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# Exploring Executive Functions Using a Distributed Circuit Model

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Review of Murray et al.

A person's ability to plan, adapt, and regulate their behavior is integral for immediate as well as long-term goals. These behaviors are collectively defined as "executive functions" and are critical components of human cognition (Kimberg et al., 1997). Because damage to the prefrontal cortex (PFC) leads to multiple symptoms of executive dysfunction, these behaviors have been classically defined as PFC-dependent (Robbins, 1996; Fellows and Farah, 2005). As experimentalists have ventured beyond the PFC, however, we have learned that connected regions such as the nucleus accumbens, ventral hippocampus, and posterior parietal cortex (PPC) also contribute to executive function (Abela and Chudasama, 2013; Donnelly et al., 2014; Buss and Spencer, 2017). These findings, coupled with the advent of technological advances such as optogenetics and functional connectivity, have led researchers to investigate the interaction of the PFC with other regions (Schmitt et al., 2017).

Building upon this premise, a recent study by Murray et al. (2017) proposed that rather than being contained within a single region, the executive functions working memory and decision making rely on *interactions* between the PPC and PFC. To demonstrate this, the authors created a distributed circuit model in which sensory information flows from the PPC into the PFC. Each region is designated a "module" and is comprised of two pools of excitatory neurons. Each pool is selective to one of two spatial, directional or object stimuli ("A" or "B") and is recurrently connected, exhibiting self-excitation. Tracing the input from stimulus A into the PPC as an example (Murray et al., 2017, their Fig. 3*A*), a long-range excitatory projection (dark blue synapse) connects "A" PPC neurons with the "A" PFC pool. These PFC neurons send reciprocal excitatory feedback (light blue synapse) to the "A" PPC pool of neurons. Within each module, both pools of neurons receive input from a common source of inhibitory neurons linearized for model simplicity (Murray et al., 2017, their Fig. 1). This results in cross-inhibition both within and between modules, with "A" input to the PPC inhibiting the "B" PPC neurons (Murray et al., 2017, their Fig. 3*A*, red) as well as "B" PFC neurons (in purple). The net effect of the model's excitation and inhibition is the *bistability* of all neurons, meaning they function within either a low (baseline) or high (persistent) state. This combination of strong synaptic excitation and lateral inhibition is the hallmark of an attractor network, which generates reverberating recurrent neural activity within a local circuit (Brunel and Wang, 2001). PFC and PPC firing rates were further modulated by the presence of NMDA receptors, which the authors include in their model in the form of a slow synaptic gating variable.

Using this computational model, Murray et al. (2017) first describe a theoretical mechanism by which neurons encode and maintain sensory input during working memory, an executive function involving the transient storage and manipulation of information within a short timeframe (Baddeley, 1992). A critical component of this definition is that during the delay between encoding and retrieval of information, a competing stimulus is introduced to disrupt the maintenance of sensory input. In the authors' model, a target stimulus representing the information to be held in working memory (i.e., "stimulus A") first engages PPC target neurons, which excite PFC target neurons through long range projections. Following the offset of the target stimulus and during the working memory delay, PPC and PFC target neurons continue to encode information due to their highly persistent recurrent activity (Murray et al., 2017, their Fig. 3*B*). One integral aspect of the model is that during the working memory delay, the introduction of a distractor stimulus (i.e., "stimulus B") may disrupt recurrent activity within the pools of PPC and PFC target neurons, preventing the encoding

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of target information. Specifically, the distractor engages the "stimulus B" pool of PPC neurons, which directly inhibits PPC target neurons and indirectly suppresses PFC target neurons (Murray et al., 2017, their Fig. 3*A*). The authors suggest that if recurrent structure of PPC and PFC target neurons is sufficiently high, working memory will be robust and the net effect of the distractor's input on target neurons will be transient (Murray et al., 2017, their Fig. 5*A*). Should recurrent structure of PPC and PFC target neurons be low, distractor PPC neurons will be highly active and disrupt working memory via inhibition of both PPC and PFC target neuron populations (Murray et al., 2017, their Fig. 5*B*).

