Clock Speed as a Window into Dopaminergic Control of Emotion and Time Perception

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Abstract

Although fear-producing treatments (e.g., electric shock) and pleasure-inducing treatments (e.g., methamphetamine) have different emotional valences, they both produce physiological arousal and lead to effects on timing and time perception that have been interpreted as reflecting an increase in speed of an internal clock. In this commentary, we review the results reported by Fayolle et al. (2015): *Behav. Process.*, *120*, 135–140) and Meck (1983: *J. Exp. Psychol. Anim. Behav. Process.*, *9*, 171–201) using electric shock and by Maricq et al. (1981: *J. Exp. Psychol. Anim. Behav. Process.*, *7*, 18–30) using methamphetamine in a duration-bisection procedure across multiple duration ranges. The psychometric functions obtained from this procedure relate the proportion 'long' responses to signal durations spaced between a pair of 'short' and 'long' anchor durations. Horizontal shifts in these functions can be described in terms of attention or arousal processes depending upon whether they are a fixed number of seconds independent of the timed durations (additive) or proportional to the durations being timed (multiplicative). Multiplicative effects are thought to result from a change in clock speed that is regulated by dopamine activity in the medial prefrontal cortex. These dopaminergic effects are discussed within the context of the striatal beat frequency model of interval timing (Matell & Meck, 2004: *Cogn. Brain Res.*, *21*, 139–170) and clinical implications for the effects of emotional reactivity on temporal cognition (Parker et al., 2013: *Front. Integr. Neurosci.*, *7*, 75).

Keywords

Fear, pleasure, interval timing, medial prefrontal cortex, cortico-striatal circuits, striatal beat frequency model

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1. Introduction

1.1. The Dual Roles of Dopamine

Dopaminergic circuits are activated by a broad range of emotions and hedonic states, i.e., from the fear of electric shock to the desire of the 'feel good' effects of cocaine and methamphetamine (Berridge & Kringlebach, 2013). Some theorists have proposed that this is why we 'like' scary things — free-falling, diving with sharks, roller coasters, haunted houses, etc. The fear and anxiety from parachuting, for example, increases the amount of dopamine that's released, thereby contributing to the perception that personal time is going faster, thereby making events in the external world seem to occur more slowly, as well as the feelings of relief and pleasure when we return to earth safely (Campbell & Bryant, 2007). But if fear serves as a survival response to a threat, or danger, why would we seek out that feeling? To really enjoy a scary situation, wouldn't we have to know that we're in a safe environment? Hence the 'Yin and Yang' between these different hedonic states — where context makes all the difference in terms of the ultimate effects on time perception (Allman et al., 2014a; Hinton & Meck, 1997a, b; Meck & MacDonald, 2007; Wittmann, 2015; Wittmann & Van Wassenhove, 2009; Wittmann et al., 2007).

Richard and Berridge (2011) have identified one of dopamine's dual effects in the nucleus accumbens, a brain region that motivates humans and other animals to seek out pleasurable rewards such as food, sex, or drugs, but is also involved in fear. Their work shows that a thin line lies between desire and dread and that dopamine influences both. Nucleus accumbens dopamine/glutamate interactions allow for the switching between desire and dread. Dopamine D1 subtype receptors act alone in the regulation of appetitive eating, but the dopamine D1 and D2 receptor subtypes act together for fear. Similar interactions of DA subtypes likely occur in the dorsal striatum as well as other brain regions (e.g., Agostino et al., 2011, 2013; Ilango et al., 2014; MacDonald et al., 2012). Moreover, the modulatory actions of dopamine D1 and D2 receptors in the cortex and striatum are mediated by activation of $GABA_A$ receptors, depending on the glutamate receptor subtypes involved (Tseng & O'Donnell, 2004).

Interestingly, dopamine/glutamate interactions in cortico-striatal circuits have been proposed as the major controlling factor of the speed of an internal clock in the seconds-to-minutes range (Agostino & Cheng, 2016; Cheng et al., 2006, 2007a; Meck, 1996; Rammsayer, 2006 – but see Avlar et al., 2015 and Balcı, 2014 for a cogent discussion of how these effects might be mediated by reward processsing). According to this proposal, increases in the 'effective' level of dopamine increases clock speed and decreases the uncertainty of temporal estimates while decreases in the 'effective' level of dopamine decreases clock speed and increases the uncertainty of temporal estimates (e.g., Coull et al., 2011; Gu et al., 2015a; Meck, 1983, 1986, 1996; Rammsayer, 1999; Shi et al., 2013; Williamson et al., 2008). Moreover,

lesions of the nigrostriatal DA pathway (e.g., dorsal striatum or substantia nigra pars compacta) severely impair timing and time perception (Meck, 2006a), whereas disruptions of the mesocortical DA pathway (e.g., prefrontal cortex or ventral tegmental area) result in the loss of control of clock speed by dopaminergic manipulations, but no impairment in timing precision (Meck 2006b). Hence, the interaction of emotion and temporal cognition is proposed to occur at the level of the prefrontal cortex which has the appropriate feedforward and feedback connections to control the characteristics of information flow (Ray & Zald, 2012). Crucially, as Ray and Zald elucidate, lateral areas of prefrontal cortex are weakly connected with key areas involved in emotion, such as the amygdala. By contrast, medial and orbital areas of prefrontal cortex have strong connections with amygdala, with medial areas having strong top-down projections to the amydala, and orbital areas receiving strong amygdala input. Single neurons in these circuits express dopamine receptors and could serve as a point of intersection between dopamine and emotion.

