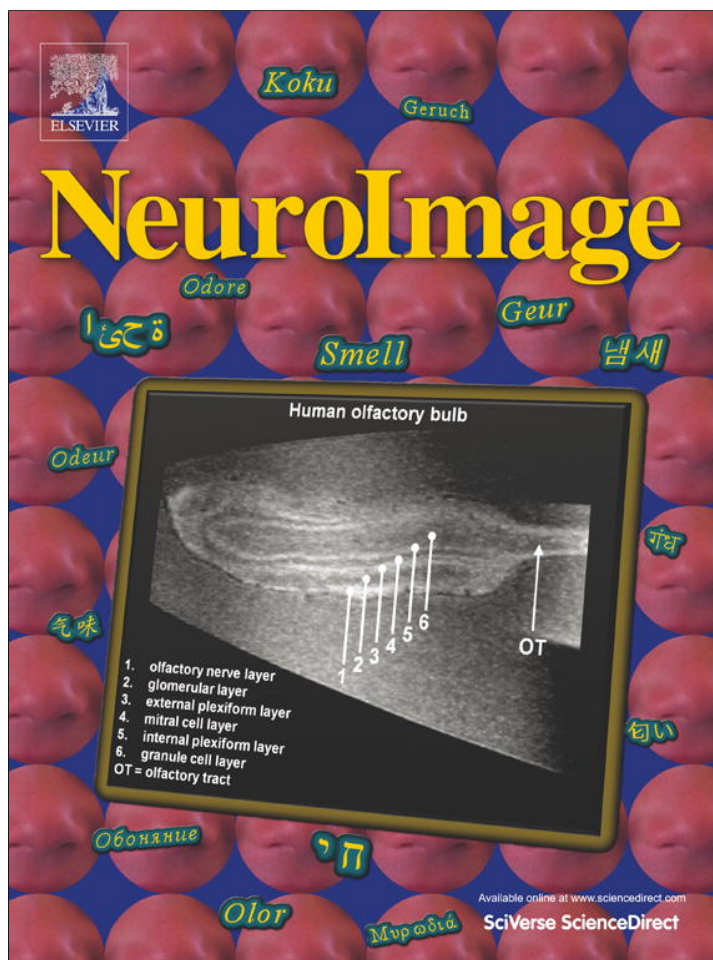


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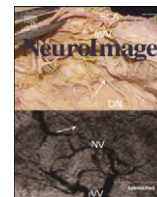
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## Neural networks related to pro-saccades and anti-saccades revealed by independent component analysis

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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.

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### 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 dorso-lateral 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 (Pierrat-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.

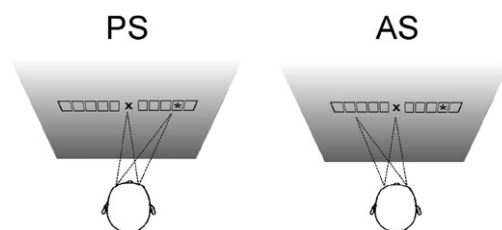
### Data acquisition

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<sup>3</sup>; matrix size =  $512 \times 512$ , TR = 25.0 ms, TE = 6.0 ms, FOV =  $22 \times 22$  cm<sup>2</sup>, flip angle =  $45^\circ$ ) 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  $128 \times 128$ , FOV of  $22 \times 22$  cm<sup>2</sup>, spatial resolution of  $1.7 \times 1.7 \times 5$  mm<sup>3</sup>, and a flip angle of  $90^\circ$ . 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.



into a coordinate system of Talairach space (Talairach and Tournoux, 1988). The functional data were then smoothed using a full-width at a half maximum isotropic Gaussian kernel of 8 mm. During the scaling procedure, voxels with low-signal intensity located outside the brain were excluded from the functional images by a clipping function.

#### Independent component analysis

The GIFT software package was used to perform a group ICA (Calhoun et al., 2001) for each task separately. The estimation determining the number of components was performed using minimum description length criteria implemented in the software (Li et al., 2007). FastICA algorithm (Hyvärinen and Oja, 2000) was applied with an estimated number of components. No scaling of the data was performed. In accordance with the approach of Calhoun et al. (2008), components were further coupled across two tasks according to spatial cross-correlation coefficients and visually inspected for the presence of artifacts.

