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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 Balci, 2014 for a cogent discussion of how these effects might be mediated by reward processing). 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 amygdala, 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 & Balci, 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

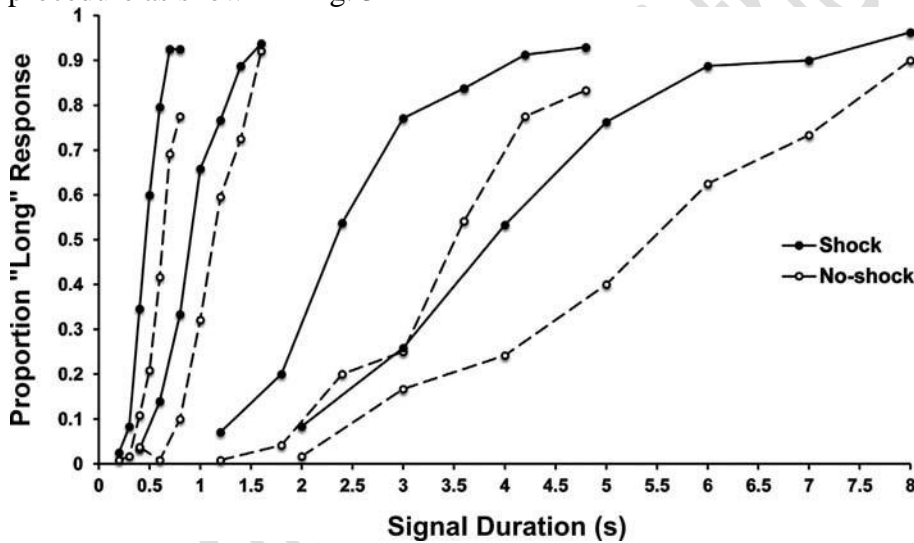


Figure 1. Mean proportion of ‘long’ responses ($p(\text{long})$) plotted against comparison durations (s) for trials with and without an electric shock in the 0.2 vs 0.8, 0.4 vs 1.6, 1.2 vs 4.8 and 2.0 vs 8.0-s duration ranges. Adapted from Fayolle et al. (2015) – Fig. 1.

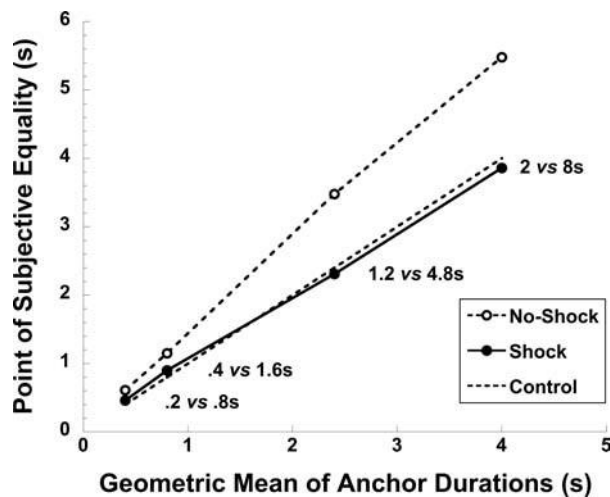


Figure 2. Mean point of subjective equality (PSE) plotted as a function of the geometric mean (GM) of the anchor duration pairs: 0.2 vs 0.8, 0.4 vs 1.6, 1.2 vs 4.8, and 2.0 vs 8.0 s. Open circles represent no-shock trials and closed circles represent shock trials. The broken line without data points 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., Foltz-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

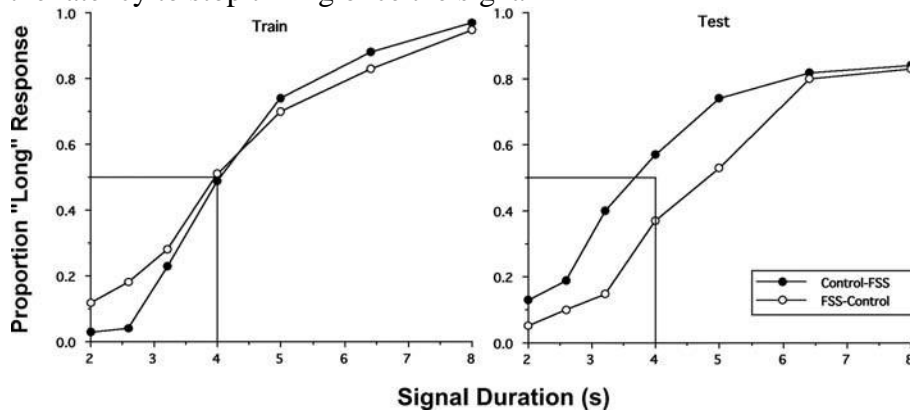


Figure 3. Median proportion ‘long’ response as a function of signal duration during seven-signal duration bisection training (left panel) and testing (right panel). Open circles indicate rats trained under continuous electric foot-shock stress (FSS) and tested without the stressor (control); closed circles 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

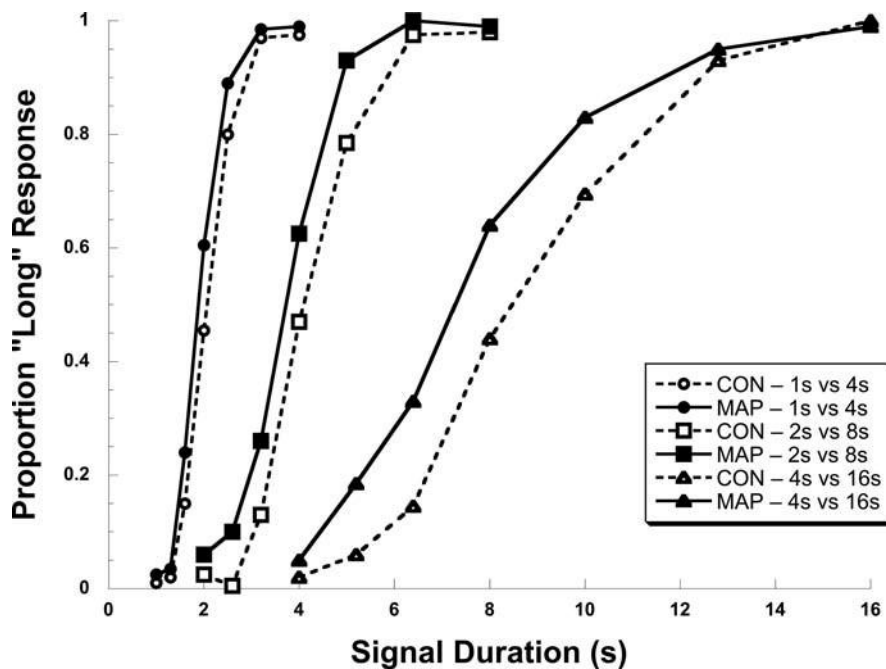


Figure 4. Median proportion 'long' response as a function of signal duration during bisection test sessions for 1 vs 4, 2 vs 8, and 4 vs 16-s anchor durations for responses with latencies less than the mean latency for each signal duration. Closed symbols indicate rats tested under the influence of methamphetamine (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).

