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Dopamine and glutamate receptor genes interactively influence episodic memory in old age

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ABSTRACT

Both the dopaminergic and glutamatergic systems modulate episodic memory consolidation. Evidence from animal studies suggests that these two neurotransmitters may interact in influencing memory performance. Given that individual differences in episodic memory are heritable, we investigated whether variations of the dopamine D2 receptor gene (rs6277, C957T) and the N-methyl-D-aspartate 3A (NR3A) gene, coding for the N-methyl-D-aspartate 3A subunit of the glutamate N-methyl-D-aspartate receptor (rs10989591, Val362Met), interactively modulate episodic memory in large samples of younger (20–31 years; n = 670) and older (59–71 years; n = 832) adults. We found a reliable gene-gene interaction, which was observed in older adults only: older individuals carrying genotypes associated with greater D2 and N-methyl-D-aspartate receptor efficacy showed better episodic performance. These results are in line with findings showing magnification of genetic effects on memory in old age, presumably as a consequence of reduced brain resources. Our findings underscore the need for investigating interactive effects of multiple genes to understand individual difference in episodic memory.

1. Introduction

Episodic memory is a heritable (e.g., McClearn et al., 1997) and polygenic (Papassotiropoulos and de Quervain, 2011) trait. We explore whether genetic predispositions of dopaminergic and glutamatergic neuromodulation interactively influence episodic memory in younger and older adults. Given increased heterogeneity of episodic memory in old age (e.g., de Frias et al., 2007), we are particularly interested in whether genetic effects are stronger in older than in younger adults.

1.1. Dopaminergic modulation of episodic memory

A large number of animal studies indicates that memory performance is impaired when dopamine (DA) receptors are blocked and enhanced when DA agonists are injected in hippocampus (for review, see Lisman and Grace, 2005). DA prolongs long-term potentiation (LTP; Frey et al., 1990, 1993; Huang and Kandel, 1995), a cellular mechanism necessary for successful memory formation and consolidation (for review, see Cooke and Bliss, 2006). In humans, molecular imaging studies have related higher D2 receptor binding in hippocampus to better recall of verbal (Takahashi et al., 2007) and pictorial (Takahashi et al., 2008) memory. Relatedly, striatal D2 receptor density has been associated with better performance across different episodic memory tasks (Bäckman et al., 2000; Cervenka et al., 2008).

1.2. Glutamatergic modulation of episodic memory

Animal and human data further suggest that glutamate also modulates episodic memory. In particular, N-methyl-D-aspartate (NMDA) receptors play a crucial role in learning and memory formation (for review, see Rezvani, 2006). Animal data show that activation of NMDA receptors is required for LTP in hippocampus (e.g., Izquierdo, 1994). In particular, NMDA receptors seem to be more critical for encoding and consolidation than for retrieval of episodic memories (e.g., Day et al., 2003; Matus-Amat et al., 2007).

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Human evidence indicates that pharmacologic blockade of NMDA receptors impairs learning and memory (Morgan et al., 2004; Rockstroh et al., 1996), whereas post-learning administration of an NMDA agonist facilitates consolidation of fearful memories (Kalisch et al., 2009).

1.3. Interactive effects of DA and glutamate on episodic memory

Computational simulations suggest that dopaminergic modulation stabilizes NMDA currents, resulting in sharpened memory representations (e.g., Durstewitz et al., 1999, 2000). Other than their separate effects, animal research also suggests that the DA and glutamate systems may interact in influencing memory performance (Adriani et al., 1998; Cestari and Castellano, 1997; Ferretti et al., 2005; Mele et al., 1996). For instance, Cestari and Castellano (1997) reported that impairment of memory consolidation by blocking NMDA receptors is potentiated by simultaneous blockade of DA receptors. Similarly, memory impairment induced by an NMDA receptor antagonist is attenuated by low doses of DA receptor agonists (Mele et al., 1996). These patterns of interactions may reflect DA-induced facilitation of NMDA receptor-dependent LTP in hippocampus (e.g., Hansen and Manahan-Vaughan, 2012; Roggenhofer et al., 2010).

