

# Atypical hemispheric dominance for attention: functional MRI topography

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**The right hemisphere is predominantly involved in tasks associated with spatial attention. However, left hemispheric dominance for spatial attention can be found in healthy individuals, and both spatial attention and language can be lateralized to the same hemisphere. Little is known about the underlying regional distribution of neural activation in these ‘atypical’ individuals. Previously a large number of healthy subjects were screened for hemispheric dominance of visuospatial attention and language, using functional Doppler ultrasonography. From this group, subjects were chosen who were ‘atypical’ for hemispheric dominance of visuospatial attention and language, and their pattern of brain activation was studied with functional magnetic resonance imaging during a task probing spatial attention. Right-handed subjects with the ‘typical’ pattern of brain organization served as control subjects. It was found that subjects with an inverted lateralization of language and spatial attention (language right, attention left) recruited left-hemispheric areas in the attention task, homotopic to those recruited by control subjects in the right hemisphere. Subjects with lateralization of both language and attention to the right hemisphere activated an attentional network in the right hemisphere that was comparable to control subjects. The present findings suggest that not the hemispheric *side*, but the intrahemispheric *pattern* of activation is the distinct feature for the neural processes underlying language and attention.**

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## Introduction

Functional imaging has increased awareness for the variability in the relation between brain function and brain structure. This variability is most striking for lateralized brain functions. Neuroimaging and

neuropsychological research indicate that the left hemisphere is specialized for language and the right for control of spatial attention in most individuals (Ojemann, 1991; Mesulam, 1999; Bookheimer, 2002). However, this is not an invariable principle. There are occasional patients with aphasias after right-hemispheric lesions, or with neglect after left-hemispheric lesions (Dronkers and Knight, 1989). The same hemisphere can even be dominant in control of both language and spatial attention (Fischer *et al*, 1991; Trojano *et al*, 1994; Alexander and Annett, 1996; Osmon *et al*, 1998; Floel *et al*, 2001; Floel and Knecht, 2002).

Recently, a number of studies have addressed the anatomical correlates of language processing in subjects with atypical right-hemisphere language dominance (Hubrich-Ungureanu *et al*, 2002; Staudt *et al*, 2002; Knecht *et al*, 2003; Jansen *et al*, 2004b). They showed that right-hemisphere recruitment for language occurs in brain areas homotopic to the left-hemisphere regions typically involved in language

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processing. Detailed studies on the lateralization of the neural substrate that underlies attentional processing in atypical cases are missing so far.

In a previous study on healthy subjects, we investigated whether functional transcranial Doppler sonography (fTCD) and functional magnetic resonance imaging (fMRI) determine hemispheric dominance of brain activation related to visuospatial attention concordantly (Jansen *et al*, 2004a). In this study, we identified three subjects who were left-hemisphere lateralized for spatial attention and right-hemisphere dominant for language and two subjects who were right-hemisphere dominant for both language and spatial attention.

This unique sample of subjects gave us the possibility to investigate two important questions: (i) the neuroanatomic correlates of visuospatial attention processing in the left hemisphere, and (ii) the influence of atypical right-hemispheric language lateralization on right-hemispheric visuospatial attention. In the present study, we therefore analyzed the data for topographical information about brain activation, which were not included in the previous study.

We hypothesized that atypical left-hemispheric dominance for attention would likewise be a mirror of right-hemispheric attentional dominance, similar to what has been shown for language (Knecht *et al*, 2003). For subjects with both language and attention lateralized to one hemisphere, we hypothesized that the intrahemispheric distribution of activation would not differ from subjects with the typical pattern. Seven subjects from the previous study, with the typical pattern of handedness (right), language (left), and attention (right) served as control group.

## Materials and methods

### Subjects

Twelve healthy volunteers (5 men), aged 24 to 30 years, were included in the study. Based on their language and attentional dominance, subjects were selected from a cohort of 15 subjects previously assessed for attentional and language dominance with both fMRI and fTCD to examine the intermethod-correlation of both techniques (Jansen *et al*, 2004a). Subjects in the study by Jansen and colleagues had been selected from a cohort of 326 healthy volunteers studied for language dominance by fTCD (Knecht *et al*, 2000a, b). A much higher percentage of the subjects chosen for the Jansen *et al* study, compared with the general population, had atypical right-hemispheric representation for language to increase the possibility to include subjects with an atypical left-hemispheric representation for spatial attention. In the present study, we chose five subjects with atypical hemispheric dominance for language and/or attention from the previous study (Jansen *et al*, 2004a) for in-depth examination of the intrahemispheric topography of atypical hemispheric lateralization. All subjects had completed the equivalent of a high school degree ('Gymnasium'). None had a serious history of medical, neurologic, or psychiatric illnesses or any brain pathology or abnormal brain morphology on T1-weighted MR images. All subjects gave their written informed consent before participation, according to the declaration of Helsinki. The subjects' characteristics are presented in Table 1.

Handedness was assessed by the Edinburgh handedness inventory (Oldfield, 1971). Hemispheric dominance for language and spatial attention was originally assessed by fTCD (see below), and confirmed by fMRI (Knecht *et al*, 2003; Jansen *et al*, 2004a).