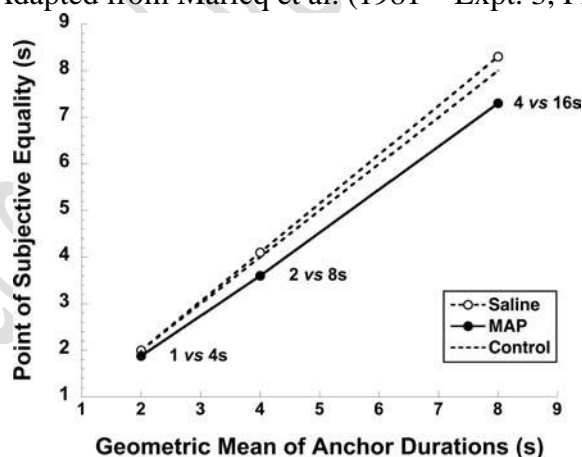


Figure 5. Mean point of subjective equality (PSE) plotted as a function of the geometric mean (GM) of the anchor duration pairs: 1 vs 4, 2 vs 8, and 4 vs 16 s. Open circles represent saline sessions and closed circles represent methamphetamine (MAP — 1.5 mg/kg, sc) sessions. The broken line without data 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 & Goldman-Rakic, 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 interval timing 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 sec-to-min range although their neural firing occurs in the msec range. The MSNs are able to detect these patterns, which are similar to musical chords, 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., Connors 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 & Droit-Volet, 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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References

- Abi-Dargham, A., Mawlawi, O., Lombardo, I., Gil, R., Martinez, D., Hunag, Y., Hwang, D.-R., Keilp, J., Kochan, L., Van Heertum, R., Gorman, J. M., & Laruee, M. (2002). Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J. Neurosci.*, *22*, 3708–3719.
- Agostino, P. V., & Cheng, R.-K. (2016). Contributions of dopaminergic signaling to timing accuracy and precision. *Curr. Opin. Behav. Sci.*, *8*, 153–160.
- Agostino, P. V., Peryer, G., & Meck, W. H. (2008). How music fills our emotions and helps us keep time. *Behav. Brain Sci.*, *31*, 575–576.
- Agostino, P. V., Golombek, D. A., & Meck, W. H. (2011). Unwinding the molecular basis of interval and circadian timing. *Front. Integr. Neurosci.*, *5*, 64. doi: 10.3389/fnint.2011.00064.
- Agostino, P. V., Cheng, R. K., Williams, C. L., West, A. E., & Meck, W. H. (2013). Acquisition of response thresholds for timed performance is regulated by a calcium-responsive transcription factor, CaRF. *Genes Brain Behav.*, *12*, 633–644.
- Akdoğan, B., & Balcı, F. (2016). Stimulus probability effects on temporal bisection performance of mice (*Mus musculus*). *Anim. Cogn.*, *19*, 15–30.
- Allan, L. G., & Gibbon, J. (1991). Human bisection at the geometric mean. *Learn. Motiv.*, *22*, 39–58.
- Allman, M. J., & Meck, W. H. (2012). Pathophysiological distortions in time perception and timed performance. *Brain*, *135*, 656–677.
- Allman, M. J., Yin, B., & Meck, W. H. (2014a). Time in the psychopathological mind. In V. Arstila & D. Lloyd (Eds), *Subjective time: The philosophy, psychology, and neuroscience of temporality* (pp. 637–654). Cambridge, MA, USA: MIT Press.
- Allman, M. J., Teki, S., Griffiths, T. D., & Meck, W. H. (2014b). Properties of the internal clock: First- and second-order principles of subjective time. *Annu. Rev. Psychol.* *65*, 743–771.
- Alzahrani, H., & Venneri, A. (2015). Cognitive and neuroanatomical correlates of neuropsychiatric symptoms in Parkinson's disease: A systematic review. *J. Neurol. Sci.*, *356*, 32–44.
- Angrilli, A., Cherubini, P., Pavese, A., & Manfredini, S. (1997). The influence of affective factors on time perception. *Percept. Psychophys.*, *59*, 972–982.
- Avlar, B., Kahn, J. B., Jensen, G., Kandel, E. R., Simpson, E. H., & Balsam, P. D. (2015). Improving temporal cognition by enhancing motivation. *Behav. Neurosci.*, *129*, 576–588.
- Balcı, F. (2014). Interval timing, dopamine, and motivation. *Timing Time Percept.*, *2*, 379–410.
- Bar-Haim, Y., Kerem, A., Lamy, D., & Zakay, D. (2010). When time slows down: The influence of threat on time perception in anxiety. *Cogn. Emot.*, *24*, 255–263.
- Barkley, R. A., Edwards, G., Laneri, M., Fletcher, K., & Metevia, L. (2001). Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). *J. Abnorm. Child Psychol.*, *29*, 541–556.
- Bartholomew, A. J., Meck, W. H., & Cirulli, E. T. (2015). Analysis of genetic and non-genetic factors influencing timing and time perception. *PLoS One*, *10*, e0143873. doi: 10.1371/journal.pone.0143873.
- Berridge, K. C., & Kringelbach, M. L. (2013). Neuroscience of affect: Brain mechanisms of pleasure and displeasure. *Curr. Opin. Neurobiol.*, *23*, 294–303.

