth Weight Children. *Pediatrics*, *124*(2), 717–728. https://doi.org/10.1542/peds.2008-2816

Baddeley, A. D. (1997). *Human memory: theory and practice. Revised edition.* Psychology Press.

Baillargeon, R., Devos, J., & Graber, M. (1989). Location memory in 8-month-old infants in a non-search AB task: Further evidence. *Cognitive Development*, *4*(4), 345–367. https://doi.org/10.1016/S0885-2014(89)90040-3

Baron, I. S., Erickson, K., Ahronovich, M. D., Litman, F. R., & Brandt, J. (2010). Spatial Location Memory Discriminates Children Born at Extremely Low Birth Weight and Late-Preterm at Age Three. *Neuropsychology*, *24*(6), 787–794. https://doi.org/10.1037/a0020382

Beauchamp, M. H., Thompson, D. K., Howard, K., Doyle, L. W., Egan, G. F., Inder, T. E., & Anderson, P. J. (2008). Preterm infant hippocampal volumes correlate with later working memory deficits. *Brain*, *131*(11), 2986–2994. https://doi.org/10.1093/brain/awn227

Beck, S., Wojdyla, D., Say, L., Betran, P., Merialdi, M., Requejo, H., & Rubens, C. (2010). *The worldwide incidence of preterm birth : a systematic review of maternal mortality and morbidity*. *April 2009*, 31–38. https://doi.org/10.2471/BLT.08.062554

Bell, M.A., Kraybill, J.H. and Diaz, A. (2013). Reactivity, Regulation, and Remembering: Associations between Temperament and Memory. In The Wiley Handbook on the Development of Children's Memory (eds P.J. Bauer and R. Fivush). doi:10.1002/9781118597705.ch29

Caravale, B., Tozzi, C., Albino, G., & Vicari, S. (2005). Cognitive development in low risk preterm infants at 3-4 years of life. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *90*(6), 474–479. https://doi.org/10.1136/adc.2004.070284

Cassiano, R. G. M., Gaspardo, C. M., Furini, G. C. B., Martinez, F. E., & Martins Linhares, M. B. (2016). Impact of neonatal risk and temperament on behavioral problems in toddlers born preterm. *Early Human Development*, *103*, 175–181. https://doi.org/10.1016/j.earlhumdev.2016.09.015

Cassiano, Rafaela G.M., Provenzi, L., Linhares, M. B. M., Gaspardo, C. M., & Montirosso, R.

(2020). Does preterm birth affect child temperament? A meta-analytic study. *Infant Behavior and Development*, *58*(March 2019), 101417. https://doi.org/10.1016/j.infbeh.2019.101417

Clark, C. A. C., & Woodward, L. J. (2010). Neonatal Cerebral Abnormalities and Later Verbal and Visuospatial Working Memory Abilities of Children Born Very Preterm. *Developmental Neuropsychology*, *35*(6), 622–642. https://doi.org/10.1080/87565641.2010.508669

Chong, S. Y., Chittleborough, C. R., Gregory, T., Lynch, J., Mittinty, M., & Smithers, L. G. (2019). The controlled direct effect of temperament at 2-3 years on cognitive and academic outcomes at 6-7 years. *PLoS ONE*, *14*(6), 1–14. https://doi.org/10.1371/journal.pone.0204189

Diamond, A., & Goldman-Rakic, P. S. (1989). Comparison of human infants and rhesus monkeys on Piaget's AB task: evidence for dependence on dorsolateral prefrontal cortex. *Experimental Brain Research*, *74*(1), 24–40. https://doi.org/10.1007/BF00248277

Espy, K. A., Stalets, M. M., Melanie, M., Senn, T. E., Cwik, M. F., & Hamby, A. (2002). Executive Functions in Preschool Children Born Preterm : Application of Cognitive Neuroscience Paradigms. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *8*(2), 83–92. https://doi.org/10.1076/chin.8.2.83.8723