Next, we have conducted an independent split-data analysis to increase validity of statistical inference and avoid circularity (Kriegeskorte et al., 2009). Odd scanning runs (set 1) of the experiment were chosen for derivation of the components, whereas even runs (set 2) were used for correlation analysis. The equivalence of the components extracted from the two sets was established through the spatial cross-correlation analysis. Set 1 enabled recognition and labelling the networks whereas set 2 enabled selection of the task-related components. Following Greicius and Menon (2004), the time course of each component of each subject underwent a correlation analysis with the task model. Correlation coefficient values provide a measure of the degree to which a network activates with the task. This analysis step is analogical to the temporal sorting feature of the GIFT toolbox since the linear regression of one variable (block model) is analogical to a correlation analysis. A component was classified as a task-related neural network if its correlation coefficient reached significance of  $p < 0.001$  in one sample  $t$ -test and its average value was larger than 0.3 (medium or strong correlation). Components were then sorted by these values and also tested for the difference in activation between the two tasks. Additionally, two neural networks of interest were compared by subtracting their positive maps from each other.

## Results

The GIFT software estimated 14 independent components for each task. Spatial cross-correlation analysis revealed a clear coupling of independent components between the PS and AS task (Fig. 2). Three of them, similar to those reported in the previous studies (Kelly et al., 2010; Varoquaux et al., 2010), were classified as artifacts. The maps of the 11 remaining neural networks are presented in Fig. 2 (all activations are reported at FDR corrected threshold  $p < 0.001$ ). Spatial cross-correlation coefficients of the split-data confirmed the coupling of independent components between set 1 of the PS task and set 1 of the AS task, as well as between the two sets in each task (Table 1). The networks were labelled and classified as those related to the task or unrelated to it (see Materials and methods section).

#### Neural networks related to the task

It has been hypothesized that there would be more task-related neural networks in the AS than in the PS, as the former is a more complex task. As we expected, only one component was classified as PS-related network, whereas four fitted to the criteria in the AS task (Fig. 3A). Their time courses are presented in Fig. 3B. A  $t$ -test on the correlation coefficients for the network common for PS and AS showed no significant difference (Fig. 3C).

#### Eye fields network

A component which showed the strongest correlation with the model (PS:  $r = 0.53$ ; AS:  $r = 0.48$ ;  $p < 0.001$ ; Fig. 3C) represents a network

of regions typically involved in a saccade task (Table 2; Fig. 3A). Activations of the lateral visual areas (from the primary to the extrastriate visual cortex) together with IPS point to the temporally coherent dorsal visual stream (DVS) which integrates the information from the retinotopic visual fields and transforms it to egocentric frames of reference e.g. relative to the eye (for review, see Kravitz et al., 2011). The IPS, also referred to as the human parietal eye field (Pierrot-Deseilligny et al., 2004), is critically important for various aspects of saccadic control, including spatial updating and the transformation of sensory input into a motor command (for review, see McDowell et al., 2008). According to study of Hu et al. (2009), IPS as a part of posterior parietal cortex plays a pivotal role in intention. Furthermore, Desmurget and Sirigu (2009) in the electrical stimulation study of the human cortex showed that the posterior parietal region is responsible for motor intention and awareness, whereas stimulation of the premotor regions triggers the movement without conscious intention and awareness. The activity of the frontal cortex within the presented network has obvious references to motor execution. The FEF is involved with both reflexive and volitional saccade initiation, whereas the SEF is responsible for volitional saccade generation (Ettinger et al., 2008a; McDowell et al., 2008; Munoz and Everling, 2004; Pierrot-Deseilligny et al., 2004). The putamen has been associated with the volitional eye movement (Petit et al., 1993; Neggers et al., 2012); however, its exact function is still unclear (Watanabe and Munoz, 2011).

A  $t$ -test on the correlation coefficients revealed no difference between the PS and AS tasks (Fig. 3C). The results suggest that this network is responsible for generating a volitional saccade to a desired direction, as both tasks equally require perception of stimuli as well as performance of eye movement. For obvious reasons, we suggest labelling it the eye field network (EFN).

