The neural correlates of orienting: An integration of fMRI and skin conductance orienting

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Received 20 June 2000; accepted 5 July 2000

In fMRI studies, the averaging of neural activity across multiple trials might obscure important psychophysiological subprocesses. The orienting response (OR) is a distinctive subprocess signalling the active orientation of attention towards potentially significant events. We sought to elucidate fMRI activity associated with visual stimuli that did or did not evoke simultaneously recorded electrodermal ORs (using customised skin conductance recording). With-OR stimuli were associated with significant activity in the hippocampus, anterior cingulate and ventromedial prefrontal cortex. Averaged analysis revealed activity only in the expected visual circuits. Our results suggest that potentially significant stimuli (with-OR) activate different functional networks to familiar (without-OR) stimuli, and that orienting may therefore be an informative subprocess to consider in cognitive fMRI studies.

NeuroReport 11:3011–3015 © 2000 Lippincott Williams & Wilkins.

Key words: Anterior cingulate; Functional magnetic resonance imaging; Hippocampus; Orienting; Skin conductance responses

INTRODUCTION

In fMRI studies to date, analysis relies on the sound method of averaging across multiple trials that correspond to a particular condition of interest. However, it is possible, particularly in paradigms designed to explore aspects of information processing, that different psychophysiological subprocesses are engaged across the trial sequence, and that these subprocesses may be obscured by an average measure. The orienting response (OR) is a distinctive subprocess to consider in this regard, given that it signals the active orientation of attention towards novel or significant events, and the mobilization of resources to process these events [1].

Our group conducted the first cognitive, short inter-stimulus-interval (ISI) event-related potential study, in which single-trial events associated with electrodermal ORs were extracted from the same dataset that was traditionally averaged. It was found that ‘with-orienting’ events are associated with a different psychophysiological response pattern to ‘without-orienting’ events [2].

In this study, we examined the neural activity underlying ‘with-orienting’ to discrete visual stimuli, compared to ‘without-orienting events’, using fMRI. ORs were delineated by simultaneous measures of skin conductance response (SCR).

The OR was first described by Pavlov [3] as a behavioural response to novel or significant environmental stimuli that directs attention towards a stimulus to extract further information. Numerous models of the OR propose that it emerges from mismatching in the comparison of novel incoming information and familiar stored information [4–9] (for review see [10]).

There is a convergence of evidence that networks underlying the generation of the OR centre on the hippocampus. Other networks implicated in the mechanisms of orienting include the anterior cingulate, ventromedial prefrontal and orbitofrontal cortices, and hypothalamus [1,4,6–10]. Of the range of indices of the OR (including heart rate, EEG desynchronization, eye movement), the most commonly used measure is the electrodermal skin conductance response (SCR) (see [10]). SCRs index the phasic changes (recorded 1–5 s after the stimulus) in autonomic arousal that signal the occurrence of an OR.

Elucidation of the networks underlying the OR has primarily involved evidence from animal and lesion studies. To date, the networks purported to underlie electrodermal orienting have not been examined using fMRI. In only two previous fMRI studies that have incorporated SCR recording, the focus was on SCR activity as an index of conditioning or as an index of spontaneous fluctuations.
in arousal associated with motivational behaviour, rather than as a specific measure of orienting [11,12].

In our study, the primary aim was to elucidate the neural activity associated with ORs that are generated in relation to discrete stimuli, using simultaneous fMRI and SCR (‘with-OR’ stimuli) recording. We observed the neural activity elicited in relation to stimuli that evoked electrodermal ORs (phasic SCRs) compared to those that did not elicit ORs. In this sense, our analysis of fMRI data followed an event-related procedure. The goal of this study was to first test this procedure in a paradigm known to produce robust fMRI activity, namely a flashing checkerboard paradigm.

One of the major issues that has plagued attempts to simultaneously assess electrodermal ORs and brain function in short ISI cognitive paradigms has been the time course of phasic SCRs (which last 4–6 s). In our study, we were able to link individual stimuli (3 s duration, 0.75 s ISI) with concomitant SCRs by the use of a sigmoid-exponential SCR model and software developed in our group [13] that allow for accurate scoring of overlapping SCRs by decomposition into their constituent parts. This quantitative SCR method was applied successfully in previous examinations of with and without-orienting ERP data, and the dynamics of SCR activity [2,14].

