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RESEARCH

## Research Report

## Memory functions of children born with asymmetric intrauterine growth restriction

Ronny Geva<sup>a,b,\*</sup>, Rina Eshel<sup>a</sup>, Yael Leitner<sup>a</sup>, Aviva Fattal-Valevski<sup>a</sup>, Shaul Harel<sup>a</sup><sup>a</sup>The Institute for Child Development and Pediatric Neurology Unit, Division of Pediatrics, Tel Aviv Sourasky Medical Center, Tel Aviv University, Israel<sup>b</sup>The Developmental Neuropsychological Laboratory at the Gonda (Goldschmied) Multidisciplinary Brain Research Center, Psychology Department, Bar-Ilan University, Ramat Gan, Israel

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## Abbreviations:

BW, birth weight

EGA, estimated gestational age

HC, head circumference

(only used once in text)

IUGR, intrauterine growth restriction

REY-AVLT, Rey Auditory

Verbal Learning Test

ROCF, Rey Osterrieth Complex

Figure Test

VADS, Visual Auditory Digit Span

## ABSTRACT

**Objective:** Learning difficulties are frequently diagnosed in children born with intrauterine growth restriction (IUGR). Models of various animal species with IUGR were studied and demonstrated specific susceptibility and alterations of the hippocampal formation and its related neural structures. The main purpose was to study memory functions of children born with asymmetric IUGR in a large-scale cohort using a long-term prospective paradigm. **Methods:** One hundred and ten infants diagnosed with IUGR were followed-up from birth to 9 years of age. Their performance was compared with a group of 63 children with comparable gestational age and multiple socioeconomic factors. Memory functions (short-term, super- and long-term spans) for different stimuli types (verbal and visual) were evaluated using Visual Auditory Digit Span tasks (VADS), Rey Auditory Verbal Learning Test (Rey-AVLT), and Rey Osterrieth Complex Figure Test (ROCF). **Results:** Children with IUGR had short-term memory difficulties that hindered both serial verbal processing system and simultaneous processing of high-load visuo-spatial stimuli. The difficulties were not related to prematurity, neonatal complications or growth catch-up, but were augmented by lower maternal education. Recognition skills and benefits from reiteration, typically affected by hippocampal dysfunction, were preserved in both groups. **Conclusions:** Memory profile of children born with IUGR is characterized primarily by a short-term memory deficit that does not necessarily comply with a typical hippocampal deficit, but rather may reflect an executive short-term memory deficit characteristic of anterior hippocampal-prefrontal network. Implications for cognitive intervention are discussed.

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## 1. Introduction

Studies have shown that fetuses, whose growth in utero is restricted, developed in an adverse preterm environment,

deficient in essential nutrients, most typically due to placental vascular insufficiency (Leitner et al., 2000; Baschat, 2004; Ergaz et al., 2005). Recent reports have shown that children born with IUGR have long-term cognitive impairments and learning

\* Corresponding author. Developmental Neuropsychological Laboratory, The Gonda (Goldschmied) Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan 52900, Israel. Fax: +972 3 5352184.

E-mail address: [gevaro@mail.biu.ac.il](mailto:gevaro@mail.biu.ac.il) (R. Geva).

difficulties in school (Low et al., 1992; Goldenberg et al., 1998; Camm et al., 2000; Hollo et al., 2002; O'Keefe et al., 2003; Geva et al., 2006). The neuropsychological basis for these difficulties is not clear (Scherjon et al., 2000). Elucidating specific neuropsychological deficits may validate animal model studies and should contribute to both understanding the long-term pathogenic sequelae of IUGR and aid in devising intervention in this high-risk surviving population. Memory may have a pivotal role in accounting for the learning difficulties experienced by children diagnosed with IUGR. The main purpose of the current study was to thoroughly explore a large-scale, prospective paradigm of memory functions in children born with IUGR.

Model studies of IUGR in various animal species have demonstrated specific susceptibility and alterations of the hippocampal formation and its related neural structures. These models of IUGR, typically induced by a period of reduced placental blood flow during the second half of pregnancy, demonstrated reduced numbers of neurons in the hippocampus and the cerebellum in conjunction with retarded dendritic and axonal growth within these structures (Cintra et al., 1990; Nyakas et al., 1996; Cintra et al., 1997; de Deungria et al., 2000; Mallard et al., 2000; Dieni and Rees, 2003; van Wassenae, 2005). In addition, histological and anatomical findings in primates and humans indicated that the hippocampus matures early during pregnancy (Kostovic et al., 1989; Berger et al., 1993; Hevner and Kinney, 1996) and is susceptible to prenatal compromise (Isaacs et al., 2003). These findings should result in a specific memory profile in children born with IUGR that is compatible with hippocampal formation-related dysfunction. Other reports indicated limbic and frontal lobe susceptibility (Makhoul et al., 2004; Geva et al., 2006). These data may suggest a unique neuropsychological profile that develops as the central nervous system (CNS) matures through childhood.