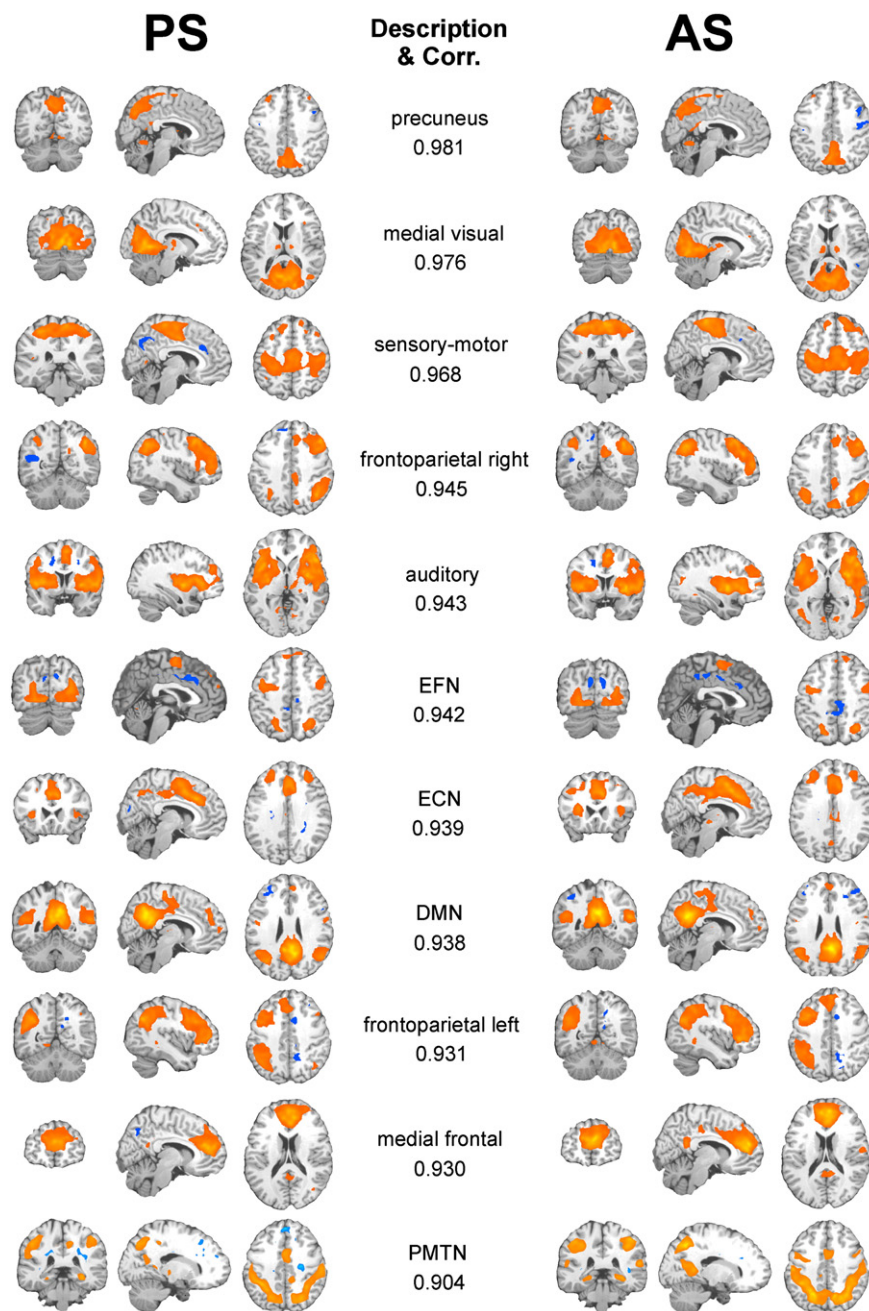
#### Parieto-medial temporal network

It was assumed that there would be a network related only to the AS task, responsible for vector inversion. The second component, correlating with the block model only in the AS task ( $r = 0.43$ ;  $p < 0.001$ ; Fig. 3C), has a rather complex anatomy. The main activations extend from the V5/MT along the IPS and reach preSMA and bilaterally the FEF (Table 2, Fig. 3A). The presence of preSMA and FEF within the network indicates the output of the information flow and cooperation with executive control network (ECN) and EFN, respectively. However, the main activation in the posterior part of the IPS is involved with another pathway, the parieto-medial temporal. Parietal activations converge in the medial precuneus and posterior cingulate cortex (PCC) and diverge to the bilateral retrosplenial cortices (RSC) and the parahippocampal cortices (PHC). Due to the similarity of the network with EFN, a differential map of the two was calculated ( $p_{\text{cor}} < 0.001$ ). The difference highlighted the connections of IPS with PHC (Fig. 4) and that is why we labelled the component parieto-medial temporal network (PMTN). Bilateral visual cortices were the only clusters with higher activation for the EFN network (Fig. 4). The results indicate that, in contrast to externally driven EFN, PMTN is driven endogenously. Although the exact mechanism triggering the vector inversion remains unclear, numerous studies have evidenced the parietal cortex to be involved in this process (Clementz et al., 2007; Dyckman et al., 2007; Medendorp et al., 2005; Moon et al., 2007; Nyffeler et al., 2007; Zhang and Barash, 2004). As a matter of fact, the strongest activation of the PMTN occurs in the posterior IPS (Table 2).

Considering (1) PMTN engagement only to the AS task, (2) the fact that it is endogenously driven, and (3) its strongest activation is in the IPS, the conclusion can be drawn that the PMTN is responsible strictly for the visuo-spatial process required to perform an anti-saccade, the vector inversion.

