



## Spatio-temporal indications of sub-cortical involvement in leftward bias of spatial attention

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### ABSTRACT

A leftward bias is well known in humans and animals, and commonly related to the right hemisphere dominance for spatial attention. Our previous fMRI study suggested that this bias is mediated by faster conduction from the right to left parietal cortices, than the reverse (Siman-Tov et al., 2007). However, the limited temporal resolution of fMRI and evidence on the critical involvement of sub-cortical regions in orienting of spatial attention suggested further investigation of the leftward bias using multi-scale measurement. In this simultaneous EEG-fMRI study, healthy participants were presented with face pictures in either the right or left visual fields while performing a central fixation task. Temporo-occipital event related potentials, time-locked to the stimulus onset, showed an association between faster conduction from the right to the left hemisphere and higher fMRI activation in the left pulvinar nucleus following left visual field stimulation. This combined-modal finding provides original evidence of the involvement of sub-cortical central attention-related regions in the leftward bias. This assertion was further strengthened by a DCM analysis designated at cortical (i.e., inferior parietal sulcus; IPS) and sub-cortical (pulvinar nucleus) attention-related nodes that revealed: 1. Stronger inter-hemispheric connections from the right to left than vice versa, already at the pulvinar level. 2. Stronger connections within the right than the left hemisphere, from the pulvinar to the IPS. This multi-level neural superiority can guide future efforts in alleviating attention deficits by focusing on improving network connectivity.

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### Introduction

Healthy individuals show a reliable bias to the left visual field (LVF) in the perception of length, size, brightness, and numerosity known as ‘pseudo-neglect’ (Bowers and Heilman, 1980). People with attention deficits show an opposite bias to the right (Hari et al., 2001), suggesting a role for the leftward bias in effective attention allocation. The leftward bias was long related to the well-documented right hemisphere (RH) superiority for spatial attention (McCourt and Jewell, 1999), known from lesion studies in humans showing higher prevalence and severity of spatial neglect following RH – compared to left hemisphere (LH) – lesions (Heilman et al., 1987; Kim et al., 1999) and from functional

magnetic resonance imaging (fMRI; Corbetta et al., 1998) and transcranial magnetic stimulation (Fuggetta et al., 2006) studies. A recent fMRI study (Siman-Tov et al., 2007) combined with dynamic causal modeling (DCM) analysis showed enhanced bilateral activation for LVF stimulation that is best explained by stronger connectivity from right to left parietal cortices than vice versa.

Classical models of spatial attention bias have underscored the role of cortical rather than sub-cortical pathways (Corbetta and Shulman, 2002). However, the fact that the leftward bias was discovered even in birds (Diekamp et al., 2005) suggests an early evolutionary role, and thus possible involvement of sub-cortical regions in its operation. Two main sub-cortical structures are likely to take part in such a mechanism: (i) the mid-brain superior colliculus (SC), a critical region for orienting of attention and gaze (Boehnke and Munoz, 2008). (ii) The thalamic pulvinar nucleus, involved in various attention-related operations such as search, selection and engagement, and in the occurrence of spatial neglect in patients (Fairhall et al., 2009). Clearly, for effective attention operation, one expects a concerted activation between high (i.e., cortical) and low (i.e., sub-cortical) levels of processing, especially for implicit processing that

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might be critical for survival. Animal studies (e.g., Burton and Jones, 1975; Petersen et al., 1987) and recent diffusion tensor imaging (DTI) studies in humans point to substantial anatomical connections between these sub-cortical and attention-related cortical regions such as the parietal cortex (Leh et al., 2008), and lesion studies point to their critical role in spatial attention operations (Karnath et al., 2002).

In order to further explore the role of sub-cortical regions in the formation of the leftward bias, we focused on two questions related to right hemisphere superiority: (i) Is the superiority confined to the attention-related cortical network or also evident at its sub-cortical nodes such as the SC and pulvinar nuclei? (ii) Is the superiority driven only by fast inter-hemispheric conduction from right to left, or also by a fast conduction within the right hemisphere between sub-cortical to cortical attention-related regions?

To answer these questions, we applied a combined electroencephalography (EEG)–fMRI approach. Simultaneous acquisition of EEG and fMRI was essential in the current study for two reasons. One is theoretical; it assured that the quality of stimulus processing (i.e., amount of attention allocation) and subjective experience was equal for the multi-scale brain measurements. Since our task involved implicit processing that might have changed with repeated stimulation, such simultaneous acquisition ensured the functional validity of our data. The other reason is methodological; sub-cortical regions cannot be traced by scalp EEG recording, and neural conduction time cannot be measured precisely with fMRI (see Debener et al., 2007 for details). Specifically, we used the superior temporal resolution of the EEG to unveil the exact temporal characteristic of inter-hemispheric transfer time based on a cross-correlation procedure while using the superior spatial resolution of the fMRI to designate activation in sub-cortical regions that is best explained by the EEG-based timing of connectivity.

