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Brain and Cognition 60 (2006) 262–271
Brain and Cognition
www.elsevier.com/locate/b&c

Using perfusion fMRI to measure continuous changes in neural activity with learning

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Accepted 22 November 2005
Available online 19 January 2006

Abstract

In this study, we examine the suitability of a relatively new imaging technique, *arterial spin labeled perfusion imaging*, for the study of continuous, gradual changes in neural activity. Unlike BOLD imaging, the perfusion signal is stable over long time-scales, allowing for accurate assessment of continuous performance. In addition, perfusion fMRI provides an absolute measure of blood flow so signal changes can be interpreted without reference to a baseline. The task we used was the serial response time task, a sequence learning task. Our results show reliable correlations between performance improvements and decreases in blood flow in premotor cortex and the inferior parietal lobe, supporting the model that learning procedures that increase efficiency of processing will be reflected in lower metabolic needs in tissues that support such processes. More generally, our results show that perfusion fMRI may be applied to the study of mental operations that produce gradual changes in neural activity.
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Keywords: Motor learning; Sequence learning; SRT; Parietal; Arterial spin-labeling; Perfusion imaging; Premotor; Plasticity; fMRI; Neuroimaging; Brain; Insula

1. Introduction

Some mental operations of interest to the cognitive neuroscientist evolve over relatively long time-scales. Examples of these include changes in emotional state, adoption of a particular cognitive "set" during the performance of a task, or the effects of sleep and alertness. A particularly salient case is the cognitive process of learning, examples of which produce enduring changes in performance that accumulate slowly over minutes to hours. Continuous motor sequence learning, in which a subject becomes skilled at the execution of an ordered set of motor movements, is of this kind (Nissen & Bullemer, 1987).

Attempts to study learning, or other slow changes in neural activity, with BOLD fMRI face the obstacle that BOLD fMRI data are rather unstable at long time scales, as the signal tends to drift up and down over time (Zarahn, Aguirre, & D'Esposito, 1997). This presents an obvious limitation for studies that attempt to discern the slow neural changes that are associated with continuous learning: it is very difficult to discriminate the changes in imaging signal that are due to learning from those that are present as drift noise.

In this study, we examine the suitability of a relatively new imaging technique for the study of continuous, gradual changes in neural activity. Arterial spin labeled (ASL) perfusion imaging permits the noninvasive quantification of regional brain tissue perfusion using labeled inflowing arterial protons as an endogenous tracer (Alsop & Detre, 1998). "Label" images include a radiofrequency irradiation,[1] aimed at the carotid and vertebral arteries, that precedes the image

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[1] It should be noted that radioactive isotopes are not used in perfusion imaging.

0278-2626/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bandc.2005.11.010

acquisition. Label images are alternated with "control" images, and the difference in signal between adjacent image pairs yields the signal due to perfusion. The perfusion effects of ASL are independent of the pulse sequence used to obtain the image after the label. For example, if echoplanar images are used, then the raw image data also contain BOLD contrast, which is attenuated during subtraction of control and labeled pairs. This allows BOLD and perfusion effects to be compared within the same data set (Wong, Buxton, & Frank, 1997). We have previously shown (Aguirre, Detre, Zarahn, & Alsop, 2002) that the perfusion fMRI signal is stable at long time scales, indicating that it may be useful for the study of slow changes in neural activity.

We obtained neuroimaging data from subjects while they performed a motor serial response time (SRT) task. During scanning, subjects performed a series of finger movements in response to visual cues over a 20 min period. Unbeknownst to the subject, there was a repeated pattern to the movements. Under these circumstances, subjects generally demonstrate a gradual and continuous decline in response time (e.g., Nissen & Bullemer, 1987). Prior imaging studies of subjects performing SRT tasks have demonstrated a reduction of neural activity in response to motor execution after training as compared to the start of training. Because the change in performance is slow and continuous, we assumed for this study that the neural correlate of performance improvement during SRT training is a gradual reduction in regional activity. Our goal in the current study was to use perfusion fMRI in an attempt to detect these neural changes. A positive result would demonstrate the ability of perfusion fMRI to measure dynamic changes in CBF over long time scales. Any effects found in the perfusion data can be contrasted with effects present in the simultaneously acquired BOLD data in each subject. Finally, because BOLD imaging is better suited to the detection of transient neural activity, we examined if the BOLD data could be used to detect trial-wise differences between correct and incorrect responses.

To foreshadow our results, insufficient power was present to detect learning effects at a map-wise level in the perfusion data. However, within regions of interest defined with a lowered map-wise threshold, separate statistical tests revealed significant correlations of CBF changes with reaction time measures of learning. These effects could not be detected within the BOLD data. However, there were measurable, event-related differences in the BOLD signal between correct and incorrect responses. Thus, this study serves as a demonstration of the potential of perfusion fMRI data to simultaneously examine rapid changes in neural activity with BOLD contrast and slow changes in neural activity with perfusion contrast.

2. Methods

2.1. Participants

Ten participants (ages 19–40, average age = 25, 5 males) were recruited from the University of Pennsylvania and received payment for participation. All subjects had normal or corrected-to-normal visual acuity, were right handed, and were free of any history of neurological or psychiatric disease. Written consent was given according to an Institutional Review Board approval from University of Pennsylvania.

2.2. Experimental procedure: SRT task

The classic serial-response (SRT) task was adopted as the learning task during perfusion fMRI scans. Subjects were required to use four fingers (left middle, left index, right middle, right index) to press keys as quickly and as accurately as possible in response to the presentation of visual cues that consisted of four white outline squares (2.65° × 2.65°, separated by 0.05°) that were arrayed horizontally on a medium gray (RGB 127) background (see Fig. 1). Each square would illuminate with a color that corresponded to those present on the response box: red, green, blue, or yellow. The spatial organization of the colors remained consistent throughout the experiment. The color target appeared for 500 ms and was followed by a 300 ms

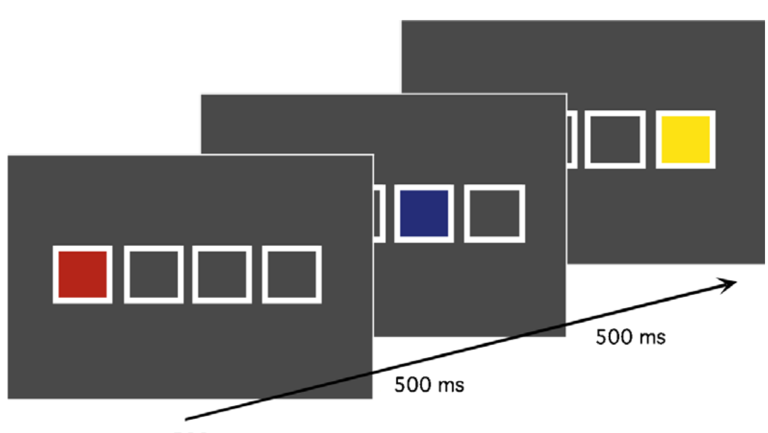

Fig. 1. Schematic drawing of the task (stimuli are not to scale). Four horizontally arrayed boxes lit up sequentially to indicate the required keypress.

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