Ready to time: response to Fifel

Eric B. Emmons[1], Benjamin J. De Corte[1], Youngcho Kim[1], Krystal L. Parker[2], Matthew S. Matell[3], Nandakumar S. Narayanan[1]

1—Department of Neurology, and 2—Department of Psychiatry University of Iowa; 3—Department of Psychology, Villanova University

CONTACT
Nandakumar Narayanan
319-353-5698
Nandakumar-narayanan@uiowa.edu
169 Newton Road
Pappajohn Biomedical Discovery Building--1336
University of Iowa, Iowa City, 52242

Text:

We greatly appreciate Fifel's thoughtful review of our work. The link to Libet's 'readiness potential' is a fascinating connection that we had not fully appreciated. The readiness potential could represent temporal processing and self-monitoring. However, correlates of temporal control are seen in many brain regions (Coull et al., 2011; Merchant and de Lafuente, 2014), and there may be higher-fidelity correlates of timing than ramping activity (Van Rijn et al., 2011; Kononowicz and van Rijn, 2014; Narayanan, 2016). Although dopamine is necessary for the temporal control of action, its precise role remains of great interest (Meck, 2006; Soares et al., 2016). Our own work suggests that dopamine via frontal D1-type receptors is critical for ~4-Hz oscillations that are both related to cognitive control and engage ramping neurons in the medial frontal cortex (Cavanagh and Frank, 2014; Parker et al., 2014a, 2015; Kim et al., 2017). Whether these dopamine-dependent 4-Hz signals or 'ramping' patterns of nigrostriatal dopamine critically facilitate temporal processing are not purely theoretical questions (Howe et al., 2013; Howard et al., 2017). Indeed, this information may have great significance for patients with disrupted decision-making processes in dopamine-dependent disorders such as Parkinson's disease and schizophrenia (Ward et al., 2011; Parker et al., 2013). Furthermore, these dynamics may also have significance in designing targeted therapies (Parker et al., 2014b, 2017; Kelley et al., 2017; Kim et al., 2017). However, as Fifel observes, these findings may have a much larger significance for elucidating the ontogeny of the volitional control of movement. The exact role of neuronal determinism and free will are, as Fifel rightly suggests, 'underdetermined.' Identifying these neuronal correlates may help better understand how to promote human agentic skills (Meyers, 1989).

Cavanagh, J.F., and Frank, M.J. (2014). Frontal theta as a mechanism for cognitive control. Trends Cogn. Sci. *18*, 414–421.

Coull, J.T., Cheng, R.-K., and Meck, W.H. (2011). Neuroanatomical and neurochemical substrates of timing. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. *36*, 3–25.

Howard, C.D., Li, H., Geddes, C.E., and Jin, X. (2017). Dynamic Nigrostriatal Dopamine Biases Action Selection. Neuron *93*, 1436–1450.e8.

Howe, M.W., Tierney, P.L., Sandberg, S.G., Phillips, P.E.M., and Graybiel, A.M. (2013). Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. Nature *500*, 575–579.

Kelley, R., Flouty, O., Emmons, E.B., Kim, Y., Kingyon, J., Wessel, J.R., Oya, H., Greenlee, J.D., and Narayanan, N.S. (2017). A human prefrontal-subthalamic circuit for cognitive control. Brain J. Neurol.

Kim, Y.-C., Han, S.-W., Alberico, S.L., Ruggiero, R.N., De Corte, B., Chen, K.-H., and Narayanan, N.S. (2017). Optogenetic Stimulation of Frontal D1 Neurons Compensates for Impaired Temporal Control of Action in Dopamine-Depleted Mice. Curr. Biol. CB *27*, 39–47.

Kononowicz, T.W., and van Rijn, H. (2014). Decoupling interval timing and climbing neural activity: a dissociation between CNV and N1P2 amplitudes. J. Neurosci. Off. J. Soc. Neurosci. *34*, 2931–2939.

Meck, W.H. (2006). Neuroanatomical localization of an internal clock: A functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. Brain Res. *1109*, 93–107.

Merchant, H., and de Lafuente, V. (2014). Introduction to the neurobiology of interval timing. Adv. Exp. Med. Biol. *829*, 1–13.

Meyers, D.T. (1989). Self, Society, and Personal Choice (New York, NY: Columbia Press).

Narayanan, N.S. (2016). Ramping activity is a cortical mechanism of temporal control of action. Curr. Opin. Behav. Sci. *8*, 226–230.

Parker, K.L., Lamichhane, D., Caetano, M.S., and Narayanan, N.S. (2013). Executive dysfunction in Parkinson's disease and timing deficits. Front. Integr. Neurosci. *7*, 75.

Parker, K.L., Chen, K.-H., Kingyon, J.R., Cavanagh, J.F., and Narayanan, N.S. (2014a). D1-Dependent 4 Hz Oscillations and Ramping Activity in Rodent Medial Frontal Cortex during Interval Timing. J. Neurosci. *34*, 16774–16783.

Parker, K.L., Narayanan, N.S., and Andreasen, N.C. (2014b). The therapeutic potential of the cerebellum in schizophrenia. Front. Syst. Neurosci. *8*, 163.

Parker, K.L., Ruggiero, R.N., and Narayanan, N.S. (2015). Infusion of D1 Dopamine Receptor Agonist into Medial Frontal Cortex Disrupts Neural Correlates of Interval Timing. Front. Behav. Neurosci. *9*, 294.

Parker, K.L., Kim, Y.C., Kelley, R.M., Nessler, A.J., Chen, K.-H., Muller-Ewald, V.A., Andreasen, N.C., and Narayanan, N.S. (2017). Delta-frequency stimulation of cerebellar projections can compensate for schizophrenia-related medial frontal dysfunction. Mol. Psychiatry.

Soares, S., Atallah, B.V., and Paton, J.J. (2016). Midbrain dopamine neurons control judgment of time. Science *354*, 1273–1277.

Van Rijn, H., Kononowicz, T.W., Meck, W.H., Ng, K.K., and Penney, T.B. (2011). Contingent negative variation and its relation to time estimation: a theoretical evaluation. Front. Integr. Neurosci. *5*, 91.

Ward, R.D., Kellendonk, C., Kandel, E.R., and Balsam, P.D. (2011). Timing as a window on cognition in schizophrenia. Neuropharmacology.