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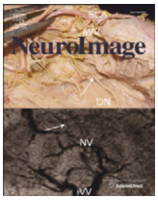

Neural networks related to pro-saccades and anti-saccades revealed by independent component analysis

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ABSTRACT

The saccadic eye movement system provides an excellent model for investigating basic cognitive processes and flexible control over behaviour. While the mechanism of pro-saccades (PS) is well known, in the case of the anti-saccade task (AS) it is still not clear which brain regions play a role in the inhibition of reflexive saccade to the target, nor what is the exact mechanism of vector inversion (i.e. orienting in the opposite direction). Independent component analysis (ICA) is one of the methods being used to establish temporally coherent brain regions, i.e. neural networks related to the task. In the present study ICA was applied to fMRI data from PS and AS experiments. The study revealed separate networks responsible for saccade generation into the desired direction, the inhibition of automatic responses, as well as vector inversion. The first function is accomplished by the eye fields network. The inhibition of automatic responses is associated with the executive control network. Vector inversion seems to be accomplished by the network comprising a large set of areas, including intraparietal sulcus, precuneus/posterior cingulate cortices, retrosplenial and parahippocampal. Those regions are associated with the parieto-medial temporal pathway, so far linked only to navigation. These results provide a new insight into understanding of the processes of the inhibition and vector inversion.

Introduction

In an extensive body of literature, the saccadic task has been referred to as a relatively pure cognitive experimental design. A pro-saccadic (PS) task requires a subject to shift attention and gaze to a target. Functional neuroimaging studies have identified a number of brain regions involved in PS, including the primary visual cortex, the intraparietal sulcus (IPS), frontal eye fields (FEF), supplementary eye fields (SEF) and dorsolateral prefrontal cortex (DLPFC) (DeSouza et al., 2003; Munoz and Everling, 2004; Pierrot-Deseilligny et al., 2004). The information from the primary visual cortex is processed through several extrastriate visual areas (Maunsell and Newsome, 1987; Vanni et al., 2001). IPS activity signifies the salience of a stimulus at a given spatial location (Colby and Goldberg, 1999) and projects to the frontal lobe. The FEF has a crucial role in executing voluntary saccades, the SEF is important for the internally guided decision of making the eye movement as well as for the initiation and performance of saccade sequences (Pierrot-Deseilligny et al., 2003), while the DLPFC is involved in suppressing automatic, reflexive responses (Munoz and Everling, 2004). Those regions connect with each other through specific neural pathways of information flow. The saccade generation process relies on the dorsal visual stream, the circuit responsible for visuospatial processing (Goodale and Milner, 1992; Milner and Goodale, 2008; Rossit et al., 2010; Valyear et al., 2006). A recent review by Kravitz et al. (2011) revealed three distinct pathways that emerge from the dorsal visual stream. According to the authors, the parietal cortex is a seed region for prefrontal, premotor and medial temporal circuits. A saccadic task is assumed to evoke two of them. The parieto-prefrontal pathway reaches to the FEF, while the parieto-premotor pathway reaches to the SEF, maintaining and mediating, respectively, controlled eye movement. So far, the third parieto-medial temporal pathway was associated strictly with navigation.

In contrast to the PS, an anti-saccadic (AS) task requires shifting attention and gaze in the direction opposite to a target. Higher cognitive demands result in significantly longer reaction times (Evdokimidis et al., 1996) and increased brain activations, for most of the regions, in comparison to those evoked by the PS (DeSouza et al., 2003; Dyckman et al., 2007; Everling and Fischer, 1998; McDowell et al., 2008). What is the exact cause of the activity increase? Performing the anti-saccades requires two additional processes. A subject must suppress the unwanted reflexive saccade and inverse the location of the target to its mirror position. Single-neuron recordings in monkeys have provided evidence that the brain inhibits the automatic response by reducing the level of preparatory activity in the saccade circuitry before the stimulus appears (Munoz and Everling, 2004). The authors point to the fact that saccade-related neurons in the superior colliculus (SC) and the FEF show a lower level of activity during the preparatory period

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on anti-saccade trials than that on pro-saccade trials. Several structures are considered as a possible source of that inhibition, the SEF (Munoz and Everling, 2004), DLPFC (Pierrot-Deseilligny, 2003) or anterior cingulate cortex (ACC) (Matsuda et al., 2004). However, the exact source of the inhibition remains unclear. As for the sensorimotor transformation responsible for inverting the location of the target, also referred to as vector inversion, numerous studies have linked this cognitive function with the parietal cortex (Clementz et al., 2007; Medendorp et al., 2005; Moon et al., 2007; Müri and Nyffeler, 2008; Zhang and Barash, 2004). Even though AS task has been widely used to study brain functions such as the inhibition of reflexive responses and target inversion, it still requires some clarification. If the processes are indeed independent, evaluating separate neural networks responsible for them should be possible and might give promising results.