The hippocampal hypothesis would have predicted a difficulty in declarative memory, such as a reduced capacity for acquisition and recall of word lists (Cohen and Eichenbaum, 1993; Zola-Morgan and Squire, 1993). Other components typically related to hippocampal formation functioning are sustaining a delay prior to stimuli retrieval from long-term memory (Lepage et al., 1998; Schacter et al., 1999) and benefiting from repeated exposure to improve learning curve. Hence, one would expect this memory profile to emerge in children diagnosed neonatally with IUGR. Limbic and frontal susceptibility would predict executive-attention-related memory difficulty (Posner and Rothbart, 2004; Vakil et al., 2004; Geva et al., 2006) that predominantly impedes short-term memory functions.

To date, a few studies have examined a discrete memory component in children with IUGR: recognition memory was examined in neonates (Gotlieb et al., 1988; Black et al., 2004), working memory was studied in children (Frisk et al., 2002) and daily memories were examined in adolescents born with IUGR (Isaacs et al., 2000). However, a systemic evaluation of the various memory systems in children with IUGR has not yet been conducted. Hence, a study that integrates various memory components is warranted. It is still not known if the difficulty experienced by children born with IUGR is primarily a short-term memory span difficulty, a processing inefficiency,

or dysfunction due to rapid decay of declarative memory traces. Furthermore, it is not clear if the difficulty is general, or specific to any one modality.

The current study of memory functions at 9 years of age in children born with IUGR, and controls matched for prematurity and socioeconomic factors explored three memory-dependent elements: (1) short-term memory span: effect of modality, (2) recall of a super-span stimuli: effect of reiteration, and (3) retrieval efficiency of complex stimuli: effect of rate delay and stimuli type (verbal and visuo-spatial).

Three hypotheses were examined in the current study. Hypothesis A stems from hippocampal findings related to IUGR both in animal models (Cohen and Eichenbaum, 1993; Zola-Morgan and Squire, 1993) and in humans (Isaacs et al., 2000). The hippocampal hypothesis thus predicted a difficulty in declarative memory, i.e., the capacity for acquisition and recall of word lists, such as those employed in the Rey Auditory Verbal Learning Test (Rey-AVLT), since these functions are largely thought to be dependent on an intact hippocampal system task (Cohen and Eichenbaum, 1993; Zola-Morgan and Squire, 1993). A deficit in obtaining a curvilinear learning function with repeated exposure would be expected. Furthermore, other memory components typically related to hippocampal formation functioning such as, a marked decay in recall after a delay would further support Hypothesis A. The rapid decay hypothesis may be tested using both verbal stimuli in the Rey-AVLT delayed recognition condition, where the subject was asked to recognize a series of stimuli that was repeatedly presented after a 20-min delay and with complex visuo-spatial stimuli in the delayed reconstruction condition of the Rey Osterrieth Complex Figure Test (ROCF).

Alternatively, the hypothesis B argument arises from recent studies on an executive-attention component, governed by dysfunctional prefrontal-related structures, that hampers short-term memory capacities. According to this hypothesis, short-term memory span would be affected, but it would not be accompanied by consolidation deficits, or by rapid decay. Finally, Hypothesis C focuses on lack of modality-specific deficit. This hypothesis is founded on absence of laterality differences in hippocampal or prefrontal-related structures with regard to the IUGR process. This hypothesis would denote equivalent memory-related difficulties in verbal and non-verbal materials both in short- and in long-term retrieval tasks. Thus, Hypothesis C may be tested in two ways: (1) by comparing levels of performance on the Rey-AVLT, that is a high-load verbal task, and the ROCF, a high-load abstract material task, both on immediate recall and a long-term delay condition; (2) by comparing modality-specific differences on Visual Auditory Digit Span (VADS): aural–oral, aural–written, visual–oral and visual–written.