#### Executive control network

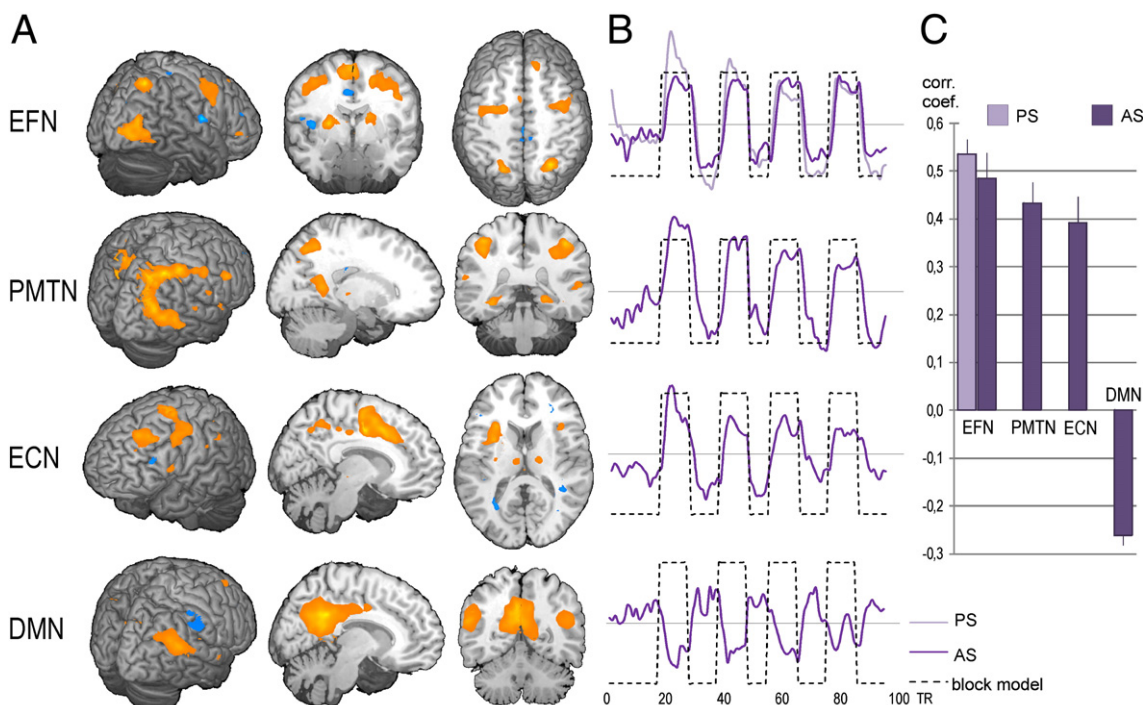
The third network correlating with the AS task ( $r = 0.39$ ;  $p < 0.001$ ; Fig. 3C) comprised the following brain regions: pre-supplementary motor area (preSMA) extending to the dorsal part of the anterior



**Fig. 2.** Independent components analysis of the PS and AS tasks. T-maps of independent components ( $p_{\text{cor}} < 0.001$ ), their labels and spatial cross-correlation coefficients. EFN = eye fields network; PMTN = parieto-medial temporal network; ECN = executive control network; DMN = default mode network.

cingulate cortex (dACC), as well as the bilateral DLPFC, FEF, anterior insula and thalamus (Table 2, Fig. 3A). Functional connectivity between those regions has been already shown by Cole and Schneider (2007) during both rest and cognitive task performance. The network has been found in many resting-state designs implementing ICA (Beckmann et al., 2005; Doria et al., 2010; Smith et al., 2009), mostly subsumed under the terminology of the executive control network (ECN). Its functions can be associated with the control of goal directed behaviour, target detection, error detection, conflict resolution, and the inhibition of automatic responses (Berger and Posner, 2000; Callejas et al., 2005; Seeley et al., 2007). In the current study, the engagement of ECN in AS tasks can be linked to a process of top-down control inhibition, i.e. suppressing automatic responses, such as reflexive saccades to the target. Indeed, all of the regions comprising the network have proven to play that inhibiting role. PreSMA enables

suppressing an automatic unwanted action and then switching to volitionally controlled action (Isoda and Hikosaka, 2007). Curtis and D'Esposito (2003) showed greater prestimulus preparatory activity in the preSMA, critically associated with reflex suppression. Although claiming inconsistency with Curtis and D'Esposito (2003), Brown et al. (2007) found DLPFC and ACC responsible for presetting, i.e. biasing, the saccade circuitry before the anti-saccade occurrence. The anterior insula has been shown to be a part of the executive system (Klein et al., 2007; Marek et al., 2010) and was found to play a role in response inhibition as well (Brass and Haggard, 2007; Swick et al., 2011). Finally, the thalamus has been associated with the definite inhibition of the prepared action and, consequently, involved in executive operations (Marzinzik and Wahl, 2008). If one considers those regions as a network, the mentioned results may become more consistent. Our findings are in agreement with those of Hwang et al. (2010)



**Fig. 3.** Task-related neural networks. (A) T-maps of task-related neural networks for AS task ( $p_{cor} < 0.001$ ). EFN = eye fields network; PMTN = parieto-medial temporal network; ECN = executive control network; DMN = default mode network. (B) Time courses of the networks for PS and AS tasks. (C) Correlation coefficients of the time courses with a task model (with standard errors).

who concluded that active inhibitory control is accomplished by multiple frontal regions rather than a single structure.

