many of us to discover that neurexins act through multiple postsynaptic partners; now it seems wise to be on the lookout for new presynaptic effectors for neuroligins. Given the overwhelming evidence linking the neurexin-neuroligin pathway to autism and schizophrenia (Südhof, 2008), these are key issues not only for fundamental neuroscience, but also for understanding and eventually developing treatments for neuropsychiatric disorders.

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Rats Exert Executive Control

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In this issue of *Neuron*, Duan et al. (2015) introduce a novel rodent model of executive control. Their neural recordings provide direct evidence for the task-set inertia theory and suggest a crucial role for the superior colliculus in executive control.

After hearing a radio report of a traffic jam as you approach a familiar intersection on the drive to work, you might opt to turn right rather than make your usual left turn to take an alternate route to your destination. We depend on our ability to alter our response to the same sensory input, such as the view of that familiar intersection, as we receive new information or as context changes on a moment-to-moment basis. Humans are not the only animals to exhibit this sort of behavioral flexibility. In fact, non-human primates have traditionally provided a powerful model system for studying cortical activity at the level of individual neurons during controlled behavior requiring this type of executive control (Miller, 2000). Now in *Neuron*, Duan et al. (2015) devise a rodent model in which animals can be trained to display such behavior, opening the door to new types of experiments, at a scale not previously possible.

One well-established behavioral paradigm for the study of executive control is the so-called Pro-/Anti-saccade task (Munoz and Everling, 2004), in which a monkey is instructed at the start of each behavioral trial to respond by directing its gaze either toward ("Pro") or away from ("Anti") a peripheral visual stimulus that appears later in the trial (Figure 1A). Rodents are both practically and scientifically appealing, due to their low cost and the ease of working with them compared with primates, coupled with recent technological breakthroughs in monitoring and manipulating individual neurons in intact rodents. There has been a push to develop more sophisticated behavioral paradigms for rodents in order to take advantage of these benefits, but it has not been clear to what extent they can be trained to perform tasks that can probe complex cognitive behaviors such as this type of executive control.

However, in this issue of *Neuron*, Duan et al. (2015) introduce a novel rodent model of executive control analogous to the Pro-/Anti-saccade primate paradigm. In this new paradigm, rats learn two sets of sensorimotor associations — they respond to a visual stimulus that may

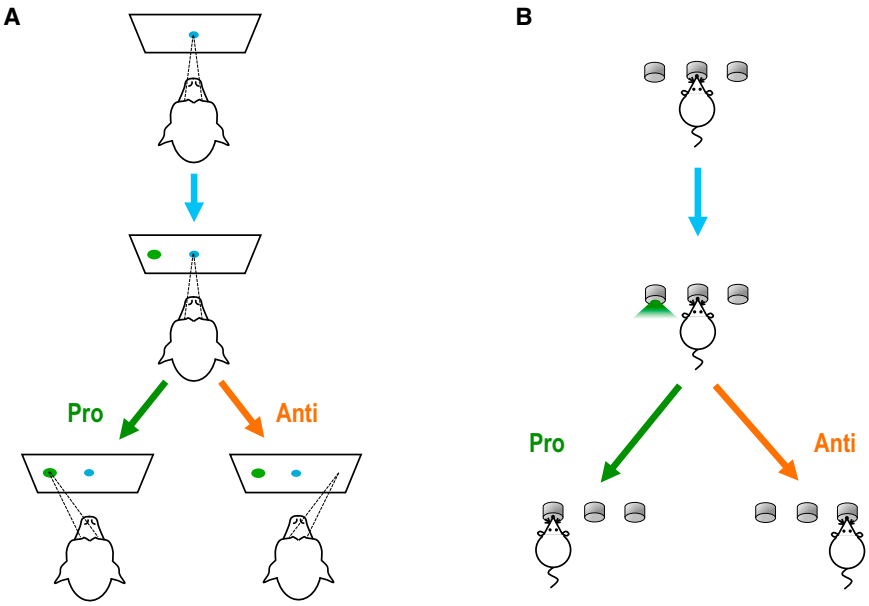

Figure 1. A Rodent Model of Rapid Sensorimotor Remapping
Inspired by the well-established pro-/anti-saccade task used to study the roles of various brain regions such as the prefrontal cortex in executive control in non-human primates (A), Duan et al. (2015) have developed a novel rodent paradigm (B) analogous to this task.

appear on the left or right either by orienting toward it ("Pro") or away from it ("Anti") (Figure 1B). This paradigm is particularly well suited for the study of rapid sensorimotor remapping, as a single-trial switch from Pro- to Anti-oriented responses requires the same stimulus to drive opposing behavioral responses on subsequent trials. Using an automated procedure, Duan et al. (2015) are able to train ~80% of their subjects to switch rapidly between Pro and Anti responses, in both a block configuration and on a trial-by-trial basis.

One feature of this sort of rapid sensorimotor remapping is an impairment in performance, quantified by an increase in errors and/or reaction time, immediately following a sensorimotor association change. Interestingly, performance is impacted by an association change regardless of how well-cued the subject is to the correct association at the onset of the trial (Monsell 2003). This performance deficit, known as "switch cost," is the focus of a large body of research on task switching in both human and non-human primates and has led to two major hypotheses as to its origin. The first, "task set reconfiguration," asserts that the assembly of a new task set is the cognitively demanding aspect of task switching and cannot be completed until the arrival of the sensory stimulus from the new task. In contrast, the second hypothesis, "task set inertia," assumes that the cognitive demand is greatest when dismantling the old task set (Allport et al., 1994; Monsell et al., 2000).

