

Research Statement

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Much of what we do feels automatic. This is well illustrated by the experience of driving a familiar commute. When driving an unfamiliar route for the first time, we fully engage. We form clear explicit memories of the experience, and we have little attention available during active navigation for other pursuits. Driving an over-learned commute for the hundredth time is quite different; many people have had the experience of sitting down in a car and suddenly finding themselves at their destination, having formed few if any explicit memories of the intervening driving time. This automation of routine series of actions is of clear adaptive value – driving to work ‘on autopilot’ frees limited attentional resources to be devoted to other tasks. However, it comes at a cost in behavioral flexibility – once an automated routine, or habit, has been initiated, attention and effort are required to deviate. The common experience of finding oneself pursuing a familiar route when today’s goal differs from the norm illustrates this inflexibility.

These two modes of behavior – flexible and attention-intensive versus inflexible and automatic – depend on different circuits in the brain. Human neuroimaging experiments have shown that navigating a novel route (in virtual reality) activates the hippocampus, while following a familiar route activates the caudate nucleus, a subset of the striatum (the input structure of the basal ganglia; Hartley et al, 2002). The striatum is also implicated in non-navigational habit-like tasks in humans (e.g. Knowlton et al, 1996; reviewed in Packard and Knowlton, 2002). In rats, the hippocampus has been repeatedly shown to be required for spatial navigation (e.g. O’Keefe and Nadel, 1973), while the striatum has a critical role in automated navigation and in habits (reviewed in Packard and Knowlton, 2002; Yin and Knowlton, 2006). These two neural systems can – a flexible spatial system involving the hippocampus and an inflexible, automated one involving the striatum – can, under some circumstances, compete with one another (Poldrack and Packard, 2003), as when we follow an automated routine by default if we are not paying sufficient attention.

Dysregulation of the striatum-dependent automation of behavior is likely to contribute to a number of neuropsychiatric conditions. Obsessive-compulsive disorder and Tourette syndrome, for example, involve the intrusive repetition of stereotyped thoughts or actions, resembling habits that have taken on a life of their own; both involve pathology of the basal ganglia (Graybiel and Rauch, 2000; Leckman and Riddle, 2000). Dysfunction of striatum-dependent habit learning in Parkinson’s disease may contribute to the characteristic dementia that accompanies the disorder as it progresses (Knowlton et al, 1996). And the compulsive drug-seeking and stereotyped patterns of thought and behavior seen in drug addiction may derive, in part, from striatum-dependent habits gone dreadfully awry (Robbins and Everitt, 1999).

Unfortunately, little work has been done to identify the cellular and molecular substrates of striatum-dependent habit learning. This is in part due to the paucity of behavioral methods and molecular tools to ask sophisticated mechanistic questions about this form of learning (in contrast to the more advanced approaches that have been brought to bear over the last two decades on hippocampus-dependent and amygdala-dependent forms of learning). **My research aims is to bring the power of mouse genetics to bear on the dissection of the molecular and cellular mechanisms of striatum-dependent learning.** We have taken the first step in this direction with a recent study of striatum-dependent learning and corticostriatal long-term potentiation (LTP) in transgenic mice in which activity of the transcription factor CREB is impaired in the dorsal striatum (Pittenger et al, 2006a); we believe that this study represented the first time that mechanisms of habit-like learning have been examined using genetic tools.

1. Striatum-dependent learning in the mouse. The use of genetic tools in the mouse to investigate the mechanisms of striatum-dependent learning is hampered by the paucity of striatum-dependent learning tasks in mice. A number of such tasks have been developed in rats, but none have been well validated in mice. Even the tasks we used in our 2006 paper (Pittenger et al, 2006a) were developed by analogy to work previously done in rats, and were not fully optimized or well validated in mice. A primary current aim in the laboratory is the establishment of clearly striatum-dependent learning tasks that can be used to assay future manipulations of the striatum, and their validation using lesions of the dorsal striatum. We have established both a cued water-maze task and (in collaboration with the laboratory of Jane Taylor) an instrumental habit

task that have many of the characteristics of habit learning and are disrupted, in mice, by lesions of the dorsal striatum (Pittenger et al, 2006b). Further characterization of these tasks is ongoing; development of other tasks, with contrasting characteristics and experimental strengths, is planned.