2. Effects of Electric Shock on Interval Timing

Fayolle et al. (2015) recently reported an extensive series of experimental conditions in which electric shocks administered to the middle finger were given to participants performing a duration bisection task during the 'to be timed' signal. A blue circle on a computer screen was used to present the signal durations and no feedback was given for the classification of signal durations. This electrical stimulation resulted in proportional leftward shifts compared to 'no-shock' control conditions across four duration ranges (0.2 *vs* 0.8 s, 0.4 *vs* 1.6 s, 1.2 *vs* 4.8 s, and 2.0 *vs* 8.0 s). These proportional effects were indexed using the point of subjective equality (PSE = 0.5 proportion 'long' response) of the observed sigmoidal functions as illustrated in Fig. 1 (see Akdoğan & Balcı, 2016, Allan & Gibbon, 1991, Kopec & Brody, 2010, and Penney et al., 2008 for theoretical discussions of how participants determine the PSE in duration bisection procedures). As one can see, the PSE was lower for the electric shock trials than for the no-shock trials, consistent with higher clock readings. In addition, electric shock significantly interacted with duration range indicating a proportional rather than an absolute change, consistent with an increase in clock speed. A linear contrast test revealed a significant effect of linearity for the interaction between electric shock and duration range with a significant linear regression between the geometric mean (GM) of each duration range and the magnitude of the difference between the shock and no-shock trials as shown in Fig. 2. As discussed by Fayolle et al. (2015 — Fig. 2), this linear function indicates a multiplicative effect of electric shock on duration judgments, which is indicative of a change in clock speed (Meck, 1983, 1986, 1996). Moreover, these effects are congruent with the effects of electric shock given to rats trained on a 2.0 *vs* 8.0 s bisection procedure as shown in Fig. 3

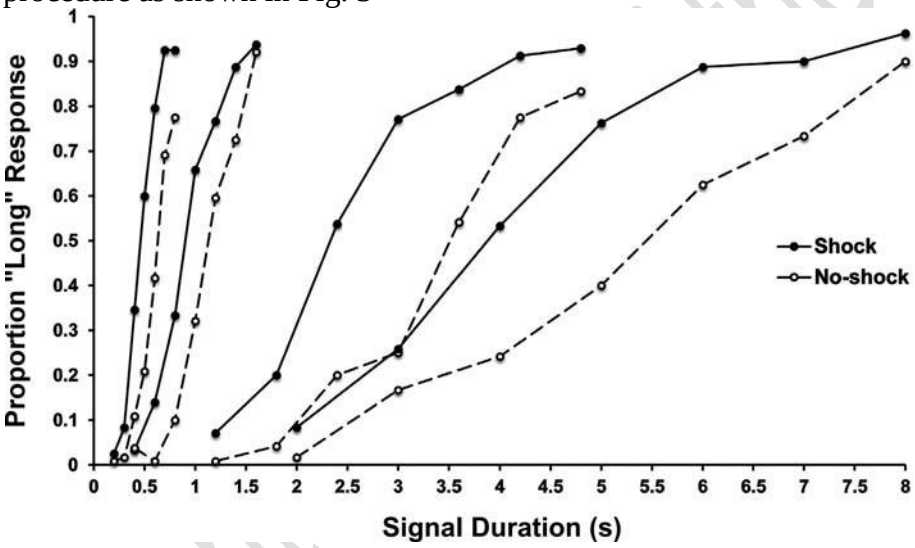

Figure 1. Mean proportion of 'long' responses (p(long)) plotted against comparison durations (s) for trials with and without an electric shock in the 0.2 *vs* 0.8, 0.4 *vs* 1.6, 1.2 *vs* 4.8 and 2.0 *vs* 8.0-s duration ranges. Adapted from Fayolle et al. (2015) – Fig. 1.