Notably, Duan et al. (2015) observe behavioral asymmetries that are both indicative of the higher cognitive demand thought to be associated with Anti responses and consistent with switch cost asymmetries observed in human and non-human primates engaged in similar tasks (Weiler and Heath, 2012). In addition to being learned more rapidly in isolation, Pro responses tend to be faster and more accurate than Anti responses (Figures 2A and 3A in Duan et al., 2015). Additionally, the reduction in performance accuracy on the first trial of a new block was significantly larger when switching from Anti to Pro relative to the switch from Pro to Anti, and animals were significantly slower to respond on the first trial of a new Pro block (Figures 3D and 3E in Duan et al., 2015). These results indicate that the Anti task is more difficult than Pro, and they show that switching from the more difficult to the easier task does indeed result in a larger switch cost.

One benefit of a rodent model for a complex cognitive ability such as executive control is that it allows for direct manipulations of neural activity at the circuit level across many subjects. To investigate neural mechanisms relevant to the observed behaviors, Duan et al. (2015) conducted reversible inactivations of two brain areas likely to be involved in Pro-/Anti-saccade responses by delivering the GABA-A agonist muscimol via bilaterally implanted cannulae in the superior colliculus (SC) and prelimbic cortex (PL), a part of the medial prefrontal cortex (mPFC). The superior colliculus is a midbrain structure with input layers that receive connections from a majority of retinal ganglion cells and project to motor output layers and is known to be involved in the generation of saccades and in visual orienting behavior in general (Felsen and Mainen, 2008). As such, it is well positioned to drive rapid responses toward a visual target, as in the Pro task. The mPFC has been shown to be involved in Anti responding in both humans and non-human primates engaged in the Pro-/Anti-saccade task (Munoz and Everling, 2004). In the rat, the PL region of the mPFC appears to play a role in the inhibition of incorrect responses and top-down control of behavior in general (Narayanan et al., 2006; Rich and Shapiro 2009) and is therefore a good candidate structure to drive performance on the presumably more cognitively demanding Anti task. Based on these observations, Duan et al. (2015) hypothesized that SC inactivation would selectively impair performance on the Pro task, while PL inactivation would impair Anti performance and leave Pro performance intact.

As predicted, PL inactivation did preferentially impact performance on the Anti task. Although both Pro and Anti performance were negatively affected by either unilateral or bilateral muscimol infusion to the PL, Anti performance was substantially more impaired (Figures 6C, 7Aii, and 7Cii in Duan et al., 2015). The results from SC inactivation were much more surprising. Unilateral SC inactivation impaired orientation contralateral to the inactivated side and improved orientation responses ipsilateral to the inactivated side, regardless of the task being

performed (Figures 6A and 6B in Duan et al., 2015). This is consistent with the expected role of the SC in generating orienting movements, but it does not distinguish between the possibility that it is crucial for Pro responses in particular from an overall orienting deficit. Bilateral SC inactivation revealed the surprising result—in a direct contradiction of the predicted effect, performance on Pro trials recovered during bilateral SC inactivation and was not significantly different from saline-infused controls (Figures 7Ai and 7Bi in Duan et al., 2015). This observation is in opposition to the hypothesis that the SC is necessary for driving Pro responses. Even more surprising, bilateral SC inactivation robustly impaired performance on the Anti trials in all animals, regardless of their baseline performance on the Anti task (Figure 7Ci in Duan et al., 2015). This result suggests an unexpected role for the SC in addition to the PFC in generating cognitively demanding Anti responses.

The preferential impairment of Anti performance during SC and PL inactivations presented a unique opportunity to directly test the contrasting hypotheses over the origin of the switch cost. Anti performance is preferentially impaired by either SC or PL inactivation, suggesting that these manipulations are selectively disrupting circuits important for Anti behavior and that both of these regions are potentially representing the Anti task set. The task set inertia hypothesis predicts that strongly activated task sets are more difficult to eliminate in order to facilitate task switching, and it further assumes that more difficult tasks require more support in memory and stronger activation in general, and so should be more effected by task set inertia. Therefore, if dismantling the existing task set is the true source of the switch cost as predicted by the task set inertia hypothesis, the switch cost should be higher when switching away from the more challenging task (Allport et al., 1994). The higher switch cost observed when switching from Anti to Pro compared to switches in the other direction is consistent with this hypothesis, but it does not provide any direct causal evidence. Remarkably, inactivation of either the SC or the PL significantly reduces, and in some cases eliminates, the cost of switching from Anti to Pro trials, while leaving the cost of switching from Pro to Anti unchanged (Figure 8 in Duan et al., 2015). To our knowledge, this is the first direct evidence that switch cost is a result of task set inertia in any model system.

In addition to providing direct support for a long-standing hypothesis on the origin of switch cost, these results constitute a significant addition to the understanding of neural mechanisms for executive control. Crucially, they indicate an unexpected role for the SC in Anti performance. This observation argues strongly against a widely held view that suppression of SC responses, likely coming from the PFC, are necessary to suppress Pro responses and allow for correct Anti performance (Johnston and Everling, 2006). Instead, the findings reported by Duan et al. (2015) are consistent with other recent challenges to that inhibition model, and they indicate that SC activation is also necessary for good performance on the Anti task. The nature of the interactions between the SC and PL were not investigated directly in this study. Ultimately, circuit-level perturbations will be necessary to fully understand the neural mechanisms supporting executive control in general, and to uncover the origins of switch cost in particular. Fortunately, a rodent model for the study of executive control, as reported here, will facilitate studies of those interactions and it will allow for other direct causal manipulations of circuits necessary for complex cognitive tasks at an unprecedented level of precision and scale.

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