**Table 1** Subjects' characteristics: age, sex, handedness, and language lateralization

Subject ID	Age (years)	Sex	Handedness <sup>a</sup>	Lateralization of language <sup>b</sup>	Lateralization of spatial attention <sup>b</sup>
<i>Atypical subjects, group I (attention left, language right)</i>					
01	25	F	-85	-5.0	4.0
02	25	M	40	-3.8	0.9
03	27	M	-100	-3.3	3.8
<i>Atypical subjects, group II (attention right, language right)</i>					
04	24	F	79	-4.1	-2.9
05	30	F	-20	-3.4	-3.2
<i>Control group (attention right, language left)</i>					
06	27	F	100	3.2	-4.1
07	24	F	20	3.4	-5.5
08	28	M	100	2.5	-3.2
09	24	M	88	2.0	-4.4
10	24	F	70	3.2	-4.8
11	27	M	100	5.0	-4.5
12	25	F	45	3.2	-3.6

<sup>a</sup>Handedness was assessed by the Oldfield score, ranging from -100 (left handedness) to +100 (right handedness)

<sup>b</sup>As assessed by fTCD: positive values indicate left-hemisphere lateralization for language/spatial attention and negative values lateralization to the right.

## Functional Transcranial Doppler Ultrasonography

**Experimental Design: Word generation (WG).** Language lateralization was assessed with a standard phonemic verbal fluency task, which is based on the Controlled Word Association Test (Lezak, 1995). Subjects were presented with a letter on a computer screen 5 secs after a cueing tone. They silently generated as many words as possible starting with the displayed letter. Task compliance was ensured by having subjects report the words after a second auditory signal, 15 secs after presentation of the letter. A third auditory signal, 5 secs later, marked the beginning of a control condition that lasted for 35 secs, and during which subjects were instructed to imagine a night sky (control condition). The following trials were presented after the same schema. One epoch lasted 60 secs (25 secs WG, 35 secs control task). Twenty epochs were recorded in total. Letters were presented in random order. 'Q', 'X', and 'Y' were excluded because few words in German start with these letters. Each letter was only displayed once.

**Line bisection.** To assess spatial attention, the Landmark Task, a variant of line bisection, which is frequently used in the assessment of visuospatial neglect (Harvey *et al*, 1995), was administered. Five seconds (secs) after a cueing tone, a horizontal line was presented for 10 secs on a computer screen (visual angle 9.3°). The horizontal line was bisected by a vertical line either in the exact middle or deviating to the right or the left by 0.1° or 0.2°. During the 10-sec period, subjects had to silently decide if the horizontal line was bisected in the middle, slightly to the left, or slightly to the right. Task compliance was ensured by having subjects report the decision verbally (middle, left, or right) after a second auditory signal at the end of the presentation of the bisected line. A third auditory signal 5 secs later marked the beginning of the control condition. The next bisected line was then presented in the same way. One epoch lasted 40 secs (20 secs for Landmark Task, 20 secs for control condition). Twenty epochs were recorded in total. Lines were bisected in the exact middle four times, and four times each displaced to the left or to the right by 0.1° or 0.2°, respectively. The sequence of conditions was randomized.

**Functional transcranial Doppler sonography data acquisition:** Using a commercially available 2 MHz transcranial Doppler ultrasonography device (Multidop T, DWL Sipplingen, Germany), the blood flow velocities within both middle cerebral arteries (MCAs) were measured continuously. Details of the technique, especially the identification of the MCAs, are described elsewhere (Ringelstein *et al*, 1990). The spectral envelope curves of the Doppler signal were stored for offline analysis.

**Functional transcranial Doppler sonography data analysis:** Analysis was performed using the software package AVERAGE (Deppe *et al*, 1997). After automatic artefact rejection, like probe displacement, data were integrated over the corresponding cardiac cycles, segmented into epochs that related to the first cueing tone and averaged. The mean velocity in the 15-sec precueing

interval ( $V_{\text{pre.mean}}$ ) was taken as a baseline value. The relative CBFV changes ( $dV$ ) were calculated by the formula

$$dV = 100 \frac{V(t) - V_{\text{pre.mean}}}{V_{\text{pre.mean}}}$$

where  $V(t)$  is the CBFV over time and  $V_{\text{pre.mean}}$  is the mean velocity in the precueing interval.

Examples of  $dV$  change related to visuospatial attention are shown in Figure 3. Differences in the velocity between both MCAs were statistically analyzed using the Wilcoxon test for each sample point.

### Calculation of $LI_{\text{FTCD}}$

The  $LI_{\text{FTCD}}$  was computed by

$$LI_{\text{FTCD}} = \frac{1}{t_{\text{int}}} \int_{t_{\text{max}} - 0.5t_{\text{int}}}^{t_{\text{max}} + 0.5t_{\text{int}}} \Delta V(t) dt$$

where

$$\Delta V(t) = dV(t)_{\text{left}} - dV(t)_{\text{right}}$$

is the difference between the relative CBFV changes in the left and right MCA. The time point  $t_{\text{max}}$  represents the latency of the absolute maximum of  $\Delta V(t)$  within the activation interval (10 to 20 secs). As integration interval, a time period of  $t_{\text{int}} = 2$  secs was chosen. A positive value of the  $LI_{\text{FTCD}}$  indicates left-hemispheric processing for spatial attention; a negative value stands for right-hemispheric dominance. The magnitude represents the degree of lateralization. The accuracy of the  $LI_{\text{FTCD}}$  of each individual is determined by its stochastically estimated confidence interval.

