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Dopamine modulates striato-frontal functioning during temporal processing

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With genesis in the ventral tegmental area and the substantia nigra pars compacta (SNc), the neurotransmitter dopamine influences brain function through three distinct pathways: the nigrostriatal, mesolimbic, and mesocortical. Dopamine plays a crucial role in a range of functions, for example: reward-related processing (Schultz et al., 1997) and reinforcement learning (Montague et al., 1996; Frank and Claus, 2006; Frank et al., 2007), working memory (Brozoski et al., 1979; Kimberg et al., 1997; Lustig et al., 2005; Cools et al., 2008), and motor function, including determining the vigor of actions (e.g., Niv et al., 2007; Smith and Villalba, 2008). Here our focus is on the role of dopamine in temporal processing, a less commonly recognized function (Meck, 1996; Buhusi and Meck, 2005; Meck et al., 2008; Jones and Jahanshahi, 2009; Allman and Meck, 2011; Coull et al., 2011 – but see Hata, 2011).

A growing body of research has sought to characterize the role of dopamine in interval timing, which can be broadly thought of as motor and perceptual timing in the milliseconds- and seconds-range. The influence of dopamine on interval timing has been demonstrated in pharmacological studies both with animals (Drew et al., 2003; Matell et al., 2006; Cheng et al., 2007; Meck et al., 2011) and humans (Rammsayer, 1993, 1997, for reviews see Meck et al., 2008; Jones and Jahanshahi, 2009; Coull et al., 2011). Using the peak-interval procedure, in which a learnt temporal interval is reproduced, animal research has established that dopamine agonists lead to the interval being underestimated, whereas dopamine antagonists lead to overestimation (e.g., Drew et al., 2003; Matell et al., 2004, 2006; MacDonald and Meck, 2005). These results have been interpreted as the effect of dopamine agonists and antagonists on speeding and slowing an "internal clock," respectively. Lesions to the SNc and the caudate–putamen (CPu) both impair temporal control on the task, while rats with lesions to the nucleus accumbens show no evidence of disrupted temporal performance (Meck, 2006a). This pattern implicates the nigrostriatal (substantia nigra–dorsal striatum) dopamine pathway in interval timing. Further, levodopa, a precursor to dopamine that is commonly used to treat Parkinson's disease (PD), restores timing performance in rats with lesions to the SNc but not in those with lesions to the CPu, which may reflect the distinct roles of these structures in temporal calculation (Meck, 2006a). Work on healthy humans has established that haloperidol, a non-specific D2 receptor antagonist, attenuates both milliseconds- and seconds-range perceptual timing (comparing the length of two stimuli), whereas remoxipride, which blocks D2 receptors in the mesolimbic and mesocortical tracts, only impairs seconds-range timing (Rammsayer, 1997). These results were considered to support the role of the nigrostriatal system in milliseconds-range timing. More recently, Wiener et al. (2011) were able to apply a more targeted investigation by studying the effect of different single-nucleotide genetic polymorphisms on perceptual timing. Participants with a polymorphism affecting the density of striatal D2 receptors showed increased variability for milliseconds- but not seconds-range perceptual timing. Conversely, participants with a polymorphism that affects an enzyme (COMT) influencing prefrontal dopamine showed greater variability only in the seconds-range. Thus, these data suggest a double dissociation, with the nigrostriatal pathway being important for milliseconds-range perceptual timing and the mesocortical pathway being important for seconds-range perceptual timing.

Parkinson's disease is a movement disorder associated with degeneration of dopaminergic neurons in the SNc. There is now a body of evidence that motor and perceptual timing within the milliseconds- and seconds-range are impaired in PD (see Jones and Jahanshahi, 2009; Allman and Meck, 2011; Coull et al., 2011). Dopaminergic medication often improves performance on perceptual (e.g., Pastor et al., 1992a; Malapani et al., 1998) and motor timing tasks (e.g., Pastor et al., 1992b; O'Boyle et al., 1996) in patients with PD; although the pattern of effects (e.g., whether accuracy or variability is affected) is variable and significant effects are not always found (e.g., Pastor et al., 1992b; O'Boyle et al., 1996; Jones et al., 2008; Harrington et al., 2011b). The variable findings might relate to the insufficiency of dopaminergic medication for fully restoring striato-frontal function (Harrington et al., 2011b), or to the inadequacy of medication withdrawal and the lingering effects of long-acting medication in patients tested "off" medication. Difficulties with interval timing have also been observed in other disorders that are associated with dopaminergic dysfunction, including schizophrenia and attention-deficit/hyperactivity disorder (ADHD; see Jones and Jahanshahi, 2009; Allman and Meck, 2011).