- Buetti, S., & Lleras, A. (2012). Perceiving control over aversive and fearful events can alter how we experience those events: An investigation of time perception in spider-fearful individuals. *Front. Psychol.*, 3, 337. doi: 10.3389/fpsyg.2012.00337.
- Buhusi, C.V. (2003) Dopaminergic effects of methamphetamine and haloperidol on the control of an internal clock. In W. H. Meck (Ed.), *Functional and neural mechanisms of interval timing* (pp. 317–338). Boca Raton, FL, USA: CRC Press.
- Buhusi, C. V., & Meck, W. H. (2002). Differential effects of methamphetamine and haloperidol on the control of an internal clock. *Behav. Neurosci.*, 116, 291–297.
- Buhusi, C. V., & Meck, W. H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nat. Rev. Neurosci.*, 6, 755–765.
- Buhusi, C. V., & Meck, W. H. (2006). Interval timing with gaps and distracters: Evaluation of the ambiguity, switch, and time-sharing hypotheses. *J. Exp. Psychol. Anim. Behav. Process.*, 32, 329–338.
- Buhusi, C. V., & Meck, W. H. (2007). Effect of clozapine on interval timing and working memory for time in the peak-interval procedure with gaps. *Behav. Process.*, 74, 159–167.
- Buhusi, C. V., & Meck, W. H. (2009a). Relativity theory and time perception: Single or multiple clocks? *PLoS One*, 4:e6268. doi: 10.1371/journal.pone.0006268.
- Buhusi, C. V., & Meck, W. H. (2009b). Relative time sharing: New findings and an extension of the resource allocation model of temporal processing. *Philos. Trans. R. Soc. B*, 364, 1875–1885.
- Buhusi, C. V., & Oprisan, S. A. (2013). Time-scale invariance as an emergent property in a perceptron with realistic, noisy neurons. *Behav. Process.*, 95, 60–70.
- Campbell, L. A., & Bryant, R. A. (2007). How time flies: A study of novice skydivers. *Behav. Res. Ther.*, 45, 1389–1392.
- Chaudhuri, K. R., & Sauerbier, A. (2016). Parkinson disease: Unraveling the nonmotor mysteries of Parkinson disease. *Nat. Rev. Neurol.*, 12, 10–11.
- Chaudhuri, K. R., & Schapira, A. H. (2009). Non-motor symptoms of Parkinsons disease: Dopaminergic pathophysiology and treatment. *Lancet Neurol.*, 8, 464–474.
- Cheng, R. K., MacDonald, C. J., & Meck, W. H. (2006). Differential effects of cocaine and ketamine on time estimation: Implications for neurobiological models of interval timing. *Pharmacol. Biochem. Behav.*, 85, 114–122.
- Cheng, R. K., Ali, Y. M., & Meck, W. H. (2007a). Ketamine “unlocks” the reduced clock-speed effect of cocaine following extended training: Evidence for dopamine-glutamate interactions in timing and time perception. *Neurobiol. Learn. Mem.*, 88, 149–159.
- Cheng, R. K., Hakak, O. L., & Meck, W. H. (2007b). Habit formation and the loss of control of an internal clock: Inverse relationship between the level of baseline training and the clock-speed enhancing effects of methamphetamine. *Psychopharmacology*, 193, 351–362.
- Church, R. M. (2003). A concise introduction to scalar timing theory. In W. H. Meck (Ed.), *Functional and neural mechanisms of interval timing*. (pp. 3–22). Boca Raton, FL: CRC Press.
- Ciullo, V., Spalletta, G., Caltagirone, C., Jorge, R. E., & Piras, F. (2016). Explicit time deficit in schizophrenia: Systematic review and meta-analysis indicate it is primary and not domain specific. *Schizophr. Bull.* 42, 505–518.
- Conners, C. K., Levin, E. D., Sparrow, E., Hinton, S. C., Erhardt, D., Meck, W. H., Rose, J. E., & March, J. (1996). Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). *Psychopharmacol. Bull.*, 32, 67–73.
- Cools, R., & D’Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol. Psychiatry*, 69, e113–e125.

- Coull, J. T., & Nobre, A. C. (1998). Where and when to pay attention: The neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *J. Neurosci.*, *18*, 7426–7435.
- Coull, J. T., Cheng, R. K., & Meck, W. H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology Rev.*, *36*, 3–25.
- Coull, J. T., Vidal, F., & Burle, B. (2016). When to act, or not to act: that's the SMA's question. *Curr. Opin. Behav. Sci.*, *8*, 14–21.
- Cravo, A. M., Rohenkohl, G., Wyart, V., & Nobre, A. C. (2013). Temporal expectation enhances contrast sensitivity by phase entrainment of low-frequency oscillations in visual cortex. *J. Neurosci.*, *33*, 40002–4010.
- Dreyer, J. K., Herrik, K. F., Berg, R. W., & Hounsgaard, J. D. (2010). Influence of phasic and tonic dopamine release on receptor activation. *J. Neurosci.*, *30*, 14273–14283.
- Droit-Volet, S. (2013). Time perception, emotions and mood disorders. *J. Physiol.*, *107*, 255–264.
- Droit-Volet, S., & Meck, W. H. (2007). How emotions colour our perception of time. *Trends Cogn. Sci.*, *11*, 504–513.
- Droit-Volet, S., Brunot, S., & Niedenthal, P. M. (2004). Perception of the duration of emotional events. *Cogn. Emot.*, *18*, 849–858.
- Droit-Volet, S., Mermillod, M., Cocenas-Silva, R., & Gil, S. (2010). The effect of expectancy of a threatening event on time perception in human adults. *Emotion*, *10*, 908–914.
- Droit-Volet, S., Fayolle, S. L. & Gil, S. (2011). Emotion and time perception: Mood elicited by films. *Front. Integr. Neurosci.*, *5*, 33. doi: 10.3389/fnint.2011.00033.
- Droit-Volet, S., Fayolle, S., Lamotte, M. & Gil, S. (2013). Time, emotion and the embodiment of timing. *Timing Time Percept.*, *1*, 99–126.
- Escoffier, N., Sheng, D. Y. J., & Schirmer, A. (2010). Unattended musical beats enhance visual processing. *Acta Psychol. (Amst.)*, *135*, 12–16.
- Escoffier, N., Herrmann, C. S., & Schirmer, A. (2015). Auditory rhythms entrain visual processes in the human brain: Evidence from evoked oscillations and event-related potentials. *Neuroimage*, *111*, 267–276.
- Failing, M., & Theeuwes, J. (2015). Reward alters the perception of time. *Cognition*, *148*, 19–26.
- Fayolle, S., Gil, S., & Droit-Volet, S. (2015). Fear and time: Fear speeds up the internal clock. *Behav. Process.*, *120*, 135–140.
- Folta-Schoofs, K., Wolf, O. T., Treue, S., & Schoofs, D. (2014). Perceptual complexity, rather than valence or arousal accounts for distractor-induced overproductions of temporal durations. *Acta Psychologica*, *147*, 51–59.
- Gable, P. A., & Poole, B. D. (2012). Time flies when you're having approach-motivated fun effects of motivational intensity on time perception. *Psychol. Sci.*, *23*, 879–886.
- Gil, S., & Droit-Volet, S. (2011). "Time flies in the presence of angry faces" ... depending on the temporal task used! *Acta Psychologica*, *136*, 354–362.
- Gil, S., & Droit-Volet, S. (2012). Emotional time distortions: The fundamental role of arousal. *Cogn. Emot.*, *26*, 847–862.
- Goldman-Rakic, P. S., Castner, S. A., Svensson, T. H., Siever, L. J., & Williams, G. V. (2004). Targeting the dopamine D1 receptor in schizophrenia: Insights for cognitive dysfunction. *Psychopharmacology*, *174*, 3–16.
- Gu, B.-M., Cheng, R. K., Yin, B., & Meck, W. H. (2011). Quinpirole-induced sensitization to noisy/sparse periodic input: Temporal synchronization as a component of obsessive-compulsive disorder. *Neuroscience*, *179*, 143–150.