Electrodermal ORs represent relatively unambiguous changes in arousal level, but can be small; traditionally an OR is defined as > 0.05 mS above baseline. Therefore, it is essential that they be recorded without noise (RF) interference in the fMRI environment. In the previous fMRI-SCR studies of arousal modulation, the focus has been on far larger SCR amplitude (eg. 2 s.d. above baseline) that was not linked directly to discrete stimuli. These studies have therefore relied on standard GSR systems and post-processing of SCR data (eg. filtering and smoothing to remove both repetitive high-frequency ‘noise’ and nonrepetitive noise, followed by resampling at the acquisition frequency) [12]. In this study, we used a fibre-optic GSR system developed in our group, which enables a minimal level of noise in the SCR data acquired simultaneously with fMRI scanning. This system allows even small SCRs to be delineated, without filtering and smoothing.

We predicted that traditional averaged analysis of fMRI data for the checkerboard stimuli would produce the commonly observed visual cortex activity. In the subaveraging analysis of stimuli (events) associated ‘with’ vs ‘without-orienting’, hippocampal-anterior cingulate-prefrontal networks would be activated.

MATERIALS AND METHODS

Subjects: Eight healthy males (mean (± s.d.) age 30.88 ± 3.8 years) participated in the study on a voluntary basis. Exclusion criteria were left handedness, and recent history of substance abuse, epilepsy or other neurological disorders, and mental retardation or head injury (assessed using the Westmead Hospital Clinical Information Base questionnaire; WHCIB).

Written consent was obtained from all subjects prior to testing in accordance with National Health and Medical Research Council guidelines.

Experimental paradigm: To produce visual sensory stimulation, we used a periodic presentation of checkerboard (test) and blank screen (control) stimuli. Four test stimulus blocks alternated with four control blocks. Stimuli were 512 pixels in height, and 384 in width, with 20% contrast. On checkerboard stimuli, checks were coloured blue and green. In test blocks, the checkerboard pattern was reversed in an alternating sequence (ie., green checks appeared blue, and vice versa on every second checkerboard stimulus). Each block comprised eight stimuli of 3 s duration, with an interstimulus interval of 0.75 s. The duration of each block was therefore 30 s. There were 32 test and 32 control stimuli in total, and the total duration of the paradigm was 4 min.

fMRI acquisition: Subjects were scanned during the checkerboard task using a Siemens 1.5 T Magnetom VISION Plus system to acquire 64 T2*-weighted images depicting BOLD (blood oxygenation level dependent) contrast for each 3 s stimulus at 18 axial non-continuous 6 mm thick plane (slices), parallel to the intercommissural (AC-PC) line: TE 40 ms, TR 3 s, matrix 128 × 128, interslice gap 0.6 mm. This EPI dataset provided full coverage of the temporal (including hippocampus and amygdala), frontal, occipital and parietal lobes.

Skin conductance recording: Electrodermal data were acquired simultaneously with fMRI data, using a fibre-optic system developed by our group to protect against interference from RF pulses in the fMRI environment. This system reduced induced currents by the inclusion of resistors in all wires, the reduction of loop area in the wires, and by the use of an optical signal that is converted back to an electrical signal once relayed out of the scanner.

Fig. 1. The sigmoid-exponential SCR model method (Lim et al., 1997) allows overlapping SCRs (as depicted above) to be decomposed and scored for both peak amplitude and latency (indicated by arrows). The modelled SCRs are curve-fitted to the SCRs using the parameters: time at which response starts, gain factor, rise time, time constant of the decay, constant (skin conductance level) and size of tail of previous SCR.
room. Resultant data were noise-free and did not require either filtering or smoothing (see Fig. 3 for example). Skin conductance was recorded using a pair of Ag/AgCl electrodes with 0.05 M sodium chloride gel placed on the distal phalanges of digits II and III of the left hand.

Selection of stimuli with and without electrodermal orienting: The presence of an electrodermal OR was determined by our customised software (Skin Conductance Response Evaluation System, SCORES) [13]. Orienting was defined as an unambiguous increase (>0.05 mS) in skin conductance with respect to each pre-stimulus baseline and occurring 1–2 s after the stimulus [15,16]. The segments of electrodermal data containing composite skin conductance signals and often overlapping responses were decomposed into phasic skin conductance responses (SCRs or orienting) and tonic skin conductance level (SCL) components using our sigmoid-exponent SCR model implemented by SCORES. This model represents the SCR in mathematical form, which enables curve-fitting and analytical separation and scoring of the SCR/SCL components (Fig. 1).

With-orienting stimuli were those in which the onset of a phasic SCR occurred within the 3 s of the stimulus. Without-orienting stimuli were classified by the failure to detect the onset of an SCR in this period.

Data analysis: Neural activity was analysed first by traditional averaging and, second by an event-related analysis of subaveraged with- and without-OR stimuli. Prior to analysis, images were first preprocessed to minimise the effects of subject motion and remove low frequency confounds [17]. The experimental design was then convolved with two Poisson functions representing haemodynamic delays of between 4 and 8 s to be auto-

statistic under the null hypothesis constructed by random permutation of the time series. Voxels significantly activated at any type I error probability could be identified by obtaining the required critical value for the statistic from the null distribution [19]. Group maps were constructed following transformation of the observed and randomized statistic maps into the standard space of Talairach and Tournoux [20] (see [21]).

