1 **RESEARCH ARTICLE**

2 # Motor Sequence Learning in the Brain: The Long and Short of It

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8 Abstract—Motor sequence learning involves predictive processing that results in the anticipation of each component of a sequence of actions. In smooth pursuit, this predictive processing is required to decrease tracking errors between the eye and the stimulus. Current models for motor sequence learning suggest parallel mechanisms in the brain for acquiring sequences of differing complexity. We examined this model by comparing shorter versus longer sequences of pursuit eye movements during fMRI. In this way we were able to identify overlapping and distinct brain areas involved in simple versus more complex oculomotor learning. Participants revealed predictive pursuit eye movements from the second presentation of the stimulus in both short and long sequences. Brain imaging results indicated activation of parallel brain areas for the different sequence lengths that consisted of the Inferior Occipital Gyrus and the Cingulate as areas in common. In addition, distinct activation was found in more working memory related brain regions for the shorter sequences (e.g. the middle frontal cortex and dorsolateral prefrontal cortex), and higher activation in the frontal eye fields, supplementary motor cortex and motor cortex for the longer sequences, independent on the number of repetitions. These findings provide new evidence that there are parallel brain areas that involve working memory circuitry for short sequences, and more motoric areas when the sequence is longer and more cognitively demanding. Additionally, our findings are the first to show that the parallel brain regions involved in sequence learning in pursuit are independent of the number of repetitions, but contingent on sequence complexity.

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INTRODUCTION

10 Many of our daily activities involve learning new sequences of movements and then executing this learned behavior (Lee and Quessy, 2003). Motor sequence learning involves the transition from reactive to predictive processing that is associated with skilled behavior, resulting in faster, more accurate movements. A good example of this transition is observed during pursuit eye movements of repeated single-velocity ramps, double-step ramps and sinusoids (Barnes and Donelan, 1999; Wells and Barnes, 1999; Barnes et al., 2000; Barnes and Schmid, 2002; Collins and Barnes, 2005; Kao and Morrow, 1994). The outcome of this learning is revealed by the early initiation (latency) of the movement, with eye velocity increasing toward a moving target prior to the brain receiving the information to drive the movement response (Kowler and McKee, 1987). Furthermore, prediction in pursuit results from the learning of not only timing, but also direction and velocity of the up-coming stimulus presentation (Barnes and Donelan, 1999; Wells and Barnes, 1999). This type of learning is often known as prediction and is inherent to all motor systems, providing compensation for the delays in internal neural processing in the brain. The pursuit system provides an excellent model for investigating early motor learning (such as those used for sequence learning) with the benefits of clear measurable behavioral markers of the acquired sequence.

A number of previous studies have shown that the learning of new motor sequences involves activation in prefrontal, premotor, anterior cingulate, and parietal brain areas (Jenkins et al., 1994; Jueptner et al., 1997). In support of these findings Toni et al. (1998) were the first to study the time-course of motor learning using fMRI and found that the dorsolateral prefrontal cortex (DLPFC), anterior cingulate and dorsal premotor cortex are involved in early learning of an eight-finger sequence. However, activity in these areas decreased as learning progressed,

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Abbreviations: ACC, anterior cingulate cortex; BG, basal ganglia; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IOG, inferior occipital gyrus; PHC, parahippocampus; PRD, predictive; RND, random; ROIs, regions of interest; SMA, supplementary motor area.

with a shift in activity to the supplementary motor area (SMA). It is logical to suggest that the differences in activation across brain region during learning are a result of increased efficiency in the brain (Schmid et al., 2001; Koch et al., 2006), facilitating the acquisition of more complex motor skills. This activation of different brain regions seems to reflect distinct learning stages (early versus late), but also, different aspects of learning such as speed or accuracy (Hikosaka et al., 1995; Rand et al., 2000).