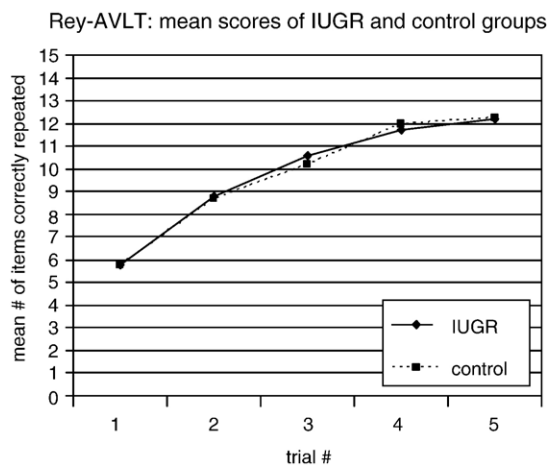
## 2. Results

To test Hypothesis A, three functions thought to involve hippocampal activity were analyzed: learning curves of immediate recall, rate of long-term decay, and recognition memory. To test the effects of repeated exposure on immediate recall of super-span stimuli, analyses of performance on

the Rey-AVLT were conducted. Both learning curves of super-span word lists presented repeatedly and benefits from reiteration were tested with the Rey-AVLT. Both groups performed within expected range on this task and exhibited a similar learning curve on repeated exposure to the super-span list (Fig. 1). Most subjects recalled six items on first exposure and learned the full list within five repeats as expected. Multivariate analysis of variance (MANOVA) with repeated measures showed that all scores were not significantly affected by group, prematurity or by prenatal complications. The Rey-AVLT scores were significantly affected by maternal education ( $F_s$ : range, 5.639–18.819,  $P$  values: range, 0.001–0.008). The full model accounted for 7%–25% of the variance explained.

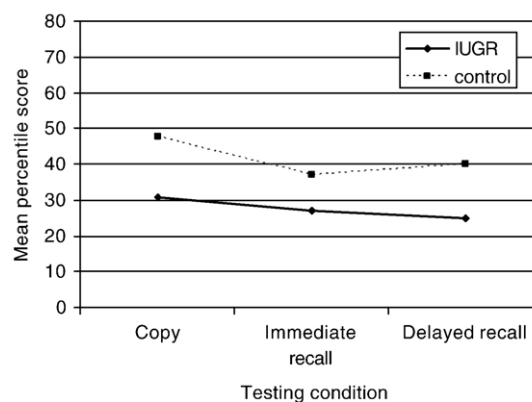
The second function examined within the framework of Hypothesis A was to test delayed recall functions (none, after 20 min) of both verbal and visuo-spatial stimuli. This was performed by analyzing performance on the ROCF and analyzing the delayed recognition recall condition of the Rey-AVLT.

The IUGR group score was significantly lower than that of the control group on all three test conditions of the ROCF (Fig. 2): design copy (with a sample present), immediate incidental recall and delayed incidental recall. The mean of the IUGR group was lower than that of the normal range, whereas the control group performed within normal range. However, it is important to note that a similar gap between the groups was maintained in all three conditions. Once past the significant attention-related difficulty evident in the copy condition, the additional demand for immediate recall and delayed recall did not further affect performance. Multivariate ANOVA for repeated scores showed that scores were significantly affected by group ( $F_{\text{copy}}=16.044$ ,  $p<0.001$ ,  $F_{\text{imm. Recall}}=6.866$ ,  $p<0.01$ ,  $F_{\text{delayed recall}}=13.056$ ,  $p<0.001$ ) and by maternal education ( $F_{\text{copy}}=9.895$ ,  $p<0.002$ ;  $F_{\text{immediate recall}}=9.332$ ,  $P=0.03$ ;  $F_{\text{delayed recall}}=5.639$ ,  $P=0.019$ ), but not by prematurity or prenatal complications. Performance on the 20-min decay as well as delayed recognition memory were within expected norms for both groups (group mean scores for decay conditions were  $10.03\pm3.13$  and  $10.53\pm2.33$  for the IUGR and



**Fig. 1 – Mean memorized items on the Rey Auditory Verbal Learning Test (Rey-AVLT) of intrauterine growth restriction (IUGR) and control groups as a function of trial conditions.**

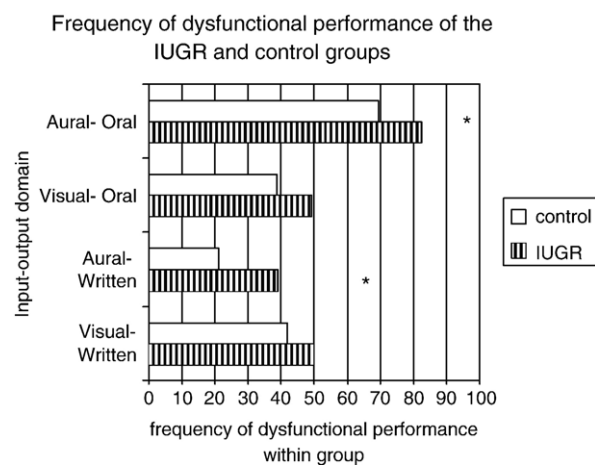
**ROCF mean percentile scores of IUGR and control groups: Copy, immediate incidental recall and delayed recall conditions**



**Fig. 2 – Mean percentile scores on the Rey Osterrieth Complex Figure Test (ROCF) of IUGR and control groups: as a function of test conditions.**

controls, respectively, and for the delayed recognition memory condition:  $10.25\pm3.39$  and  $10.84\pm2.42$  for the IUGR and control groups, respectively). Repeated measures  $F=1.208$ , NS). Overall, no differences between the groups were found on this measure.