There is consensus from imaging studies that the basal ganglia, particularly the dorsal striatum, are engaged during interval timing (e.g., Rao et al., 2001; Harrington et al., 2004, 2010, 2011a,b; Jahanshahi et al., 2006, 2010; Coull et al., 2008, for reviews see Meck et al., 2008; Jones and Jahanshahi, 2009; Coull et al., 2011). The basal ganglia are closely connected to the cortex through a series of striato-cortical loops (Alexander et al., 1986). Recording from neural ensembles in animal studies supports the role of both striatal and cortical regions in encoding temporal intervals (e.g., Matell et al., 2003, 2011; Lebedev et al., 2008; Höhn et al., 2011), whilst cortical lesions in rats attenuate temporal performance (Meck, 2006b). Further, patients with cortical lesions and healthy individuals with short-lasting TMS-induced disruption to cortical function demonstrate difficulties on temporal

tasks (Jones et al., 2004; Coslett et al., 2009). Thus there has been increasing interest in explaining and exploring how interval timing might be distributed across key cortical and subcortical regions. The obvious mediator for this relationship is dopamine. To better examine the effects of dopamine on striato-frontal function in PD, we investigated the neural correlates of motor timing in a repetitive tapping task, in patients tested both "on" and "off" apomorphine, a non-selective dopamine receptor agonist (Jahanshahi et al., 2010). Using effective connectivity analysis, we established that task-related coupling between the left head of the caudate nucleus and the prefrontal cortex was increased when the patients were "on" medication compared to the "off" state. The data support the proposal that dopamine modulates the coupling between frontal and striatal regions during motor timing. Fronto-striatal connectivity in PD has also been investigated during a perceptual timing task where the durations of two stimuli were compared (Harrington et al., 2011b). Consistent with the previous study, greater activation of the putamen and superior frontal gyrus was observed "on" compared to "off" medication during the decision phase of the perceptual timing task. However, the dominant finding was that connectivity between the basal ganglia and cortex was greater "off" than "on" medication during this task.

A challenge for the field has been to develop a biologically plausible model of interval timing. The striatal beat frequency model (Matell and Meck, 2000, 2004) proposes that the striatum receives cortical and thalamic oscillatory activity that serves as a clock signal. Using a process of coincidence detection, striatal spiny neurons fire when a criterion number of neuronal inputs oscillate with the same beat frequency. It is suggested that nigrostriatal phasic dopamine signals the onset and offset of a timed interval, whereas tonic dopamine alters the frequencies of the cortical oscillations, thus directly modulating the speed of the "internal clock." According to this model, dopamine is a critical mediator of temporal calculations (see Allman and Meck, 2011; Oprisan and Buhusi, 2011).

Interval timing fits under the broad umbrella of temporal processing, which includes circadian rhythms through to the psychological relationship between time and memory. The different types of temporal experience are poorly defined and understood (Grondin, 2010), and the relationship between these various types of temporal processing has received little attention. A complete account of interval timing should seek to position this process within the wider context of temporal processing. Particularly, an unexplored question is whether the role of dopamine in interval timing can be integrated with ostensibly distinct areas of dopamine-focused research that have a temporal component. The temporal difference model of learning proposes that the phasic activity of midbrain dopamine neurons code the time discrepancy between the expected and actual delivery of reward, calculating a reward prediction error (e.g., Montague et al., 1996; Schultz et al., 1997; Hollerman and Schultz, 1998). Dopamine neurons in the substantia nigra have also been implicated in temporal discounting, which is the waning of reward value with increasing delay, and in the temporal uncertainty inherent in delayed rewards (Kobayashi and Schultz, 2008). Related to this, administration of dopamine antagonists to healthy participants increases the degree of temporal discounting, i.e., the relative value of delayed rewards decreases, leading to impulsive behavior (Pine et al., 2010). Other work proposes that tonic levels of dopamine in the nucleus accumbens play an important role in response vigor (i.e., the rate of responding) by calculating the average rate of reward (Niv et al., 2007), a process that has an intrinsic temporal component. Finally, mesocortical dopamine is critical for working memory (Brozoski et al., 1979; Kimberg et al., 1997; Cools et al., 2008), which is essentially the process of maintaining information "on line" over a time interval. To date, the investigation of the role of dopamine in reward prediction error, reinforcement learning, temporal discounting, working memory, response vigor, and interval timing have remained largely distinct fields. There may be a value in exploring whether the temporal components of these tangential fields can be integrated with research that seeks to formulate a role for dopamine in modulating interval timing.

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