ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 26 (2005) 801 – 812

Cerebellum and M1 interaction during early learning of timed motor sequences

V.B. Penhune[a,c,*] and J. Doyon[b,c]

[a]Department of Psychology, Concordia University, SP-A 244, 7141 Sherbrooke St. W, Montreal, Canada QC H4B 1R6
[b]Department of Psychology, University of Montreal, F-414-6, 90, Avenue Vincent d'Indy, C.P. 6128, succ. Centre-ville, Montréal, Canada H3C 3J7
[c]McConnell Brain Imaging Centre, Montreal Neurological Institute, Canada

Received 20 October 2004; revised 21 January 2005; accepted 23 February 2005
Available online 7 April 2005

We used positron emission tomography (PET) to examine within-day learning of timed motor sequences. The results of this experiment are novel in showing an interaction between cerebellum and primary motor cortex (M1) during learning that appears to be mediated by the dentate nucleus (DN) and in demonstrating that activity in these regions is directly related to performance. Subjects were scanned during learning (LRN) across three blocks of practice and during isochronous (ISO) and perceptual (PER) baseline conditions. CBF was compared across blocks of learning and between the LRN and baseline conditions. Results demonstrated an interaction between the cerebellum and M1 such that earlier, poorer performance was associated with greater activity in the cerebellar hemispheres and later, better performance was associated with greater activity in M1. Inter-regional correlation analyses confirmed that as CBF in the cerebellum decreases, blood flow in M1 increases. Importantly, these analyses also revealed that activity in cerebellar cortex was positively correlated with activity in right DN and that DN activity was negatively correlated with blood flow in M1. Activity in the cerebellar hemispheres early in learning is likely related to error correction mechanisms which optimize movement kinematics resulting in improved performance. Concurrent DN activity may be related to encoding of this information and DN output to M1 may play a role in consolidation processes that lay down motor memories. Increased activity in M1 later in learning may reflect strengthening of synaptic connections associated with changes in motor maps that are characteristic of learning in both animals and humans.

Keywords: Motor-skill learning; Cerebellum; Dentate nucleus; Motor cortex; Basal ganglia; Human

* Corresponding author. Department of Psychology, Concordia University, SP-A 244, 7141 Sherbrooke St. W, Montreal, Canada QC H4B 1R6. Fax: +1 514 848 4523.

E-mail addresses: vpenhune@vax2.concordia.ca (V.B. Penhune), julien.doyon@umontreal.ca (J. Doyon).

Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2005.02.041

Introduction

A growing body of evidence in both animals and humans has demonstrated plastic neuronal changes in the brain with learning of a motor skill (Doyon and Ungerleider, 2002; Doyon et al., 1996, 1999, 2002, 2003; Gandolfo et al., 2000; Graybiel, 1995; Hikosaka et al., 2002b; Kleim et al., 2002a; Nudo et al., 1996; Thach, 1996). These experiments can be roughly divided into two categories: those that have focused on early rapid changes occurring over minutes (Classen et al., 1998; Doyon et al., 1996, 1999, 2002; Imamizu et al., 2000; Karni et al., 1995; Nezafat et al., 2001; Pascual-Leone et al., 1994; Shadmehr and Holcomb, 1997; Toni et al., 1998; Van Mier et al., 1998); and those that have examined relatively slowly developing changes occurring over days or weeks (Karni et al., 1995; Kleim et al., 2004; Lu et al., 1998; Nezafat et al., 2001; Nudo et al., 1996; Pascual-Leone et al., 1995; Penhune and Doyon, 2002). The results of these experiments have demonstrated the involvement of specific regions of motor cortex, the cerebellum and basal ganglia (BG) depending of the stage of motor learning. Drawing on work in experimental animals, Kleim et al. (2002a, 2004) has hypothesized that early rapid plasticity of motor maps in M1 may be mediated by unmasking of latent connections, while longer-term changes are mediated by synaptogenesis and strengthening of cortical connections (Rioult-Pedotti et al., 1998). In the cerebellum, early learning is probably mediated by error-correction mechanisms instantiated in the climbing fiber system of the cerebellar cortex (Ito, 2000), while later learning may involve plastic changes in regions of the cerebellar hemispheres and/or the cerebellar nuclei specific to the effector and internal model for the task (Imamizu et al., 2000; Lu et al., 1998; Nezafat et al., 2001). In the BG, it has been proposed that anterior putamen is more involved in early learning, while the posterior region is more important for later learning (Jueptner and Weiller, 1998; Miyachi et al., 2002).

More recently, it has been proposed that distinct cortico-cerebellar and cortico-striatal systems may be important for different stages of learning (Doyon and Ungerleider, 2002; Doyon et al., 2003), different modalities of learning (Doya, 2000, 2003) or for learning different aspects of the same task (Hikosaka et al., 2002a; Middleton and Strick, 2000). Strikingly, however, there is little data allowing comparison of the neural mechanisms underlying the early and late periods of learning on the same task (Karni et al., 1995; Kleim et al., 2004; Nezafat et al., 2001). In a previous study of across-day learning (Penhune and Doyon, 2002), we showed that a dynamic network including the cerebellum, basal ganglia and motor cortical regions were differentially active on Day 1 of practice, after 5 days of training and at delayed recall. Based on these results, we proposed that the cerebellum is critically involved in optimizing movement kinematics during early learning, but that later learning and delayed recall are mediated by the BG and motor cortical regions. Therefore, the present experiment was designed to examine within-day changes in the cortico-cerebellar and cortical–striatal networks. Most importantly, the experiment was designed to allow the direct assessment of the relationship between behavioral measures of learning and changes in the pattern of active brain regions and to allow the examination of the interaction between different brain regions across the course of learning.