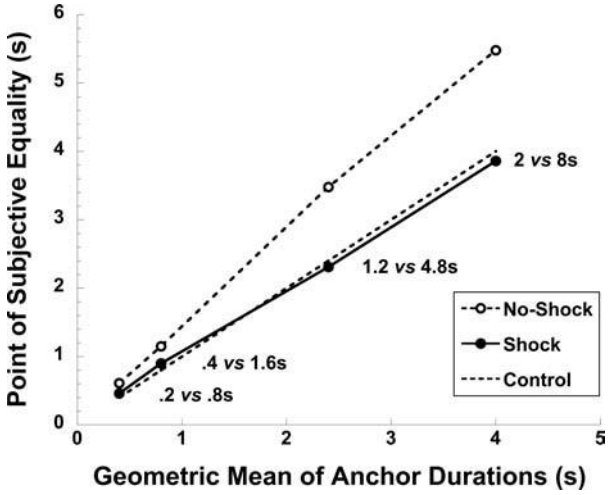

Figure 2. Mean point of subjective equality (PSE) plotted as a function of the geometric mean (GM) of the anchor duration pairs: 0.2 *vs* 0.8, 0.4 *vs* 1.6, 1.2 *vs* 4.8, and 2.0 *vs* 8.0 s. Open circles represent no-shock trials and closed circles represent shock trials. The broken line without data points represents the 'ideal' participant that bisects each of the anchor duration pairs at the GM as described by Allan and Gibbon (1991). Adapted from Fayolle et al. (2015 – Fig. 2).

(Meck, 1983 — white noise served as the 'to be timed' signal and feedback was given for the classification of anchor durations). Although not measured in these timing experiments, fear conditioning using electric shock has been shown to increase the release of dopamine in the prefrontal cortex of rats (Yoshioka et al., 1996).

It's important to note that in the Fayolle et al. (2015) procedure, the electric shocks were delivered at a random time during the 'to be timed' signal and the earlier the shock was delivered the more participants classified the duration as being 'long'. This suggests that the effects on clock speed are more attributable to the reaction to the shock than it's anticipation. Moreover, given that no baseline control condition was provided without 'no-shock' and 'shock' signals, one could just as easily interpret the results as reflecting a decrease in clock speed following a 'no shock' safety signal. This explanation is particularly attractive given that the 'shock' condition produced PSE values close to the GM for all four duration ranges, as predicted by the *similarity decision rule* of scalar timing theory as used by Allan and Gibbon (1991), Church (2003), and Meck (1983).

When other investigators have studied the effects of signaling no or low reward *vs* high reward on time perception, they've found that the greater valued signal was perceived to last longer (Failing & Theeuwes, 2015). Unlike the Fayolle et al. (2015) study, however, the effects of reward were a fixed duration and did not increase proportionally with the durations being timed. As a consequence, the authors argued for an effect on attention that influences the saliency of a stimulus and how quickly participants start timing a signal rather than an arousal effect that influences clock speed throughout the trial (e.g., Folta-Schoofs et al., 2014; Lake et al., 2014, in press; Lui et al., 2011). In juxtaposition, the effects of footshock stress reported by Meck (1983) reflect a constant state of arousal because the electric shock was being delivered continuously, in a non-pulsed fashion during both training and testing sessions, but for different treatment groups in each phase of the experiment (see Fig. 3 left and right panels).

Attention can be viewed as a dynamic process that entrains to the periodicity of information availability (e.g., Agostino et al., 2008; Coull & Nobre, 1998; Cravo et al., 2013; Escoffier et al., 2010, 2015; Henry & Hermann, 2014; Samaha et al., 2015). As such, oscillations in attention can be driven and/or synchronized with ongoing oscillations used as the time base for interval timing (Gu et al., 2015b). In addition, attention can be used to selectively increase or decrease the rate of this oscillatory time base for different stimuli, thereby explaining modality differences (e.g., Penney et al., 2000, 2014) and supporting simultaneous temporal processing (Buhusi & Meck, 2009a). Short-term attentional

modification of temporal processing might only affect the detection of the signal and the latency to start timing (e.g., additive, 'start gun' effect, Failing & Theeuwes, 2015), whereas long-term attentional modification would be expected to affect not only the latency to begin timing, but also the rate of temporal integration during the entire signal (multiplicative, 'clock speed' effect), as well as the latency to stop timing once the signal