To examine Hypothesis B, the test conditions of short-term memory skills of children born with IUGR, and scores from the VADS test were analyzed. Chi-squared ( $\chi^2$ ) analysis for frequency of suboptimal/borderline performance on short-term memory retrieval showed that children born with IUGR more frequently experienced difficulties with the immediate recall of digit span (DS) than matched controls (46.06% vs. 28.62%, respectively,  $p<0.05$ , Fig. 3). Their difficulties were more frequent than in controls, particularly in conditions of auditory input and verbal expression. Tests of between-subject effects showed that both prematurity and IUGR affected overall performance on VADS average over the four test conditions: prematurity effect:  $F=5.048$ ,  $p=0.026$ ; IUGR effect:  $F=6.906$ ,  $p=0.009$ ).



**Fig. 3 – Frequency of dysfunctional performance on the Visual Auditory Digit Span (VADS) of the IUGR and control groups as a function of modality.**

The aural–oral condition affected over 82% of the children born with IUGR. The least affected condition for the control group was the oral–written (80% of the group performed within expected range).

To test Hypothesis C, a study of immediate memory span and rate of deficient functioning as a function of input-specific modality (aural vs. visual) and output modality (oral vs. written) was conducted. To test if the effect of IUGR on audible stimuli was general, expressed both in attention to input and in retrieval output, conditions were recorded regarding input (aural and visual) vs. output modalities (verbal and written). A general linear model with repeated measures for the factor of input–output mode (auditory or visual) was conducted. Analysis showed a significant input by group interaction ( $F=6.160$ ,  $p=0.014$ ) and no effect of the output mode (verbal or written, NS).

Finally, to test the variables best predicting the specific short-term memory difficulties encountered by children born with IUGR, the main effect of prematurity on performance was not significant. As the IUGR effect was particularly evident in the aural–oral condition, ANOVA analyses of the aural–oral condition revealed that it is significantly affected by group ( $F=4.589$ ,  $p=0.034$ ) or by the CI ( $F=4.123$ ,  $p=0.044$ ). However it is not affected by neonatal complications, prematurity, anthropometric catch-up growth, or by maternal education. The VADS data showed that children born with IUGR have short-term memory difficulties that are particularly pronounced when input is dependent upon attention to aural stimuli.

### 3. Discussion

Recent reports pointed to increased susceptibility to learning deficits among children born prematurely who had been diagnosed with IUGR. The pathogenic brain process is not clear. It is important to study the effects of IUGR on memory skills using a prospective paradigm in order to explore one of the major mechanisms that may account for learning deficits in this high-risk population. Recent reports have suggested two possible explanatory sources. On the one hand, animal models demonstrated hippocampal formation changes as a result of induced IUGR (Mallard et al., 2000; van Wassenae, 2005). On the other hand, a report on human infants was suggestive of decreased frontal lobe development (Makhoul et al., 2004). Each of these mechanisms is suggestive of a different memory profile in children born with IUGR.

The current study used a long-term prospective paradigm and a control group matched for prematurity and socioeconomic factors to characterize the memory profile of children born with IUGR and to explore which of two suggested underlying hypotheses accounts better for the memory deficit: a hippocampal hypothesis or a frontal executive hypothesis. To accomplish these aims, the study tested several major elements of memory functions, including attention sensitive memory functions, i.e., short-term memory recall, and tests of hippocampal formation-related memory symptoms: super-span learning curve and benefits from reiteration, as well as testing the effects of stimulus delay and rate of decay of memory traces using both sequential verbal material and simultaneous visuo-spatial design.

To comply with the study's aims, it was essential to use a large-scale prospective long-term follow-up paradigm. This was highly important as the subject's self-selection by learning difficulties or self-selection by socioeconomic resources are major concerns when studying long-term effects of a developmental pathogenic process in humans. Hence, this concern was markedly reduced using a prospective paradigm. Furthermore, the relatively innocuous demographic characteristics of the sample allowed for a relatively direct observation of the effects of placental vascular insufficiency on preterm development, as opposed to maternal malnutrition and poor health that may confound the outcome findings.