Motor sequence learning in this experiment was conceptualized as the optimization with practice of specific parameters of motor response that result in improved precision and accuracy of performance. This is similar to the type of motor learning examined in studies of serial finger tapping (Karni et al., 1995) and force field learning (Nezafat et al., 2001). This contrasts with other paradigms, such as the serial reaction time task (SRT) that emphasize implicit or explicit learning of the order of a sequence of movements. The task used was the timed motor sequence task (TMST) developed in our previous study of across-day learning (Penhune and Doyon, 2002). The TMST requires subjects to reproduce a temporally complex sequence of finger taps in synchrony with a visual stimulus (Fig. 1, panel A). Subjects were scanned across three blocks of learning on the same task along with two baseline conditions. In order to identify changes in the pattern of active regions during learning, subtraction analyses contrasted blood flow across blocks of learning and between the learning and baseline conditions. To confirm the results of the subtraction analyses, normalized blood flow was extracted from regions identified in the subtraction analysis. Most importantly, regression analyses were performed to examine the relationship between behavioral measures of performance and blood flow across blocks of learning. Finally, inter-regional regression analyses were conducted to examine the interaction of the cerebellar and motor cortical regions seen to be active across blocks of learning. The results of this experiment are novel in showing a direct relationship between blood flow and performance, and in showing an interaction between the cerebellum and M1 during learning.

Materials and methods

Subjects

Subjects were 12 healthy, right-handed volunteers selected to have no more than 1 year of musical training or experience (6 female, 6 male, average age = 24.8). Subjects were paid for their participation, and gave informed consent. The experimental protocol was approved by the Research Ethics Committee of the Montreal Neurological Institute.

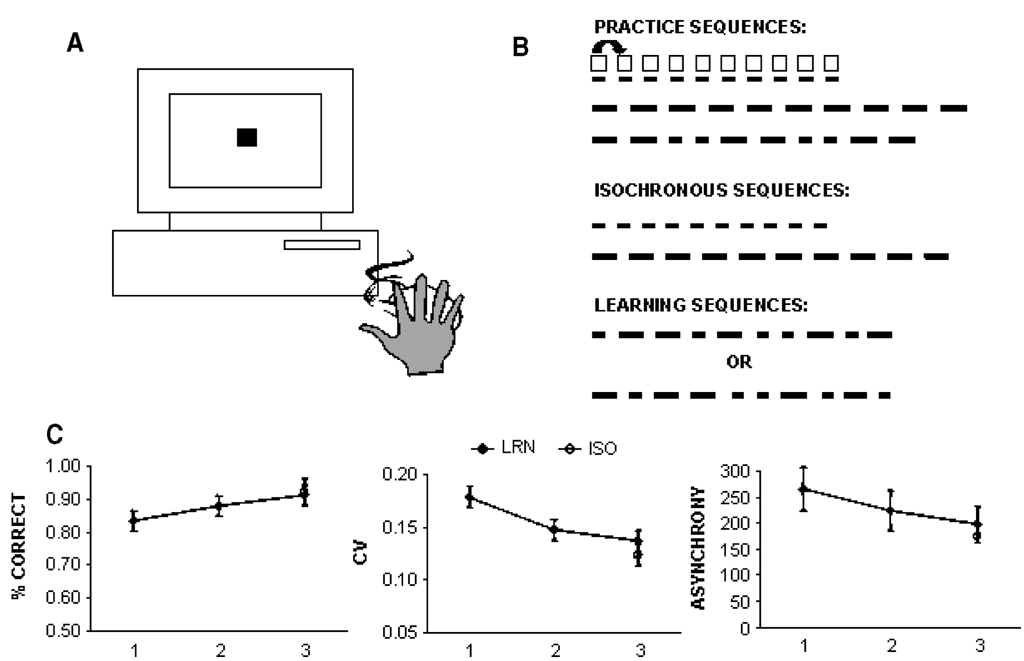

Fig. 1. Illustrates the experimental setup, stimulus sequences and behavioral results. Stimulus sequences were made up of white squares which appeared sequentially at the center of the computer screen (panel A). Squares appeared for either short (250 ms) or long durations (750 ms), represented by the short or long line lengths (panel B). The ISI was 500 ms. For each condition, one example of each sequence type is illustrated. For the learning condition, subjects were tested on only one of the two possible sequences. Panel C contains graphs of performance measures (percent correct; coefficient of variation and response asynchrony) for the learned (LRN) and isochronous (ISO) sequences across blocks of practice (BLK1, 2 and 3). All measures showed significant improvement between BLK1 and BLK3; response asynchrony showed significant differences between all three blocks of practice. Pairwise comparisons contrasting BLK3 to ISO showed no significant differences in for any of the measures.