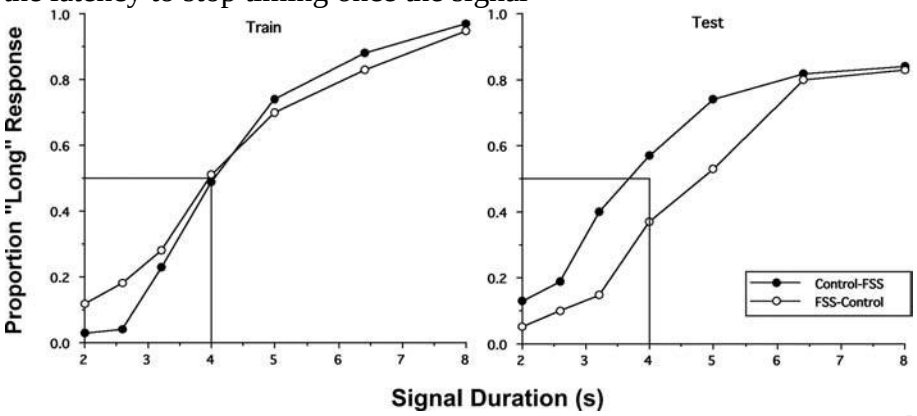

Figure 3. Median proportion 'long' response as a function of signal duration during seven-signal duration bisection training (left panel) and testing (right panel). Open circles indicate rats trained under continuous electric foot-shock stress (FSS) and tested without the stressor (control); closed circles indicate rats trained without the stressor and tested under continuous FSS. Connecting horizontal and vertical brackets indicate where the 'ideal' participant would bisect the pair of 2 *vs* 8 s anchor durations at the GM of 4 s based upon the similarity decision rule described by Allan and Gibbon (1991). Adapted from Meck (1983 – Expt. 2, Fig. 6).

offsets (Meck, 1983; Meck et al., 1985). In this sense, attention and timing are viewed as being tightly linked (Meck & Benson, 2002), although it's possible to have one without the other (e.g., Lustig & Meck, 2005) and to dissociate some aspects of attention from changes in clock speed (e.g., Buhusi, 2003; Buhusi & Meck, 2002, 2006, 2009b; Lake & Meck, 2013; Penney et al., 1996; Tipples, 2008, 2010, 2011, 2015).

3. Effects of Methamphetamine on Interval Timing

Along the same lines, Lake and Meck (2013) recently showed that amphetamine (indirect dopamine agonist) given to participants performing a duration reproduction (peak-interval) procedure for 7.0 and 17.0 s intervals resulted in proportional leftward shifts for those participants who didn't rate the drug extremely high in terms of 'drug liking' and hence weren't distracted from the timing task. In contrast, haloperidol (direct dopamine antagonist) produced proportional rightward shifts in these same participants. The proportional leftward shifts in peak time for the Gaussian-shaped response functions indicate an increase in clock speed, whereas the proportional rightward shifts indicate a decrease in clock speed — with both effects occurring as a function of the drug-induced changes in the 'effective' levels of dopamine. It should be noted that the PSE for a sigmoidal function and peak time for a Gaussian function are formally related (Yin et al., in press). Moreover, these effects are reminiscent of the earlier psychopharmacological experiments conducted with rats and mice trained on both the duration bisection and peak-interval procedures in which indirect dopamine agonists such as cocaine and methamphetamine (MAP) produced proportional leftward shifts, whereas dopamine antagonists such as haloperidol produced proportional rightward shifts in timing functions (e.g., Maricq & Church, 1982; Maricq et al., 1981; Matell et al., 2004, 2006; Meck, 1983, 1986, 1996). Duration bisection data as a function of signal range and MAP injection are shown in Fig. 4 (Maricq et al., 1981 — house light off served as the 'to be timed' signal and feedback was given for the classification of anchor durations).

In addition to the proportional leftward shifts observed following MAP *vs* saline injections, linear contrast test revealed a significant effect of linearity for the interaction between MAP and duration range with a significant linear regression between the GM of each duration range and the magnitude of the difference between the MAP and saline injection sessions as shown in Fig. 5.

All things being equal, a faster clock should be a more accurate clock, thereby leading to improved sensitivity to time and lower difference limens (DL) – which wasn't observed by Fayolle et al. (2015) or Maricq et al. (1981) where no change