According to their hemispheric dominance for language and spatial attention, subjects were divided into three groups:

**Group I (subjects 01–03):** Right hemispheric dominance for language, left hemispheric dominance for spatial attention.

**Group II (subjects 04–05):** Right hemispheric dominance for both language and spatial attention.

**Group III (subjects 06–12):** Left hemispheric dominance for language, right hemispheric dominance for spatial attention.

Group I thus comprised 'atypical' subjects with dissociated lateralization of language and attention, and Group II 'atypical' subjects with associated lateralization of language and attention. Group III (subjects with the standard or typical pattern of hemispheric lateralization) served as a control.

A missing dissociation of lateralization of attention and language is often associated with cognitive deficits. Therefore, subjects who lacked dissociation between lateralization for language and for visuospatial attention were tested *post hoc* with the Leistungspruefsystem (LPS) for adults < 50 years (Sturm *et al*, 1993) to assess for verbal and nonverbal intelligence. To screen for attentional deficits, digit span was assessed using the subtest of the Wechsler Memory Scale (WMS) (Wechsler and Stone, 1974), and visual span using the Corsi-tapping test (Lezak,

1995). Speed of processing, mental flexibility, and attention were examined with the Trail Making Test (Spreeen and Strauss, 1991).

### Magnetic Resonance Imaging Experimental Design

For the purpose of functional imaging studies, hemispheric lateralization for attention may be assessed in a number of ways (for a review see Cabeza and Nyberg, 2000). In the present study, we chose to examine lateralization for spatial attention with the Landmark task. Subjects had to decide whether prebisected horizontal lines are divided in the exact center, or slightly to the right or left of the center (Figure 1). This task was chosen, although it is not without criticism (Halligan *et al*, 1989; Ferber and Karnath, 2001), because it corresponds to deficits frequently encountered in patients experiencing visuospatial neglect after stroke (Harvey *et al*, 1995; Heilman, 1997; Marshall, 1998; Mesulam, 1999).

The control task used in the present study was devised to incorporate all aspects of the experimental task except the bisection judgment itself (Fink *et al*, 2000, 2002). It controls for the visual input, the neural responses resulting from the hand used for the responses that indicate subjects' performance, and the decision component involved in the task *per se*. In this way, we depicted the neural substrates that are specific to the visuo-spatial judgments associated with the experimental task.

Five seconds after a color change (duration 0.5 secs), subjects were presented with a horizontal line for 5 secs on a computer screen (visual angle 9.3°). The horizontal line was either bisected by a vertical line in the exact middle or slightly deviating to the left or the right (Landmark task) or presented together with a waveform-shaped line (control task). During the 5-sec period, subjects silently decided where the horizontal line

was bisected (Landmark task), or where the waveform-shaped line was presented (control task), respectively. Immediately after the line presentation, subjects were instructed to report their decision by pressing corresponding buttons on a response pad with both hands. After 2 secs, another color change marked the beginning of the next epoch. Six Landmark tasks were followed by six control tasks. This sequence was repeated seven times.

### Magnetic Resonance Imaging Data Acquisition

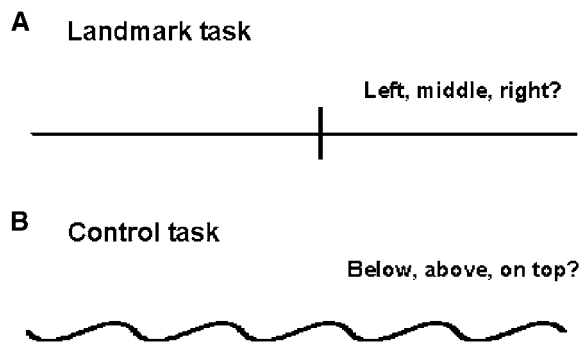
All MRI data were acquired on a neuro-optimized GE 1.5T whole body scanner equipped with a standard circular polarized head coil. Functional images were acquired using a T<sub>2</sub>\*-weighted gradient echo EPI sequence (TE = 40 ms, TR = 2 secs, flip angle 90°, slice thickness 7 mm, 1 mm gap, matrix 64 × 64, FOV 200 mm, in-plane resolution 3.125 × 3.125 mm). Sixteen axial slices orientated parallel to the AC-PC line covering the whole head were taken. Additional high-resolution T<sub>1</sub>-weighted anatomic images were acquired (TE = 8 ms, TR = 24 ms, flip angle 30°, matrix 256 × 256, FOV 250 mm, 124 sagittal slices, slice thickness 1.5 mm).

### Magnetic Resonance Imaging Data Analysis

All calculations and image manipulations were performed on an Enterprise 450 (SUN Microsystems Computers) using MATLAB (www.mathworks.com) and SPM99 (www.fil.ion.ucl.ac.uk/spm). Statistical parametric map (SPM) was used for realignment, normalization, smoothing, and statistical analysis to create statistical parametric maps of significant relative regional BOLD response changes (Friston *et al*, 1995a, b).