The primary finding of the study was that children born with asymmetric IUGR have memory difficulties relative to controls carefully matched for prematurity, familial and socioeconomic factors. This deficit may underlie the learning difficulties encountered by children born with IUGR (Hawdon et al., 1990; Szatmari et al., 1990). The specific memory profile found is highly significant as it has both empirical and clinical implications regarding the long-term pathophysiological process related to IUGR. The memory profile was essentially comprised of deficits in short-term memory task together with preserved recognition memory, super-span learning and memory and normal rate of decay. The profile is compatible with executive-attention deficit.

As short-term memory was implicated, it is important to examine whether it is a result of an attention difficulty, or a limited working memory capacity. A comparison between the children's scores on the VADS and on the Rey-AVLT supports the orientation-attention deficit, rather than the limited working memory capacity hypothesis. The reason for this being that the VADS tests immediate memory spans, and the Rey-AVLT places high loads on the working memory system by presenting a demand to learn super-span lists via repeated exposure and an opportunity to use mnemonic strategies. The data demonstrated that IUGR affects specifically the VADS, but not the Rey-AVLT. Therefore, the comparison between performances on both tasks supports the notion that difficulties experienced by children with IUGR are mostly in preliminary orientation, rather than in active maintenance for processing of complex stimuli. The difficulties perceived may probably arise from an initial attention deficiency that restricts orientation to the full set of presented stimuli (Cowan et al., 1999). Indeed, recent reports indicated an attention deficit in children born with IUGR that is evident in the neonatal phase (Tolsa et al., 2004). In fact, recent studies demonstrated that premature neonates born with IUGR have attention difficulties and difficulties in recognition processes neonatally, at 2 weeks of age post-birth (Cowan et al., 1999). Their deficient attention performance was related to a significant reduction in their cerebral volume, particularly in cortical grey matter (Tolsa et al., 2004). Similarly, attention and executive dysfunctions were shown to persist throughout the first decade of life in children born with asymmetric IUGR (Geva et al., 2006).

The hippocampal hypothesis predicted that the IUGR group could exhibit deficits in the Rey-AVLT task, as this test requires learning a super-span list of words by repeated exposure and immediate recall (Kilpatrick et al., 1997). Performance on the Rey-AVLT is based upon encoding-



relating stimuli (Petrides and Milner, 1982; Cohen and Eichenbaum, 1993; Karlsgodt et al., 2005) and withstanding a long-term delay (Kohler et al., 1998). Fusiform and parahippocampal responses are expected to mediate successful encoding that consequently reflects attentional orienting to specific stimuli within a long list rendered distinctive by virtue of its temporal context (Strange et al., 2002). The comparison between the IUGR and the carefully matched control groups showed that performance on the Rey-AVLT task was preserved. Both groups performed equally well on this task and exhibited similar learning curves, similar decay after 20-min interval and intact recognition memory.

This profile indicated that given appropriate orientation and exposure and an opportunity to form relationships among stimuli, the immediate recall of children with IUGR is not significantly different from that of matched controls. Contrary to expectations, typical hippocampal formation-related memory symptoms: difficulties in recognition memory, in benefits from reiteration and in rapid decay, were not found to characterize specifically children born with IUGR. Thus, the hippocampus hypothesis does not appear to be supported (Bachevalier and Vargha-Khadem, 2005).

Nevertheless, recent findings using imaging paradigms point to involvement of hippocampus activity during encoding, rather than during maintenance of memory traces (Karlsgodt et al., 2005) and to a contributing role of the perirhinal cortex in the encoding process that supports free recall (Strange et al., 2002). Therefore, it may be that the encoding difficulty encountered by children diagnosed with IUGR is partially related to anterior hippocampal contribution. However, this hypothesis cannot be fully supported in view of lack of evidence for prototypical hippocampal-related functioning, particularly during retrieval in recognition memory (Lepage et al., 1998; Schacter et al., 1999; Manns et al., 2003). These findings underscore a note of caution with regard to deduction from induced models of IUGR to spontaneous asymmetric IUGR, in view of differences in CNS mechanisms and differences in experimental procedures.

Is the initial short-term memory difficulty specific to certain stimuli type? In order to provide an answer, immediate memory of both verbal material, and graphic-abstract material, were evaluated. Findings showed that children with IUGR experienced immediate recall difficulties irrespective of stimuli type. This was evident both by shortened DS on the VADS and by lower ROCF scores on immediate reproduction that could not be explained by lower graphomotor abilities.