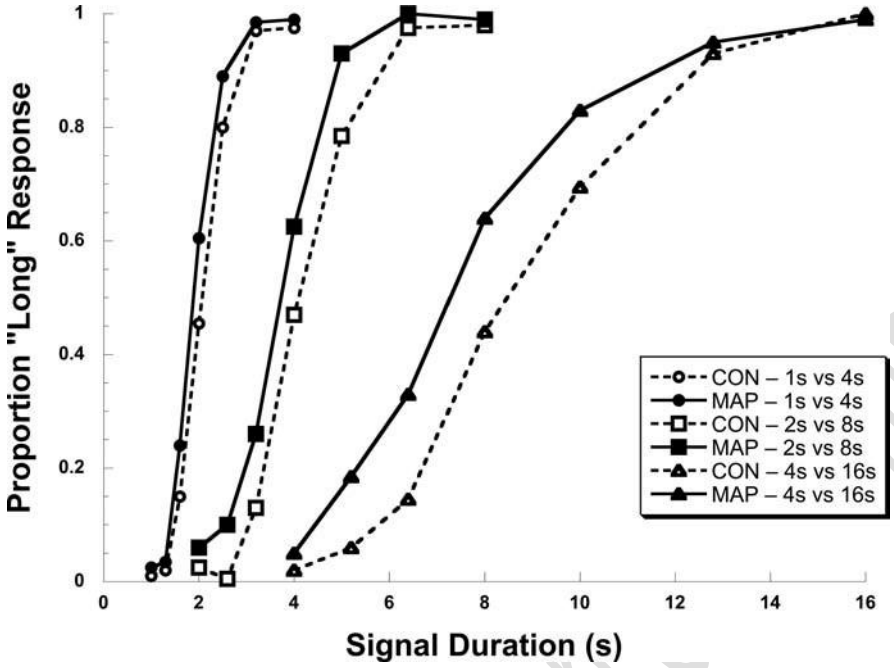

Figure 4. Median proportion 'long' response as a function of signal duration during bisection test sessions for 1 *vs* 4, 2 *vs* 8, and 4 *vs* 16-s anchor durations for responses with latencies less than the mean latency for each signal duration. Closed symbols indicate rats tested under the influence of methamphetamine (MAP — 1.5 mg/kg, sc) and open symbols indicate rats tested under saline control conditions. Adapted from Maricq et al. (1981 – Expt. 3, Fig. 7).

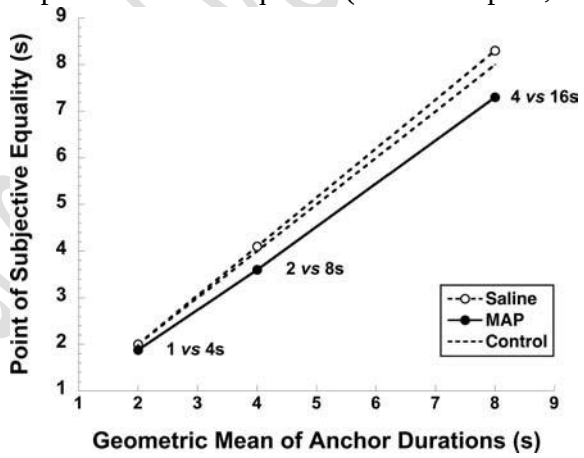

Figure 5. Mean point of subjective equality (PSE) plotted as a function of the geometric mean (GM) of the anchor duration pairs: 1 *vs* 4, 2 *vs* 8, and 4 *vs* 16 s. Open circles represent saline sessions and closed circles represent methamphetamine (MAP — 1.5 mg/kg, sc) sessions. The broken line without data points represents the 'ideal' participant that bisects each of the anchor duration pairs at the GM as described by Allan and Gibbon (1991). Data taken from Maricq et al. (1981 – Expt. 3). in DL was reported. While lower DLs are sometimes observed following dopaminergic drug administration

(Cheng et al., 2006), the myriad effects of systematically administered drugs or electric shock delivered to the finger or foot would be expected to produce unwanted sources of variability in the processes affecting duration discrimination. Moreover, individual differences in baseline PSE values, perhaps reflecting differences in clock speed between underestimators and overestimators (see Lustig & Meck, 2005), have been shown to be correlated with the level of neural activation in the right supplementary motor area (SMA) as well as the pre-SMA, putamen, and right pallidum using event-related fMRI (Tipples et al., 2013, 2015; but see Coull et al., 2016; Kononowicz & Penney, 2016; Kononowicz & Van Rijn, 2014 and Van Rijn et al., 2011 for a discussion of the role of the SMA in timing).

4. Medial Prefrontal Cortex and Dopamine Activity

A considerable amount of experimental work has shown that dopamine in the medial prefrontal cortex is crucial for the temporal control of behavior. Humans with lesions of the medial frontal cortex have increased variability in time production tasks (Picton et al., 2006). Neuroimaging studies have repeatedly implicated medial frontal regions in timing tasks, in addition to cerebellar and basal ganglia networks (e.g., Coull et al., 2011; Merchant et al., 2013a; Spencer, 2015; Teki et al., 2012). Notably, medial frontal regions in humans and rodents can have similar patterns of neuronal activity (Narayanan, 2016; Narayanan et al., 2013; Parker et al., 2015a), facilitating mechanistic investigation of temporal processing in rodents.

Disrupting rodent medial frontal cortex impairs performance of operant tasks requiring temporal control of action (e.g., Kim et al., 2009; Laubach et al., 2015; Narayanan & Laubach 2006; Narayanan et al., 2012; Xu et al., 2014). Single neurons in medial frontal cortex (e.g., Narayanan & Laubach 2009; Niki & Watanabe 1979; Parker et al., 2014) and medial premotor cortex (Merchant et al., 2013b) are strongly modulated during timing tasks. Specifically, medial frontal neurons appear to 'ramp', or have linear changes in firing rate with time (e.g., Kim et al., 2013; Parker et al., 2014). This pattern of activity has been shown to encode temporal processing by other brain areas and modeling studies have demonstrated that ramping activity can be key for integration of temporal information (e.g., Hass & Durstewitz, 2014; Narayanan, 2016; Reutimann et al., 2004; Simen et al., 2011).

