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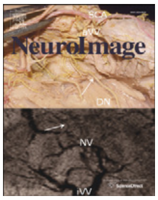

Changing the structure of complex visuo-motor sequences selectively activates the fronto-parietal network

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ABSTRACT

Previous brain imaging studies investigating motor sequence complexity have mainly examined the effect of increasing the length of pre-learned sequences. The novel contribution of this research is that we varied the structure of complex visuo-motor sequences along two different dimensions using *mxn* paradigm. The complexity of sequences is increased from 12 movements (organized as a 2×6 task) to 24 movements (organized as 4×6 and 2×12 tasks). Behavioral results indicate that although the success rate attained was similar across the two complex tasks (2×12 and 4×6), a greater decrease in response times was observed for the 2×12 compared to the 4×6 condition at an intermediate learning stage. This decrease is possibly related to successful chunking across sets in the 2×12 task. In line with this, we observed a selective activation of the fronto-parietal network. Shifts of activation were observed from the ventral to dorsal prefrontal, lateral to medial premotor and inferior to superior parietal cortex from the early to intermediate learning stage concomitant with an increase in hyperset length. We suggest that these selective activations and shifts in activity during complex sequence learning are possibly related to chunking of motor sequences.

Introduction

Most of our day to day activities involve acquiring and performing complex sequences of actions to achieve a desired goal, from lacing shoes to driving an automobile (Sun and Giles, 2001). Behavioral and neural correlates of motor sequence learning have been extensively studied using various paradigms (see Rhodes et al., 2004; Halsband and Lange, 2006 for reviews). Earlier neuroimaging studies that investigated sequence complexity have primarily manipulated the sequence length (e.g. 4, 8, 12 and 16 elements in Sadato et al., 1996; 1, 4, 12 and 16 elements in Catalan et al., 1998, 1999 and 4 to 8 elements in Boecker et al., 1998, 2002). However, these earlier studies equated sequence complexity (as defined by the sequence length) with the total number of movements to be learned. The length of the sequence forms only one possible dimension of complexity. Other manipulations of sequence complexity contrast between repeated and heterogeneous sequence of finger movements (for example, 11111 vs. 12312 Harrington et al., 2000; Haaland et al., 2004). They found that when sequence length is controlled, RT increases independently with the number of different responses or the number of transitions (e.g. 12222 vs. 12111 vs. 12122 vs. 12121; 12333 vs. 12133 vs. 12131). In the aforementioned paradigms one element is presented at a given time. These studies, however, have not addressed the complexity of motor sequences when the amount of information to be processed at a given time is systematically varied.

Miller (1956) introduced the concept of capacity limits on the amount of information that can be processed in immediate memory. By organizing information into a series of chunks, we can stretch the information bottleneck (Miller, 1956). Behavioral studies show that motor sequences are hierarchically organized with chunks of sub-sequences separated by long time gaps and increased number of errors (Rosenbaum et al., 1983). Chunking refers to the process whereby the motor sequence is recoded as an efficient representation performed with specific patterns of timing. Each chunk acts as a single memory unit and thereby overcoming the limitations of working memory, which was previously proposed to be 7 ± 2 items (Miller, 1956) and later argued to be around 4 (Cowan, 2001). In a recent

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study, Bo and Seidler (2009) observed that the visuo-spatial working memory capacity predicted the number of chunks and the rate of learning that the subjects could perform.

In previous behavioral studies, chunks were externally specified, such as change in pattern of movements (repetition, inversion and transposition, Koch and Hoffmann, 2000) or a temporal delay in response–stimulus interval (Verwey and Dronkert, 1996; Verwey et al., 2009). Spontaneous reorganization of unstructured sequences into a number of motor chunks has also been investigated (Sakai et al., 2003; Verwey and Eikelboom, 2003; Verwey et al., 2010). Particularly, according to this behavioral research, motor chunks include only 3–5 key movement elements and longer sequences are typically chunked already (Bo and Seidler, 2009; Terrace, 2001; Verwey, 2003). According to Verwey (2003; Verwey and Eikelboom, 2003) individual differences concealed shorter chunks within longer chunks consistent with a hierarchical representation of motor sequences (Bapi et al., 2005; Rosenbaum et al., 1983). However, longer chunk-size has also been reported (Kennerley et al., 2004 with chunk-size of 7 movements). Sakai et al. (2003) reported chunk-size between 1 and 5 sets of 2 elements each i.e. a maximum of 10 movements constituted a chunk, while performing a 20 movement long-sequence structured as a 2×10 task. Thus, increased complexity would be related to increased number of chunks and the phenomenon of chunking is intricately linked to performance of complex motor sequences. Although chunking in motor sequence learning has been extensively studied behaviorally, it has gained less attention in neuroimaging studies (see also Bor et al., 2003; Graybiel, 1998; Kennerley et al., 2004; Verwey et al., 2002).