Moreover, in contrast to the ECN detected with resting-state designs, here the network includes the FEF regions. The result suggests that the FEF is the output of the inhibition process conducted by the network. The results are in agreement with the findings of inhibition of saccade neurons in the FEF and SC before the target appears (Munoz and Everling, 2004); however, the SC could not be detected in the present study, due to the artifacts on the edge of the scanning field-of-view.

#### Default mode network

The component correlating negatively, close to the threshold of component classification, with the AS task ( $r = -0.26$ ;  $p < 0.001$ ; Fig. 3C) comprises the following brain regions: the posterior midline region, the bilateral inferior parietal lobes and the superior frontal gyrus (Table 2, Fig. 3A). This map corresponds to the default mode network (DMN), which is one of the most consistent finding of the fMRI experiments implementing functional connectivity methods,

**Table 1**

Spatial cross-correlation of components between pro-saccade (PS) and anti-saccade (AS) tasks derived from set 1 and equivalence through the spatial correlation established between set 1 and set 2.

Description	Spatial correlation		
	PS vs. AS - set1	PS - set1 vs. set2	AS - set1 vs. set2
Frontoparietal right	0.961	0.936	0.920
Medial visual	0.960	0.965	0.965
Sensory-motor	0.959	0.938	0.890
Frontoparietal left	0.936	0.891	0.859
DMN	0.929	0.908	0.826
Medial frontal	0.922	0.826	0.780
Auditory	0.902	0.887	0.910
Precuneus	0.854	0.858	0.959
EFN	0.850	0.734	0.876
ECN	0.842	0.837	0.800
PMTN	0.797	0.706	0.772

either in resting-state designs (Beckmann et al., 2005; Calhoun et al., 2008; Damoiseaux et al., 2006; Smith et al., 2009), or task-based experiments (Mazoyer et al., 2001; Raichle et al., 2001; for review, see Buckner et al., 2008). It has been also shown that attentional demand on the task leads to greater deactivation of the network (Mayer et al., 2010; McKiernan et al., 2003; Persson et al., 2007; Singh and Fawcett, 2008) due to the reallocation of processing resources from the DMN to the brain areas involved in the task performance. Greicius and Menon (2004) have proven that sensory stimuli for most subjects were not sufficiently challenging to disrupt the network. Since DMN was detected but unrelated to PS performance, it seems that this task did not engage the subjects sufficiently enough. In contrast, the negative correlation of DMN in the AS task suggests that either higher demand for inhibition (ECN) or vector inversion (PMTN) was a reason why internally generated cognitive processes were disrupted during the task.

#### Neural networks unrelated to the tasks

Seven of the detected neural networks are engaged neither in the PS nor in the AS task. All of them are similar to those identified previously (Beckmann et al., 2005; Calhoun et al., 2008; Damoiseaux et al., 2006; Smith et al., 2009; St Jacques et al., 2011; Varoquaux et al., 2010).

The component with parietal and prefrontal activations is referred to as a frontoparietal network (Calhoun et al., 2008; Smith et al., 2009). Its common feature across studies is lateralization, as there are separate components observed for the left and right hemispheres. The results obtained in the current study also show lateralization with a maximum of parietal activation in the angular gyrus and few maxima of prefrontal activation along the inferior frontal sulcus.

Both medial frontal and precuneus components should be referred to as the systems rather than the network, as they show one main cluster of activation. Medial frontal is considered as a part of the DMN (Buckner et al., 2008; Raichle et al., 2001); however, it was found as a separate component in some ICA studies (Calhoun et al., 2008; Damoiseaux et al., 2006; Varoquaux et al., 2010). The second system is centred in the medial part of the Brodmann area 7 (BA7),



**Table 2**  
Talairach coordinates of maximum positive activations in the networks related to the anti-saccade task derived from set 1.