In order to examine the effective connectivity in the aforementioned attentional network, a model-driven analysis was pursued with a DCM procedure (Friston et al., 2003). DCM is based on Bayesian rules to model task-independent intrinsic connectivity between regions, task-dependent modulations of these regions, and direct inputs to the system. Hence, DCM assesses mutual influences of neural regions, and how these influences are affected by the experimental conditions (Friston et al., 2003; Penny et al., 2004). As an extension of our previous work, the model tested inter-hemispheric conduction between the right and left pulvinar nuclei in addition to the right and left intraparietal sulcus (IPS) (Siman-Tov et al., 2007). Furthermore, the model tested the intra-hemispheric conduction between the pulvinar nucleus and the IPS of each hemisphere separately.

## Materials and methods

### Subjects

Fifteen volunteers participated in this simultaneous EEG–fMRI study. Three participants were excluded from the final analysis after reporting neurological disorders such as attention deficit hyperactive disorder (ADHD) or due to left-handedness, and hence 12 right-handed healthy subjects were included in the analysis [3 males, mean age: 24.5 y (range: 21–30), mean education: 13.7 y (range: 12–16)]. All had normal or corrected-to-normal vision. None had any neurological or psychiatric symptoms, or any structural brain abnormality. Due to technical problems in EEG data acquisition, two subjects were removed from the EEG study prior to data analysis. The Ethical Committee of the Tel Aviv Sourasky Medical Center approved the study and all subjects signed an informed consent form.

### Visual stimuli and experimental design

Stimuli were black and white pictures of neutral faces and geometric patterns of  $3.7^\circ$  (width)  $\times$   $4.7^\circ$  (height). The face stimuli

were derived from those used by Siman-Tov et al. (2007), and included faces with a neutral expression taken from two databases: The Averaged Karolinska Directed Emotional Faces (KDEF) database (Lundqvist et al., 1998) and the Pictures of Facial Affect (Ekman and Friesen, 1976). The pattern stimuli were simple black and white patterns taken from a pool of pictures used in our laboratory for clinical purposes and the Internet. There were 40 pictures of faces and 39 pictures of patterns, presented randomly with Psychtoolbox implemented in MATLAB 7.0.4 software.

The experiment included 4 consecutive sessions, each consisting of 181 repetitions (6.6 min), composed of blocks of left or right visual fields (LVF/RVF)  $\times$  stimuli type (face/pattern) presented in a pseudorandom order (Fig. 1A). Each session started with 6 blank trials, a first short block of house pictures that was discarded afterwards, and 12 stimuli blocks of 10 events, separated by rest blocks of 3–5 blank trials.

Fig. 1B illustrates the order of an experimental trial. The event duration was 2.2 s, starting with a central gray fixation dot, presented for 500 ms. Following this, a picture of a face or a pattern was presented parafoveally ( $5^\circ$  angle from the center of the picture) to the right or left of the fixation, for 200 ms. Then, the color of the central fixation dot was changed to either blue or red for 500 ms, and returned to gray for 1400 ms for the remaining time of the event. The picture onset was shifted by a random jitter of 0–200 ms after the 500 ms fixation; however, it always disappeared before the color change of the central fixation dot. In addition, the color change of the central dot was shifted by a random jitter of 0–300 ms after the picture disappeared, to prevent time locking of the evoked neural responses to the gradient switching. The inter-trial interval was adjusted according to the jitters of the picture onset and color change onset, in order to achieve an event duration of 2.2 s.

Participants were asked to report the color change of the central fixation dot via a response box using their right thumb for a red dot and left thumb for a blue dot. To achieve visual field segregation, participants were explicitly instructed to ignore the pictures and to maintain fixation throughout the experiment.

### Data acquisition

#### fMRI acquisition

MRI scans were conducted using a 3-Tesla GE scanner (Signa excite, Milwaukee, WI, USA). All images were acquired using a GE four channel head coil. The scanning session included conventional anatomical MR images (T1-WI, T2-WI, T2-FLAIR), and three-dimensional spoiled gradient (3D-SPGR) echo sequence [field of view (FOV) – 250 mm; matrix size –  $256 \times 256$ ; voxel size –  $0.98 \times 0.98 \times 1$ ]. Functional images included T2\*-weighted images at the same locations as the anatomical images [FOV – 200 mm, matrix size –  $64 \times 64$ , voxel size –  $3.1 \times 3.1 \times 3.5$ , TR/TE/FA = 2200/35/90, 33–34 axial slices (depending on initial alignment) of 3.5 mm without gap].

#### EEG acquisition

Continuous EEG data was recorded simultaneously with fMRI acquisition throughout the experimental sessions. EEG was collected using an MR-compatible system including a 32-channel BrainCap electrode cap with sintered Ag/AgCl ring electrodes (30 EEG channels, 1 ECG channel, and 1 EOG channel under the left eye; Falk Minow Services, Herrsching-Breitbrunn, Germany; Fig. 2A) and BrainAmp-MR EEG amplifier (Brain Products, Munich, Germany). The reference electrode was placed between Fz and Cz. Raw EEG was sampled at 5 kHz and recorded using Brain Vision Recorder software (Brain Products). Previous studies at our laboratory showed good signal-to-noise ratio of the EEG data in the combined approach (Ben-Simon et al., 2008; Sadeh et al., 2008).

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