The first five images of each session, during which the MR signal reaches a steady state, were discarded. The remaining scans of each individual were realigned to the first image (corresponding to the sixth acquired image of the time series) to correct for movement artefacts. Sinc interpolation was used in the transformation. A mean functional image volume was constructed for each subject from the realigned images and coregistered with the anatomic image. The functional images were normalized to a template brain image created by the Montreal Neurological Institute (MNI) (Evans *et al*, 1994). The coregistered anatomic image was used to determine the parameters for the spatial normalization process (Friston *et al*, 1995a). The resulting voxel size in standard stereotactic coordinates was 2 × 2 × 2 mm<sup>3</sup>. The normalized images were smoothed using an isotropic Gaussian kernel (FWHM: 6 mm for single subject analysis, 10 mm for group analysis).

After preprocessing, statistical analysis was performed on individual data. The experimental conditions (judgment of prebisected lines/control task) were modelled using a boxcar function convolved with a hemodynamic response function (hrf) in the context of the general linear model used by SPM99. The time series was filtered with



**Figure 1** (A) Activation task. Subjects were presented with a horizontal line, bisected by a vertical line either in the exact middle or slightly deviating to the left or the right. They had to decide where the horizontal line was bisected. (B) Control task. As in the activation task, a horizontal line was shown, together with a waveform-shaped line. Subjects had to decide whether the line was overlapping with, above or below the horizontal line.

the hrf as low-pass filter. Specific effects were examined by applying appropriate linear contrasts to the parameter estimates for the experimental conditions, resulting in a *t*-statistic for every voxel. These *t*-statistics constitute an SPM and can be interpreted by referring to the probabilistic behavior of Gaussian random fields.

To obtain activation maps across subjects, the functional data within the control group were combined in a ‘fixed-effect’ analysis as the most sensitive approach involved to identify areas in attentional processing (Friston *et al*, 1999). For the ‘atypical’ subjects, we did not perform a group analysis. On the one hand, the group sizes were too small; on the other hand, one could not expect *a priori* that the ‘atypical’ subjects show the same kind of ‘atypicality’, that is, activate the same brain regions among each other. Their respective individual activation pattern was compared with the typically activated brain region of the control group.

The anatomical localizations of activated brain regions were determined by reference to a standard stereotactic atlas (Talairach and Tournoux, 1988), using the T2T applet (<http://neurologie.uni-muenster.de/ger/dienstleistungen/index.html>) (Deppe *et al*, 2003).

## Results

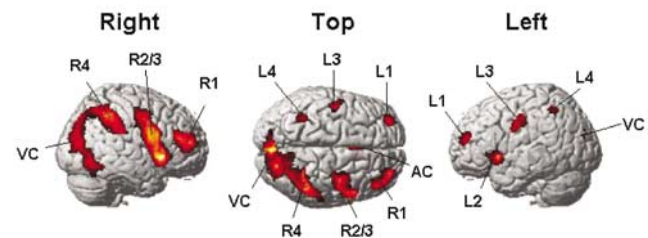
### Behavioral Testing

Subjects with associated lateralization for language and attention (subjects 4 and 5), often associated with cognitive deficits, showed normal or above normal scores on standard psychological testing (Table 2). Notably, performance on nonverbal tasks was not below overall performance.

### Brain Regions Activated by the Control Group (Right-Hemisphere Dominance for Spatial Attention, Left-Hemisphere Dominance for Language)

Figure 2 and Table 3 summarizes for the control group the regions with increased neural activity associated with the Landmark task ( $P < 0.01$ , corrected for multiple comparisons). Only clusters with a size of at least 100 activated voxels are displayed. Additionally, to illustrate the differences between the individual activation and the group activation, the activated pattern of a representative subject is provided in Figure 3A.

Increases in neural activity were observed in the ventrolateral prefrontal cortex (R1 and L1, resp.), the lateral orbito-frontal cortex (R2 and L2, resp.), the dorsolateral frontal cortex (R3 and L3, resp.), and the lateral parietal cortex (R4 and L4, resp.). These activations were observed in the right as well as in the left hemispheres, although the extent of activation was higher in the right hemisphere. Additionally, there was bilateral activation in the anterior cingulate cortex (AC) and the visual cortex (VC).



**Figure 2** Activation in the control group. Relative increases in neural activity associated with the landmark task relative to the control task ( $P < 0.01$  corrected for multiple comparisons).

**Table 2** Neuropsychologic examination of the two subjects (subjects 4 and 5) with lateralization of both language and spatial attention to the right hemisphere

(A) Verbal and nonverbal intelligence

Subject ID.	Verbal knowledge (LPS, subtest 1+2)	Reasoning (LPS, subtest 4)	Word fluency (LPS, subtest 5)	Visual perception (LPS, subtest 9)	Figure-ground perception (LPS, subtest 10)	Closure (LPS, subtest 12)
04	70	85	70	50	70	70
05	50	90	90	70	90	50

(B) Attention

Subject ID.	Concentration: speed/accuracy (d2 test)	Digit span (WAIS)	Visual span (Corsi block tapping)	Cognitive speed (TMT, part A)/ mental flexibility (TMT, part B)
04	90/50	17	25	> 10/75
05	100/90	60	60	90/90

Values are expressed in percentiles.