Murray et al. (2017) also describe how their distributed circuit model functions during perceptual decision making, an executive function requiring the accumulation and integration of sensory information before executing an action (Shadlen and Newsome, 2001). The saccadic target selection task (Schall and Thompson, 1999) is used as an example in which competing visual information from a target and distractor is presented before selecting the target as a correct outcome. Visual input is fed directly to the PPC ("selection") module, where there is competition between target and distractor selective neurons. During a successful discrimination trial the PPC target population receives greater input than the distractor population, sending feedforward excitatory input to a cluster of target neurons within the PFC or "action" module (Murray et al., 2017, their Fig. 7*C*, top). The high recurrent structure within the PFC module facilitates the steep firing rate ramping observed during the action, contrasted with the weaker recurrent structure of the PPC module, which enables the integration of perceptual information over a longer timeframe (Murray et al., 2017, their Fig. 7*A*). The authors also found that reaction time correlated with the complexity of discriminating stimuli (Murray et al., 2017, their Fig. 7*B*, top). Discrimination trials in which the contrast between target and distractor was high (i.e., 51.2%) resulted in reaction times twice as fast relative to trials in which contrast was low (0–12.8%). Interestingly, modeling the removal of PFC feedback to the PPC resulted in slower but more accurate responses during low-contrast trials (Murray et al., 2017, their Fig. 7*C*), which is consistent with the phenomenon of speed–accuracy tradeoff.

One critical component of the authors' model is that persistent cortical activity is required for maintenance of working memory and correct choices during decision making. This assumption has been supported within the literature for over 45 years, with Fuster and Alexander (1971) among the first to identify continuously firing PFC neurons during a delayed response task. More recent evidence reveals persistent activity is also observed throughout a range of cortical regions, including auditory, somatosensory, and the parietal cortices (Zylberberg and Strowbridge, 2017). However, one consideration that remains unaddressed by the author's distributed circuit model is that of sequential neuronal activity. Originally observed in the rhesus monkey frontal cortex by Batuev et al. (1980), this "relay race" of activity refers to neurons firing in a specific pattern during a *fraction* of the task (delay/choice) rather than throughout. These data have been corroborated in modern electrophysiological experiments and across species, with choice-specific sequences of neurons observed in the mouse PPC and PFC during decision making tasks (Harvey et al., 2012; Schmitt et al., 2017). One possibility is that instead of being mutually exclusive, *both* persistent and sequential cortical activity mediates executive functions. This hypothesis is supported by Baeg et al. (2003), who observed both continuously active and sequence-specific PFC neurons during a working memory task. Diversifying Murray et al.'s (2017) circuitry to create a mixed selectivity model (which includes populations of sequence-specific neurons in addition to those that persistently fire) may provide a more biologically relevant simulation of cortical activity during tests of executive function.

The authors of this study provide an integrated computational approach for studying executive function, where the strength of PPC and PFC circuits are regulated through both local and long-range inputs. Through these connections, the PPC and PFC function as a coordinated network in which recurrent activity facilitates filtering distractions and choosing outcomes. Visualization and experimental manipulation of these circuits is the logical next step in assessing the model's biological validity. This frontoparietal distributed circuit model was primarily built using nonhuman primate physiological and behavioral data, and is additionally supported by anatomical literature (reciprocal projections have been traced between dorsal PFC and PPC/area 7, see Cavada and Goldman-Rakic, 1989; Leichnetz, 2001). As experimentalists are now turning to transgenic mice to dissect and investigate entire neuronal populations using functional imaging (Carrillo-Reid et al., 2017), this leaves the question as to whether the frontoparietal circuit described by Murray et al. (2017) exists within the rodent brain. Neuroanatomists have confirmed the rodent PPC (comprised of the rostrolateral, anterior and anteromedial visual cortices) is homologous to extrastriate regions within the primate visual "dorsal stream", and it has further been implicated in visual decision making processes (Wang and Burkhalter, 2007; Wang et al., 2012; Licata et al., 2017). Screening of the current Allen Mouse Brain Connectivity Atlas (http://connectivity.brain-map.org/, accessed March, 2018) reveals reciprocal connections between rodent PPC and the ventrolateral orbitofrontal cortex, a recognized homolog of primate dorsolateral PFC (Uylings et al., 2003). These data suggest the frontoparietal circuit is maintained in the rodent model, which can therefore be visualized and monitored for the authors' proposed ramping and recurrent network activity *in vivo*.

The distributed circuit model developed by Murray et al. (2017) bridges the PFC and PPC neural substrates using computational principles and experimental data. The authors provide a framework to guide investigators in their examination of nonhuman primate as well as rodent frontoparietal circuitry, highlighting the continued need for experimental and computational collaboration. It is through these partnerships that neuroscientists can continue making significant progress in the investigation and modeling of interacting neural networks throughout the brain.

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