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Effects of aging and dopamine genotypes on the emergence of explicit memory during sequence learning

Nicolas W. Schuck [a,b,*], Peter A. Frensch [b], Brit-Maren M. Schjeide [c], Julia Schröder [c,d], Lars Bertram [c], Shu-Chen Li [a,e]

[a] Max Planck Institute for Human Development, Center for Lifespan Psychology, Lentzealle 94, 14195 Berlin, Germany
[b] Humboldt-Universität zu Berlin, Department of Psychology, Unter den Linden 6, 10099 Berlin, Germany
[c] Max Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Neuropsychiatric Genetics Group, Ihnestraße 63, 14195 Berlin, Germany
[d] Charité – Universitätsmedizin Berlin, Evangelisches Geriatriezentrum Berlin, Charitestraße 1, 10117 Berlin, Germany
[e] TU Dresden, Department of Psychology, Chair of Lifespan Developmental Neuroscience, Zellescher Weg 17, 01062 Dresden, Germany

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ABSTRACT

The striatum and medial temporal lobe play important roles in implicit and explicit memory, respectively. Furthermore, recent studies have linked striatal dopamine modulation to both implicit as well as explicit sequence learning and suggested a potential role of the striatum in the emergence of explicit memory during sequence learning. With respect to aging, previous findings indicated that implicit memory is less impaired than explicit memory in older adults and that genetic effects on cognition are magnified by aging. To understand the links between these findings, we investigated effects of aging and genotypes relevant for striatal dopamine on the implicit and explicit components of sequence learning. Reaction time (RT) and error data from 80 younger (20–30 years) and 70 older adults (60–71 years) during a serial reaction time task showed that age differences in learning-related reduction of RTs emerged gradually over the course of learning. Verbal recall and measures derived from the process-dissociation procedure revealed that younger adults acquired more explicit memory about the sequence than older adults, potentially causing age differences in RT gains in later stages of learning. Of specific interest, polymorphisms of the dopamine- and cAMP-regulated neuronal phosphoprotein (*DARPP*-32, rs907094) and dopamine transporter (*DAT*, VNTR) genes showed interactive effects on overall RTs and verbal recall of the sequence in older but not in younger adults. Together our findings show that variations in genotypes relevant for dopamine functions are associated more with aging-related impairments in the explicit than the implicit component of sequence learning, providing support for theories emphasizing the role of dopaminergic modulation in cognitive aging and the magnification of genetic effects in human aging.

1. Introduction

Convergent data from brain and behavioral levels underscore that memory is a multifaceted function that involves multiple brain circuitries and cognitive processes (Cohen & Squire, 1980; Reber & Squire, 1994; Squire & Zola-Morgan, 1991; for reviews see Squire, 2004, 2009). A prominent model proposed by Cohen and Squire (1980) posits a basic distinction between declarative and non-declarative memory, and similar views have proposed to distinguish between explicit (verbally reportable) and implicit (not verbally reportable) learning (*e.g.*, Reber, 1989; for reviews see Cleeremans, 1997; Frensch & Rünger, 2003). In this view, declarative or explicit memory refers to memory contents and episodes that can be consciously recalled and is primarily implicated by the hippocampus and adjacent areas, which are commonly referred to as medial-temporal lobe (MTL). Non-declarative or implicit memory, in contrast, subsumes a number of different types of memory that are not dependent on the MTL and mostly inaccessible by conscious recall. Motor skill acquisition is an example of non-declarative/implicit memory and the striatum has been found to be a key component of the neural network underlying this ability (Doyon & Benali, 2005).

One of the commonly applied paradigms for studying motor skill acquisition is the serial reaction time (SRT) task (Nissen & Bullemer, 1987), in which participants learn sequential regularities of successive stimulus locations and their corresponding motor responses. Nissen and Bullemer showed that in this task participants acquired

* Corresponding author at: Princeton Neuroscience Institute, Princeton University, Princeton, NJ 08540, USA. Tel.: +1 609 258 4480.
E-mail address: nschuck@princeton.edu (N.W. Schuck).

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motor skills without being aware of what was learned or the learning process itself, and further studies showed that this learning co-occurred with activation in the striatum (Aizenstein et al., 2006; Atallah, Lopez-Paniagua, Rudy, & O'Reilly, 2007; Rauch et al., 1997). Relatedly, studies on the underlying neurochemical processes have suggested that implicit learning is, in part, implicated by dopaminergic receptor mechanisms in the striatum (Karabanov et al., 2010) and is modulated by the gene encoding the dopamine transporter protein (*DAT*, Simon et al., 2011), which is active mostly in the striatum (Heinz et al., 2000). At the same time, it has been reported that motor skill acquisition is preserved in amnesic patients, suggesting that is it hippocampus independent and dissociable from declarative/explicit memory (Nissen & Bullemer, 1987; Reber & Squire, 1994).