WAIS = Wechsler Adult Intelligence Scale; TMT = Trail Making Test; LPS = Leistungspruefsystem.

**Table 3** Brain regions activated by the control group (attention right, language left)

Cluster number	Region of Activation	Brodmann area	MNI-Coordinates			T-value
			X	Y	Z	
<i>Left hemisphere</i>						
L1	Superior frontal gyrus	BA 10	-32	54	20	6.95
L2	Inferior frontal gyrus	BA 47	-34	20	-4	7.39
L3	Precentral gyrus	BA 6	-20	-16	0	6.27
			-50	-6	32	6.14
L4	Superior parietal lobule, inferior parietal lobule	BA 7, 40	-44	-12	40	6.10
			-34	-50	52	6.68
<i>Right hemisphere</i>						
R1	Superior frontal gyrus, middle frontal gyrus	BA 10, 46	32	54	16	8.57
			42	40	18	6.95
R2/3	Inferior frontal gyrus, Insula, precentral gyrus, middle frontal gyrus	BA 6, 45, 47	50	6	24	11.36
			42	16	-4	10.25
			38	18	2	10.20
			38	-6	42	10.14
R4	Superior parietal lobule, inferior parietal lobule, gyrus supramarginalis, precuneus	BA 7, 40	16	-84	36	9.45
			16	-80	42	9.06
			46	-42	40	8.82
			14	-66	52	7.52
			30	-60	48	7.40
			60	-26	26	5.39
<i>Bilateral activation</i>						
VC	Visual cortex	BA 17, 18, 19	4	-82	0	8.45
			0	-84	14	8.37
			4	-86	26	8.28
			26	-78	30	7.62
			-18	-84	22	6.03
			18	-62	-12	4.78
AC	Anterior cingulate cortex	BA 32	6	12	38	8.10
			10	26	30	6.85

### Brain Regions Activated by Atypical Subjects from Group I (Left-Hemisphere Dominance for Spatial Attention, Right-Hemisphere Dominance for Language)

Table 4 summarizes the brain regions that were activated by the subjects 1–3 during the Landmark task ( $P < 0.001$ , uncorrected). Figure 3B provides the activation pattern of a representative subject. All three subjects activated brain regions homotopic to those activated by the control group.

### Brain Regions Activated by Atypical Subjects from Group II (Right-Hemisphere Dominance for Both Spatial Attention and Language)

Table 5 summarizes the brain regions that were activated by the subjects 4 and 5 during the visuospatial task ( $P < 0.001$  uncorrected). Figure 3C provides the activation pattern of a representative subject. Both subjects activated the same brain regions as the control group. There was no influence of the atypical right-hemisphere language lateraliza-

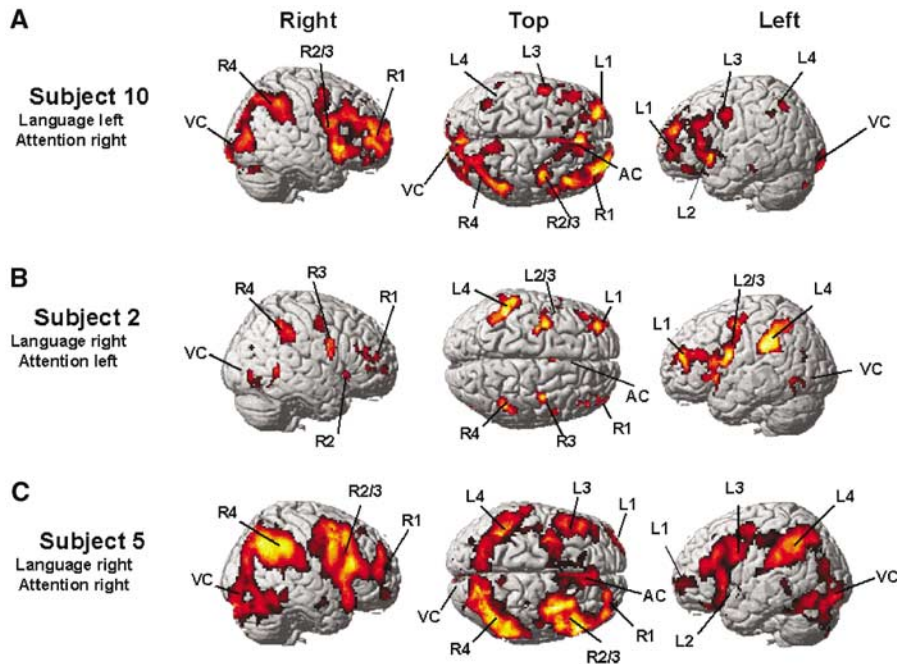
tion on the intrahemispheric visuospatial attention activation pattern.

## Discussion

To the best of our knowledge, this is the first study that examines the functional neuroanatomic correlates of atypical left-hemispheric attentional processing, and the influence of atypical right-hemisphere language dominance on the functional organization of right-hemispheric visuospatial attention.

Our data showed that

- (i) in subjects with atypical left-hemisphere dominance for spatial attention, recruitment of brain areas occurs in regions homotopic to the regions typically activated by subjects with 'normal' right-hemisphere dominance;
- (ii) for subjects with both language and spatial attention lateralized to one hemisphere, the intrahemispheric activation pattern during a visual-spatial attention task does not differ from subjects with the typical pattern of hemispheric dominance.