Performance on either VADS or the ROCF was also not modulated by rate of anthropometric catch-up. This result regarding lack of catch up effect on memory complements similar findings with another procedure: the self-ordered pointing task (Petrides and Milner, 1982), used with diverse head-growth groupings of children with IUGR (Frisk et al., 2002).

The working memory finding points to a possible lack of orientation of attention in children born with IUGR that precedes and maintains perception processes. It may very well be that an infant programming deficit, evident neonatally (Tolsa et al., 2004), persists and impedes upon working memory and executive functions (Geva et al., 2005; Geva et

al., 2006). Attention difficulty alluded to in the neonatal phase due to IUGR persists throughout the first decade of life and affects short-term memory of both verbal and abstract materials.

The primary memory difficulty encountered by the IUGR group was a short-term memory span deficit, both for verbal (digits) and non-verbal stimuli (complex abstract pattern). This pattern, as well as a visuo-spatial processing difficulty evident on the ROCF complies with frontal lobe (Sami et al., 2003) and/or perihippocampal cortical region-related changes. This memory profile is not typically expected from a hippocampal or diencephalic damage (Cave and Squire, 1992; Di Stefano et al., 2000). These findings may imply that structural deficiencies detected prenatally and neonatally that affect attention are not well compensated for and place children born with IUGR at risk for short-term memory deficit, that may undermine learning and cognitive competence in their later development.

### 3.1. Empirical implications

The data are indicative of functional deficits related to the prefrontal systems and not necessarily a hippocampal formation source. The hippocampal hypothesis would have predicted a difficulty in declarative memory, such as the capacity for acquisition and recall of word lists, as tested by the Rey-AVLT, since it is largely thought to depend on an intact hippocampal system (Cohen and Eichenbaum, 1993; Zola-Morgan and Squire, 1993). Other memory components typically related to hippocampal formation functioning are those of sustaining a delay and benefiting from repeated exposure. The rapid decay hypothesis was tested with both verbal stimuli, in the Rey-AVLT delayed recognition condition where the subject was asked to recognize a series of stimuli that was repeatedly presented after 20-min delays, and with complex visuo-spatial stimuli in the delayed recall condition of the ROCF. The children in the IUGR group did not show abnormal decay as a function of a 20-min delay from last exposure on either task. On both measures the reduced level of performance was maintained, and no greater deficit was evident in the experimental group relative to the control group. Furthermore, it was found that the ability of children with IUGR to benefit from repeated exposure of complex stimuli, such as super-span lists of words or complex abstract figures and the ability to withstand delay prior to recall are not specifically affected by IUGR.

Hence, performance on both components, characteristic of hippocampal formation damage, does not support the hippocampal hypothesis. Furthermore, in order to fully exclude the hippocampal hypothesis, it is important to include the factors of reward association learning and context (Deadwyler et al., 1985; Tulving and Markowitsch, 1998), in future studies.

Recent reports note continued myelination in the subicular and presubicular regions, a key relay zone between the hippocampus and many cortical areas throughout adolescence and adulthood (Bachevalier and Vargha-Khadem, 2005). Therefore, it is recommended that hippocampal-related functions, such as episodic memory in adolescents who were exposed to IUGR, be followed-up.

### 3.2. Clinical implications

The deficit profile has important clinical significance as it implies two intervention directions to improve learning by children who were diagnosed with IUGR. Firstly, the data suggest that the major memory deficit encountered by children with IUGR is short-term memory that may be accounted by a lack of sufficient attention allocation to the novel stimuli, rather than a deficit in processing the information. Manipulating the level of directed attention by facilitating orientation should benefit learning performance. Furthermore, processing of complex stimuli, either verbal or abstract is not specifically affected by IUGR when exposure is repeated and rehearsed. Hence, clinical interventions in children with IUGR should focus on increasing arousal and directing attention in addition to reiteration, rather than concentrating on slowing presentation rate or simplifying the novel material.

In summary, children born with IUGR do experience short-term memory difficulties. These difficulties are evident with both verbal material and complex visuo-spatial domain. Decoding difficulties are most pronounced when aural–oral integration skills and/or high-load abstract material analyses are required. Deficits may reflect an executive short-term memory deficit characteristic of anterior hippocampal–prefrontal network. Later phases of processing, consolidation and retrieval, typically affected by hippocampal formation network, were not shown to be affected specifically by IUGR.

