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Differential effects of amphetamine and haloperidol on temporal reproduction: Dopaminergic regulation of attention and clock speed

Jessica I. Lake, Warren H. Meck*

Department of Psychology and Neuroscience, Genome Sciences Research Building II, 3rd Floor, 572 Research Drive, PO Box 91050, Duke University, Durham, NC 27708, USA

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ABSTRACT

Healthy volunteers were tested on 7-s and 17-s peak-interval timing procedures following D-amphetamine (20 mg—oral), haloperidol (2 mg—oral), and placebo treatments in order to assess the dopaminergic regulation of temporal processing. Individual differences were observed in the drug effects such that two different patterns of timing behavior emerged. In the first pattern, D-amphetamine produced proportional leftward shifts of the timing functions while haloperidol produced proportional rightward shifts. This symmetrical pattern of results suggests that clock speed is regulated by the effective level of dopamine, i.e., D-amphetamine increases clock speed and haloperidol decreases clock speed. The second pattern was the opposite of the first pattern and was revealed by D-amphetamine producing proportional rightward shifts of the timing functions while haloperidol produced no reliable effect. This asymmetrical pattern of results is consistent with an explanation in which attention toward the stimulant-induced euphoria produced by D-amphetamine diminishes the attentional resources available for temporal processing, thereby diluting any drug-induced changes in clock speed. The result of increased competition and time-sharing between these two dimensions (e.g., attention towards feelings of euphoria versus attention towards the passage of time) leads to the underestimation/overproduction of temporal intervals. Interestingly, participants that displayed the 'clock-speed' pattern liked D-amphetamine significantly less than participants that displayed the 'attention' pattern and were more variable in a simple reaction time task than other participants. These results suggest that individuals with a higher degree of sensitivity to time are also more sensitive to their feelings of stimulant-induced euphoria and drug liking—suggesting that internal clock and reward pathways share common dopaminergic pathways.

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1. Introduction

Dopamine (DA) plays an integral role in the modulation of cognitive processes. While its importance in timing and time perception is well established (Allman & Meck, 2012; Coull, Cheng, & Meck, 2011), studies examining the effects of dopaminergic (DAergic) drug administration on timing processes in humans have been limited. Previous work with rats and mice has shown that indirect DA agonists, such as cocaine and methamphetamine, result in the overestimation of time, as indicated by horizontal leftward shifts in the psychophysical functions relating the probability of a response to signal duration (e.g., Abner, Edwards, Douglas, & Brunner, 2001; Buhusi & Meck, 2002; Cevik, 2003; Cheng, Ali, & Meck, 2007; Cheng, Hakak, & Meck, 2007; Cheng, MacDonald, & Meck, 2006; Cheung et al., 2006; Chiang et al., 2000; Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; Matell, Bateson, & Meck, 2006; Matell, King, & Meck, 2004; Meck et al., 2012). In contrast, the administration of DA receptor antagonists, such as haloperidol and raclopride, lead to an underestimation of time, as indicated by horizontal rightward shifts in psychophysical functions (e.g., Buhusi & Meck, 2002; Cheng & Liao, 2007; Drew, Fairhurst, Malapani, Horvitz, & Balsam, 2003; Lustig & Meck, 2005; MacDonald & Meck, 2005; MacDonald & Meck, 2006; Maricq & Church, 1983). Taken together, these results suggest that effective levels of DA modulate the speed of an internal clock in the multiple-seconds range (Buhusi & Meck, 2005; Gu, Cheng, Yin, & Meck, 2011; Jones & Jahanshahi, 2011; Casini, Ramdani-Beauvir, Burle, & Vidal, in press).

In line with rodent studies, pharmacological challenges in humans have resulted in temporal distortions consistent with changes in clock speed (Arushanya, Baida, Mastyagin, Popova, & Shikina, 2003). Rammsayer (1993), Rammsayer (1997), Rammsayer (1999) has found that DA antagonists impair time perception in the range of milliseconds and seconds, attributing these effects to DAergic modulation of the basal ganglia, a structure believed to

* Corresponding author. Tel.: +1 919 660 5765.
E-mail address: meck@psych.duke.edu (W.H. Meck).