Fan, R., Portuguez, M., & Nunes, M. (2013). Cognition, behavior and social competence of preterm low birth weight children at school age. *Clinics*, *68*(7), 915–921. https://doi.org/10.6061/clinics/2013(07)05

Fernandez-Baizan, C., Arias, J. L., & Mendez, M. (2019). Spatial orientation assessment in preschool children : Egocentric and allocentric frameworks. *Applied Neuropsychology: Child*, 1–23. https://doi.org/10.1080/21622965.2019.1630278

Fitzpatrick, A., Carter, J., & Quigley, M. A. (2016). Association of gestational age with verbal ability and Spatial Working Memory at age 11. *Pediatrics*, *138*(6). https://doi.org/10.1542/peds.2016-0578

Flamand, V. H., Nadeau, L., & Schneider, C. (2012). Brain motor excitability and visuomotor coordination in 8-year-old children born very preterm. *Clinical Neurophysiology*, *123*(6), 1191–1199. https://doi.org/10.1016/j.clinph.2011.09.017

Garon, N., Smith, I. M., & Bryson, S. E. (2014). A novel executive function battery for preschoolers: Sensitivity to age differences. *Child Neuropsychology*, *20*(6), 713–736. https://doi.org/10.1080/09297049.2013.857650

Gilmore, R., & Johnson, M. H. (1995). Working memory in infancy 6 month-olds performance on two versions of the oculomotor delayed response task. In *Journal of Experimental Child Psychology* (Vol. 59, pp. 397–418).

Grossmann, T. (2013). Mapping Prefrontal Cortex Functions in Human Infancy. *Infancy*, *18*(3), 303–324. https://doi.org/10.1111/infa.12016

Lemola, S., Oser, N., Urfer-maurer, N., Brand, S., Holsboer-, E., Bechtel, N., Grob, A., Weber, P., & Datta, A. N. (2017). Effects of gestational age on brain volume and cognitive functions in generally healthy very preterm born children during school-age : A voxel-based morphometry study. *PLoS ONE*, 1–13.

Lind, A., Nyman, A., Lehtonen, L., & Haataja, L. (2019). Predictive value of psychological assessment at five years of age in the long-term follow-up of very preterm children. *Child Neuropsychology*, *00*(00), 1–12. https://doi.org/10.1080/09297049.2019.1674267

Loe, I. M., Chatav, M., & Alduncin, N. (2015). Complementary assessments of executive function in preterm and full-term preschoolers. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *21*(3), 331–353. https://doi.org/10.1080/09297049.2014.906568

Lowe, J., Maclean, P. C., Shaffer, M. L., & Watterberg, K. (2009). Early Working Memory in Children Born With Extremely Low Birth Weight: Assessed by Object Permanence. *Journal of Child Neurology*, *24*(4), 410–415.

Matthews, A., Ellis, A. E., & Nelson, C. A. (1996). Development of Preterm and Full-Term Infant Ability on AB , Recall Memory , Transparent Barrier Detour , and Means-End Tasks. *Child Development*, *67*, 2658–2676.

Mürner-Lavanchy, I., Ritter, B. C., Spencer-Smith, M. M., Perrig, W. J., Schroth, G., Steinlin, M., & Everts, R. (2014). Visuospatial working memory in very preterm and term born children—Impact of age and performance. *Developmental Cognitive Neuroscience*, *9*, 106–116. https://doi.org/10.1016/j.dcn.2014.02.004

Newbury, J., Klee, T., Stokes, S., & Moran, C. (2016). Interrelations between working memory, processing speed and language development in the age range 2-4 years. *Journal of Speech, Language and Hearing Research*, *Oct 1;59*(5), 1146–1158. https://doi.org/10.1044/2016

Oakes, L. M., Hurley, K. B., Ross-Sheehy, S., & Luck, S. J. (2011). Developmental changes in infants' visual short-term memory for location. *Cognition*, *118*(3), 293–305. https://doi.org/10.1016/j.cognition.2010.11.007.Developmental

