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Neuromodulation of Pupil Diameter and Temporal Perception

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Review of Suzuki et al.

A wide range of behavior depends on the ability to perceive the passage of time and to remember and compare short durations (0.5–5 s). For example, noticing that an internet connection is slower than normal relies on observing present lag and comparing it with the normal lag stored in memory. The mechanisms by which the brain tracks and compares time from second to second is not understood; indeed, there is debate in the literature as to whether dedicated time-keeping mechanisms exist or whether timing-related behaviors emerge from the intrinsic properties of other circuits (Grondin, 2010). However, fMRI studies have implicated a few key brain areas in the perception of short durations. Subcortically, the basal ganglia are likely to be involved in the encoding of short durations (Rao et al., 2001). Cortically, the right prefrontal cortex (Lewis and Miall, 2006) as well as the area comprising supplementary motor area extending to anterior cingulate cortex (ACC) (Kudo et al., 2004) show increased blood oxygenation during a task in which subjects had to estimate an elapsed duration by pressing a button.

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Perception of elapsing time can be expanded or compressed compared with veridical time. A particularly uninteresting seminar seems to drag on, but a night out with close friends seems to be over too soon. Neuromodulators, such as norepinephrine (NE), acetylcholine (ACh), dopamine, serotonin, and others, could potentially mediate these temporal distortion effects. Neuromodulators alter the dynamics of neuronal circuits (Marder, 2012) and thus could either alter timing circuits, if they exist, or change the temporal properties of other circuits.

Suzuki et al. (2016) sought to establish a link between the NE system and perception of short durations because NE has been related to timing behaviors (Rammsayer et al., 2001), but it has not been as well characterized in its temporal distortion effects as other neuromodulators. Pupil diameter has been used as an indirect measure of activity in the locus ceruleus (LC) (Aston-Jones and Cohen, 2005; Joshi et al., 2016), the source of NE for much of the brain. Therefore, Suzuki et al. (2016) measured pupil diameter during a delayed saccade task in Japanese macaques to infer the relationship between NE and temporal perception. They trained the animals to make a saccade to a briefly flashed cue, but only after a self-paced delay of 1000–1700 ms. After filtering out impulsive saccades made immediately after cue presentation, the authors sorted saccades by latency and split them into thirds: early, middle, and late. During the saccade itself, pupil diameter was not significantly different between early and late saccades. In the time preceding and immediately following the cue presentation, however, pupil diameter was significantly larger in the early saccade group than in the late group. Furthermore, saccade latency and pupil diameter during this time were negatively correlated.

Decreased saccade latency can be explained by an expansion of internal time such that intervals are perceived as longer: the animal would overestimate the elapsed time since cue presentation and saccade earlier. Therefore, the authors conclude that increased pupil diameter is related to subjective time expansion and that NE release may therefore expand the perception of passing time (Suzuki et al., 2016). The authors rule out some other explanations of the pupil diameter-related saccade latency. For example, pupil diameter is not correlated with saccade latency on the impulsive trials, suggesting that the effect is not from pupil-linked facilitation of the occulomotor system (Suzuki et al., 2016).

Although NE levels likely correlate with the observed effect on saccadic latency, the interpreted effect on the perception of time may conflict with the adrenergic perceptual effects observed elsewhere in the literature. In a delayed reward task, rats administered clonidine, an NE agonist, had increased delay in the timing of their responses; on the other hand, rats administered idazoxan, an NE antagonist, had reduced delay (Penney

et al., 1996). These results can be interpreted to mean that an increase in NE activity contracts perceived time, whereas a decrease in NE activity expands it. This is in opposition to the hypothesis proposed by Suzuki et al. (2016).

Reboxetine, an NE reuptake blocker, increased accuracy and performance in a temporal discrimination task (Rammsayer et al., 2001). Thus, in the present study, increased NE might be expected to increase the accuracy of the comparison between the correct interval stored in memory and the time elapsed since the cue. However, the shortest latency saccades, associated with increased NE, show the worst timing performance in the task. A large fraction of the shortest latency saccades occur before the required 1000 ms had elapsed (Suzuki et al., 2016). However, the tasks used in these two studies have different cognitive requirements: comparing an elapsing interval with one stored in memory (Suzuki et al., 2016) and comparing two consecutively presented intervals (Rammsayer et al., 2001). The effects may be mediated by different mechanisms, which could explain the discrepancy.