- Gu, B.-M., Jurkowski, A. J., Lake, J. I., Malapani, C., & Meck, W. H. (2015a). Bayesian models of interval timing and distortions in temporal memory as a function of Parkinson's disease and dopamine-related error processing. In A. Vatakis & M.J. Allman (Eds), *Time distortions in mind: Temporal processing in clinical populations* (pp. 284–329). Boston, MA, USA: Brill Academic Publishers.
- Gu, B.-M., Van Rijn, H., & Meck, W. H. (2015b). Oscillatory multiplexing of neural population codes for interval timing and working memory. *Neurosci. Biobehav. Rev.*, 48, 160–185.
- Harrington, D. L., & Rao, S. M. (2015). Timing in neurogenerative disorders of the basal ganglia. In A. Vatakis & M. J. Allman (Eds), *Time distortions in mind: Temporal processing in clinical populations* (pp. 190–225). Boston, MA, USA: Brill Academic Publishers.
- Harrington, D. L., Castillo, G. N., Reed, J. D., Song, D. D., Litvan, I., & Lee, R. R. (2014). Dissociation of neural mechanisms for intersensory timing deficits in Parkinson's disease. *Timing Time Percept.*, 2, 145–168.
- Hashimoto, Y., & Yotsumoto, Y. (2015). Effect of temporal frequency spectra of flicker on time perception: Behavioral testing and simulations using a striatal beat frequency model. *Timing Time Percept.*, 3, 201–222.
- Hass, J., & Durstewitz, D. (2014). Neurocomputational models of time perception. *Adv. Exp. Med. Biol.*, 828, 49–71.
- Heilbronner, S. R., & Meck, W. H. (2014). Dissociations between interval timing and intertemporal choice following administration of fluoxetine, cocaine, or methamphetamine. *Behav. Process.*, 101, 123–134.
- Henry, M. J., & Herrmann, B. (2014). Low-frequency neural oscillations support dynamic attending in temporal context. *Timing Time Percept.*, 2, 62–86.
- Hinton, S. C., & Meck, W. H. (1996). Increasing the speed of an internal clock: The effects of nicotine on interval timing. *Drug Dev. Res.*, 38, 204–211.
- Hinton, S. C., & Meck, W. H. (1997a). How time flies: Functional and neural mechanisms of interval timing. In C. M. Bradshaw & E. Szabadi (Eds), *Time and behaviour: Psychological and neurobiological analyses* (pp. 409–457). New York, NY, USA: Elsevier.
- Hinton, S. C., & Meck, W. H. (1997b). The “internal clocks” of circadian and interval timing. *Endeavour*, 21, 82–87.
- Howland, R. H. (2012). The use of dopaminergic and stimulant drugs for the treatment of depression. *J. Psychosoc. Nurs. Ment. Health Serv.*, 50, 11–14.
- Hwang-Gu, S.-L., & Gau, S. S.-F. (2015). Interval timing deficits assessed by time reproduction dual tasks as cognitive endophenotypes for attention-deficit/hyperactivity disorder. *PLoS One*, 10, e0127157. doi: 10.1371/journal.pone.0127157.
- Ilango, A., Kesner, A. J., Keller, K. L., Stuber, G. D., Bonci, A., & Ikemoto, S. (2014). Similar roles of substantia nigra and ventral tegmental dopamine neurons in reward and aversion. *J. Neurosci.*, 34, 817–822.
- Jahanshahi, M., Jones, C. R. G., Dirnberger, G., & Frith, C. D. (2006). The substantia nigra pars compacta and temporal processing. *J. Neurosci.*, 26, 12266–12273.
- Jones, C. R. G., & Jahanshahi, M. (2014). Contributions of the basal ganglia to temporal processing: Evidence from Parkinson's disease. *Timing Time Percept.*, 2, 87–127.
- Jones, C. R. G., and Jahanshahi, M. (2015). Striatal and frontal pathology: Parkinson's disease and patients with lesions of the basal ganglia and frontal cortex. In A. Vatakis & M. J. Allman (Eds), *Time distortions in mind: Temporal processing in clinical populations* (pp. 250–280). Boston, MA, USA: Brill Academic Publishers.