According to a review by McDowell et al. (2008) an evaluation of functional connectivity between regions supporting saccade generation would be extremely useful for complementing functional anatomy information. Although Hwang et al. (2010) applied a functional connectivity analysis to the fMRI data of the AS and PS task, the authors focus their study exclusively on the inhibitory control, ignoring the vector inversion process. The goal of their study was to characterize the age-related development (from childhood to adulthood) of the effectively connected regions rather than contribute to understanding the processes involved in the AS task. Therefore, to the best of our knowledge, this study is the first that responded to McDowell et al. (2008) recommendation. To achieve that, an independent component analysis (ICA) has been implemented in the functional magnetic resonance imaging (fMRI) study. ICA is a developing data-driven approach more and more often used in neuroimaging studies (Bell and Sejnowski, 1995; McKeown et al., 1998). In contrast to fixed model-based approaches, like the General Linear Model (GLM), it does not rely on poorly defined models, unknown timing of neuronal activity or variability of hemodynamic response. Therefore, it may give more insight into the data and detect responses that would not have been revealed by a GLM analysis (McKeown et al., 1998; Moeller et al., 2011). Recently growing interest in resting-state connectivity aims to identify common and repetitive brain networks (Beckmann et al., 2005; Calhoun et al., 2008; Damoiseaux et al., 2006; Smith et al., 2009; Varoquaux et al., 2010). The ICA method allows also for a straightforward analysis of more complex brain imaging experiments including those concerning neurological disorders (Greicius, 2008). Moreover, the implementation of ICA to cognitive experimental data enables distinguishing brain networks related to task what can improve understanding of the cognitive functions (St Jacques et al., 2011).

The aim of our research was to investigate the neural networks responsible for separate functions in pro-saccadic and anti-saccadic tasks. To achieve that we applied ICA to fMRI data, as the method allows the distinctions of temporally coherent neural networks. Comparison and identification of each component with those reported in the literature enabled us to recognize artifacts and associate neural networks with their function. A correlation analysis of their time course with block model provided us with the distinction between task-related and task-unrelated neural networks. We hypothesized that there will be AS-related separate network responsible for the inhibition of automatic responses as well as separate network involved in vector inversion. Not only we achieved that but also detected a parietal-medial temporal pathway that was never before associated with anti-saccades nor detected with the ICA.

Materials and methods

Participants

Fifteen healthy, male volunteers, with a mean age of 27.4 years (SD = 5.6) participated in the study. All of them were right handed, had normal vision, no neurological or sleep-related disorders, no history of head injury, were non-smokers, and drug-free. The subjects were informed about the procedure and goals of the study and gave their written consent. They had performed a training session to get familiar with the MR scanner and with the experimental procedure. The study was approved by the Bioethics Commission at the Jagiellonian University.

Procedure

Pro-saccadic (PS) and anti-saccadic (AS) tasks were used in the block design study (Fig. 1). In both tasks a fixation point was displayed in the centre of the screen for 30 s; then, a target stimulus was randomly presented at one of the five right- or five left-side situated squares, while the fixation point remained continuously visible (overlap paradigm). The subjects were instructed to direct their attention and gaze straight ahead toward the fixation point and, when the target appeared, to execute an eye movement to it and then to move back to the fixation point (PS task). In the AS task the subjects were asked not to follow the stimulus, but to target their attention and gaze at the point in the opposite direction and at the same distance from the fixation point as the original target. There were five scanning runs, each containing a 5 min PS and 5 min AS task session. Every task session was combined with nine blocks, five blocks of fixation point presentations and four blocks of target presentations, preceded with verbal information about the type of task. Blocks of targets consisted of 18 stimuli (each presented for 1500 ms with a gap of 500 ms between the targets). Each block lasted 30 s.

Data acquisition

Magnetic resonance imaging (MRI) was performed using a 1.5 T General Electric Signa scanner (GE Medical Systems, Milwaukee, WI). High-resolution, whole-brain anatomical images were acquired using a T_1-weighted sequence. A total of 60 axial slices were obtained (voxel dimension = $0.4 \times 0.4 \times 3$ mm^3; matrix size = 512×512, TR = 25.0 ms, TE = 6.0 ms, FOV = 22×22 cm^2, flip angle = 45°) for coregistration with the fMRI data. Functional T_2^*-weighted images were acquired using a whole-brain echo planar pulse sequence (EPI) with a TE of 60 ms, matrix size of 128×128, FOV of 22×22 cm^2, spatial resolution of $1.7 \times 1.7 \times 5$ mm^3, and a flip angle of 90°. One session was composed of 100 images for each of the 20 axial slices, taken at an interleaved fashion with a TR of 3 s. The first three images of each session were excluded from the functional analysis to allow for the T1 equilibrium effects.

Data analysis

Data preprocessing

Standard preprocessing procedure was applied using Analysis of Functional NeuroImage software (Cox, 1996). Firstly, each 3D image was time-shifted so that the slices were aligned temporally. After head motion correction, the functional EPI data sets were zero-padded to match the spatial extent of the anatomic scans, and then coregistered. Anatomical and functional images were transformed

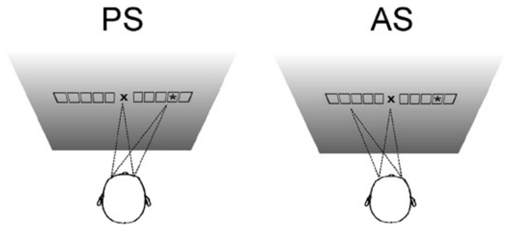

Fig. 1. Tasks used in the study. In the pro-saccadic (PS) task subjects were asked to direct their attention and gaze to the target, while in the anti-saccadic (AS) task to opposite direction.