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# Dopamine modulates attentional control of auditory perception: DARPP-32 (PPP1R1B) genotype effects on behavior and cortical evoked potentials ☆

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ABSTRACT

Using a specific variant of the dichotic listening paradigm, we studied the influence of dopamine on attentional modulation of auditory perception by assessing effects of allelic variation of a single-nucleotide polymorphism (SNP) rs907094 in the DARPP-32 gene (dopamine and adenosine 3′, 5′-monophosphate-regulated phosphoprotein 32 kilodations; also known as PPP1R1B) on behavior and cortical evoked potentials. A frequent DARPP-32 haplotype that includes the A allele of this SNP is associated with higher mRNA expression of DARPP-32 protein isoforms, striatal dopamine receptor function, and frontal–striatal connectivity. As we hypothesized, behaviorally the A homozygotes were more flexible in selectively attending to auditory inputs than any G carriers. Moreover, this genotype also affected auditory evoked cortical potentials that reflect early sensory and late attentional processes. Specifically, analyses of event-related potentials (ERPs) revealed that amplitudes of an early component of sensory selection (N1) and a late component (N450) reflecting attentional deployment for conflict resolution were larger in A homozygotes than in any G carriers. Taken together, our data lend support for dopamine's role in modulating auditory attention both during the early sensory selection and late conflict resolution stages.


## 1. Introduction

Research on neuromodulation of cortical functions indicates that dopaminergic systems are critically involved in working memory and attentional control (for reviews, see Arnsten & Pilszka, 2011; Seamans & Yang, 2004). Most studies on dopamine modulation of working memory maintenance have focused on processes related to prefrontal D1 and D2 receptors (Durstewitz, Seamans, & Sejnowski, 2000; Phillips, Ahn, & Floresco, 2004; Williams & Goldman-Rakic, 1998; Vijyayraghavan et al., 2007). Given that multiple circuits connect striatal regions with regions in the frontal cortex (Alexander, DeLong, & Strick, 1986; Pennartz et al., 2009), recent human research has begun to investigate the role of striatal dopamine in working memory and attention (e.g., Cools, Clark, & Robbins, 2004; Frank, Loughry, & O'Reilly, 2001; Landau, Lal, O'Neil, Baker, & Jagust, 2005; Lewis, Dove, Robbins, Barker, & Owen, 2003; McNab & Klingberg, 2008).

### 1.1. Dopamine and attention: evidence from animal and human studies

Lesion studies in rats have shown that unilateral striatal dopamine depletion increases reaction times of responses contralateral to the lesion side in tasks that require visual attentional orienting (Brown & Robbins, 1989; Carli, Evenden, & Robbins, 1985;

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Ward & Brown, 1996). Deficits in selective attention processes (i.e., the inability to ignore irrelevant stimuli in blocking paradigms) have also been observed in rats with pharmacologically induced hyperdopaminergic activity (Crider, Blockel, & Solomon, 1986). A more recent study by Brown et al. (2010) investigating neurofibromatosis-1 mutant mice with reduced striatal dopamine function found impairments in non-selective and selective attention mechanisms as assessed by a variety of locomotor activities. Moreover, the mutants' attention dysfunctions could be reversed by treatment with methylphenidate, a dopamine agonist commonly used for treating attentional-deficit hyperactivity disorder (ADHD). Of particularly interest for the present study, Bao, Chan, and Merzenich (2001) found that pairing a tone with a transient dopamine signal through stimulation of the ventral tegmental area (VTA) increases the corresponding representation area in the auditory cortex, the selectivity of neural responses, and firing synchrony in response to the specific tone.

In human research, a recent receptor imaging studies used 6-[$^{18}$F]fluoro-L-DOPA (FDOPA) as a radioligand for assessing dopamine synthesis in the striatum. Vernaleken et al. (2007) found that changes in prefrontal blood-oxygen-level-dependent (BOLD) signal during attentional control were positively correlated with dopamine synthesis capacity in the ventral and dorsal striatum. Similarly, it has been observed that changes in BOLD signal in the anterior cingulate cortex and the dorsal lateral prefrontal cortex while processing affective stimuli correlate positively with striatal dopamine synthesis in the caudate and putamen, which indicates that striatal dopamine contributes to attentional processing of affective stimuli (Siessmeier et al., 2006). Furthermore, striatal dopamine synthesis capacity is also related to working memory performance, with dopamine synthesis capacity being higher in individuals with better working memory performance (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). More specifically, as regarding dopamine's effect on mechanisms of selective attention, an early positron emission tomography (PET) study, which used $^{11}$C-labeled raclopride as the radioligand, found evidence for transient striatal dopamine release while young adults played a video game that required sustained and selective visual attention (Koepp et al., 1998). Also of relevance to the current study, earlier pharmacological studies that used target detection dichotic listening paradigms found that catecholamine antagonists (e.g., haloperidol or droperidol) attenuated the processing negativity, which reflected selective attention, only in later time windows, i.e. at least 200 ms after stimulus onset (Kähkönen et al., 2001; Shelley et al., 1997). On the other side of the coin, a recent study showed that dopamine agonist (rotigotine) improved hemispatial neglect of patients' performance in visual search tasks that required selective attention (Gorgoraptis et al., 2012).

