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BRAIN RESEARCH

Research Report

Memory functions of children born with asymmetric intrauterine growth restriction

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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.

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

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difficulties in school (Low et al., 1992; Goldenberg et al., 1998; Camm et al., 2000; Hollo et al., 2002; O'Keeffe 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 Wassenaer, 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