Cortical regions receive dopamine from medial midbrain dopamine neurons in the ventral tegmental area and medial substantia nigra (Williams & GoldmanRakic, 1998). In the cortex, pharmacologically blocking D1 but not D2 dopamine receptors impairs temporal control of action, and attenuates temporal expectation during a reaction time task (Narayanan et al., 2012; Parker et al, 2015b). Similarly, optogenetically disrupting medial prefrontal neurons expressing D1 dopamine receptors (D1DR) impairs interval timing by decreasing sensitivity to time and thereby increasing the spread and reducing the slope of timing functions (Narayanan et al., 2012 — see also Cheng et al., 2007b). Parker et al. (2014; 2015b) have recently shown that focal infusion of the D1DR agonist SKF82958 or D1DR antagonist SCH 23390 into the medial prefrontal cortex of rats during an intervaltiming task impairs timing behavior without changing overall firing rates of medial prefrontal cortex neurons. Moreover, ramping patterns of neuronal activity that are thought to reflect temporal processing are attenuated following infusion of either a D1DR agonist or antagonist (Parker et al, 2014; 2015b). Focal infusion of D1DR antagonists altered medial prefrontal cortex local field potentials by attenuating delta activity between 1 and 4 Hz, while focal D1DR agonist infusions enhanced delta power and attenuated alpha power between 8 and 15 Hz. These data support the proposal that the influence of D1-dopamine signals on medial prefrontal cortex activity adheres to a U-shaped curve, and that temporal cognition requires optimal levels of dopamine in frontal cortex (e.g., Cools & D'Esposito, 2011; Vijayraghavan et al., 2007). This line of work is broadly consistent with past work demonstrating that prefrontal D1DRs play a key role in cognitive processes such as working memory (Abi-Dargham et al., 2002; Goldman-Rakic et al., 2004; Ward et al., 2012), and because prefrontal systems might exert top-down control of emotional circuits in the striatum and amygdala.

In a similar manner, an inverted U-shaped profile of clock speed *vs*. dopamine levels was proposed to account for the results of MAP administration to heterozygous and homozygous dopamine transporter knock-out mice (Meck et al., 2012). The observation was that initial increases in dopamine lead to increases in clock speed that are then followed either by decreases in clock speed and/or disruption of the temporal control of behavior as dopamine levels continue to rise as a function of the interaction between drug dose and gene dose. The restriction of variations in clock speed that support optimal timing behavior to a relatively narrow range of dopamine activity may be related to local dendrodendritic inhibitory feedback mechanisms as well as striatonigral feedback from the caudate, thus leading to unstable patterns of activity with sustained increases in dopamine levels or receptor activity that may interfere with cortico-striatal timing mechanisms (Coull et al., 2011; Matell & Meck, 2004; Trih et al., 2003; Ward et al., 2009).

5. Striatal Beat Frequency Model and Dopamine Activity

In the striatal beat frequency (SBF) model of interval timing (e.g., Allman & Meck, 2012; Coull et al, 2011; Hashimoto & Yotsumoto, 2015; Matell & Meck, 2000, 2004; Muller & Nobre, 2014; Murai et al., 2016; Van Rijn et al., 2014) duration estimation is based upon the coincidence detection of oscillatory processes in cortico-striatal circuits. The SBF model supposes that: at the onset of a 'to be timed' signal, populations of cortical (and thalamic) neurons phase reset (and synchronize) and begin oscillating at their endogenous periodicities. Dopamine release from the ventral tegmental area at the onset of the signal is believed to play a part in this resetting function for cortical neurons while also acting as a 'start gun', and dopamine release from the substantia nigra pars compacta at signal onset works in a similar fashion to reset the weights of the synaptic connections in the dorsal striatum (Buhusi & Meck, 2005; Jahanshahi et al., 2006; Kononowicz, 2015; Matell & Meck, 2004). The detection of coincident activation of specific cortical oscillation patterns is the role of striatal medium spiny neurons (MSNs). The adjustment of cortico-striatal synaptic weights allows the MSNs to discriminate and become 'tuned' to specific patterns of coincident oscillatory activity, thus increasing their likelihood of firing upon similar patterns of cortical activation in the future. This property accounts for the close correspondence to aspects of interval timing and working memory performance, which are held to depend on the same neural representation of a specific stimulus (Gu et al., 2015b; Lustig et al., 2005; MacDonald et al., 2007). Given that oscillatory activation repeats itself at regular intervals (its period) and changes in a systematic manner as a function of time (its phase), these cortical oscillatory patterns, when observed across neurons differing in their intrinsic periodicity, can represent time intervals in the secto-min range although their neural firing occurs in the msec range. The MSNs are able to detect these patterns, which are similar to musical cords, by acting as coincidence detectors or 'perceptrons' (e.g., Buhusi & Oprisan, 2013, Oprisan & Buhusi, 2014). Striatal output travels to the thalamus along two pathways: the direct (dopamine D1 receptor mediated) and indirect (dopamine D2 receptor mediated), then loops back to the cortex and striatum, influencing the rate of oscillatory activity and permitting alterations in clock speed by changing the input to MSNs (Oprisan & Buhusi, 2011). Differential activity in the direct and indirect pathways of the basal ganglia may serve to start, stop (pause), or reset the timing process (Matell & Meck, 2004). Consequently, the SBF model has the advantage of being consistent with the known psychophysics, neuropharmacology, and neuroanatomy of interval timing while at the same time making testable predictions regarding the functioning of its components (e.g., Allman et al., 2014b; Coull et al., 2011; Hashimoto & Yotsumoto, 2015; Kononowicz, 2015; Kononowicz & van Rijn, 2014, 2015; Kononowicz et al., 2015; Merchant et al., 2013a; Oprisan & Buhusi, 2013; Oprisan et al., 2014; Tomasi et al., 2015; Van Rijn et al., 2011; Yin & Meck, 2014).