**Figure 3** Landmark activation pattern of representative subjects ( $P < 0.001$ , uncorrected for multiple comparisons) with (A) the typical pattern of lateralization, and (B, C) an atypical representation for language- and attention lateralization. In their respective dominant hemisphere, the ‘atypical’ subjects showed an intrahemispheric activation pattern similar to the control group. Only cluster with a size of at least 10 contiguous voxels are displayed. Of note, the sites of maximal brain activation in the respective clusters are almost identical to the control group (Tables 3–5).

**Table 4** Brain regions activated by group 1 (attention left, language right)

Cluster number	Region of Activation	Brodmann area	MNI-Coordinates			T-value
			X	Y	Z	
<b>(a) Subject 1</b>						
<i>Left hemisphere</i>						
L1	Superior frontal gyrus, middle frontal gyrus	BA 10	-30	42	8	3.78
L2/L3	Inferior frontal gyrus, precentral gyrus, insula	BA 6, 47	-28	42	22	2.59 <sup>a</sup>
			-46	4	24	5.33
			-52	-2	30	4.47
			-26	20	-4	3.88
L4	Precuneus, inferior parietal lobule, supramarginal gyrus	BA 7, 40	-22	-68	36	5.59
			-54	-40	36	5.48
			-34	-56	42	4.18
<i>Right hemisphere</i>						
R1	Superior frontal gyrus, middle frontal gyrus	BA 10	34	48	20	2.57 <sup>a</sup>
R2	Inferior frontal gyrus (extending into temporal lobe)	BA 47	42	18	-10	5.97
			46	14	-20	5.26
			34	30	-10	4.78
R3			No activation at $P < 0.05$			
R4	Inferior parietal lobule, superior parietal lobule (extending into the temporal and occipital cortex)	BA 7, 40	38	-66	24	4.54
			26	-60	0	2.74 <sup>b</sup>
			32	-58	42	2.68 <sup>b</sup>
<i>Bilateral activation</i>						
VC	Visual cortex	BA 18, 19	-2	-80	-22	3.29
			6	-64	-6	3.23
AC	Anterior cingulate cortex	BA 32	-6	32	32	3.59
			0	26	30	3.50
			-2	24	28	3.39
<b>(b) Subject 2</b>						
<i>Left hemisphere</i>						
L1	Superior frontal gyrus, middle frontal gyrus	BA 10	-32	54	20	5.54
			-36	48	8	4.97
			-36	60	10	4.06

Table 4 Continued

Cluster number	Region of Activation	Brodmann area	MNI-Coordinates			T-value
			X	Y	Z	
L2	Inferior frontal gyrus, insula (extending into temporal lobe)	BA 47	-58	14	0	5.04
			-34	16	0	4.61
			-40	16	-2	4.21
L3	Precentral gyrus, middle frontal, gyrus inferior frontal gyrus	BA 6, 9	-50	2	22	6.07
			-46	2	26	5.92
			-30	-12	56	4.69
L4	Inferior parietal lobule, supramarginal gyrus	BA 40	-44	-38	32	6.43
			-48	-44	50	5.40
			-54	-28	28	4.80
<i>Right hemisphere</i>						
R1	Superior frontal gyrus, middle frontal gyrus	BA 10	34	46	12	3.95
			38	50	16	3.85
			44	52	14	3.74
R2	Inferior frontal gyrus, insula	BA 47	36	18	-2	4.27
			30	16	8	3.78
R3	Precentral gyrus, middle frontal gyrus, inferior frontal gyrus	BA 6, 9, 44	38	0	26	5.18
			38	-8	48	5.04
			52	2	24	4.19
R4	Inferior parietal lobule, supramarginal gyrus	BA 40	44	-48	48	4.89
			50	-38	38	4.77
			52	-44	30	3.69
<i>Bilateral activation</i>						
VC	Visual cortex	BA 19	50	-78	0	4.37
			50	-76	-4	4.19
			-50	-64	-4	4.20
			-52	-62	-8	4.07
AC	Anterior cingulate cortex	BA 32	-4	20	34	5.23
			0	30	24	4.54
			4	2	46	4.32
<i>(c) Subject 3</i>						
<i>Left hemisphere</i>						
L1	Superior frontal gyrus, middle frontal gyrus	BA 10, 46	-36	56	20	5.76
			-42	56	10	4.03
			-32	66	10	3.96
L2	Inferior frontal gyrus, insula	BA 11, 47	-22	26	-14	5.13
			-24	26	-22	4.70
			-34	18	0	4.33
L3	Precentral gyrus, middle frontal gyrus	BA 6, 9	-42	6	20	6.73
			-34	-10	48	6.71
			-48	4	38	5.08
L4	Inferior parietal lobule, superior parietal lobule, precuneus	BA 7, 40	-26	-80	38	6.68
			-44	-50	42	6.65
			-34	-54	42	6.06
<i>Right hemisphere</i>						
R1	Superior frontal gyrus, middle frontal gyrus	BA 10	32	50	18	2.67 <sup>c</sup>
R2	Inferior frontal gyrus	BA 47	38	16	-8	3.43
R3	Precentral gyrus, middle frontal gyrus	BA 6	42	-4	56	5.24
			30	-6	44	4.31
R4	Inferior parietal lobule, superior parietal lobule, precuneus	BA 7, 40	24	-64	50	6.44
			32	-52	50	6.09
			40	-40	36	5.27
<i>Bilateral activation</i>						
VC	Visual cortex	BA 17, 18	48	-76	-4	3.87
			38	-82	-8	3.69
			26	-92	-16	3.37
AC	Anterior cingulate cortex	BA 32	10	16	26	5.20
			-8	18	40	4.92