Region	Side	x	y	z	T
<i>EFN</i>					
Inferior occipital gyrus	R	14	-82	-6	11.29
	L	-24	-86	-2	9.73
Posterior IPS	L	-22	-70	46	11.07
	R	28	-64	48	15.10
SEF	M	0	-6	62	10.99
FEF	R	52	-2	30	7.46
	L	-42	-12	40	10.74
Superior frontal gyrus	M	12	38	48	6.81
Putamen	R	24	-6	6	14.64
	L	-16	-2	12	8.88
<i>ECN</i>					
Dorsal ACC	M	8	12	40	15.79
PreSMA	M	2	2	52	19.96
FEF	R	32	0	52	15.12
	L	-18	-2	60	13.41
DLPFC	R	30	34	38	7.33
	L	-26	34	38	11.49
Anterior insula	R	36	18	10	6.82
	L	-30	20	10	12.76
Thalamus	R	16	-16	8	8.33
	L	-10	-18	8	6.35
<i>PMTN</i>					
Posterior IPS	R	30	-62	40	17.15
	L	-26	-62	42	17.60
Anterior IPS	R	40	-40	52	14.50
	L	-44	-44	44	16.34
V5/MT	R	48	-52	-2	14.40
	L	-42	-64	16	14.23
PreSMA	M	-2	2	48	5.88
Lateral FEF	R	56	10	32	10.25
	L	-48	8	28	18.31
FEF	R	28	-6	52	6.94
	L	-34	-4	48	12.66
Supramarginal gyrus	L	-56	-26	24	10.65
PHC	R	30	-34	-10	13.79
	L	-24	-42	-8	11.03
RSC	R	16	-50	6	10.39
	L	-8	-50	6	10.48
precuneus/PCC	M	-6	-60	48	10.31
<i>DMN</i>					
Posterior midline region	M	2	-52	26	41.49
Inferior parietal lobe	R	54	-58	20	19.25
	L	-38	-72	32	12.17
Superior frontal gyrus	L	-22	28	48	12.66
	R	22	28	48	10.20

Note: Side refers to the location of the activation, where M=medial, L=left, and R= right hemisphere. T values refer to the maximum of cluster ( $p_{cor}<0.001$ ). FEF=frontal eye field; SEF=supplementary eye field; IPS=intraparietal sulcus; ACC=anterior cingulate cortex; preSMA=presupplementary motor area; DLPPFC=dorsolateral prefrontal cortex; PHC=parahippocampal cortex; RSC=retrosplenial cortex; PCC=posterior cingulate cortex.

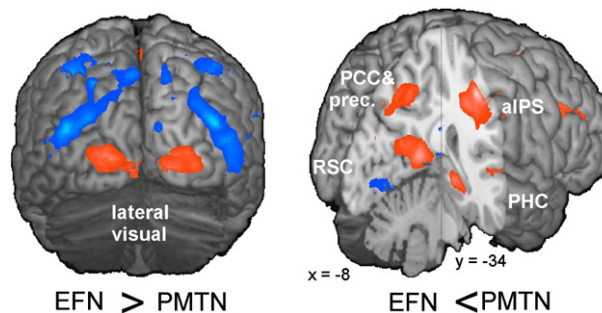
which corresponds to the precuneus. As reported in a review by Cavanna and Trimble (2006), the precuneus plays a role in a wide spectrum of highly integrated tasks, such as visuospatial imagery, episodic memory retrieval, and self-processing.

The remaining task-unrelated networks can be linked to sensory modalities: the primary visual cortex (medial visual), the somatosensory and motor cortices (sensory-motor) as well as the primary and secondary auditory cortices (auditory).

**Discussion**

*Application of the ICA in separating brain functions*

The goal of this research was to separate the neural networks responsible for different processes in saccadic tasks. The PS task



**Fig. 4.** Comparison of eye fields network (EFN) and parieto-medial temporal network (PMTN). Differential map of PMTN and EFN ( $p_{cor}<0.001$ ). PCC= posterior cingulate cortex, RSC=retrosplenial cortex, alPS=anterior intraparietal sulcus, PHC= parahippocampal cortex. The difference (PMTN>EFN) highlighted the connections of the IPS with PHC, i.e. parieto-medial temporal pathway.

requires only EFN for a volitional saccade generation. The AS task, in addition to the PS task, requires involvement of ECN for the inhibition of the reflexive saccades to the target and the activation of the PMTN for the sensorimotor transformation of target location to its mirror position, i.e. vector inversion. ICA has proven to be a powerful technique, considering it enabled distinction of brain functions within a single experimental design. It also eliminates artifacts from the data and proves temporal coherence of the regions. Furthermore, the resemblance of the networks among many studies, with either resting-state or task designs, speaks for the great reliability of the ICA. However, one should not look for an identical set of regions for network identification. It seems that key regions of the network provide enough information to identify it, whereas additional activations suggest functional connections specific to a given task (e.g. FEF occurrence in the ECN). Finally, in the present study, the ICA has revealed activations that were not reported in previous studies implementing the same task design, i.e. a parieto-medial temporal pathway within the PMTN. The medial temporal activations in the AS task might be too subtle in comparison to the frontal or parietal activations and, in consequence, mistakenly neglected when standard analysis methods are applied to the fMRI data. We state that this pathway indeed plays an important role in the vector inversion process. Its functions are discussed in detail below.