As noted above, the SBF model proposes that tonic dopamine levels in the frontal cortex are important in setting the tonic firing rate of cortical projections to the striatum. Increases or decreases in this rate could thus result in increases or decreases in the rate of cortical oscillations, resembling a

pacemaker-like mechanism. At the same time, phasic dopaminergic signals may have more transient effects on timing circuitry. Phasic dopamine release to the cortex and striatum has been demonstrated in response to appetitive and aversive stimuli, cues that predict such stimuli, and novel/salient stimuli (e.g., Land et al., 2014; Narayanan et al., 2012). Phasic burst firing of dopaminergic neurons results in changes in dopaminergic concentrations in target areas that last up to a few seconds (e.g., Dreyer et al., 2010). These brief bursts of dopamine may trigger low frequency oscillations as well as ramping activity in the cortex that in turn interacts with oscillatory activity in the striatum.

While phasic dopaminergic firing is thought to play a role in the 'start gun' process (Kononowicz, 2015; MacDonald et al., 2012, 2014; Matthews et al., 2014), such phasic dopamine bursts may also mediate the transient physiological arousal component of temporal distortion induced by emotional stimuli (Droit-Volet & Meck, 2007; Lake et al., 2016; Schirmer, 2014). The input pathway inducing phasic bursting of dopaminergic midbrain neurons could influence the latency after stimulus onset that these neurons fire, with earlier bursting resulting in increases in temporal estimates. Alternatively, in the same way that tonic dopamine may change the rate of cortical oscillation frequencies, transient increases in dopamine around salient events might temporarily increase the rate of cortical oscillations, resulting in short-lived increases in temporal estimates associated with emotional reactions and/or psychiatric illness (e.g., Mathalon & Sohal, 2016; Péron et al., 2013; Schirmer et al., 2016; Vinogradov & Herman, 2016).

6. Clinical Correlations

Dopamine is a key neurotransmitter not only in human behavior, but also in human psychiatric and neurological diseases. For instance, Parkinson's disease (PD) is characterized by deficits in dopamine as well as other neurotransmitters (Narayanan et al., 2013). PD patients have deficits in emotional processing as well as in temporal control of action. PD patients have both deficits in recognizing negative emotions in others, and suffer from severe apathy as well as depression and anxiety (Alzahrani & Venneri, 2015; Chaudhuri & Sauerbier, 2016; Chaudhuri & Schapira, 2009). PD patients also have reliably impaired perceptual and motor timing with increased clock-speed variability and impaired temporal memories, suggesting a complex deficit involving both cortical and basal ganglia function (Harrington & Rao, 2015; Harrington et al., 2014; Jones & Jahanshahi, 2014, 2015; Merchant et al., 2013a; Parker et al., 2013, 2015a). Moreover, dopaminergic drugs for Parkinson's disease can modulate temporal processing (Buhusi & Meck, 2005; Gu et al., 2015a; Malapani et al., 1998), but do not reliably improve emotional function in PD patients (e.g., Chaudhuri & Schapira, 2009; Péron et al., 2014).

Another salient disease is schizophrenia. Patients with schizophrenia can have altered prefrontal D1DRs that in turn impair striatal function (Abi-Dargham et al., 2002; Meyer-Lindenberg et al., 2002). While a heterogeneous disease, schizophrenia patients have markedly impaired emotional processing, with decreased ability to recognize emotion, decreased ability to experience hedonic experiences, profoundly altered motivation as well as co-morbid depression and anxiety (Kring & Caponigro, 2010). Several decades of work has described patients with schizophrenia also suffer from disrupted perceptual timing (Ciullo et al., 2016; Ward et al., 2012). As in Parkinson's disease, several drugs that are effective for schizophrenia (including haloperidol) act on dopaminergic receptors, with some potently blocking striatal D2 signaling and others such as clozapine, risperidone, and aripiprazole with partial action on dopamine receptors in addition to serotonin and norepinephrine receptors (e.g., Buhusi & Meck, 2007; Heilbronner & Meck, 2014; MacDonald & Meck, 2005).