- Kim, J., Jung, A. H., Byun, J., Jo, S., & Jung, M. W. (2009). Inactivation of medial prefrontal cortex impairs time interval discrimination in rats. *Front. Behav. Neurosci.*, 3, 38. doi: 10.3389/neuro.08.038.2009.
- Kim, J., Ghim, J.-W., Lee, J. H., & Jung, M. W. (2013). Neural correlates of interval timing in rodent prefrontal cortex. *J. Neurosci.*, 33, 13834–13847.
- Kliegl, K. M., Watrin, L., & Huckauf, A. (2015). Duration perception of emotional stimuli: Using evaluative conditioning to avoid sensory confounds. *Cogn. Emot.*, 29, 1350–1367.
- Kononowicz, T. W. (2015). Dopamine-dependent oscillations in frontal cortex index “start-gun” signal in interval timing. *Front. Hum. Neurosci.*, 9, 331. doi: 10.3389/fnhum.2015.00331.
- Kononowicz, T. W., & Penney, T. B. (2016). The contingent negative variation (CNV): timing isn’t everything. *Curr. Opin. Behav. Sci.*, 8, doi: 10.1016/j.cobeha.2016.02.022.
- Kononowicz, T. W., & Van Rijn, H. (2014). Decoupling interval timing and climbing neural activity: A dissociation between CNV and N1P2 amplitudes. *J. Neurosci.*, 34, 2931–2939.
- Kononowicz, T. W., & Van Rijn, H. (2015). Single trial beta oscillations index time estimation. *Neuropsychologia*, 75, 381–389.
- Kononowicz, T. W., Sander, T., & Van Rijn, H. (2015). Neuroelectromagnetic signatures of the reproduction of supra-second durations. *Neuropsychologia*, 75, 201–213.
- Kopec, C. D., & Brody, C. D. (2010). Human performance on the temporal bisection task. *Brain Cogn.*, 74, 262–272.
- Kring, A. M., & Caponigro, J. M. (2010). Emotion in schizophrenia: Where feeling meets thinking. *Curr. Dir. Psychol. Sci.*, 19, 255–259.
- Lake, J. I. (2016). Recent advances in understanding emotion-driven temporal distortions. *Curr. Opin. Behav. Sci.*, 8, 214–219.
- Lake, J. I., & Meck, W. H. (2013). Differential effects of amphetamine and haloperidol on temporal reproduction: Dopaminergic regulation of attention and clock speed. *Neuropsychologia*, 51, 284–292.
- Lake, J. I., LaBar, K. S., & Meck, W. H. (2014). Hear it playing low and slow: How pitch level differentially influences time perception. *Acta Psychologica*, 149, 169–177.
- Lake, J. I., LaBar, K. S., & Meck, W. H. (in press). Emotional modulation of interval timing and time perception. *Neurosci. Biobehav. Rev.*
- Lake, J. I., Meck, W. H., & LaBar, K. S. (2016). Discriminative fear learners are resilient to temporal distortions during threat anticipation. *Timing Time Percept*, 4, 63–78.
- Land, B. B., Narayanan, N. S., Liu, R. J., Gianessi, C. A., Brayton, C. E., Grimaldi, D. M., Sarhan, M., Guarnieri, D. J., Deisseroth, K., Aghajanian, G. K., & DiLeone, R. J. (2014). Medial prefrontal D1 dopamine neurons control food intake. *Nat. Neurosci.* 17, 248–253.
- Langer, J., Wapner, S., & Werner, H. (1961). The effect of danger upon the experience of time. *Am. J. Psychol.*, 74, 94–97.
- Laubach, M., Caetano, M. S., & Narayanan, N. S. (2015). Mistakes were made: Neural mechanisms for the adaptive control of action initiation by the medial prefrontal cortex. *J. Physiol. Paris*, 109, 104–117.
- Levin, E. D., Conners, C. K., Sparrow, E., Hinton, S. C., Erhardt, D., Meck, W. H., Rose, J. E., & March, J. (1996). Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychopharmacology*, 123, 55–63.
- Levin, E. D., Conners, C. K., Silva, D., Hinton, S. C., Meck, W. H., March, J., & Rose, J. E. (1998). Transdermal nicotine effects on attention. *Psychopharmacology*, 140, 135–141.
- Linazasoro, G., & van Blercom, N. (2007). Severe stuttering and motor tics responsive to cocaine. *Parkinsonism Relat. Disord.*, 13, 57–58.

- Lui, M. A., Penney, T. B., Schirmer, A. (2011). Emotion effects on timing: Attention versus pacemaker accounts. *PLoS One*, 6, e21829. doi: 10.1371/journal.pone.0021829.
- Lustig, C., & Meck, W. H. (2005). Chronic treatment with haloperidol induces deficits in working memory and feedback effects of interval timing. *Brain Cogn.*, 58, 9–16.
- Lustig, C., Matell, M. S., & Meck, W. H. (2005). Not “just” a coincidence: Frontal-striatal synchronization in working memory and interval timing. *Memory*, 13, 441–448.
- MacDonald, C. J., & Meck, W. H. (2005). Differential effects of clozapine and haloperidol on interval timing in the supraseconds range. *Psychopharmacology*, 182, 232–244.
- MacDonald, C. J., Cheng, R. K., Williams, C. L., & Meck, W. H. (2007). Combined organizational and activational effects of short and long photoperiods on spatial and temporal memory in rats. *Behav. Process.*, 74, 226–233.
- MacDonald, C. J., Cheng, R. K., & Meck, W. H. (2012). Acquisition of “Start” and “Stop” response thresholds in peak-interval timing is differentially sensitive to protein synthesis inhibition in the dorsal and ventral striatum. *Front. Integr. Neurosci.*, 6, 10. doi: 10.3389/fnint.2012.00010.
- MacDonald, C. J., Fortin, N. J., Sakata, S., & Meck, W. H. (2014). Retrospective and prospective views on the role of the hippocampus in interval timing and memory for elapsed time. *Timing & Time Percept.*, 2, 51–61.
- Malapani, C., Rakitin, B., Levy, R., Meck, W. H., Deweer, B., Dubois, B., & Gibbon, J. (1998). Coupled temporal memories in Parkinson’s disease: A dopamine-related dysfunction. *J. Cogn. Neurosci.*, 10, 316–331.
- Maricq, A. V., & Church, R. M. (1983). The differential effects of haloperidol and methamphetamine on time estimation in the rat. *Psychopharmacology*, 79, 10–15.
- Maricq, A. V., Roberts, S., & Church, R. M. (1981). Methamphetamine and time estimation. *J. Exp. Psychol. Anim. Behav. Process.*, 7, 18–30.
- Matell, M. S., & Meck, W. H. (2000). Neuropsychological mechanisms of interval timing behaviour. *BioEssays*, 22, 94–103.
- Matell, M. S., & Meck, W. H. (2004). Cortico-striatal circuits and interval timing: Coincidence detection of oscillatory processes. *Cogn. Brain Res.*, 21, 139–170.
- Matell, M. S., King, G. R., & Meck, W. H. (2004). Differential modulation of clock speed by the chronic administration of intermittent versus continuous cocaine. *Behav. Neurosci.*, 118, 150–156.
- Matell, M. S., Bateson, M., & Meck, W. H. (2006). Single-trials analyses demonstrate that increases in clock speed contribute to the methamphetamine-induced horizontal shifts in peak-interval timing functions. *Psychopharmacology*, 188, 201–212.
- Mathalon, D. H., & Sohal, V. S. (2016). Neural oscillations and synchrony in brain dysfunction and neuropsychiatric disorders: It’s about time. *JAMA Psychiatry*, 72, 840–844.
- Matthews, W. J., & Meck, W. H. (2014). Time perception: The bad news and the good. *WIREs Cogn. Sci.*, 5, 429–446.
- Matthews, W. J., Terhune, D. B., Van Rijn, H., Eagleman, D. M., Sommer, M. A., & Meck, W. H. (2014). Subjective duration as a signature of coding efficiency: Emerging links among stimulus repetition, prediction coding, and cortical GABA levels. *Timing Time Percept. Rev.*, 1, 1–11.
- Meck, W. H. (1983). Selective adjustment of the speed of internal clock and memory processes. *J. Exp. Psychol. Anim. Behav. Process.*, 9, 171–201.
- Meck, W. H. (1986). Affinity for the dopamine D2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock. *Pharmacol. Biochem. Behav.*, 25, 1185–1189.
- Meck, W. H. (1996). Neuropharmacology of timing and time perception. *Cogn. Brain Res.*, 3, 227–242.
- Meck, W. H. (2005). Neuropsychology of timing and time perception. *Brain Cogn.*, 58, 1–8.

