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Impairment on a self-ordered working memory task in patients with early-acquired hippocampal atrophy

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ABSTRACT

One of the features of both adult-onset and developmental forms of amnesia resulting from bilateral medial temporal lobe damage, or even from relatively selective damage to the hippocampus, is the sparing of working memory. Recently, however, a number of studies have reported deficits on working memory tasks in patients with damage to the hippocampus and in macaque monkeys with neonatal hippocampal lesions. These studies suggest that successful performance on working memory tasks with high memory load require the contribution of the hippocampus. Here we compared performance on a working memory task (the Self-ordered Pointing Task), between patients with early onset hippocampal damage and a group of healthy controls. Consistent with the findings in the monkeys with neonatal lesions, we found that the patients were impaired on the task, but only on blocks of trials with intermediate memory load. Importantly, only intermediate to high memory load blocks yielded significant correlations between task performance and hippocampal volume. Additionally, we found no evidence of proactive interference in either group, and no evidence of an effect of time since injury on performance. We discuss the role of the hippocampus and its interactions with the prefrontal cortex in serving working memory.

1. Introduction

One of the striking features of both adult- and developmental-onset amnesia produced by damage to the hippocampus is the sparing of working memory (e.g. Milner, 1966; Cave and Squire, 1992). Typically, despite their severe and chronic impairment in episodic or event memory (Allen et al., 2014; Baddeley et al., 2011, 2010; Hurley et al., 2011; Vargha-Khadem, 1997), amnesic patients often display normal working memory on such standard tasks as digit span and block span (but see Rose et al., 2012). Given this profile, it might be surmised that the hippocampus makes no contribution to working memory, an ability that is therefore often assumed to be served instead by neocortical regions, especially the prefrontal areas implicated in the maintenance and manipulation of on-line information (Brahmbhatt et al., 2008; Molteni et al., 2008; Vuontela et al., 2009). However, because of their reciprocal neuroanatomical connections (Aggleton et al., 2015; Barbas and Blatt, 1995; Carmichael and Price, 1995; Goldman-Rakic et al., 1984; Kondo et al., 2005; Saleem et al., 2008), severe damage to the hippocampus can potentially compromise the working memory function of the prefrontal cortex.

Heuer and Bachevalier (2011) induced bilateral hippocampal lesions in neonatal monkeys and tested the animals as adults on (a) a self-ordered object-sequence task known to depend on the functional integrity of the dorsolateral prefrontal cortex (DLPFC), and (b) a session-unique delayed non-matching-to-sample task known to depend on the integrity of the ventrolateral prefrontal cortex (VLPFC). Results indicated a selective deficit in the self-ordered working memory task. In contrast, there was no effect of

Abbreviations: aMCI, amnesic mild cognitive impairment; CMS, children memory scale; DLPFC, dorsolateral prefrontal cortex; ECMO, extracorporeal membrane oxygenation; FSIQ, full scale IQ; IFG, inferior frontal gyrus; RT, response time; SOPT, self-ordered pointing task; TGA, transposition of the great arteries; VLPFC, ventrolateral prefrontal cortex; WAIS, Wechsler adult intelligence scale; WISC-IV, Wechsler intelligence scale for children IV; WMS, Wechsler memory scale.

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the neonatal hippocampal lesions on the session-unique, delayed non-matching-to-sample task, suggesting that the VLPFC of the hippocampal-lesioned monkeys was functionally intact. In a subsequent report, Heuer and Bachevalier (2013) contrasted the performance of the same monkeys on two different serial order working memory tasks that measure memory for temporal order of stimuli, one being DLPFC-dependent, and the other not. Once again, results confirmed that the operated monkeys were impaired only on the more complex temporal order list—*viz,* the version that is dependent on the functional integrity of the DLPFC. Taking the results of the two studies together, the authors conclude that early hippocampal lesions "...yield significant deficits in...monitoring of information in working memory. The results further suggest that the deficits may relate to an alteration of hippocampal-prefrontal interactions" (Heuer and Bachevalier, 2013, p. 11).

To compare directly the contributions of prefrontal cortex and the medial temporal lobes to performance on the Self-ordered Pointing Task (SOPT), Petrides and Milner (1982) studied groups of adult patients with unilateral surgical excisions of one or the other of these two brain regions. The results confirmed the sensitivity of the SOPT to frontal lobe lesions, especially for removals on the left side, but also indicated that patients with large temporal lobe removals extending medially and posteriorly (i.e. those involving radical excisions of the hippocampus along with parahippocampal gyrus and entorhinal cortex) were impaired as well. These patients showed material-specific deficits on the verbal or non-verbal versions of the SOPT consistent with the side of surgery; i.e. left hemispheric surgery resulted in impaired performance on tasks involving low- and high-imagery words, whereas right hemispheric surgery resulted in impaired performance on tasks involving abstract designs and representational drawings. Relevant to the current study, the report by Petrides and Milner (1982) also highlighted the effects of memory load, with both frontal and medial temporal lobe lesions yielding error rates that increased as a function of increasing number of items in each test block.

