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Repetition priming and cortical arousal in healthy aging and Alzheimer's disease

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ABSTRACT

Repetition priming refers to a form of implicit memory in which prior exposure to a stimulus facilitates Q2 the subsequent processing of the same or a related stimulus. One frequently used repetition priming task is word-stem completion priming. In this task, participants complete a series of beginning word stems with the first word that comes to mind after having viewed, in an unrelated context, words that can complete some of the stems. Patients with Alzheimer's disease (AD) exhibit a significant deficit in word-stem completion priming, but the neural mechanisms underlying this deficit have yet to be identified. The present study examined the possibility that the word-stem completion priming deficit in AD is due to disruption of ascending neuromodulatory systems that mediate cortical arousal by comparing word-stem completion priming and behavioral measures of spatial orienting and phasic alerting. Results showed that in healthy elderly controls higher levels of phasic alerting were associated with a sharpening of the temporal dynamics of priming across two delay intervals: those with higher levels of alerting showed more immediate priming but less delayed priming than those with lesser levels of alerting. In patients with AD, priming was impaired despite intact levels of phasic alerting and spatial orienting, and group status rather than individual levels of alerting or orienting predicted the magnitude of their stem-completion priming. Furthermore, the change in priming across delays they displayed was not related to level of alerting or orienting. These findings support the role of the noradrenergic projection system in modulating the level of steady-state cortical activation (or "cortical tonus") underlying both phasic alerting and the temporal dynamics of repetition priming. However, impaired priming in patients with AD does not appear to be due to disruption of this neuromodulatory system.

1. Introduction

Repetition priming refers to a fundamental form of implicit memory in which prior exposure to a stimulus facilitates the subsequent processing of the same or a related stimulus. Numerous demonstrations of intact repetition priming in profoundly amnesic patients suggest that this form of priming does not depend upon declarative or explicit memory processes mediated by medial temporal lobe structures that are damaged in these patients (e.g., Graf et al., 1984; Shimamura and Squire, 1984; Warrington and Weiskrantz, 1968, 1974). Repetition priming may, however, reflect the temporary modification of perceptual, lexical and semantic representations stored in neocortical regions that remain intact in patients with circumscribed amnesia (Gabrieli et al., 1994; Squire, 1987; Tulving and Schacter, 1990). In support of this possibility, functional neuroimaging studies have shown that repetition of a stimulus is accompanied by a reduction of activation (i.e., repetition suppression) within those neocortical areas involved in the initial processing of the stimulus (e.g., Henson, 2003; Wiggs and Martin, 1998). This repetition suppression may represent the neural correlate of the behavioral repetition priming effect (i.e., neural priming), but this has yet to be fully resolved (see Gotts et al., 2012 for a review and discussion).

One repetition priming task that has been used extensively is word-stem completion priming. In this task participants are exposed to a series of words and later asked to complete a series of beginning word stems with the first word that comes to mind. Unknown to the participant, some of the stems can be completed with the previously exposed words and others cannot. Priming is reflected in the increased likelihood of completing the word stems with previously presented words rather than other appropriate words that were not presented (an unprimed baseline). Priming on

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word-stem completion tasks occurs without explicit memory for the words that were previously exposed, and is not diminished in patients with circumscribed amnesia (e.g., Graf et al., 1984).

Behavioral studies have shown that word-stem completion priming is dependent upon both perceptual and conceptual processes (Graf et al., 1985; Nelson et al., 1987; Nelson and Friedrich, 1980). Consistent with these behavioral findings, neuroimaging studies have shown that stimulus repetition in this task is associated with reduced neural activation within modality-specific regions in striate and extrastriate cortex and within amodal regions of inferior temporal and frontal cortex (e.g., Buckner et al., 2000). Similar distinctions between perceptual and conceptual aspects of neural priming have been demonstrated with other repetition priming tasks (Schacter et al., 2007; Wig et al., 2009, 2005). This suggests the possibility that multiple neural mechanisms underlie repetition priming effects (e.g., Race et al., 2009; Schacter et al., 2007). One mechanism may be that initial stimulus presentation leads to increased cortical tuning or sharpening of perceptual and semantic representations within posterior and temporal cortical regions, respectively. This cortical tuning may, in turn, lead to a reduction in overall neural activation within these cortical regions and facilitation in processing a stimulus during its subsequent presentations (Henson, 2003; Wiggs and Martin, 1998). A second mechanism may be that initial stimulus presentation leads to reduced activation in prefrontal regions involved in the controlled retrieval of conceptual information (e.g., Badre and Wagner, 2007). Reduced activation may result from a decreased reliance on top-down processing due to increased efficiency in bottom-up processing of conceptual information (Henson, 2003; Race et al., 2009) or from increased efficiency of interactions between prefrontal regions and temporal regions following stimulus presentation (Gotts et al., 2012). In support of this latter possibility, stimulus repetition has been found to increase neural synchrony between prefrontal and temporal cortical regions, with the timing of this increased synchrony correlated with the magnitude of behavioral priming (Ghuman et al., 2008).

