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Impaired context reversal learning, but not cue reversal learning, in patients with amnestic mild cognitive impairment

Einat Levy-Gigi[a,*], Oguz Kelemen[b], Mark A. Gluck[a], Szabolcs Kéri[c,d]

[a] Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, USA
[b] Bács-Kiskun County Hospital, Kecskemét, Hungary
[c] Department of Physiology, Faculty of Medicine, University of Szeged, Szeged, Hungary
[d] National Psychiatry Center, Budapest, Hungary

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ABSTRACT

It has been proposed that reversal learning is impaired following damage to the orbitofrontal and ventromedial frontal cortex (OFC/VMFC) and to the medial temporal lobe (MTL), including the hippocampal formation. However, the exact characteristics of the MTL-associated reversal learning deficit are not known. To investigate this issue, we assessed 30 newly diagnosed patients with amnestic mild cognitive impairment (aMCI) and 30 matched healthy controls. All patients fulfilled the aMCI criteria of the Mayo Clinic Alzheimer's Disease Research Center and underwent head magnetic resonance imaging that confirmed MTL atrophy. Reversal learning was assessed using a novel reinforcement learning task. Participants first acquired and then reversed stimulus–outcome associations based on negative and positive feedback (losing and gaining points). Stimuli consisted of a cue (geometric shapes) and a spatial context (background color or pattern). Neuropsychological assessment included tasks related to the MTL (paired associates learning), dorsolateral prefrontal cortex (DLPFC) (extradimensional shift, One-touch Stockings of Cambridge), and OFC/VMFC (Holiday Apartment Task). Results revealed that, relative to controls, patients with aMCI exhibited a marked reversal learning deficit, which was highly selective for the reversal of context. The acquisition of stimulus–outcome associations and cue reversal learning were spared. Performance on the context reversal learning task significantly correlated with the right hippocampal volume. In addition, patients with aMCI had deficits on tests related to DLPFC but not to OFC/VMFC. However, DLPFC dysfunctions were not associated with context reversal learning. These results suggest that MTL deficits in aMCI selectively affect context reversal learning when OFC/VMFC functions are spared. This deficit is not influenced by the valence of the outcome (positive or negative feedback) and by executive dysfunctions.

1. Introduction

Adapting to environmental changes is one of the most fundamental challenges for every organism. Conditions that once were rewarding may become disadvantageous and non-adaptive and vice versa. Cognitive flexibility, including attentional set-shifting and reversal learning, is a crucial element of adaptation (Frank & Claus, 2006; Robbins & Arnsten, 2009). Clinical studies and animal models have shown that frontal lobe lesions cause marked cognitive rigidity (Chudasama & Robbins, 2006). Specifically, lesion to the dorsolateral prefrontal cortex (DLPFC) and its rodent analogues results in deficits on tasks requiring the shifting of attentional sets, whereas damage to the orbitofrontal and ventromedial frontal cortex (OFC/VMFC) is associated with reversal learning impairment (Birrell & Brown, 2000; Dias, Robbins, & Roberts, 1996). Additional brain regions implicated in reversal learning are the cortico-striatal system and the medial temporal lobe (MTL), including the hippocampal formation (e.g., Cools, Clark, Owen, & Robbins, 2002; Marston, Everitt, & Robbins, 1993; Myers, Deluca, Hopkins, & Gluck, 2006; Shohamy, Myers, Hopkins, Sage, & Gluck, 2009; Swainson et al., 2000). However, the potential difference between the roles of these brain regions is not fully understood.

During discrimination learning, individuals form an attentional set of stimulus dimensions relevant for responding (e.g., discrimination of stimuli according to their shape). In attentional set-shifting tasks, individuals must change the attentional set to efficiently respond to newly relevant stimulus dimensions (e.g., shifting from shape to color). In reversal learning, participants first acquire a stimulus discrimination rule, and then learn to reverse this choice without a change in the relevant stimulus dimension

* Corresponding author at: Center for Molecular and Behavioral Neuroscience, Rutgers University, 197 University Ave, Newark 07102, NJ, USA.
Tel.: +1 973 353 3669; fax: +1 973 353 1272.
E-mail address: levygigie@gmail.com (E. Levy-Gigi).

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(Chudasama & Robbins, 2006). Although this model explains a wide range of behavioral phenomena, current discrimination learning paradigms do not take into consideration that stimulus dimensions regularly occur in a specific context (Vakil, Raz, & Levy, 2007). For example a central stimulus dimension (e.g., a shape) can be presented against a peripheral context (e.g., a color or a texture background). In this case, the central dimension, or cue, refers to the "what" information, whereas the peripheral background refers to the "where" information (Eichenbaum, Yonelinas, & Ranganath, 2007).

In discrimination and reversal learning, both cue and context may be relevant (Wickens, 1987). Cue and context may serve as conditioned stimuli predicting the probability of reinforcement (Good & Honey, 1991). Context can also serve as an occasion setter, indicating whether a specific cue will be reinforced or not (Penick & Solomon, 1991). Therefore, a cue can be reinforced in a distinctive context but not in another one (Bouton, 1993). While the MTL is not necessary to mediate each type of contextual conditional learning, it is critical for contextual occasion setting (Bouton, 1993; Eichenbaum et al., 2007; Gluck & Myers, 2001; Myers & Gluck, 1994; Mayes, Macdonald, Donlan, Pears, & Meudell, 1992).