<sup>a</sup>Active at  $P = 0.006$ .<sup>b</sup>Active at  $P = 0.004$ .<sup>c</sup>Active at  $P = 0.004$ .

**Table 5** Brain regions activated by group 2 (both attention and language right)

Cluster number	Region of Activation	Brodmann area	MNI-Coordinates			T-value
			X	Y	Z	
<b>(a) Subject 4</b>						
Left hemisphere						
L1			no activation at $P < 0.05$			
L2	Insula	BA 47	-30	16	4	3.75
L3	Precentral gyrus	BA 6	-26	-8	-44	3.79
			-36	-12	42	3.66
			-40	-12	44	3.55
L4	Inferior parietal lobule, superior parietal lobule, precuneus, supramarginal gyrus	BA 7, 40	-24	-46	34	4.48
			-34	-48	34	3.89
			-30	-52	46	3.61
Right hemisphere						
R1	Superior frontal gyrus, middle frontal gyrus	BA 10	26	48	22	2.73 <sup>a</sup>
R2	Inferior frontal gyrus, insula, precentral gyrus	BA 44, 45, 47	38	24	4	3.79
			58	4	10	3.92
R3	Precentral gyrus, middle frontal gyrus	BA 6	28	-10	32	4.44
			32	-12	46	3.99
			44	-8	44	3.48
R4	Inferior parietal lobule, supramarginal gyrus	BA 40	46	-46	46	5.23
			36	-54	58	4.30
			44	-44	40	5.00
Bilateral activation						
VC	Visual cortex	BA 18	-24	-72	14	3.58
AC	Anterior cingulate cortex	BA 32	6	20	44	3.04
			8	18	36	2.38 <sup>b</sup>
<b>(b) Subject 5</b>						
Left hemisphere						
L1	Superior frontal gyrus, middle frontal gyrus	BA 10	-42	58	0	7.36
			-38	60	0	7.01
L2	Inferior frontal gyrus, insula	BA 44, 45, 47	-32	22	-10	7.96
			-34	24	-14	7.91
			-44	20	8	6.92
L3	Middle frontal gyrus	BA 6	-28	-6	48	12.62
			-36	-4	60	7.04
L4	Precuneus, inferior parietal lobule, superior parietal lobule	BA 7, 40	-40	-54	54	10.52
			-26	-70	46	9.92
			-26	-64	38	9.87
Right hemisphere						
R1 <sup>c</sup>	Superior frontal gyrus, middle frontal gyrus	BA 10, 46	42	52	16	10.46
			32	60	20	4.93
R2 <sup>c</sup>	Inferior frontal gyrus	BA 44, 45, 47	52	16	6	9.21
			36	18	-8	6.17
R3 <sup>c</sup>	Precentral gyrus, middle frontal gyrus	BA 6, 9	34	0	48	12.10
			36	2	52	12.09
			48	4	32	11.23
R4	Precuneus, inferior parietal lobule, superior parietal lobule (extending into visual cortex)	BA 7, 40	22	-70	40	13.15
			28	-6	48	12.94
			36	-66	42	12.24
Bilateral activation						
VC	Visual cortex	BA 17, 18, 19	-18	-94	-10	7.68
			18	-94	-22	7.64
			26	-90	-22	7.09
AC	Anterior cingulate cortex	BA 32	10	10	48	8.79
			-8	12	42	6.25

<sup>a</sup>Active at  $P = 0.003$ .<sup>b</sup>Active at  $P = 0.009$ .<sup>c</sup>R1, R2, R3 are at  $P = 0.001$  (uncorrected) and so extensively activated that they are part of a contiguous cluster.

## Intrahemispheric Pattern of Activation for Spatial Attention Tasks

The pattern of activation in our control group (of 'typical' subjects) is in line with findings of a previous study by Fink and colleagues who used a similar paradigm (Landmark task) in healthy volunteers (Fink *et al*, 2000, 2001). During the Landmark task, these authors found activation predominantly in the right superior and inferior parietal cortex, as well as prefrontal cortex and anterior cingulate. The intrahemispheric pattern of activation in their study was also similar to the activations found in our subjects with left-hemispheric attentional dominance.

The present study concurs with findings on atypical language lateralization (Knecht *et al*, 2003) by showing that distinct intrahemispheric brain regions are activated in spatial attentional tasks, regardless of hemispheric dominance and regardless of language lateralization. Taken together, the two studies strongly support the notion that the intrahemispheric pattern and not the interhemispheric side is the distinct feature for the neural processes underlying language and spatial attention. In the following sections, we will discuss the implications of these findings from a theoretical and clinical perspective.