## 4. Experimental procedure

### 4.1. Subjects

All children with IUGR (birth weight [BW] below the 10th percentile) who were diagnosed at birth were eligible to participate, with the exception of those with genetic disorders and unrelated co-morbidities. All neonates in this study, IUGR and controls alike, were born at the Lis Maternity Hospital between January 1, 1992, and December 31, 1995, and were admitted to the neonatal unit of the Dana Children's Hospital, Tel Aviv Medical Center, that serves the residential area of Tel Aviv. The study was approved by the Tel Aviv Sourasky Medical Center Helsinki Committee for studies on human subjects. Informed parental and subject consent was obtained in all cases. Inclusion criteria were mid-second trimester to third trimester onset IUGR (verified clinically and/or by ultrasound), absence of fetal infections, congenital malformations, such as congenital heart disease and metabolic and chromosomal disorders at birth. Estimated gestational age (EGA) was calculated according to the date of the last menstrual period. Pathological studies of the placentas revealing vascular placental insufficiency were confirmed (Leitner et al., 2000).

Subjects were followed-up periodically for 9–10 years (Geva et al., 2006). No major CNS-related pathogenic processes, such as meningitis, traumatic brain injury, or severe anomalies were noted in any of the non-excluded subjects in the current report.

The experimental group (N=63) comprised children who were born with appropriate BW for their GA. This group of

9-year olds was randomly sampled according to birth registries kept at the municipal well-baby clinic and the registry of the public school contiguous to the clinic in the same community in the Tel Aviv municipal area. The group was selected to be comparable for testing age, parental ages, maternal education, parental occupation and EGA (Table 1). This cohort was quite unique as it offered an opportunity to observe the direct effects of prematurity and IUGR, irrespective of major confounds, such as teen motherhood or poor care (Ergaz et al., 2005). Furthermore, the cohort was not characterized by very short gestational periods and included only one child with extremely low BW, thus the full spectrum effect of IUGR pathogenic process could be studied without load of the extreme cases in the cohort (Geva et al., 2006).

As shown in Table 1, group means and distributions were comparable on other neonatal/obstetrical, parental, familial and socioeconomic measures of EGA, maternal and paternal ages, maternal and paternal education, paternal occupation and socioeconomic variables regarding level of proficient work and family structure. Groups differed significantly regarding BW and head circumference and thus on their cephalization index as expected (Harel et al., 1985a,b). They also differed, as expected, in propensity for neonatal complications (Fattal-Valevski et al., 1999; Gutbrod et al., 2000).

### 4.2. Data analysis

The unpaired *t* test was used to determine differences in outcome measures at 9 years of age and evaluated short-term memory input modalities: aural–visual, output modalities: verbal–written, stimuli type: verbal (VADS) (Koppitz, 1981; Talley, 1986) and visuo-spatial (ROCF) (Osterreith, 1944), super-span memory capacities using repeated exposure (Rey-AVLT, Vakil et al., 2004), and delayed incidental recall of both verbal and visuo-spatial stimuli. A *p* value <0.05 was considered to be statistically significant. Data are presented as mean ± standard error (*m* ± *SE*). Multivariate ANOVA of the outcome measures with the following covariates was conducted: (1) prematurity; (2) maternal education; (3) neonatal complications (>3); (4) gender and (5) catch up, to control the effects of these factors on outcome in addition to the effect of IUGR.

Ranked order scores were analyzed using Chi-square ( $\chi^2$ ) of frequency within each participating group.

### 4.3. Materials and procedures

Digit span capacities were tested using the VADS Test (Koppitz, 1981). The child was presented with digit spans of increasing lengths. After each trial was presented the child was asked to duplicate the sequence in the same order. If performance matched the presented sequence, a 'span+1' was to be administered; if the response was incorrect, an additional sequence with identical span length was repeated. Scoring was dependent upon the maximum response to span length. The test comprised four conditions: (1) an aural–oral span condition: aural stimuli were presented at a rate of 1 digit per second in a monotone intonation and constant volume; the child was asked to repeat the sequence immediately the examiner completed presentation of the full span; (2) a visual–oral span condition: the child was shown a series of cards.