Omizzolo, C., Scratch, S. E., Stargatt, R., Kidokoro, H., Thompson, D. K., Lee, K. J., Cheong, J., Neil, J., Inder, T. E., Doyle, L. W., & Anderson, P. J. (2014). Neonatal Brain Abnormalities and Memory and Learning Outcomes at 7 Years in Children Born Very Preterm. *Memory*, *22*(6), 605–615. https://doi.org/10.1080/09658211.2013.809765

Pazzaglia, F., & Cornoldi, C. (1999). The role of distinct components of visuo-spatial working memory in the processing of texts. *Memory (Hove, England)*, *7*(1), 19–41. https://doi.org/10.1080/741943715

Pelphrey, K. A., Reznick, J. S., Goldman, B. D., Sasson, N., Morrow, J., Donahoe, A., & Hodgson, K. (2004). Development of visuospatial short-term memory in the second half of the 1st year. *Developmental Psychology*, *40*(5), 836–851. https://doi.org/10.1037/0012-1649.40.5.836

Piaget, J. (1954). The construction of reality in the child. In M. Cook (Ed.), *The construction of reality in the child.* (pp. xiii, 386–xiii, 386). Basic Books. https://doi.org/10.1037/11168-000

Potijk, M. R., De Winter, A. F., Bos, A. F., Kerstjens, J. M., & Reijneveld, S. A. (2012). Higher rates of behavioural and emotional problems at preschool age in children born moderately preterm. *Archives of Disease in Childhood*, *97*(2), 112–117. https://doi.org/10.1136/adc.2011.300131

Reznick, J. S., Morrow, J. D., Goldman, B. D., & Snyder, J. (2004). The onset of working memory in infants. *Infancy*, *6*(1), 145–154. https://doi.org/10.1207/s15327078in0601_7

Roid, G. H., & Sampers, J. L. (2011). Merrill-Palmer-R. Escalas de desarrollo. Madrid, Spain: TEA.

Saavalainen, P., Luoma, L., Bowler, D., Määttä, S., Kiviniemi, V., Laukkanen, E., & Herrgård, E.

(2007). Spatial span in very prematurely born adolescents. *Developmental Neuropsychology*, *32*(3), 769–785. https://doi.org/10.1080/87565640701539535

Sajaniemi, N., Hakamies-Blomqvist, L., Mäkelä, J., Avellan, A., Rita, H., & von Wendt, L. (2001). Cognitive development, temperament and behavior at 2 years as indicative of language development at 4 years in pre-term infants. *Child Psychiatry and Human Development*, *31*(4), 329–346. https://doi.org/10.1023/A

Spencer, J. P., Smith, L. B., & Thelen, E. (2001). Tests of a Dynamic Systems Account of the A-not-B Error: The Influence of Prior Experience on the Spatial Memory Abilities of Two-Year-Olds. *Child Development*, *72*(5), 1327–1346. https://doi.org/Doi 10.1111/1467-8624.00351

Sun, J., Mohay, H., & Callaghan, M. O. (2009). A comparison of executive function in very preterm and term infants at 8 months corrected age. *Early Human Development*, *85*(4), 225–230. https://doi.org/10.1016/j.earlhumdev.2008.10.005

Suor, J. H., Stuge-Apple, M., Davies, P. T., & Cicchetti, D. (2017). A life history approach to delineating how harsh environments and hawk temperament trains differencially shape children's problem-solving skills. *Journal of Child Psychology and Psychiatry*, *58*(8), 902–909. https://doi.org/10.1126/science.1249098.Sleep

Tokariev, M., Vuontela, V., Lönnberg, P., Lano, A., Perkola, J., Wolford, E., Andersson, S., Metsäranta, M., & Carlson, S. (2019). Altered working memory-related brain responses and white matter microstructure in extremely preterm-born children at school age. *Brain and Cognition*, *136*(July), 103615. https://doi.org/10.1016/j.bandc.2019.103615