## Theories on Cerebral Lateralization

A major phenomenon of human brain function is its ubiquitous lateral cerebral specialization (Geschwind and Galaburda, 1985; Gazzaniga, 2000). The key features of this specialization have traditionally been the left hemisphere's superiority for language and speech and the right hemisphere's superiority for tasks such as attentional monitoring. This division was thought to result from the fact that the left hemisphere has marked limitations in perceptual functions, and the right hemisphere prominent limitations in its cognitive functions (Gazzaniga, 2000). Other researchers have suggested that lateralization of language and control of spatial attention dissociate because the cerebral hemispheres differ fundamentally in their computational modes, with the left being biased for symbolic and the right for analogue processes (Corballis, 1997). Relative hemispheric specialization for global and local processing has also been proposed to account for lateralization of cognitive functions (Robertson and Lamb, 1991; Fink *et al*, 1997; Barrett *et al*, 1998).

A growing body of lesion studies (Fischer *et al*, 1991; Trojano *et al*, 1994; Alexander and Annett, 1996; Osmon *et al*, 1998) and activation studies (Flöel *et al*, 2001, 2003; Flöel and Knecht, 2002; Hubrich-Ungureanu *et al*, 2002; Staudt *et al*, 2002; Knecht *et al*, 2003) inform us, however, that other patterns of hemispheric specialization may occur. For language, a number of studies have addressed the functional topography in subjects with atypical right-hemisphere language dominance (Hubrich-

Ungureanu *et al*, 2002; Staudt *et al*, 2002; Knecht *et al*, 2003; Jansen *et al*, 2004b). The underlying neuroanatomic correlates for attention are largely unknown, however. In the present study, we have addressed this issue, and found that also for spatial attention, atypical hemispheric dominance shows a mirror-reverse pattern of brain activation, compared with the 'standard' pattern.

These findings suggest that atypically lateralized brain functions in general are localized to homotopic sites within the respective hemisphere. Intrahemispheric pattern rather than hemispheric side seems to be a hard-wired pattern of brain organization, at least in healthy individuals (see examples of cross-modal plasticity in chronic deafferentation, review in Burton, 2003).

## Neuropsychologic Implications

Our data further suggest that the brain may organize in a way that language and spatial attention can exist within the same hemisphere without penalty to brain function. The subjects in our study with lateralization of both language and attention to the right hemisphere displayed normal intellectual, linguistic, and spatial performance. Although we did not perform detailed morphometric MRI analysis, we inspected the MRIs for evidence of structural damage. No such changes were detected. Therefore, brain lesions early in life, which might have been involved in the development of atypical lateralization for language and attention, are highly unlikely in our case.

On the basis of studies in patients with early-onset seizures (Saykin *et al*, 1989; Strauss *et al*, 1990; Helmstaedter *et al*, 1994), it has been hypothesized that the limited computational capacities would not allow one hemisphere to be dominant for both language and spatial attention without detrimental effects to linguistic and spatial abilities ('crowding hypothesis') (Saykin *et al*, 1989; Strauss *et al*, 1990; Carlsson *et al*, 1994; Helmstaedter *et al*, 1994; Mariotti *et al*, 1998; Staudt *et al*, 2002). However, in contrast to previous studies on the crowding phenomenon (Saykin *et al*, 1989; Strauss *et al*, 1990; Carlsson *et al*, 1994; Helmstaedter *et al*, 1994; Mariotti *et al*, 1998; Staudt *et al*, 2002), no negative behavioral consequences could be ascertained in our subjects. Most importantly, we did not find major discrepancies between verbal and nonverbal performance. We believe that the decisive difference to the previous studies, which all examined populations with left-hemispheric damage or seizures, is that our subjects do not have any evidence of (left-hemispheric) damage.

## Clinical Relevance

Our findings show that all patterns of cerebral lateralization may occur in healthy subjects, and

that in certain individuals, different functions may lateralize independently from each other. Clinicians need to be aware of the possibility of combined linguistic and visuospatial impairments of variable degrees after left- or right-hemispheric damage.

Our results are also of direct clinical relevance in patients where fMRI is used to determine cortical 'attention areas' before brain surgery (e.g., tumor or epilepsy surgery). Perhaps the most difficult task in the interpretation of fMRI data is the differentiation between 'artificial' and 'real' activation. From our results, it can be concluded that in patients with atypical hemispheric dominance of a cognitive function, activation should be expected in homotopic brain regions. Activation outside these expected locations should be interpreted with caution.

## Conclusion

In the present study, we showed that not hemispheric side, but the intrahemispheric pattern, is the distinct feature of localization for attention and language (Gazzaniga, 2000). Differences in hemispheric side for lateralized brain functions need not be accompanied by impaired function, as proposed by lesion studies (Saykin et al, 1989; Strauss et al, 1990; Staudt et al, 2002). Rather, all patterns of cerebral lateralization may be implemented in the healthy human brain. The present results add to the evidence that atypical lateralization as such does not reflect disorganization of the neural basis of language. It is still unknown, however, why some people develop an atypical pattern of hemispheric lateralization, while the majority of healthy individuals adheres to the standard pattern. Genetic, hormonal, and environmental factors may affect embryonic development and the side of cerebral lateralization, an issue for further investigation.

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