**Table 1 – Demographic description of the participating groups**

		IUGR (N=110)	Control (N=61)	Significance
Obstetric/Neonatal	Birth weight	1853.6±416.8 (<0.5th %ile)	2829.7±761.7 (WNL)	<0.001
	Neonatal HC (cm)	30.5±1.9 (>0.10th %ile)	33.5±4.3 (WNL)	<0.001
	Neonatal CI <sup>a</sup>	1.72±0.41	1.27±0.30	<0.05
	Complicated hospital stay (%>3 comp) <sup>b</sup>	66.4	27.4	<0.001
	Estimated gestation age	37.0±2.6	36.7±6.9	NS
	Prenatal complications score <sup>b</sup>	9.4±7.1	11.3±7.8	NS
	Neonatal complications score <sup>b</sup>	11.7±12.8	8.9±13.9	NS
	Prematurity (%<37)	29.1	33.8	NS
	ELBW (%<750)	0.009	0	NS
	Maternal smoking (%)	12.8	21.4	NS
Demographic	Gender (%M)	49.1	44.3	NS
	Age at test (months)	112	111	NS
	Weight at 9 years (kg.)	27.93±0.716 (WNL)	31.06±0.610 (WNL)	<0.005
	HC at 9 years (g)	51.2±1.8 (WNL)	52.1±2.6 (WNL)	<0.05
	Height at 9 years (cm)	131.28±6.1 (WNL)	135.0±6.7 (WNL)	<0.001
Parental	Maternal age at delivery	30.5±5.8	30.5±4.6	NS
	Paternal age at delivery	33.6±6.3	32.5±4.5	NS
	Maternal education (Y)	13.0±2.3	13.5±3.6	NS
	Maternal health	19.6±1.9	20.0±0.0	NS
	Paternal health	19.5±2.7	18.6±5.3	NS
	Parental occupation <sup>c</sup>	4.4±3.1	5.0±2.6	NS
	Parental education (Y)	12.8±2.6	12.9±2.9	NS
Familial–Community	Parity (%)	0.23±0.623	0.38±0.719	NS
	Socioeconomical status <sup>d</sup>	1.5±1.1	1.6±1.2	NS
	# of children in family	2.4±1.1	3.0±1.2	NS
	Child's place in family	2.0±1.1	2.0±0.8	NS

WNL=within normal limits; IUGR=intrauterine growth restriction, ELBW=extremely low birth weight, NS=nonsignificant.

<sup>a</sup> Cephalization index=Head Circumference×10<sup>2</sup>/Birth Weight (g) (Harel et al., 1985a,b) adapted from Fattal-Valevski et al.

<sup>b</sup> Cephalization index=Head Circumference×10<sup>2</sup>/Birth Weight (g) (Harel et al., 1985a,b) adapted from Fattal-Valevski et al.

<sup>c</sup> Coded on a 9-level scale (1=non proficient, 2=proficient, 3=farmer, 4=hand artisan, 5=salesman, 6=clerkship, 7=managerial, 8=free profession, 9=academic research).

<sup>d</sup> Composite score based on maternal education parental occupation and welfare aid.

Each card contained a printed (72-point font) digit span presented for 5–10 s until the child signaled readiness to commence. At that point the card was covered; (3) an aural-written span condition: spans were presented aurally as depicted in condition 1 (aural–oral) and the child was asked to write the sequence on a blank sheet of paper as soon as the examiner finished performing the sequence; (4) a visual-written span condition: stimuli were set similar to those presented in condition 2 (visual–oral). The child was asked to respond in a similar fashion as that of condition 3. All conditions were introduced in a fixed order.

The REY-AVLT (Vakil et al., 2004) was used for the super-span list learning test. The list comprises 15 items that are repeated 5 times. Immediately after each trial the subject was asked to repeat the list. An intrusive list was then presented, after which the subject's recall of the items in the second list was recorded and another recall trial of the first list was then conducted. A delayed recall after 20 min was also administered in conjunction with a 32-word list that was finally presented for recognition. The test is sensitive to CNS compromise in children. Use of both the VADS and REY-AVLT are effective for evaluating auditory memory of children suspected of having learning difficulties (Talley, 1986).

The subjects' immediate memory and delayed recall of the non-verbal information was evaluated by the ROCF test (Osterreith, 1944) using three phases: (A) the subject was

asked to copy the ROCF. Thereafter, immediate incidental recall of the figure was tested by asking the child to reconstruct it from memory. Incidental delayed recall of the figure was tested 20 min after the immediate recall phase.

Subjects were tested individually by an experienced certified psychologist, who was blinded to the subjects' group affiliation. No compensation or travel fees were given for participation. Performance was coded using standardized scores based on the norms for each test and coded also for optimality (optimal, questionable, suboptimal/dysfunctional). Psychological specialists who were blind to the subject's group assignment rated the specific domains of functioning using percentile scores of performance in the VADS, REY-AVLT and the ROCF; scores were ranked to three levels: within and above 1 SD from the mean of the population was rated as normal; scores ranging between 1 and 2 SDs below the mean were rated as suspected abnormal; and scores that were below 2 SDs from the population's mean were coded as abnormal/dysfunctional. Scores were rechecked by a trained experimenter blinded to patients' appearance and group. Inter-rater agreement was higher than 95%.

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