1.4. Study aims and hypotheses

Thus far, human studies investigating interactive influences of DA and NMDA modulation of episodic memory are lacking. We therefore examined the effects of the DA D2 gene (DRD2) and the NR3A gene, coding for the N-methyl-D-aspartate 3A (NR3A) subunit of the glutamate NMDA receptor, on episodic memory in young and old adults. Carriers of the DRD2 C/C genotype have higher D2 receptor densities in neocortical and limbic regions, including the hippocampus (Hirvonen et al., 2009). The DRD2 C/C genotype has also been associated with better backward serial memory, particularly in older adults (Li et al., 2013). Less is known about the NR3A gene. An electroencephalographic study reported that the NR3A T/T genotype is associated with better prefrontal information processing (Gallinat et al., 2007), presumably reflecting higher NMDA receptor efficacy. Relative to carriers of the NR3A T/T genotype, C/C homozygotes showed reduced frontal P300 amplitudes during an auditory oddball task.

Given the role of DA and glutamate in modulating episodic memory and their potential interaction, we expected that individuals with genetic predispositions for both higher receptor efficacy with respect to D2 (i.e., DRD2 C/C) and NMDA (i.e., NR3A T/T) receptors would show better episodic memory performance than those carrying fewer advantageous genotypes. We tested this hypothesis using an item and associative recognition memory task (Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003). Further, the resource modulation hypothesis predicts magnified genetic effects in populations with lower structural and neurochemical brain resources (Lindenberger et al., 2008). Thus, we expected that the 2 polymorphisms would modulate episodic memory to a greater extent in older than in younger adults.

2. Methods

2.1. Participants

A total number of 788 young (20–31 years; 52.2% female) and 1222 old (59–71 years; 60.5% female) adults were recruited via newspaper announcements and advertisements in public transportation. All participants reported normal or corrected to normal vision, were right-handed, as indexed by the Edinburgh Handedness Index (Oldfield, 1971), and had completed at least 8 years of education. Older participants scored over 27 on the Mini Mental State Examination. No participant was on medications that may affect memory, and none reported a history of head injury, medical (e.g., heart attack), neurologic (e.g., epilepsy), or psychiatric (e.g., depression) disease.

2.2. Genotyping

DNA was extracted from peripheral blood using standard methods. The polymorphisms of the DRD2 (C957T, rs6277) and the NR3A gene (Val362Met, rs10989591) were genotyped using the commercially available TaqMan Open Array multiplex genotyping system (C_11339240_10 for rs6277 and C_1792848_10 for rs10989591; TaqMan Open Array Genotyping Plate; Applied Biosystems, Forster City, CA, USA), following established procedures (Schjeide et al., 2011). The genotype frequencies in younger adults were: DRD2–160:399:229 (C/C:C/T:T/T) and NR3A–84:348:356 (T/T:C/T:C/C). The corresponding distributions for the older sample were DRD2–278:591:353 (C/C:C/T:T/T) and NR3A–145:568:509 (T/T:C/T:C/C). In both age groups, both polymorphisms were in Hardy–Weinberg equilibrium ($ps > 0.05$).

2.3. Experimental task

Participants underwent two cognitive testing sessions one week apart. Each session lasted about 3 hours and participants were tested in groups of six individuals of the same age. The cognitive battery assessed episodic memory, working memory, executive functioning, perceptual speed, and psychometric intelligence. Responses were made via button boxes and keyboards. The episodic memory task of interest in this study is described in the following.

We used an item and associative recognition memory task (Naveh-Benjamin, 2000). The task involved 4 different conditions. During the study phase, 30 word pairs were presented sequentially for 6 seconds in each condition. The pairs consisted of semantically unrelated German nouns. Participants were instructed to study the items either as 2 single words (item instruction) or as a pair of words (pair instruction). Following study, participants had to count backwards in steps of 3 (i.e., 335–332–329) for 90 seconds to prevent rehearsal and minimize the influence of short-term memory. Then the test phase followed with either an item or an associative recognition test. In the item conditions, participants decided whether or not a word had been presented during study. Half of the presented words were old, and the other half was new. In the associative conditions, participants indicated whether or not a word pair had been presented at study phase. Half of the pairs were old, and the other half consisted of pairs formed by recombining words in the previously studied list of pairs. In recognition, 30 words or word pairs were presented for 4 seconds each. The combination of the 2 factors, study instruction and recognition test, resulted in 4 different conditions: (1) item instruction–item test, (2) pair instruction–item test, (3) item instruction–associative test, and (4) pair instruction–associative test.

2.4. Data-based exclusion criteria

Participants with negative hits minus false alarms or more than 20% non-responses in any of the conditions were excluded from analyses (15% of younger adults and 30% of older adults), because this indicates that the task was not performed appropriately. In the total sample, the gene-gene interaction remained reliable in older adults ($n = 1222$), as reported in the following. The relative proportion of excluded subjects did not differ across the 4 genotype groups ($ps > 0.10$ in both younger and older adults). The final