Twilhaar, E. S., De Kieviet, J. F., Aarnoudse-Moens, C. S. H., Van Elburg, R. M., & Oosterlaan, J. (2017). Academic performance of children born preterm: A meta-analysis and meta-regression. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, 322–330. https://doi.org/10.1136/archdischild-2017-312916

Urben, S., Jonge, L. V. H. De, Barisnikov, K., Pizzo, R., Monnier, M., Lazeyras, F., Tolsa, C. B., Hüppi, P. S., Pizzo, R., Monnier, M., Lazeyras, F., Tolsa, C. B., & Hüppi, P. S. (2015). Gestational age and gender influence on executive control and its related neural structures in preterm-born children at 6 years of age. *Child Neuropsychology*, *7049*(June 2016), 0–20. https://doi.org/10.1080/09297049.2015.1099619

Vicari, S., Caravale, B., Carlesimo, G. A., Casadei, A. M., & Allemand, F. (2004). Spatial working memory deficits in children at ages 3-4 who were low birth weight, preterm infants. *Neuropsychology*, *18*(4), 673–678. https://doi.org/10.1037/0894-4105.18.4.673

Vieira, M. E. B., & Linhares, M. B. M. (2016). Quality of life of individuals born preterm: a systematic review of assessment approaches. *Quality of Life Research*, *25*(9), 2123–2139. https://doi.org/10.1007/s11136-016-1259-9

Wilcox, T., Nadel, L., & Rosser, R. (1996). Location Memory in Healthy Preterm and Full-Term Infants. *Infant Behavior and Development*, *19*, 309–323.

Woodward, L. J., Edgin, J. O., Thompson, D., & Inder, T. E. (2005). Object working memory deficits predicted by early brain injury and development in the preterm infant. *Brain*, *128*(11), 2578–2587. https://doi.org/10.1093/brain/awh618

Table 1. Main sociodemographic data of control and preterm sample

		Controls (N=65)	**Preterm (N=15)**
		Mean (Standard deviation)	
Mother's age		37.21 (4.02)	34.30 (3.79)
Father's age		38.38 (3.74)	37.40 (4.52)
		N (%)	
Girls		33 (50.8%)	10 (50%)
Boys		32 (49.2%)	10 (50%)
Mothers' studies	Primary	1 (1.7%)	0 (0%)
	Secondary	8 (13.3%)	7 (35%)
	Technical	19 (31.7%)	4 (20%)
	Bachelor's degree	32 (53.3%)	9 (45%)
Fathers' studies	Primary	0 (0%)	2 (10%)
	Secondary	16 (30.2%)	7 (35%)
	Technical	15 (28.3%)	9 (45%)
	Bachelor's degree	22 (41.5%)	2 (10%)
Mothers' diseases		3 (4.7%)*	3 (15%)*
Fathers' diseases		9 (16.1%)*	2 (10%)*

*Number and percentages of parents who presented at least one disease or condition. The diseases of the parents are listed in order of decreasing frequency: psychological (anxiety and depression) (N=9), allergies (N=9), asthma (N=6), metabolic (diabetes and hypertension) (N=4), and neurological (multiple sclerosis) (N=1).

Table 2. Neonatal variables of preterm sample

	Mean (Standard deviation)	Range
Birth weight (grams)	1800.75 (376.07)	1170-2425
Gestational age (weeks)	32.90 (1.91)	30-36
APGAR test (1 min)	8.30 (1.21)	
APGAR test (5 min)	9.55 (0.76)	
	Frequency (%)	
Multiple delivery	40%	
In vitro fecundation (IVF)	10%	
C-section delivery	35%	
Maternal corticosteroids	75%	
Maternal antibiotics	65%	
Maternal chorioamnionitis	5%	
Maternal arterial hypertension	10%	
Surgery during NICU	0%	
Endotracheal intubation	0%	
Continuous positive airway pressure	45%	
Mechanical ventilation	0%	
Inotropic	10%	
Surfactant	10%	
Respiratory distress syndrome	0%	
Necrotizing enterocolitis	0%	
Patent ductus arteriosus	0%	
Transfused anemia	0%	
Early onset sepsis	0%	
Late onset sepsis	5%	
Apnea	30%	
Intraventricular hemorrhage (Grade I*)	25%	