One way in which motor learning can be classified is via a serial process when the flow of information shifts from spatial memory to the development of a motor skill via serial sensorimotor transformations. Another possibility of learning in the brain is via parallel processing, whereby spatial and motor information are acquired independently and processed in parallel (Alexander et al., 1986; Hikosaka et al., 1999). Hikosaka et al. (1999) proposed that serial processing may apply to simple movements, such as reaching, but that this serial process would be repetitive and inefficient for more complex sequences of actions. To optimize these demanding brain computations, Hikosaka et al. (1999, 2002a,b), Sakai et al. (1998) proposed a motor learning model that supports the notion that prior to learning a sequence, performance relies on the sensorimotor information flow (serial sensorimotor or visual-to-motor processing) and is predominantly a form of 'spatial' memory. However, with practice, performance becomes non-reliant on this serial sensorimotor transformation and is taken over by two parallel acquisition mechanisms: 1) an explicit short-term *spatial* coordinate system; and 2) an implicit long-term *motoric* storage system. The acquisition by the spatial sequence process occurs early (in the order of milliseconds) and is highly flexible, relying on attention and working memory mechanisms. Acquisition achieved by the motoric system occurs more slowly (i.e. minutes/hours), and in the later stages of learning (i.e. days/months) performance retains speed without awareness (Hikosaka et al., 1999, 2002a,b). There is a gradual shift between these parallel sequential processes from the initial fast acquisition (observed in anticipatory movements associated with pre-SMA and DLPFC activation in monkeys) toward motor cortices in later stages (automatic movements). Consistent with Hikosaka et al. (1999, 2002a,b) findings in humans and non-human primates, Sakai et al. (1998) fMRI study also describes a transition between an early ''declarative stage" of learning in frontal brain areas (DLPFC and pre-SMA), to a later more procedural learning stage in parietal brain regions (precuneus and intraparietal sulcus).

One important feature of the model described here, is that the learning of a sequence occurs via spatial and motor mechanisms independently and each system has its own input–output (spatial or motor coordinates). However, accurate and quick performance of a sequence means that the two parallel sequence processes must communicate (possibly in pre-SMA or PMA), ideally with the spatial sequence guiding the motor sequence (Hikosaka et al., 1999). However, Hikosaka et al. (1999) noted that the parallel arrangement means that a sequence can be acquired by either of these mechanisms (initiated by spatial or motor mechanisms), thus, a sequence might be acquired rather implicitly by the motor sequence mechanism, as with implicit SRT learning (Pascual-Leone et al., 1994). Additionally, when disrupting the motor sequence process the spatial process may continue to acquire the sequence, but with errors (e.g., SMA, Hikosaka et al., 1998). Nakahara et al. (2001) examined neural network models of sequence learning and also found that the parallel (independent) systems required communication or a 'monitor' (pre-SMA) but that subsequent manipulations of the model suggested that the model is robust even if one mechanism fails (or it is destroyed), as the other can take over and still learn the sequence although not perfectly (i.e., implicit or motor vs. explicit or spatially accurate).

In smooth pursuit tracking, the reactive to predictive transition into a steady-state occurs quickly (after a single presentation) when implementing repeated short sequences of ramps (see Collins and Barnes, 2005). This probably reflects the low attention and working memory requirement needed for such a simplistic task. However, the question still remains as to how the system copes with more complex sequences of actions that require enhanced attention and go beyond the short-term memory (prediction) buffer capacity (see Collins and Barnes, 2005). Collins and Barnes (2005) found that the predictive drive in smooth pursuit is optimal during short sequences, but is affected by increased cognitive load (added ramps to a sequence), resulting in learning at a slower rate. They suggested this slower learning may reflect the additional working memory requirements, but that learning was indeed possible in the more complex sequences. This finding provides evidence of the robustness of the sequence-learning processing. However, it is still unclear whether the learning of complex sequences results in a slower, spatial to motor serial transition, or alternatively the system immediately implements a more implicit (slower) motor mechanism to acquire the sequence. Furthermore, previous studies have shown areas involved in very short-term predictive mechanisms, including frontal eye fields (FEF), supplementary eye fields (SEF), DLPFC and anterior cingulate cortex (ACC) (Schmid et al., 2001; Lencer et al., 2004; Burke and Barnes, 2008; Ding et al., 2009); but have failed to examine longer more complex sequence lengths. Thus, knowledge of how prediction in the early stages of learning is used for more complex motor skills' acquisition is not yet understood.

The present study aimed to identify the brain areas involved in sequence learning in oculomotor tracking, by addressing a previously unexplored effect of varying sequence length on the BOLD activation in these areas of interest. Our study differs from previous studies in that we compared learning in short (4 ramp) and long (8 ramp) sequences of eye movements using directly comparable stimuli, where only the sequence length (i.e., number of ramps) varied within the fMRI scanner. Furthermore, based on previous studies (mentioned above) we predict the outcome will show distinct parallel circuitry for the activation of shorter (more spatial) versus longer (more motoric) sequence lengths.