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Research report

Motor skill learning and offline-changes in TGA patients with acute hippocampal CA1 lesions

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ABSTRACT

Learning and the formation of memory are reflected in various memory systems in the human brain such as the hippocampus based declarative memory system and the striatum-cortex based system involved in motor sequence learning. It is a matter of debate how both memory systems interact in humans during learning and consolidation and how this interaction is influenced by sleep. We studied the effect of an acute dysfunction of hippocampal CA1 neurons on the acquisition (on-line condition) and off-line changes of a motor skill in patients with a transient global amnesia (TGA). Sixteen patients (68 ± 4.4 yrs) were studied in the acute phase and during follow-up using a declarative and procedural test, and were compared to controls. Acute TGA patients displayed profound deficits in all declarative memory functions. During the acute amnestic phase, patients were able to acquire the motor skill task reflected by increasing finger tapping speed across the on-line condition, albeit to a lesser degree than during follow-up or compared to controls. Retrieval two days later indicated a greater off-line gain in motor speed in patients than controls. Moreover, this gain in motor skill performance was negatively correlated to the declarative learning deficit. Our results suggest a differential interaction between procedural and declarative memory systems during acquisition and consolidation of motor sequences in older humans. During acquisition, hippocampal dysfunction attenuates fast learning and thus unmasks the slow and rigid learning curve of striatum-based procedural learning. The stronger gains in the post-consolidation condition in motor skill in CA1 lesioned patients indicate a facilitated consolidation process probably occurring during sleep, and suggest a competitive interaction between the memory systems. These findings might be a reflection of network reorganization and plasticity in older humans and in the presence of CA1 hippocampal pathology.

Abbreviations: TGA, transient global amnesia; DWI, diffusion-weighted imaging; CA, cornu ammonis.

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1. Introduction

Learning and the formation of memory within a behavioral context requires an adaptive plasticity that is reflected in the presence of multiple memory systems in the human brain (Sherry & Schacter, 1987; Willingham, 1997). Learning of declarative or relational memory such as facts and events is thought to rely on the hippocampus and the medial temporal lobe system whereas non-declarative procedural learning such as acquisition of a new motor skill, habits or sequence learning is thought to be mediated by cortical–striatal–cerebellar based circuits (McDonald & White, 1993; Mishkin, Malamut, & Bachevalier, 1984; Squire, 2004; Willingham, Salidis, & Gabrieli, 2002). The declarative memory system is considered flexible and being involved in forming rapid associations between novel events that are spatially and temporally distributed, whereas the striatum based learning system is assumed to perform a gradual stimulus-response binding by trial and error and to be slower and more rigid (Keisler & Shadmehr, 2010; Krakauer & Shadmehr, 2006; Mishkin et al., 1984). Learning of a motor skill such as the sequential finger tapping task is associated with activity within the cortical-striatal-cerebellar circuit during encoding, consolidation and retrieval (Albouy et al., 2008; Debas et al., 2010, 2014; Doyon, Penhune, & Ungerleider, 2003; Karni et al., 1998). With regard to consolidation of newly formed memory, it has been shown that sleep has an important effect on the consolidation of both, motor sequence learning and declarative memories (Debas et al., 2014; Diekelmann & Born, 2010; Walker & Stickgold, 2004).

Initially, the different 'dual' memory systems have been considered rather functionally independent as suggested by early findings from chronically amnesiac patients after bilateral medial temporal-lobe excision or hippocampal lesions. These patients were capable of acquiring and maintaining motor skills (Corkin, 1968), habits (Hay, Moscovitch, & Levine, 2002; Knowlton, Mangels, & Squire, 1996), perceptual sequence learning and motor tasks (Cohen & Squire, 1980; Gabrieli, Corkin, Mickel, & Growdon, 1993; Reber & Squire, 1994; Tranel, Damasio, Damasio, & Brandt, 1994).

Recent evidence shows an involvement of the hippocampus in motor sequence learning and overnight consolidation of motor memory (Albouy et al., 2008, 2015; Schendan, Searl, Melrose, & Stern, 2003; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). Imaging data in younger subjects studying motor sequence learning suggest an activation of the striatum whereas the hippocampus is deactivated during acquisition indicating a competitive interaction of both systems during acquisition of motor sequence memory (Albouy et al., 2008, Albouy, Sterpenich et al., 2013; Poldrack & Packard, 2003). During overnight consolidation, this interplay is thought to turn into a cooperative interaction between striatum and hippocampus (Albouy et al., 2008). In older subjects, however, the interaction between the striatal and the hippocampal memory seem to be differentially organized as both, the striatal and hippocampal system are activated during learning (Rieckmann, Fischer, & Backman, 2010). This suggests an age dependent adaptive plasticity of the interaction between striatal and hippocampal components during motor sequence learning and consolidation (Rieckmann et al., 2010). Conversely, animal data show that lesions to either the hippocampus or striatum result in a double dissociation in learning paradigms suggesting an interaction or even an antagonism between memory systems (Logothetis et al., 2012; Packard & Teather, 1997; Schroeder, Wingard, & Packard, 2002). The nature of the interaction is thus still a matter of debate (Albouy, Sterpenich et al., 2013; Robertson, 2012).

To further elucidate the interaction between the hippocampal and striatal system in motor sequence learning and off-line changes and to mechanistically specify the hippocampal involvement in particular, we studied the effects of transiently lesioned hippocampal CA1 neurons on learning and off-line changes of a sequence finger tapping task in patients with a transient global amnesia (TGA). The TGA is a rare amnestic syndrome that is characterized by a sudden onset of a selective, but transient amnesia following damage of the hippocampus whereby procedural memory is thought to remain intact (Bartsch et al., 2010; Eustache et al., 1997; Evers, Frese, & Bethke, 2002). The time course of the acute amnestic syndrome is limited up to 24 h. In patients with a TGA, highly focal lesions confined to the CA1 field of the hippocampal cornu ammonis (CA-) can be detected in high-resolution magnetic resonance imaging (MRI) (Bartsch, Alfke, Deuschl, & Jansen, 2007; Bartsch et al., 2006). These MRI lesions can be considered the structural correlate of the amnestic deficit reflecting a transient diaschisis of CA1-dependent circuits in terms of functional disconnection of the hippocampus (Bartsch, Dohring, Rohr, Jansen, Deuschl, 2011; Bartsch et al., 2006, 2008, 2010).

2. Patients and methods

2.1. Study cohort

Sixteen patients (68 ± 4.4 yrs, 5 males) were studied after presenting to our neurological emergency unit and fulfilling the following diagnostic criteria of a TGA (Bartsch et al., 2010): i) the presence of an anterograde amnesia, that was ii) witnessed by an observer, iii) no clouding of consciousness or loss of personal identity, iv) cognitive impairment was limited to amnesia, v) no focal neurological or epileptic signs, vi) no recent history of head trauma or seizures, and vii) resolution of symptoms within 24 h. Patients were studied by one neurologist who remained 24/7 on-call for this study. Additionally, 16 healthy subjects [62.9 ± 8.8 yrs ($p = .054$), 6 males] were recruited as a control group for the motor sequence learning. All persons were right handed. Every participant gave informed consent to the study, which was approved by the Ethical Committee of the University of Kiel and which was conducted according to the Declaration of Helsinki. The recruitment of a relatively high number of TGA patients is the result of a regional stroke awareness program with very early admittance of large numbers of patients with suspected stroke to our neurological emergency unit. Some of the results have been published in abstract form (Bartsch et al., 2011).

2.2. Neurological assessment

All patients had a standard neurological examination on admission and follow-up and underwent a structured interview