1.1. Implicit motor skill acquisition and aging

The distinction between explicit and implicit memory has also been a focus in the research on memory aging. A number of studies have shown little or no implicit memory impairments in older adults (Bo & Seidler, 2010; Fleischman, Wilson, Gabrieli, Bienias, & Bennett 2004; Howard & Howard, 1989; Light & Singh, 1987; for a review, see Rieckmann & Bäckman, 2009). This finding stands in contrast to the apparent age-related deficit in explicit memory, but it is confined to less complex statistical regularities (*e.g.* deterministic and lower order transitions between sequence elements, Howard & Howard, 1997; Howard et al., 2004) and does not apply to the use of chunks (Verwey, 2010; Verwey, Abrahamse, Ruitenberg, Jiménez, & de Kleine, 2011), although in younger adults implicit learning can capture higher order statistics of the sequence structure (Schuck, Gaschler, & Frensch, 2012; Schuck, Gaschler, Keisler, & Frensch, 2012). At the same time, aging is associated with apparent declines in dopaminergic modulation in various extrastriatal (*e.g.*, Kaasinen et al., 2000) and striatal (*e.g.*, Erixon-Lindroth et al., 2005) regions. Furthermore deficiencies of dopaminergic modulation in these brain circuitries contribute to various common cognitive impairments in old age (see Bäckman, Nyberg, Lindenberger, Li, and Farde, 2006; Li, Lindenberger, and Bäckman 2010, for an empirical review; see Li, Lindenberger, and Sikström, 2001, for a theoretical integration) and have been linked to deficiencies in striatal mechanisms underlying learning (Eppinger, Schuck, Nystrom, & Cohen, 2013). Additionally, longitudinal (Raz et al., 2005) and cross-sectional (Walhovd et al., 2011) research on changes in regional brain volumes has shown that the extent of volume shrinkage in the striatum is comparable to the decline in hippocampal volume.

In light of the above-mentioned relations between implicit learning and striatal dopamine on the one hand and the partially spared implicit learning abilities in older adults during sequence learning on the other hand, we investigated the effects of aging and dopamine-regulating factors on the implicit and explicit aspects of sequence learning in the SRT task. Therefore our key research question was whether genetic variations that influence dopamine functioning in older adults influence their learning and memory in the SRT task.

1.2. The DAT and DARPP-32 genes and motor skill acquisition

A recent receptor imaging study showed that sequence learning is modulated by striatal dopamine receptor density (Karabanov et al., 2010). It is thus of specific interest to investigate genotype effects of genes relevant for striatal dopamine function and how the genotype effects interact with age. To study the impact of dopamine-regulating factors, we took the candidate gene approach (see Green et al., 2008). Specifically, we investigated the impact of genetic variations in two genes known to be associated with striatal dopamine signaling, the dopamine- and cAMP-regulated neuronal phosphoprotein (*DARPP-32*, also known as the protein phosphatase 1 regulatory subunit 1B, *PPP1R1B*; location: 17q12) gene (Brené et al., 1994) and the dopamine transporter (*DAT*, *i.e. SLC6A3*; location: 5p15) gene (Vandenbergh, Persico, & Hawkins, 1992). The *DARPP-32* gene is particularly involved in integration of dopaminergic signal transmission in striatal dopamine receptors (Svenningsson et al., 2004). The DARPP-32 protein is highly expressed in striatal medium-sized spiny neurons and has a broad spectrum of effects on D1 as well as D2 receptors (Yger & Girault, 2011). Animal research has shown that manipulations of DARPP-32 implicate motor behavior in rodents (Bateup et al., 2010) as well as the occurrence of L-DOPA induced involuntary movements in a rodent model of Parkinson's Disease (Santini et al., 2007). In humans, it has been shown that a common haplotype that also includes the single nucleotide polymorphism (SNP) rs907094 of this gene is associated with striatal activation and volume (Meyer-Lindenberg et al., 2007) as well as performance in a reinforcement learning task (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007; Hämmerer et al., 2013). Specifically, homozygotes of the *DARPP-32* rs907094 A allele ("A/A" carriers) performed better than carriers of the G allele (*i.e.*, A/G or G/G, henceforth "any G"). In addition to these effects, a recent paper has shown that the *DARPP-32* rs907094 polymorphism is related to attentional regulation (Li, Passow et al., 2013). Given the complexity of DARPP-32's effects on the dopamine system, a recent summary also concluded that "the contribution of DARPP-32 in human behavior remains poorly understood" (Yger & Girault, 2011). The animal research that highlighted a role of DARPP-32 in motor functions and its known role in DA function in general indicate that there is a further need to study the effects of DARPP-32 on human behavior. Moreover, research has shown that the expression of DARPP-32 increases with advancing age (Colantuoni et al., 2008), and hence *DARPP-32* provides an interesting candidate gene in the study of aging and motor skill acquisition. Finally, DARPP-32 is often assumed to be an integrator of neural dopaminergic signal transmission (Svenningsson et al., 2004), and hence its interactions with other DA-relevant genes are of particular interest.

The second gene we investigated, *DAT*, is also implicated in striatal dopaminergic neurotransmission and regulates the reuptake of dopamine from the synaptic cleft (Heinz et al., 2000). It has been shown that the various number tandem repeat (VNTR) in exon 15 affects gene expression (Fuke et al., 2001). The VNTR 9-repeat allele ("9-repeats") is associated with lower protein availability *in vitro* (Miller & Madras, 2002; VanNess, Owens, & Kilts, 2005) and *in vivo* (Cheon, Ryu, Kim, & Cho, 2005; Heinz et al., 2000; Jacobsen & Staley, 2000; van de Giessen et al., 2009). This decreased availability of DAT likely leads to increased availability of striatal dopamine in the synaptic cleft. In line with these findings, evidence from behavioral genetic studies shows that the *DAT* VNTR 9-repeat allele is associated with better working memory (Brehmer et al., 2009) and episodic memory (Li, Papenberg et al., 2013; Schott et al., 2006), although some studies did not replicate such an association (Boonstra et al., 2008; Rommelse et al., 2008). Of particular interest, Simon et al. (2011) reported an association between implicit learning and the *DAT* VNTR genotype, with 9-repeat carriers learning more than 10/10 homozygotes in an sequential triplet learning task.

In summary, we investigated two dopamine relevant genes. One gene, *DAT*, has been shown to affect implicit learning in younger adults. The second gene, *DARPP-32*, is not well studied in humans, but is known to affect motor behavior in animals, is increasingly expressed with advancing age and plays a particular role in the integration of DA signaling processes. Hence *DAT* and *DARPP-32* are ideal candidate genes to investigate interactive