The current study was designed to investigate the relationship between PFC and MTL functioning and cue and context reversal learning. We developed a novel task comparing reversal learning for cue and context. Fig. 1 depicts stimuli with two dimensions, a central shape (cue) embedded in a color/pattern context. The first phase of the task includes a discrimination learning procedure in which cards consisting of a cue and a context predict a specific outcome (reward or punishment, i.e. winning or losing points). In the subsequent reversal phase, there are two possibilities: shared cue – the cue is unchanged but appears in a new context; shared context – a new cue is presented in the original context. The new cards are associated with the opposite outcome relative to the discrimination learning phase. Therefore, if the original card predicts reward, then the new card will predict punishment and vice versa. Participants must reverse the original discrimination rule in order to adapt to the new condition (Fig. 1 and Table 1).

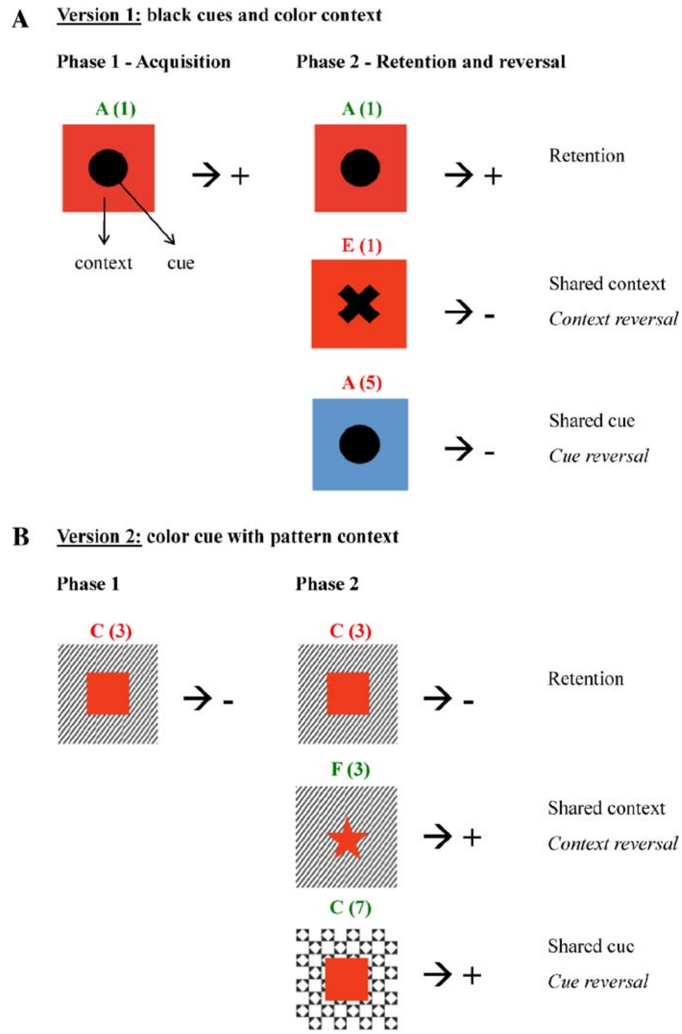

Fig. 1. Illustration of the cue and context reversal task. In cue change, new cards share the same context with the original card, but they have a new cue. In context change, new cards share the same cue with the original card, but the cue is presented in a new context. The task has two versions, one with black cues and color context (A) and the other with color cues and pattern context (B). Letters "A–G" refer to the eight cue shapes, and numbers "1–8" refer to the eight contexts (colors and patterns). Green is assigned to positive outcome (+), red to negative outcome (−) (see also Table 1). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Phases of the cue and context reversal task.

Phase 1: acquisition	Phase 2: retention and reversal
A (1) ➔ +	A (1) ➔ +
	E (1) ➔ -
	A (5) ➔ -
B (2) ➔ +	B (2) ➔ +
	F (2) ➔ -
	B (6) ➔ -
C (3) ➔ -	C (3) ➔ -
	F (3) ➔ +
	C (7) ➔ +
D (4) ➔ -	D (4) ➔ -
	G (4) ➔ +
	D (8) ➔ +

A–G, eight cue shapes; 1–8, eight contexts (colors and patterns). Green refers to positive outcome (+), red refers to negative outcome (−).

In order to investigate the role of MTL and PFC in cue and context reversal learning, we assessed a group of patient with newly diagnosed amnestic mild cognitive impairment (aMCI) and matched healthy controls. In contrast to patients with dementia, individuals with aMCI show relatively spared general cognitive abilities and daily functioning. However, they exhibit declarative memory impairments, which can be explained by MTL dysfunctions (Collie & Maruff, 2000; Gauthier et al., 2006; Petersen et al., 1999; Shi, Liu, Zhou, Yu, & Jiang, 2009; Whitwell et al., 2007). The majority of individuals with aMCI also exhibit executive dysfunctions, indicating the pathology of the PFC (Kramer et al., 2006; Price et al., 2010; Schmitter-Edgecombe & Sanders, 2009). Beyond the fact that aMCI serves as a model condition for the impairment of multiple cognitive systems, which is, however, not entirely generalized in the early stage of the disorder, the context and cue reversal learning paradigm may provide an opportunity to develop new clinical testing tools.

We used neuropsychological tests sensitive to DLPFC, OFC/VMFC, and MTL functions in order to investigate the contri-