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play an integral role in timing processes and, specifically, in the regulation of clock speed (Meck, 2006a,b; Meck, Penney, & Pouthas, 2008). The importance of DAergic input to the basal ganglia in timing performance is supported by a recent study showing that DA precursor depletion reduced activity in the putamen and that this change in activity was correlated with impaired timing performance (Coull, Hwang, Leyton, & Dagher, in press). Additionally, patients with Parkinson's disease (PD), a disorder characterized by the degradation of DAergic input to the striatum, demonstrate temporal processing deficits when tested off medication. These deficits are frequently ameliorated with administration of the DA precursor levodopa (L-dopa) and/or DA agonists (e.g., apomorphine) to PD patients (Artieda, Pastor, Lacruz, & Obeso, 1992; Jahanshahi et al., 2010; Malapani et al., 1998), although effects may be dependent on the dose and other factors affecting optimal DA levels (Allman & Meck, 2012; Pouthas & Perbal, 2004; Rakitin, Scarmeas, Li, Malapani, & Stern, 2006). Similar restorative effects of L-dopa on timing behavior have been observed in rats with lesions of the substantia nigra pars compacta (Meck, 1996; Meck, 2006b).

At the same time, timing in the multiple-seconds range requires attention and working memory processes (Buhusi & Meck, 2009a; Lejeune, 1998; Lewis & Miall, 2003; Macar & Vidal, 2009; Thomas & Weaver, 1975), functions that are generally associated with prefrontal regions, as well as other regions thought to underlie executive functioning, such as the anterior cingulate (Landau, Lal, O'Neil, Baker, & Jagust, 2009; Lustig, Matell, & Meck, 2005). In addition to influences on clock speed, DA also modulates performance on these executive functions (Farid et al., 2009; Floresco & Magyar, 2006; Jones & Jahanshahi, 2011). Based on such evidence, it has been suggested that DAergic modulation of attention and working memory can influence temporal accuracy (Rammsayer, 1999). Using variable feedback probabilities, Lustig and Meck (2005) found that rightward shifts in timing functions increased with the number of trials since feedback. Supporting the role of DA in modulating working memory, this study found that rightward shifts associated with the decay of the feedback effects were enhanced with the administration of the DA receptor blocker haloperidol. Taken together, investigations of DAergic modulation of timing performance in humans support the role of DAergic signals in mediating temporal distortions by influencing activity in cortico-striatal circuits (for reviews see Allman & Meck, 2012; Coull et al., 2011; Droit-Volet, in press; Jones & Jahanshahi, 2011).

Nevertheless, an understanding of how pharmacological manipulations of effective DA levels influence time perception in humans has been limited by a number of factors. First, studies have largely measured temporal accuracy (e.g., Rammsayer 1993, 1997, 1999; Weiner & Ross, 1962), without assessing whether DAergic drugs result in systematic shifts in psychometric timing functions when 'train vs. test' comparisons are made, evidence of which would be consistent with changes in clock speed (Meck & Benson, 2002). Additionally, few studies have compared the effects of both DA agonists and antagonists within the same individuals (Buhusi & Meck, 2002; Maricq & Church, 1983). Lastly, direct comparisons between the timing performance of humans and non-human subjects have been limited by the fact that the majority of human studies have not used the types of duration reproduction tasks typically used in studies with lower animals, e.g., the peak-interval (PI) procedure (see Church, Miller, Meck, & Gibbon, 1991; Church, Meck, & Gibbon, 1994; Maricq et al., 1981).