Although it does seem likely that NE affects the perception of time, it may not fully explain the effects observed in the current study. Other neuromodulators may also be involved in pupil diameter and temporal perception. Although pupil diameter is correlated with LC activity, it is also correlated with activity in several other brain structures, including the intermediate layer of the superior colliculus, inferior colliculus, and ACC (Joshi et al., 2016). Indeed, Joshi et al. (2016) suggest that NE's influence on pupil diameter is indirect because the latency to pupil diameter change is greater after LC stimulation than these other brain areas. Thus, it is possible that some other structure or circuit in the brain may more directly relate to both pupil diameter and time perception.

Although pupil diameter is most often linked to NE levels, levels of other neuromodulators may also correlate with pupil diameter. For example, serotonergic agonists can increase pupil diameter (Schmid et al., 2015), whereas metergoline, a serotonergic antagonist, decreases pupil diameter (Vitiello et al., 1997). Moreover, pupil diameter correlates with expected risk, which is associated with cholinergic activity (Yu and Dayan, 2005; Preuschoff et al., 2011). Thus, it seems likely that the activity of neuromodulatory systems beyond NE may relate to pupil diameter. There has been a surprising lack of study on the direct relationships of neuromodulators to pupil diameter, however. These relationships could be tested by simultaneously measuring pupil diameter and neuromodulator concentrations in ACC, superior colliculus, or other brain regions using fast-scan cyclic voltammetry or microdialysis techniques.

The effects on saccadic latency and temporal distortion observed by Suzuki et al. (2016) may also be the result of other neuromodulators. For example, the cholinergic system may be affecting the storage of the behavioral delay interval in memory. Increasing ACh with physostigmine, a cholinesterase inhibitor, shifts the distribution of responses earlier on delayed response task; ACh antagonists had the opposite effect (Meck and Church, 1987). This effect was not immediate but instead gradually shifted the distribution of response timing over many trials. Because the effect was gradual, the authors speculated that cholinergic disturbances may distort the storage of correct durations in memory, altering the performance only after the accumulation of several trials (Meck and Church, 1987; Meck, 1996). If increased pupil diameter and ACh levels are correlated, this alternative hypothesis could explain the precocious saccades associated with large pupil diameter: increased ACh could shorten the task-specific saccade delay stored in memory, causing an early saccade. This alternative hypothesis could be tested with the current data. The effects of pupil diameter on saccadic latency should start small and build with successive trials of either large or small pupil diameter.

Neuromodulators in addition to NE and ACh also affect temporal perception and pupil diameter. Antipsychotics that target D2 dopamine receptors increase perceived duration (Meck, 1986), and dopamine antagonists impair processing of intervals in the same range used by Suzuki et al. (2016) (Rammsayer et al., 2001). Serotonin receptor agonism has been shown to interfere with perception of time intervals >2 s (Wittmann et al., 2007), and serotonergic manipulations can influence interval detection and the stored memory of duration (Ho et al., 2002). To add even more complexity, the circuit-level effects induced by neuromodulators depend on the preexisting state of the network and may also be influenced by neuromodulator–neuromodulator interactions (Marder et al., 2014). Additionally, temporal perception across magnitudes of time duration is implemented by different mechanisms; each time scale responds differently to each of the neuromodulators (Rammsayer et al., 2001; Grondin, 2010).

In conclusion, time perception is altered by many different neuromodulators, including norepinephrine, acetylcholine, dopamine, and serotonin. These neuromodulators act together to alter the circuit dynamics of timing related circuits, and they can all change the internal sense of time. Suzuki et al. (2016) provide an important contribution to understanding how pupil diameter, dynamic modulatory systems, and perception of time interrelate, but more work needs to be done to understand this complex neurobiological process. The effects of neuromodulators on pupil diameter need to be more directly assessed. To determine whether time perception can be altered directly by neuromodulator release, optogenetics and electrical stimulation could be used in the neuromodulatory nuclei: the LC, basal forebrain, dorsal raphe nucleus, and ventral tegmental area. Understanding how the different neuromodulators affect time perception will give a better understanding of both how time is modeled in the brain and how the temporal perception system can be altered.

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