- Meck, W. H. (2006a). Neuroanatomical localization of an internal clock: A functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. *Brain Res.*, 1109, 93–107.
- Meck, W. H. (2006b). Frontal cortex lesions eliminate the clock speed effect of dopaminergic drugs on interval timing. *Brain Res.*, 1108, 157–167.
- Meck, W. H. (2007). Acute ethanol potentiates the clock-speed enhancing effects of nicotine on timing and temporal memory. *Alcohol Clin. Exp. Res.*, 31, 2106–2113.
- Meck, W. H., & Benson, A. M. (2002). Dissecting the brain's internal clock: How frontal-striatal circuitry keeps time and shifts attention. *Brain Cogn.*, 48, 195–211.
- Meck, W. H., & MacDonald, C. J. (2007). Amygdala inactivation reverses fear's ability to impair divided attention and make time stand still. *Behav. Neurosci.*, 121, 707–720.
- Meck, W. H., Church, R. M., & Gibbon, J. (1985). Temporal integration in duration and number discrimination. *J. Exp. Psychol. Anim. Behav. Process.*, 11, 591–597.
- Meck, W. H., Cheng, R. K., MacDonald, C. J., Gainetdinov, R. R., Caron, M. G., & Çevik, M. Ö. (2012). Gene-dose dependent effects of methamphetamine on interval timing in dopamine-transporter knockout mice. *Neuropharmacology*, 62, 1221–1229.
- Merchant, H., Harrington, D. L., & Meck, W. H. (2013a). Neural basis of the perception and estimation of time. *Ann. Rev. Neurosci.*, 36, 313–336.
- Merchant, H., Pérez, O., Zarco, W., & Gámez, J. (2013b). Interval tuning in the primate medial premotor cortex as a general timing mechanism. *J. Neurosci.*, 33, 9082–9096.
- Meyer-Lindenberg, A., Miletich, R. S., Kohn, P. D., Esposito, G., Carson, R. E., Quarantelli, M., Weinberger, D. R., & Berman, K. F. (2002). Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat. Neurosci.*, 5, 267–271.
- Muller, T., & Nobre, A. C. (2014). Perceiving the passage of time: Neural possibilities. *Ann. NY Acad. Sci.*, 1326, 60–71.
- Murai, Y., Whitaker, D., & Yotsumoto, Y. (2016). The centralized and distributed nature of adaptation-induced misjudgments of time. *Curr. Opin. Behav. Sci.*, 8, 117–123.
- Narayanan, N. S. (2016). Ramping activity is a cortical mechanism of temporal control of behavior. *Curr. Opin. Behav. Sci.*, 8, 226–230.
- Narayanan, N. S., & Laubach, M. (2006). Top-down control of motor cortex ensembles by dorsomedial prefrontal cortex. *Neuron*, 52, 921–931.
- Narayanan, N. S., & Laubach, M. (2009). Delay activity in rodent frontal cortex during a simple reaction time task. *J. Neurophysiol.*, 101, 2859–2871.
- Narayanan, N. S., Land, B. B., Solder, J. E., Deisseroth, K., & DiLeone, R. J. (2012). Prefrontal D1 dopamine signaling is required for temporal control. *Proc. Natl Acad. Sci. USA*, 109, 20726–20731.
- Narayanan, N. S., Cavanagh, J. F., Frank, M. J., & Laubach, M. (2013). Common medial frontal mechanisms of adaptive control in humans and rodents. *Nat. Neurosci.*, 16, 1888–1895.
- Nesse, R. M. (2005). Natural selection and the regulation of defenses. *Evol. Hum. Behav.*, 26, 88–105.
- Niki, H., & Watanabe, M. (1979). Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Res.*, 171, 213–224.
- Noreika, V., Falter, C. M., & Rubia, K. (2013). Timing deficits in attention-deficit/hyperactivity disorder (ADHD): Evidence from neurocognitive and neuroimaging studies. *Neuropsychologia*, 51, 235–266.
- Noulhiane, M., Mella, N., Samson, S., Ragot, R., & Pouthas, V. (2007). How emotional auditory stimuli modulate time perception. *Emotion*, 7, 697–704.
- Ogden, R. S., Moore, D., Redfern, L., & McGlone, F. (2014). The effect of pain and the anticipation of pain on temporal perception: A role for attention and arousal. *Cogn. Emot.*, 29(5), 910–922.