Periventricular leukomalacia	0%

NICU: Neonatal Intensive Care Unit

* Participants in our sample only showed intraventricular hemorrhage in level I

Table 3. Descriptive data of standard scores from Merrill-Palmer R scores of control and preterm children

	12 months		15 months		18 months		22 months	
	Control (N=16)	**Preterm (N=20)**	**Control (N=16)**	**Preterm (N=17)**	**Control (N=18)**	**Preterm (N=15)**	**Control (N=15)**	**Preterm (N=15)**
	Mean (Standard deviation)							
MPR General Index	107.14 (7.03)	98.70 (6.54)	103.63 (4.57)	102.41 (4.10)	86.53 (9.58)	96.14 (10.57)	87.27 (7.63)	96.80 (7.62)
MPR Cognition	111.79 (7.36)	97.20 (7.41)	105.50 (8.27)	106.12 (4.52)	89.24 (9.93)	96.93 (8.07)	86.67 (2.55)	89.47 (1.26)
MPR Fine Motor Skills	97.50 (9.57)	101.20 (7.97)	97.94 (7.74)	97.12 (6.80)	86.00 (13.66)	98.07 (11.34)	92.67 (7.57)	97.33 (2.54)
MPR Receptive Language	95.71 (2.97)	-*	97.56 (6.72)	94.41 (0.50)	92.24 (8.54)	96.86 (12.19)	92.53 (9.99)	95.27 (2.22)
MPR Visuomotor coordination	102.14 (11.83)	94.95 (6.58)	102.19 (7.43)	99.35 (4.66)	83.59 (13.82)	96.36 (10.01)	83.93 (6.75)	91.00 (2.14)

*** No data are available for Receptive Language measures in 12-month-old preterm children due to age-corrected adaptation. It was therefore necessary to start at the level (0.5 on the scale) at which there are no scoring items for these variables.*

Table 4. Correlations between Baby-mnemo (BM) measures and Hide and Seek (HS) with Merrill-Palmer R (MPR) subscales in preterm children (N=20)

		BM Location	**BM Delay**	**BM Update**	**HS Retention**	**HS Update**	**HS Correct answers**
MPR General Index	Spearman correlation	**.357****	**.485****	**.373****	**.585****	**.362****	**.571****
	P value	**.003**	**.000**	**.002**	**.000**	**.003**	**.000**
MPR Cognition	Spearman correlation	**.341****	**.399****	**.313***	**.518****	**.332****	**.485****
	P value	**.005**	**.001**	**.011**	**.000**	**.006**	**.000**
MPR Fine Motor Skills	Spearman correlation	**.370****	**.478****	**.338****	**.526****	**.381****	**.556****
	P value	**.002**	**.000**	**.006**	**.000**	**.002**	**.000**
MPR Receptive Language	Spearman correlation	.197	**.446****	**.304***	**.323***	**.300***	**.431****
	P value	.167	**.001**	**.030**	**.021**	**.032**	**.002**
MPR Visuomotor Coordination	Spearman correlation	**.316****	**.396****	**.280***	**.570****	**.381****	**.587****
	P value	**.010**	**.001**	**.023**	**.000**	**.002**	**.000**

Figure captions

Figure 1. Front view of the Baby-Mnemo device (A) and the Hide and Seek (B) device. (A) Four push buttons are available with their 4 corresponding platforms. A blanket is employed to partially cover the device. (B) Four small boxes with lids inside a larger box with lid are available to hide the object.