Earlier neuroimaging studies indicate the involvement of the fronto-parietal network along with the premotor cortex in complex motor sequence learning (see Honda and Shibasaki, 1998 for a review). With increasing sequence complexity, increased activation in premotor, precuneus, and posterior parietal areas was observed, with decreases in activation in inferior parietal, and superior and dorsal frontal areas (Boecker et al., 1998, 2002; Catalan et al., 1998; Sadato et al., 1996). Harrington et al. (2000) observed that cerebellum and superior parietal areas were positively correlated with the number of fingers used and dorsal premotor area was positively correlated with the increase in the number of finger transitions. Haaland et al. (2004) found that the parietal and the premotor cortices activated more in the left than the right hemisphere when complex sequences were compared with simple sequences irrespective of the hand used. However, the role of fronto-parietal network in relation to complexity of sequences to be learned still remains inconclusive (Honda and Shibasaki, 1998) — whether the activation is exclusively due to the learning or performance of complex sequences of increased sequence length.

Most of the earlier fMRI studies investigating motor sequence complexity used over-learned sequences (Boecker et al., 1998, 2002; Catalan et al., 1998, 1999; Sadato et al., 1996) or briefly practiced sequences (Haaland et al., 2004; Harrington et al., 2000) and as such did not address different learning stages during complex motor sequence learning. Bapi et al. (2006) demonstrated that distinct neural representations subserve different stages of visuo-motor sequence learning (see also Hikosaka et al., 1999; Nakahara et al., 2001). Jenkins et al. (1994) and Jueptner et al. (1997a,b) observed activation in the dorsal prefrontal cortex (Brodmann area: 9/46) and in the caudate nucleus during learning of new sequences compared to pre-learned sequences. Sakai et al. (1998) observed transition of activity from frontal areas in the early stages to the parietal areas by the late stages of sequence learning, reflecting acquisition and retrieval of visuo-motor sequences. These earlier studies on visuo-motor learning (Jenkins et al., 1994; Jueptner et al., 1997a, 1997b; Sakai et al., 1998) suggest that the fronto-parietal cortices would have different roles during different stages of complex sequence learning (Boecker et al., 1998, 2002; Catalan et al., 1998; Haaland et al., 2004; Harrington et al., 2000; Honda and Shibasaki, 1998; Sadato et al., 1996).

The *mxn* sequence learning paradigm (Bapi et al., 2000; Hikosaka et al., 1995) allows us to increase the complexity of sequence in two dimensions (*m*, *n*) without changing the sequence length (i.e. total number of movements to be learned). In the *mxn* sequence learning paradigm (Bapi et al., 2000), visual stimuli consisting of *m* illuminated squares on a 3×3 grid are displayed on a computer monitor. Subjects learn to press *m* corresponding keys (called a *set*) successively on a keypad in response to the visual stimuli. The order of key presses has to be discovered by trial and error. The complete sequence consists of *n* such sets (called a *hyperset*). For example, the 2×6 task (Fig. 1a) consists of learning a sequence of 12 movements by incrementally learning 6 sets of 2 elements each. The sequence length (12) is simply obtained by the multiplication of set length (2) and hyperset length (6). In our study, the amount of information to be processed at a time is represented by a *set*. The complexity of sequences is increased from 12 movements (organized as the 2×6 task) to 24 movements (organized as 4×6 and 2×12 tasks). This design allows us to investigate the effect of complexity along two dimensions (set length and hyperset length) without varying the sequence length (Fig. 1b). We hypothesize that frontal areas are more active during early learning stages in which participants engage in trial and error learning of the sequence, and the parietal areas would be more active after initial learning (Jenkins et al., 1994; Sakai et al., 1998). Additionally, our design allows us to investigate brain areas involved in the process of chunking motor sequences. Due to the limitations on immediate memory span (Cowan, 2001; Miller, 1956) and based on previous findings on typical chunk lengths (Bo and Seidler, 2009; Verwey, 2003), we hypothesized that a smaller set-size (such as in 2×6, 2×12 tasks) would enable spontaneous chunking across several sets (Sakai et al., 2003), while increasing the set-size (such as in the 4×6 task) will limit the chunk formation to single sets (Pammi et al., 2004). In this context, our study should reveal different neural activations corresponding to *mxn* tasks in which chunking across sets is facilitated compared to when chunking is limited to single sets. The two dimensions of complexity would also point to possible differences during chunk formation and execution (Verwey, 2001; Verwey et al., 2010).

Materials and methods

Subjects

Eighteen right-handed normal volunteers (15 males and 3 females with a mean of 23.65 years) participated in this study. Of these 17 subjects were considered for data analysis as one subject did not show learning in the 2×6 task. Subjects were paid for their participation and written informed consent was obtained. The ethics committee of the Brain Activity Imaging Center (BAIC), Advanced Telecommunications Research Institute International (ATR), Kyoto, Japan approved the experimental protocol.

Stimuli

Subjects lay supine in the scanner and visual stimuli were projected on a mirror in front of them. In the *mxn* sequence learning task (Bapi et al., 2000; Hikosaka et al., 1995), a *set* of *m* squares was illuminated simultaneously in white color on a 3×3 grid display against gray background (Fig. 1a). The grid measured 3.7 cm×3.7 cm on the rear screen and the viewing angle was approximately 5°×5°. For each *set*, subjects learned by trial-and-error the correct order of successively pressing *m* corresponding keys on a 3×3 keypad placed near their right hand. The complete visuo-motor sequence of *mxn* key-presses was composed of *n* such *sets* (called a *hyperset*), which was incrementally acquired by trial and error. Subjects were