- Ohman, A., & Mineka, S. (2001). Fears, phobias, and preparedness: Toward an evolved module of fear and fear learning. *Psychol. Rev.*, *108*, 483–522.
- Oprisan, S. A., & Buhusi, C. V. (2011). Modeling pharmacological clock and memory patterns of interval timing in a striatal beat- frequency model with realistic, noisy neurons. *Front. Integr. Neurosci.* *5*, 52. doi: 10.3389/fnint.2011.00052.
- Oprisan, S. A., & Buhusi, C. V. (2013). How noise contributes to time-scale invariance of interval timing. *Phys. Rev. E Stat. Nonlin. Soft Matter. Phys.*, *87*, 052717. doi: 10.1103/PhysRevE.87.052717.
- Oprisan, S. A., & Buhusi, C. V. (2014). What is all the noise about in interval timing? *Phil. Trans. R. Soc. B*, *369*, 20120459. doi: 10.1098/rstb.2012.0459.
- Oprisan, S. A., Dix, S., & Buhusi, C. V. (2014). Phase resetting and its implications for interval timing with intruders. *Behav. Process.*, *101*, 146–153.
- Parker, K. L., Lamichhane, D., Caetano, M. S., & Narayanan, N. S. (2013). Executive dysfunction in Parkinson's disease and timing deficits. *Front. Integr. Neurosci.*, *7*, 75. doi: 10.3389/fnint.2013.00075.
- Parker, K. L., Chen, K-H., Kingyon, J. R., Cavanagh, J. F., & Narayanan, N. S. (2014). D1-dependent 4 Hz oscillations and ramping activity in rodent medial frontal cortex during interval timing. *J. Neurosci.*, *34*, 16774–16783.
- Parker, K. L., Chen, K-H., Kingyon, J. R., Cavanagh, J. F., & Narayanan, N. S. (2015a). Medial frontal ~4-Hz activity in humans and rodents is attenuated in PD patients and in rodents with cortical dopamine depletion. *J. Neurophysiol.*, *114*, 1310–1320.
- Parker, K. L., Ruggiero, R. N., and Narayanan, N. S. (2015b). Infusion of D1 dopamine receptor agonist into medial frontal cortex disrupts neural correlates of interval timing. *Front. Behav. Neurosci.*, *9*:294. doi: 10.3389/fnbeh.2015.00294.
- Penney, T. B., Holder, M. D., & Meck, W. H. (1996). Clonidine-induced antagonism of norepinephrine modulates the attentional processes involved in peak-interval timing. *Exp. Clin. Psychopharm.*, *4*, 82–92.
- Penney, T. B., Gibbon, J., & Meck, W. H. (2000). Differential effects of auditory and visual signals on clock speed and temporal memory. *J. Exp. Psychol. Hum. Percept. Perform.*, *26*, 1770–1787.
- Penney, T. B., Gibbon, J., & Meck, W. H. (2008). Categorical scaling of duration bisection in pigeons (*Columba livia*), mice (*Mus musculus*), and humans (*Homo sapiens*). *Psychol. Sci.*, *19*, 1103–1109.
- Penney, T. B., Yim, E. N. K., & Ng, K. K. (2014). Distractor expectancy effects on interval timing. *Timing Time Percept.*, *2*, 1–19.
- Péron, J., Frühholz, S., Vérin, M., & Grandjean, D. (2013). Subthalamic nucleus: A key structure for emotional component synchronization in humans. *Neurosci. Biobehav. Rev.*, *37*, 358–373.
- Péron, J., Grandjean, D., Drapier, S., & Vérin, M. (2014). Effect of dopamine therapy on nonverbal affect burst recognition in Parkinson's disease. *PLoS One*, *9*, e90092. doi: 10.1371/journal.pone.009009.
- Picton T. W., Stuss, D. T., Shallice, T., Alexander, M. P., & Gillingham, S. (2006). Keeping time: Effects of focal frontal lesions. *Neuropsychologia*, *44*, 1195–1209.
- Ptáček, R., Kuželová, H., & Stefano, G. B. (2011). Dopamine D4 receptor gene DRD4 and its association with psychiatric disorders. *Med. Sci. Monit.*, *17*: RA215–RA220.
- Rammsayer, T. H. (1999). Neuropharmacological evidence for different timing mechanisms in humans. *Q. J. Exp. Psychol. B*, *52*, 273–286.
- Rammsayer, T. H. (2006). Effects of pharmacologically induced changes in NMDA receptor activity on human timing and sensorimotor performance. *Brain Res.*, *1073–1074*, 407–416.

- Ray, R. D., & Zald, D. H. (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neurosci. Biobehav. Rev.*, *36*, 479–501.
- Reutimann, J., Yakovlev, V., Fusi, S., & Senn, W. (2004). Climbing neuronal activity as an event-based cortical representation of time. *J. Neurosci.* *24*, 3295–3303.
- Richard, J. M., & Berridge, K. C. (2011). Nucleus accumbens dopamine/glutamate interaction switches modes to generate desire versus dread: D1 alone for appetitive eating but D1 and D2 together for fear. *J. Neurosci.*, *31*, 12866–12879.
- Rommelse, N. N., Arias-Vásquez, A., Altink, M. E., Buschgens, C. J., Fliers, E., Asherson, P., Faraone, S. V., Buitelaar, J. K., Sergeant, J. A., Oosterlaan, J., & Franke, B. (2008). Neuropsychological endophenotype approach to genome-wide linkage analysis identifies susceptibility loci for ADHD on 2q21.1 and 13q12.11. *Am. J. Hum. Genet.*, *83*, 99–105.
- Samaha, J., Bauer, P., Cimaroli, S., & Postle, B. R. (2015). Top-down control of the phase of alpha-band oscillations as a mechanism for temporal prediction. *Proc. Natl Acad. Sci. USA*, *112*, 8439–8444.
- Schapira, A. H. V., Bezard, E., Brochie, J., Calon, F., Collingridge, G. L., Ferger, B., Hengerer, B., Hirsch, E., Jenner, P., Le Novère, N., Obeso, J., Schwarzschild, M. A., Spampinato, U., & Davidai, G. (2006). Novel pharmacological targets for the treatment of Parkinson's disease. *Nat. Rev. Drug Discov.*, *5*, 845–854.
- Schirmer, A. (2014). *Emotion*. Thousand Oaks, CA, USA: SAGE.
- Schirmer, A., Escoffier, N., Cheng, X., Feng, Y., & Penney, T. B. (2016). Detecting temporal change in dynamic sounds: On the role of stimulus duration, speed, and emotion. *Front. Psychol.*, *6*, 2055. doi: 10.3389/fpsyg.2015.02055.
- Shaw, P., Stringaris, A., Nigg, J., & Leibenluft, E. (2014). Emotion dysregulation in attention deficit hyperactivity disorder. *Am. J. Psychiatry*, *171*, 276–293.
- Shi, Z., Jia, L., & Müller, H. J. (2012). Modulation of tactile duration judgments by emotional pictures. *Front. Integr. Neurosci.*, *6*, 24. doi: 10.3389/fnint.2012.00024.
- Shi, Z., Church, R. M., & Meck, W. H. (2013). Bayesian optimization of time perception. *Trends Cogn. Sci.*, *17*, 556–564.
- Simen, P., Balci, F., de Souza, L., Cohen, J. D., & Holmes, P. (2011). A model of interval timing by neural integration. *J. Neurosci.*, *31*, 9238–9253.
- Singer, H. S., Szymanski, S., Giuliano, J., Yokoi, F., Dogan, A. S., Brasic, J. R., Zhou, Y., Grace, A. A., & Wong, D. F. (2002). Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. *Am. J. Psychiatry*, *159*, 1329–1336.
- Smith, S. D., McIver, T. A., Di Nella, M. S. J., & Crease, M. L. (2011). The effects of valence and arousal on the emotional modulation of time perception: Evidence for multiple stages of processing. *Emotion*, *11*, 1305–1313.
- Spencer, R. M. C. (2015). Timing in the cerebellum and cerebellar disorders. In A. Vatakis & M.J. Allman (Eds), *Time distortions in mind: Temporal processing in clinical populations* (pp. 226–249). Boston, MA, USA: Brill Academic Publishers.
- Teki, S., Grube, M., & Griffiths, T. D. (2012). A unified model of time perception accounts for duration- based and beat-based timing mechanisms. *Front. Integr. Neurosci.*, *5*, 90. doi: 10.3389/fnint.2011.00090.
- Thönes, S., & Oberfeld, D. (2015). The perception in depression: A meta-analysis. *J. Affect. Disord.*, *175*, 359–372.
- Tipples, J. (2008). Negative emotionality influences the effects of emotion on time perception. *Emotion*, *8*, 127–131.
- Tipples, J. (2010). Time flies when we read taboo words. *Psychon. Bull. Rev.*, *17*, 563–568.