While the PI procedure using durations in the multiple-seconds range (e.g., 7–21 s) has rarely been studied with the administration of DAergic drugs in humans (e.g., Lustig & Meck, 2005; Malapani et al., 1998; Meck, 2005), many human studies have successfully implemented this timing procedure in other contexts (e.g., Fortin et al., 2009; Hinton & Meck, 2004; Levin et al., 1996; Levin et al., 1998; Lustig & Meck, 2005; Malapani, Deweer, & Gibbon, 2002; Rakitin et al., 1998; Rakitin, Stern, & Malapani, 2005; Wearden & McShane, 1988). Notably, some discrepancies in timing performance between human and non-human subjects on the PI and other timing procedures have been demonstrated (e.g., Church et al., 1994; Lejeune & Wearden, 2006; Rakitin et al., 1998; Wearden & Lejeune, 2008; Wearden & McShane, 1988). While the mechanisms underlying the performance divergence between humans and non-human animals on the PI procedure remain unclear, these cross-species differences leave open the possibility that humans may not demonstrate the characteristic leftward and rightward shifts in psychometric functions associated with the administration of DA agonists and antagonists, respectively, that are observed in nonhuman animal studies.

Indirect evidence suggests that the influence of DAergic drugs on mood changes may be important in modulating temporal processing in humans. At sufficient dosages, DA agonists increase drug-liking scores and reports of drug-induced euphoria (Drevets et al., 2001; McCloskey, Palmer, & de Wit, 2010), while DA antagonists decrease elation (Brauer & de Wit, 1997). At the same time, positive mood has been shown to influence performance on tasks of executive functioning (Mitchell & Phillips, 2007), purportedly through associated changes in DA (Ashby, Isen, & Turken, 1999; Dreisbach et al., 2005). The direction of positive mood-induced effects may depend on the type of task assessed. For example, positive mood is thought to enhance cognitive flexibility and thus, may improve performance on tasks that rely on the integration of novel information and set switching (e.g., Ashby et al., 1999; Dreisbach & Goschke, 2004; Dreisbach, 2006). However, cognitive flexibility may come at the expense of other executive functions, such as directed attention and working memory (Cools & D'Esposito, 2011). Enhanced positive affect has been shown to increase distractibility and reduce the maintenance of task-related information (Dreisbach & Goschke, 2004; Dreisbach, 2006). While few studies have examined the effects of mood on time perception (Droit-Volet & Meck, 2007; Droit-Volet, Fayolle, & Gil, 2011), changes in attention and working memory capacity have consistently been shown to influence performance on timing tasks in humans (Brown, 1985; Macar, Grondin, & Casini, 1994; Lustig & Meck, 2001; Lustig & Meck, 2005; Gamache, Grondin, & Zakay, 2011). Individuals with ADHD, a disorder characterized by attentional and working memory deficits, demonstrate deficits in temporal processes (Barkley, Murphy, & Bush, 2001; Smith, Taylor, Rogers, Newman, & Rubia, 2002). Attention-sharing between temporal and non-temporal tasks, which limits resources available to devote to timing, results in temporal underestimation in healthy participants (Macar et al., 1994). As positive mood is associated with increased distractibility and reduced maintenance resources, the induction of a positive mood may reduce the attentional resources that can be allocated to temporal processing.

As positive moods impair directed attention and working memory and these processes, in turn, are important in influencing timing performance, we hypothesized that DA agonist-induced euphoric feelings may modulate interval timing. Based on evidence of individual differences in drug-liking scores and their correlation with baseline lapses in attention (e.g., McCloskey et al., 2010), we assessed whether these individual differences predicted the effects of DA agonists on temporal processing. In the PI procedure, attentional distraction shifts psychometric timing functions to the right (Buhusi & Meck, 2009a; Meck, 2005), producing a shift in the opposite direction of the canonical leftward shift resulting from an increase in clock speed (Meck, 1996; Meck, 2007; Buhusi and Meck, 2002; Buhusi and Meck, 2007). To demonstrate dissociations in temporal processing based

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