Figure 2. Comparison of preterm children and controls on memory tasks. (A) Comparison on Baby-mnemo at 22 months. Significant differences were found in the Location and Update phases. (B) Comparison on Hide and Seek at 12 months. Significant differences were observed on Errors and Correct answers. $*p<0.05$; $**p<0.01$

Figure 3. Comparison of preterm children by age on memory tasks. (A) Comparison on Baby-mnemo phases. Significant differences were found on Delay at 22 months compared to 12 and 15 months. (B) Comparison on Hide and Seek measures. Significant differences were observed on Retention between 12 and 22 months, and on Update, Correct answers, and Errors between 12 and 22 months and between 18 and 22 months. $**p<0.01$

Figure 1.

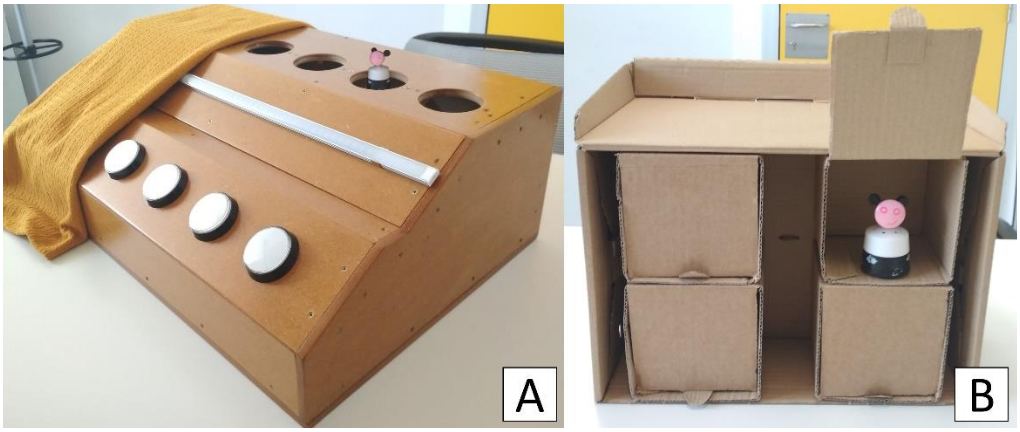

Figure 2

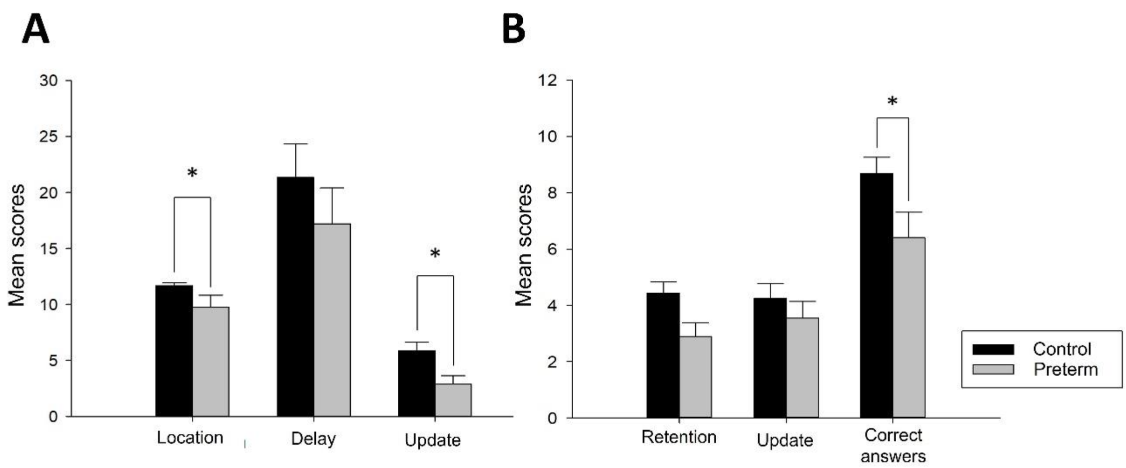

Figure 3