- Tipples, J. (2011). When time stands still: Fear-specific modulation of temporal bias due to threat. *Emotion*, 11, 74–80.
- Tipples, J. (2015). Rapid temporal accumulation in spider fear: Evidence from hierarchical drift diffusion modelling. *Emotion*, 15, 742–751.
- Tipples, J., Brattan, V., & Johnston, P. (2013). Neural bases for individual differences in the subjective experience of short durations (less than 2 seconds). *PLoS One*, 8, e54669. doi: 10.1371/journal.pone.0054669.
- Tipples, J., Brattan, V., & Johnston, P. (2015). Facial emotion modulates the neural mechanisms responsible for short interval time perception. *Brain Topogr.*, 28, 104–112.
- Tomasi, D., Wang, G.-J., Studentsova, Y., & Volkow, N. D. (2015). Dissecting neural responses to temporal prediction, attention, and memory: Effects of reward learning and interoception on time perception. *Cereb. Cortex*, 25, 3856–3867.
- Trih, J. V., Nehrenberg, D. L., Jacobsen, J. P., Caron, M. G., & Wetsel, W. C. (2003). Differential psychostimulant-induced activation of neural circuits in dopamine transporter knockout and wild type mice. *Neuroscience*, 118, 297–310.
- Tseng, K. Y., & O'Donnell, P. (2004). Dopamine-glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signaling mechanisms. *J. Neurosci.*, 24, 5131–5139.
- Van Rijn, H., Kononowicz, T. W., Meck, W. H., Ng, K. K., & Penney, T. B. (2011). Contingent negative variation and its relation to time estimation: A theoretical evaluation. *Front. Integr. Neurosci.*, 5, 91. doi: 10.3389/fnint.2011.00091.
- Van Rijn, H., Gu, B.-M., & Meck, W. H. (2014). Dedicated clock/timing-circuit theories of time perception and timed performance. *Adv. Exp. Med. Biol.*, 829, 75–99.
- Vijayraghavan, S., Wang, M., Birnbaum, S. G., Williams, G. V., & Arnsten, A. F. T. (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat. Neurosci.*, 10, 376–384.
- Vinogradov, S., & Hermann, A. (2016). Psychiatric illnesses as oscillatory connectomopathies. *Neuropsychopharmacology*, 41, 387–388.
- Volkinburg, H. V., & Balsam, P. (2014). Effects of emotional valence and arousal on time perception. *Timing Time Percept.*, 2, 360–378.
- Ward, R. D., Kellendonk, C., Simpson, E. H., Lipatova, O., Drew, M. R., Fairhurst, S., Kandel, E. R., & Balsam, P.D. (2009). Impaired timing precision produced by striatal D2 receptor overexpression is mediated by cognitive and motivational deficits. *Behav. Neurosci.*, 123, 720–730.
- Ward, R. D., Kellendonk, C., Kandel, E. R., & Balsam, P.D. (2012). Timing as a window on cognition in schizophrenia. *Neuropharmacology*, 62, 1175–1181.
- Watts, F., & Sharrock, R. (1984). Fear and time-estimation. *Percept. Mot. Skills*, 59(2), 597–598.
- Williams, S. M., & Goldman-Rakic, P. S. (1998). Widespread origin of the primate mesofrontal dopamine system. *Cereb. Cortex*, 8, 321–345.
- Williamson, L. L., Cheng, R. K., Etchegaray, M., & Meck, W. H. (2008). “Speed” warps time: Methamphetamine’s interactive roles in drug abuse, habit formation, and the biological clocks of circadian and interval timing. *Curr. Drug Abuse Rev.*, 1, 203–212.
- Wittmann, M. (2015). Modulations of the experience of self and time. *Consc. Cogn.*, 38, 172–181.
- Wittmann, M., & Van Wassenhove, V. (2009). The experience of time: Neural mechanisms and the interplay of emotion, cognition and embodiment. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, 364(1525), 1809–1813.
- Wittmann, M., Leland, D. S., Churan, J., & Paulus, M. P. (2007). Impaired time perception and motor timing in stimulant-dependent subjects. *Drug Alcohol Depend.*, 90(2-3), 183–192.
- Xu, M., Zhang, S.-Y., Dan, Y., & Poo, M.-M. (2014). Representation of interval timing by temporally scalable firing patterns in rat prefrontal cortex. *Proc. Natl Acad. Sci. USA*, 111, 480–485.

- Yin, B., & Meck, W. H. (2014). Comparison of interval timing behaviour in mice following dorsal or ventral hippocampal lesions with mice having δ opioid receptor gene deletion. *Philos. Trans. R. Soc. B*, 369, 20120466. doi: 10.1098/rstb.2012.0466.
- Yin, B., Lusk, N. A., & Meck, W. H. (in press). Interval-timing protocols and their relevancy to the study of temporal cognition and neurobehavioral genetics. In V. Tucci (Ed.) *Neuro-phenome: Cutting-edge approaches and technologies in neurobehavioral genetics*. Hoboken, NJ, USA: Wiley-Blackwell.
- Yoshioka, M., Matsumoto, M., Togashi, H., & Saito, H. (1996). Effects of conditioned fear stress on dopamine release in the rat prefrontal cortex. *Neurosci. Lett.*, 209, 201–203.