In striking contrast to preserved repetition priming in patients with circumscribed amnesia, patients with Alzheimer's disease (AD) are impaired on word-stem completion priming tasks (for reviews, see Fleischman, 2007; Fleischman and Gabrieli, 1998; Meiran and Jelicic, 1995; Millet et al., 2010). The neural mechanisms underlying impaired priming in patients with AD have yet to be identified. The presence of intact repetition priming on perceptual identification tasks in AD patients who have stem-completion priming deficits (e.g., Fleischman et al., 1995; Keane et al., 1991) suggests that the neural mechanisms mediating perceptual priming are intact in these patients. Thus, their stem-completion priming deficit may be due instead to disruption within the neural systems that mediate conceptual priming. This view is consistent with the observation that AD pathology is typically more extensive in temporal and frontal cortical regions that support conceptual processing than in posterior sensory regions that support perceptual/structural processing (Brun and Englund, 1981; Terry and Katzman, 1983) and with findings that AD leads to a systematic disruption of corticocortical projections that connect distinct but functionally related cortical regions (Braak and Braak, 1991; Delacoste and White, 1993; Delacourte et al., 1999; Hof and Morrison, 1999; Morrison and Hof, 2002; Price and Morris, 1999). In this view, impaired repetition priming in AD results from degradation of semantic representations stored within temporal lobe neocortical regions or reduced efficiency in interactions between frontal and temporal neocortical regions due to impaired corticocortical connectivity.

Other findings, however, suggest that a disruption in conceptual priming may not completely account for the stem-completion priming deficit in patients with AD. First, posterior perceptual systems have been found to be disrupted in AD (e.g., Festa et al., 2005; Hof and Morrison, 1990; Paxton et al., 2007; Velarde et al., 2012) and perceptual repetition priming is not entirely intact (e.g., Backman et al., 2000; Bondi and Kaszniak, 1991; Heindel et al., 1990, 1998). Second, meta-analyses of word-stem completion priming studies in AD have confirmed the overall presence of a significant priming deficit (Meiran and Jelicic, 1995; Millet et al., 2010), but have also noted considerable variability in the magnitude of the deficit. Even though there appears to be a substantial impairment overall (e.g., Bondi et al., 1993; Keane et al., 1991; Perani et al., 1993; Randolph, 1991) some studies show only mild impairment or even normal priming (e.g., Deweer et al., 1994; Huberman et al., 1994). Attempts to explain the variation in the results of these studies in terms of differences in cognitive processes engaged by the particular procedures of the word completion task that was used, or by differences in the characteristics of the subjects in the various studies, have been largely unsuccessful (Fleischman, 2007; Fleischman and Gabrieli, 1998; Meiran and Jelicic, 1995; Millet et al., 2010). Nevertheless, the variability suggests that something other than conceptual processes may contribute to impaired priming in AD. One possibility supported by recent neural network simulation models is that impaired repetition priming reflects disruption of neuromodulatory systems that enhance the processing of neural signals rather than disruption of the neural systems themselves (Gotts, 2003).

The possibility that the word-stem completion priming deficit of patients with AD is due to disruption of ascending neuromodulatory systems is consistent with neuroanatomical studies that show neuron loss in the nucleus basalis of Meynert and the locus coeruleus in AD (Bondareff et al., 1982, 1987; Mann et al., 1986; Whitehouse et al., 1982; Zweig et al., 1988). These structures are the primary locus of ascending cholinergic and noradrenergic projection systems in the brain that are thought to enhance sensory processing by increasing the signal-to-noise ratio of target neurons in the neocortex (Carrasco et al., 2000; Dosher and Lu, 2000; Lu and Dosher, 2000; Picciotto et al., 2012; Sara, 1985a; Servan-Schreiber et al., 1990). Evidence for a potential role of ascending neuromodulatory systems in the priming deficit of patients with AD comes from a combined pharmacological/fMRI study in healthy adults that demonstrated attenuated behavioral expression of word-stem completion priming, and abolishment of the neural repetition suppression effects normally observed within left extrastriate, middle frontal and inferior frontal cortices, following administration of a cholinergic antagonist (Thiel et al., 2001).

Behavioral studies have implicated the cholinergic system in the modulation of spatially selective orienting of attention (e.g., Davidson et al., 1999; Davidson and Marrocco, 2000; Murphy and Klein, 1998; Stewart, Burke and Marrocco, 2001; Witte et al., 1997) and the noradrenergic system in the modulation of nonselective phasic and tonic alerting processes (Aston-Jones et al., 1999; Foote and Morrison, 1987; Sara, 1985a,b, Sara and Bouret, 2012). Moreover, AD patients have been found to display deficits in both spatial orienting and phasic alerting (e.g., Faust and Balota, 1997; Festa-Martino et al., 2004, Maruff and Currie, 1995; Parasuraman et al., 1992; Tales et al., 2002). Thus, to the degree that behavioral measures of orienting and alerting reflect the corresponding integrity of the cholinergic and noradrenergic systems, respectively, then disruptions to either system may contribute to the priming deficit of AD patients. However, this deficit may be influenced more by disruption to the alerting system than the spatial orienting system because the noradrenergic system projects more diffusely to all cortical regions in order to influence the level of steady-state cortical activation (i.e., “cortical tonus”) and modulate the moment-by-moment efficiency of sensory processing (Aston-Jones et al., 1999; Sara, 1985a,b; Sara and Bouret, 2012).

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