2. **The interaction of striatum-dependent and hippocampus-dependent learning.** Our cued watermaze task is performed in both a spatial and cued version; the cued version depends on the dorsal striatum. Unexpectedly, we find that lesions of the dorsal striatum, which disrupt performance of the cued version of the task, enhance learning of the spatial version. We interpret this as strong evidence of competition between the two learning systems. Further characterization of this fascinating phenomenon is ongoing.
3. **CREB in striatum-dependent learning.** The transcription factor CREB is implicated in a wide range of different forms of learning and synaptic plasticity (e.g. Pittenger and Kandel, 1998; Carlezon et al, 2005). In published work we have established that disruption of CREB activity through transgenic expression of a dominant-negative CREB mutant, KCREB, impairs both synaptic plasticity and memory in both the hippocampus and the striatum (Pittenger et al, 2002, 2006). As we develop and validate new striatum-dependent learning tasks, we are testing the effect of this transgenic disruption of CREB activity in the dorsal striatum on them.
4. **Targeting subregions of the dorsal striatum.** Both arguments from connectivity and data from rats suggest that the subregions of the dorsal striatum – the dorsomedial striatum, corresponding roughly to the primate caudate, and the dorsolateral striatum, corresponding to the putamen – are functionally distinct (e.g. Yin and Knowlton, 2006). We are developing methods to target functional disruptions specifically to dorsolateral and dorsomedial striatum, in order to probe functional dissociations. Initial experiments are being performed using stereotactic excitotoxic lesions.

We are also developing adeno-associated viruses to allow the localized disruption of CREB function in striatal subregions, in collaboration with the laboratory of Ralph DiLeone. In the future, this approach will be used to target other molecular disruptions to striatal subregions, in an ongoing effort to analyze functional (and perhaps mechanistic) differences between them.

5. **The role of interneurons: new techniques to target molecular manipulations to defined neuronal populations.** The network-level function of the striatum is critically regulated by interneurons; the same is true of most, if not all, regions of the brain (e.g. Freund and Buszaki, 1996; Soltesz, 2006). It is increasingly clear that disruption of defined populations of interneurons may contribute to the pathophysiology of depression (e.g. Rajkowska et al, 2007), schizophrenia (e.g. Lewis and Moghaddam, 2006), Tourette syndrome (Kalanithi et al, 2005), and other neuropsychiatric disorders. In the striatum, several distinct populations of interneurons coordinate network-level activity; in particular, the parvalbumin-expressing fast-spiking interneurons are critically involved in coordinating network oscillations (Berke et al, 2004). (This is the same interneuron population that has been shown to be impoverished in severe cases of Tourette syndrome; Kalanithi et al, 2005). In order to dissect the mechanisms of this regulation and better understand the pathophysiology of neuropsychiatric disorders in which interneuron function is disrupted, it would therefore be of immense value to be able to target specific molecular manipulations to defined populations of interneurons.

Unfortunately, currently available techniques do not allow such targeting. Targeting a molecular manipulation to a defined neuronal subtype can sometimes be accomplished in transgenic mice (e.g. Meyer et al, 2002), but rarely can this technique be used to target only the neurons in a specific brain region. Brain region targeting can be achieved using recombinant viruses (e.g. Hommel et al, 2003); but this approach does not allow selective manipulation of a neuronal subtype of interest. In work supported by the Tourette Syndrome Association, therefore, we are developing techniques to combine the advantages of these two approaches to allow more precise targeting of defined interneuronal populations than has hitherto been possible. In a first application of our approach, we are seeking to specifically ablate the parvalbumin-expressing fast-spiking neurons of the dorsal striatum, both to better understand their function in regulating neuronal network function and behavior, and to generate a conceptually novel model of Tourette syndrome.

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