*Parieto-medial temporal pathway*

One of the key findings of the study is the involvement of the parieto-medial temporal pathway in the AS task. The results obtained here show that the pathway is part of the PMTN, which is responsible for vector inversion. Numerous studies have already linked the parietal cortex with this sensorimotor transformation (Clementz et al., 2007; Dyckman et al., 2007; Medendorp et al., 2005; Moon et al., 2007; Nyffeler et al., 2007; Zhang and Barash, 2004). Zhang and Barash (2004) employed a memory-delay version of the AS task in their electrophysiological study with monkeys. The authors found the activity in monkey analogue of human IPS, 50 ms after the visual neurons on the opposite side of the brain. Another study proved that those findings also apply to the human brain. Medendorp et al. (2005) conducted an event-related fMRI experiment with a memory-delayed saccade task. They observed IPS activity in response to target location presented in the contralateral visual field. However, when a cue for a delayed anti-saccade trial appeared, the activity shifted from one hemisphere to the other. Nyffeler et al. (2007) reported a patient with a small right-sided posterior parietal stroke who performed rightwards anti-saccades markedly hypometric (i.e. undershooting) whereas normal leftwards anti-saccades and pro-saccades. This anti-saccade inaccuracy was ascribed to the impairment of visual vector inversion. The authors claim to provide the evidence that visual vector inversion could be an intrinsic property of the posterior parietal cortex.

As far as we know, there is no literature linking vector inversion with the medial temporal lobe. However, numerous studies associate its function with spatial memory (Bachevalier and Nemanic, 2008; Bohbot et al., 2000; Ploner et al., 2000). Ploner et al. (2000) found that patients with right parahippocampal lesions were impaired in their ability to remember locations in the left visual hemifield and made saccades to those locations after delays of 30 s. Buffalo et al. (2006) showed that anterior PHC activates selectively to spatial encoding. It seems that the connections between IPS and PHC can be ascribed to encoding and/or retrieving spatial information. PCC, with the direct interconnectivity to IPS (Kravitz et al., 2011), contributes to the translation between egocentric representations of space in the parietal cortex and the allocentric representations in the parahippocampal cortices (Vogt et al., 1992). Dean and Platt (2006) provide evidence that this translation applies to the saccadic task, as they found PCC encoding the location of saccade's target in allocentric coordinates. Studies with navigation tasks revealed that the PHC encodes a representation of the local scene that allows it to be remembered, whereas the RSC directs one's movement towards navigational targets that are not currently visible (Epstein, 2008). If one considers a representation of the inverse target location as a local scene, the findings have obvious implementation in the AS task. Finally, our results of PMTN involvement in vector inversion are in agreement with Bird and Burgess's review (2008), according to which the PHC, with its strong connections to RSC and IPS, is a key region for the processing of visuospatial information (from the dorsal visual stream).

Our results extend the findings that link the parietal cortex with vector inversion. We suggest that the inversion of the target's location is driven endogenously by a temporally coherent brain pathway, which includes the IPS, precuneus/PCC, RSC and PHC. The parieto-medial temporal pathway due to its junction of bilateral activations in the medial PCC and precuneus can be responsible for parietal shift from one hemisphere to the other, which was reported by Medendorp et al. (2005). Moreover, a right-sided posterior parietal stroke affecting only the performance of rightwards anti-saccades and not rightwards pro-saccade (Nyffeler et al., 2007) could be explained by a lesion of parieto-medial temporal pathway, leaving EFN unaffected. In summary, PMTN performs sensorimotor transformation, i.e. vector inversion, with parieto-medial temporal pathway being responsible for the sensory transformation of target location and prefrontal connections integrating with EFN in the motor command.

#### *Associations to the neural framework of visuospatial processing*

A recent review by Kravitz et al. (2011) introduced a new neural framework of visuospatial processing. The authors proposed three major pathways emerging from the dorsal visual stream with distinct anatomy and functionality. The first one, parieto-prefrontal pathway, links the parieto-occipital circuit with the prefrontal cortices, including FEF, and is responsible for the initiation of volitional eye movements. The second, parieto-premotor pathway, connects IPS with SEF and one of its functions is mediating eye movements. The third pathway, parieto-medial temporal, projects indirectly from the angular gyrus to medial temporal lobe. The latter includes PCC, RSC as well as PHC and is claimed to be crucial for navigation. The authors do not exclude the possibility that it may contribute to other forms of visuospatial function.