The issue of memory load was recently addressed in other reports, where it has been suggested that whether the hippocampus plays a role in working memory depends on both memory load (Axmacher et al., 2010, 2007; Jeneson et al., 2012, 2011, 2010) and memory lag (Elliott and Dolan, 1999; Jeneson et al., 2012, 2011; Olson et al., 2006; Owen et al., 1995). Jeneson and Squire (2012) argued that 'supra-span' demands (i.e. higher memory loads and longer delays) require long-term memory and, therefore, the participation of the hippocampus, since working memory capacity is overloaded. Others suggest that the hippocampus is involved in the performance of a working memory task when the task requires relational memory, irrespective of whether working- or long-term memory is involved (Hannula et al., 2006; Watson et al., 2013); when information coding and binding occurs (Nee and Jonides, 2013, 2008; Oztekin et al., 2009); when dealing with novel stimuli (Rose et al., 2012); during on-line maintenance of the stimuli for the purpose of active processing (Voss et al., 2011; Warren et al., 2011), or simply during higher order visual spatial processing (reviewed in Cowell et al., 2010; Lee et al., 2012).

We examined the consequences of relatively selective hippocampal damage on performance on the SOPT after early injury in humans. From a cohort with a documented history of hypoxic-ischaemic events early in life, we recruited a large group of patients who showed a moderate to severe degree of hippocampal damage. The timing of the hippocampal lesions, and the time lag between lesion-onset and test in this group of patients resemble the rhesus monkeys studied by Heuer and Bachevalier (2011, 2013). In the current study we focused on the relation between memory-load and the role of the hippocampus. Building on the growing evidence that degree of hippocampal activation is correlated with memory load (e.g. Jeneson et al., 2012, 2011, 2010), we attempted to relate the degree of hippocampal atrophy to behavioural performance on the SOPT. This approach contrasts with one that treats hippocampal atrophy as present or absent, as is often the case in patient studies. We adapted the abstract designs version of the SOPT developed by Petrides and Milner (1982), a visual working memory task with varying memory loads, to suit the young age level of our patients and controls. Low memory load trials fall within the span traditionally associated with working memory (Alvarez and Cavanagh, 2004; Cowan, 2001; Luck and Vogel, 1997), whereas high-memory-load trials would potentially exceed working memory span. We hypothesised that the patients' performance would show a hippocampal-dependent load-effect, i.e., the greater the hippocampal atrophy, the lower the memory load it could maintain. Theoretically, the hippocampal-dependent load effect could also be demonstrated in healthy controls. It is therefore conceivable that at high memory-loads, healthy controls would also find it difficult to hold in mind the order of pointing they generated in each block. Under such circumstances it would be predicted that *both* patients and controls would surpass the limits of their working memory capacity and make increasing number of errors at high memory loads.

Lastly, our patient group is unique inasmuch as the hippocampal damage in each case was acquired in infancy or early childhood. This could have a different effect on function than it would in adults who had developed normally and only later sustained damage to the hippocampus. We therefore also tested the relationship between elapsed time since damage and behavioural performance on the SOPT.

2. Materials and methods

2.1. Participants

Eighteen patients (age range = 10–33, mean age = 16.7 ± 6.6, 10M, 8F) with confirmed bilateral hippocampal atrophy and Full Scale IQ (FSIQ) within the normal range (FSIQ ≥ 85) participated in the study. Patients had sustained hippocampal damage as a result of a hypoxic-ischaemic event early in life (during infancy or early childhood) due to various aetiologies (acute respiratory failure followed by Extracorporeal Membrane Oxygenation (ECMO) treatment, n = 6; Transposition of the Great Arteries (TGA) and open heart surgery, n = 5; neonatal asphyxia, n = 4; pre-term birth, n = 1; hypoglycaemia, n = 1; epilepsy related, n = 1). Hippocampal atrophy was defined as ≥15% volume reduction on each side (volume reduction averaged across hemispheres: range = 15.7–61.9%, mean = 34.9 ± 15.9%), relative to the mean of a group of healthy controls (n = 64; mean = 3248.64 ± 255.45 mm^3). Table 1 presents patients' clinical and demographic information. Eighteen healthy volunteers (age range = 9–38, mean age = 18.1 ± 8.9, 10M, 8F) also participated in the study. Participants had no genetic syndromes, no overt neurological deficits (e.g. hemiplegia), no central visual or auditory impairments, and all were native English speakers. The two groups were matched for gender. Participants completed these tests as part of a larger study. They were assessed over two to three days and were compensated for their time and expenses. The study was approved by the Local Research Ethics Committee and all participants, and/or their parents/guardians, read an information sheet and gave written informed consent before the start of the study.

2.2. Behavioural testing

For the SOPT, participants were shown an array of abstract designs. The designs were based on those developed by Petrides and Milner (1982), but created anew by a member of our research team, so they are easy to distinguish from one another but difficult