A third disease where dopamine, emotion and time interact is attention- deficit-hyperactivity disorder (ADHD). Both children and adults with ADHD have marked emotional dysregulation, in which they have difficulty inhibiting emotions and allocating attention to emotional stimuli (Shaw et al., 2014). Children with ADHD have impaired motor timing when producing time intervals (Barkley et al., 2001; Hwang-Gu et al., 2015; Rommelse et al., 2008). Moreover, a core treatment for ADHD

are various indirect dopamine agonists such as methylphenidate, methamphetamine, and nicotine, which as detailed above, have clear effects on interval timing (e.g., Conners et al., 1996; Hinton & Meck, 1996; Levin et al., 1996, 1998; Meck, 2007; Noreika et al., 2013).

Dopaminergic signaling is involved in numerous diseases and neurological/ psychiatric conditions, such as depression, bipolar disorder, dystonia, drug addiction, Huntington's disease, obsessive-compulsive disorder, stuttering, Tourette's syndrome(e.g., Allman & Meck, 2012; Gu et al., 2011; Linazasoro & van Blercom, 2007; Ptáček et al., 2011; Singer et al., 2002). Furthermore, many commonly prescribed drugs powerfully modulate dopaminergic signaling. Thus, understanding the precise mechanism of dopaminergic control of emotion and clock speed is of great clinical relevance, as it may help provide insight into symptoms of Parkinson's disease, schizophrenia, and ADHD, as well as help develop and tune current and novel therapies and genetic tests for these and other human diseases including drug abuse, anxiety, and depression (e.g., Bartholomew et al., 2015; Howland, 2012; Lake, 2016; Lake et al., in press; Meck, 2005; Schapira et al., 2006; Thönes & Oberfeld, 2015; Tomasi et al., 2015; Wittmann et al., 2007).

7. Conclusions

The idea that transient physiological arousal mediates the effect of emotion on time perception finds considerable empirical support from studies that have asked participants to judge the duration of emotional stimuli. A consistent finding is that individuals overestimate the duration of faces expressing states of high arousal (e.g., angry expressions) and moreover, this effect is increased in individuals with high levels of anxiety and self-reported fearfulness (Bar-Haim et al., 2010; Tipples, 2008, 2011, 2015). For angry facial expressions this pattern has been replicated by the same research group and also, separate research groups (for a review see; Droit-Volet, 2013; Droit-Volet et al., 2013) using different tasks (Gil & DroitVolet, 2011). The overestimation effect generalizes to different types of emotional stimuli including emotional sounds (Noulhiane et al., 2007), aversively conditioned stimuli (Droit-Volet et al., 2010; Ogden et al., 2014), highly arousing negative images (Angrilli et al., 1997; Droit-Volet et al., 2011; Gil & Droit-Volet, 2012; Shi et al., 2012; Smith et al., 2011) and highly feared stimuli (Buetti & Lleras, 2012; Langer et al., 1961; Watts & Sharrock, 1984).

The sensitivity of time to the effects of threat-related stimuli and individual differences in fearfulness (and anxiety) supports the idea that time is modulated by the operation of a system that responds to potential threats (Ohman & Mineka, 2001) or similarly, the dread system described by Richard and Berridge (2011). In our evolutionary past, failing to experience unpleasant feelings and rapidly prepare a response would have been costly (Nesse, 2005). Consequently, stimuli rated as highly arousing and negative are easy to find (for researchers in this area) and unpleasant arousal is readily evoked in laboratory settings especially in individuals predisposed to feel anxiety and fear.

The relatively scarcity of studies reporting effects for pleasant stimuli should not be taken as evidence for threat-specific effects: Overestimation of time has been reported for pleasant arousing images (Volkinburg & Balsam, 2014), happy facial expressions (Droit-Volet et al., 2004) and also, for neutral stimuli associated with pleasant, high arousal stimuli using an evaluative conditioning procedure (Kliegl et al., 2015). There is some evidence of differential effects of pleasant and unpleasant stimuli on timing and this evidence includes an underestimation effect for both pleasant (Gable & Poole, 2012) and unpleasant stimuli (Lui et al., 2011). The engagement of attentional processes is one explanation for these exceptions to the overestimation effect for arousing emotional stimuli: Perhaps under some circumstances individuals withdraw attention from unpleasant images and spend longer inspecting pleasant images (e.g., 'pleasure seeking'). However, and in summary of the effects for emotional stimuli, the overwhelming evidence is for overestimation due to emotional arousal – an effect that is consistent with dopamine-mediated increases in transient physiological arousal.

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