### 1.2. Dopamine and attention: clinical and molecular genetic evidence

Evidence from clinical research also converges on the view that dysfunctional dopaminergic signaling in the cortical–striatal–thalamic–cortical pathways is one of the causes underlying symptoms of ADHD, such as impaired attentional regulation and poor impulse control (see Arnsten & Pilszka, 2011; Swanson et al., 2007 for reviews). Abnormality of dopamine signaling in the prefrontal cortex contributes to hypoactivation of the ventral prefrontal and inferior parietal regions (see Casey & Durston, 2006). Furthermore, in ADHD patients alterations in striatal dopamine transporter (DAT) density (see Fusar-Poli, Rubia, Rossi, Sartori, & Balottin, 2012 for a meta-analysis of nine receptor imaging studies) as well as reduced volumes of striatal regions, such as the caudate nucleus and the globus pallidus that are rich in dopamine, were observed (Castellanos et al., 2002). Depending on the history of psychostimulant exposures, relative to healthy controls drug naïve ADHD patients tend to show lower DAT density in the striatum (e.g., Hesse, Ballaschke, Barthel, & Sabri, 2009; Volkow et al., 2007), whereas patients with prior medication treatments tend to show higher DAT density (Fusar-Poli et al., 2012). Altered dopamine transporter density in ADHD patients could change mechanisms of recycling dopamine back into the presynaptic terminal, and consequently would result in suboptimal extracellular dopamine levels (Jones et al., 1998; Shumay, Folwer, & Volkow, 2010).

Recent molecular genetic studies also showed that the dopamine transporter gene (DAT1) 10R/10R genotype, associated with lower levels of striatal synaptic dopamine and smaller caudate volume, is a risk factor for ADHD (Durston et al., 2005). Investigations of the effects of DAT1 gene genotype on spatial attention in healthy children and adolescents showed that DAT 10R homozygotes tend to perform below the levels of DAT 9R carriers (Bellgrove et al., 2007). Relatedly, a recent study of attentional regulation in healthy younger adults reported that DAT 9R carriers showed a larger effect of inhibition of return, likely reflecting greater attentional flexibility (Colzato, Pratt, & Hommel, 2010). Furthermore, another genotype also relevant for striatal dopamine function (i.e., the D2 receptor gene, DRD2 C957T) has been found to be associated with individual differences in attentional blink, in line with PET imaging studies suggesting a role for striatal dopamine in the regulation of attentional resources (Colzato, Slagter, de Rover, & Hommel, 2011).

### 1.3. DARPP-32 gene, dopamine modulation, and cognition

Another well-studied molecular candidate for striatal dopamine signaling is the DARPP-32 protein (now also known as PPP1R1B, protein phosphatase 1, regulatory inhibitor subunit 1B), which is richly expressed in the striatum. The DARPP-32 protein is phosphorylated by dopamine D1 receptor stimulation, and dephosphorylated by D2 receptor stimulation (Nishi, Snyder, & Greengard, 1997). The protein modulates striatal dopamine cellular excitability and synaptic plasticity related to the dopamine receptors (Calabresi et al., 2000; Fienberg et al., 1998; Gould & Manji, 2005). It should be noted, however, given that the striatum integrates excitatory glutamatergic inputs, and there are other neuromodulators, such as adenosine and nitric oxide, which also regulate striatal phosphorylation, it is likely that DARPP-32 also interacts with other neurotransmitters besides dopamine (Svenningsson et al., 2004).

Although as reviewed above the effects of a few other dopamine genes (e.g., the DRD2 or the DAT genotypes) on attention or working memory functions have been studied, much less is known about the potential contributions of the DARPP-32 gene on attentional mechanisms. Extant findings, however, suggest that DARPP-32 may also regulate executive control and attention functions in the frontal cortex via the frontal–hippocampal–striatal pathway. For instance, other than expressions in the striatum, the DARPP-32 protein is also expressed in other regions innervated by dopaminergic projections, such as in the anterior cingulate cortex (Narita et al., 2010) and other regions of the prefrontal cortex (Albert et al., 2002; Kunii et al., 2011). Moreover, the DARPP-32 protein has been shown to modulate the functional interaction between the striatum and the prefrontal cortex (Meyer-Lindenberg et al., 2007; Frank & Fossella, 2011) that is critically involved in attention-demanding tasks (e.g., Casey, 2005; Cools et al., 2004; Nagano-Saito et al., 2008). There is also evidence indicating that variations in the DARPP-32 gene affect the functional connectivity between the inferior frontal gygus and the parahippocampus during an associative emotional memory task (Curcic-Blake et al., 2012). Thus, individual differences in mRNA