The results obtained in the current study provide evidence that the new framework applies to the neural mechanism underlying the performance of saccades in humans. The parieto-prefrontal and parieto-premotor pathways together with the dorsal visual stream form EFN. Although the two pathways have a distinct anatomy and function, saccadic tasks evoke both of them coherently. Their presence within the EFN network confirms that the network is responsible for both maintaining and mediating eye movement. The parieto-medial temporal pathway described by Kravitz et al. (2011) shows

strong similarities with the one obtained here, present in PMTN. They both project from the parietal cortex through PCC and RSC to the PHC, and in both cases, their function is associated with processing spatial information. It seems we have found another visuospatial function of the parieto-medial temporal pathway, which is the vector inversion.

#### *Neural networks unrelated to the tasks*

It seems adequate that some of the detected neural networks are not involved in the task. The components linked to sensory modalities are activated at some level during the whole time of scanning due to constant wakefulness. The medial frontal system is separated from the DMN in our study, similarly to previous research (Calhoun et al., 2008; Damoiseaux et al., 2006; Varoquaux et al., 2010). Damoiseaux et al. (2006) explained this division with the finding that the medial anterior part of the DMN shows more variation of the BOLD signal. Mantini et al. (2007) found that fMRI signal fluctuations in the medial prefrontal cortex are strongly connected with the gamma power of the EEG signal, whereas the rest of the DMN is linked with alpha and beta power. This division may also be associated with genetic factor of dopamine levels in brain, recently proven to affect the BOLD deactivations of medial frontal and medial parietal regions in PS and AS task (Ettinger et al., 2008b). The fact that DMN is related to the AS task, whereas medial frontal is not, might be a substantial information for further research in exploring the functions of those regions.

As expected, the frontoparietal network was not involved in the saccadic tasks. St Jacques et al. (2011) found the left frontoparietal network to be related to memory retrieval task and being linked to the processing of semantic information that guide the construction of an autobiographical memory. However, region similarities, i.e. parietal and frontal activations, with the EFN network make it crucial for recognizing the two in future studies. It is very often that activations within IPS and FEF are referred to as a frontoparietal network (Brown et al., 2007; Corbetta et al., 1998; Connolly et al., 2002; Matsuda et al., 2004; Medendorp et al., 2011), what might raise inconsistencies. Since ICA enabled distinction of the two networks, we propose to follow EFN labelling for the network comprising IPS, FEF and SEF, whereas frontoparietal labelling for the network activating widely inferior frontal sulcus and angular gyrus.

As for the precuneus system, we expected it to be task-related because numerous studies have linked its function to visuospatial processing (see review by Cavanna and Trimble, 2006). However, this brain region is large enough to contribute to multiple functions. In our study, the precuneus was found to be divided into three functionally distinct parts. The inferior part of the precuneus is located in the posterior midline region of the DMN. The anterior part of the precuneus is involved in vector inversion performed by the PMTN, whereas the posterior part resulted as a separate component. The latter was not engaged in any task, so no conclusions regarding its functions can be drawn. Whatsoever, the finding is in agreement with the versatility of precuneus functions reported by Cavanna and Trimble (2006). The presentation of neural networks unrelated to the task may contribute to future ICA-based conclusions or at least it can provide clarification of the network anatomy. Future studies could address the issue whether the task-unrelated but detected networks play any role in a given task.

#### **Conclusions**

The findings provide evidence that volitional eye movements, i.e. pro-saccades and anti-saccades, are the result of activity and interactions of separate neural networks. The eye fields network (EFN) is the most and equally activated in both tasks. Its function involves the perception of stimulus location, initiation and successful generation



of saccade into the chosen direction. The parieto-medial temporal network (PMTN), the executive control network (ECN), and the default mode network (DMN) were only AS-related. The PMTN is responsible for the sensorimotor transformation of the target's location referred to as the vector inversion. The inversion is driven endogenously by a temporally coherent brain pathway within the PMTN, which includes the IPS, precuneus/PCC, RSC and the PHC. The ECN is responsible for the inhibition, i.e. suppressing automatic responses, such as reflexive saccades. Negative activation of DMN only for AS task results from higher cognitive demands for the inhibition and/or vector inversion processes.

Revealing neural networks involved in the saccadic task has important implications for the understanding and potentially distinguishing the higher-order cognitive functions (McDowell et al., 2008). The identification of neural networks in the current study provides an insight into understanding the processes of inhibition and vector inversion. The former is realised by the set of brain regions (ECN), and not by a particular one. The presence of FEF within ECN confirms previous electrophysiological findings that this is the region that needs to be suppressed in order to withhold an eye movement. Vector inversion is not an intrinsic property of the parietal cortex but rather a property of its connection to the medial temporal lobe. As far as we know, a parieto-medial temporal pathway was never before associated with anti-saccades nor detected with the ICA. Our findings highlight the importance of applying novel analysis method, such as ICA, to fMRI experiments. The modifications of the experimental procedure, e.g. using an event-related design of the delayed saccade tasks or increasing the salience of the cue, may help to further investigate the exact nature of the processing within these networks.

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