In the average analysis of the overall checkerboard response, the ON (reversing checkerboard) periods of stimulation were contrasted with the OFF (blank screen) periods in the experimental design.

In subsequent subaveraging analysis, responses obtained during periods of checkerboard stimulation in which ORs were observed were contrasted with periods of checkerboard stimulation when no ORs were observed.

RESULTS

Traditional averaging: Checkerboard stimuli, when compared to a baseline (blank screen) condition, produced the typical pattern of robust neural activity in the visual cortices. Highly significant ($p = 0.000006$) and robust activity was observed bilaterally in the extrastriate visual regions, including lingual, fusiform and inferior occipital gyri (encompassing Brodmann areas 17, 18, 19 and 37; Fig. 2). Less prominent but still significant ($p = 0.0002$) activity was also observed bilaterally in the nucleus lenticularis. Talairach coordinates (in millimetres) for this activity were $-32$, $0$, $-3$ (left hemisphere) and $32$, $4$, $-3$ (right).

With- and without-OR subaveraging: The mean number of stimuli associated with an SCR, subaveraged to derive the with-orienting condition ($A_1$) was $8.75 \pm 4.16$, and the mean amplitude of these SCRs was $0.12 \pm 0.7 \mu S$. Figure 3 depicts an example SCR; the SCR waveform is typical of electrodermal Orienting recorded in a standard setting and confirms the lack of interference from RF pulses generated in the fMRI environment.

Significant and specific with-orienting activity was observed in OR-related networks, including the right anterior

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**Fig. 2.** Generic brain activity for the 8 subjects for averaged analysis. Voxel activated in response to the checkerboard pattern are coloured yellow, with radiological presentation (left side of brain on right side of image and vice versa). Significant striate and extrastriate visual circuit activity is shown within lingual (GL), fusiform (GF) and inferior occipital (GOI) gyri, encompassing Brodmann Areas (BA) 17, 18, 19 and 37. Talairach coordinates (in mm), referring to the voxel with the maximum FPQ in each cluster were (a) 22, $-84$, $-24$ and $-14$, $-91$, $-24$; (b) 18, $-91$, $21$ and $-14$, $-91$, $21$ and $-14$, $-91$, $-21$; (c) 18, $-91$, $-18$, and $-18$, $-91$, $-18$ and (d) 22, $-88$, $-15$ and $-14$, $-94$, $-15$. 
cingulate (p = 0.00003), left hippocampus (p = 0.002), and medial prefrontal gyrus (p = 0.001; Fig. 4).

Some activity was still observed in the bilateral lingual (p = 0.00008), bilateral fusiform (left, p = 0.0005; right, p = 0.002), and right inferior occipital gyrus (p = 0.001), but this activity was substantially circumscribed compared to that revealed in averaged analysis. Additional bilateral with-orienting activity was observed in the cerebellum (left, p = 0.0008; right, p = 0.0002), and within the inferior (left, p = 0.001), medial (left, p = 0.006; right, p = 0.005), and superior (right, p = 0.001) temporal gyri. Talaraich coordinates and approximate Brodmann areas for each region of activity are listed in Table 1.

Consideration of data for individual subjects revealed that all subjects showed anterior cingulate activity, and seven of the eight subjects showed hippocampal activity.

DISCUSSION
This preliminary study served to demonstrate that the extraction of fMRI activity according to the presence or absence of an electrodermal OR produces meaningful brain network activity that is distinct from that produced in a traditional averaged fMRI analysis. Moreover, the delineation of ‘with-orienting’ activity has further elucidated the networks underlying the OR in humans.

Averaged analysis of activity elicited by checkerboard, contrasted with control, stimuli produced a robust pattern of striate and extrastriate visual cortex activity, within the inferior occipital, lingual and fusiform gyri (see Fig. 3), and encompassing areas 17, 18, 19 and 37. This pattern is consistent with findings from fMRI studies of visual activation, using checkerboard and related visual stimulation [22–24]. Less prominent activity was also observed bilater-
ally in the nucleus lentiformis, which has been associated with visual processing in animal studies [25].

When the fMRI activity over the same session of averaged fMRI data, was subaveraged for with-OR checkerboard stimuli, markedly different network activity was elucidated. Specific with-OR activity was evident in the nucleus lentiformis, which has been associated with the observations of Critchley et al. [12] that phasic increases in arousal may produce a corresponding increase in visual cortex activity, and that cerebellum may be involved in the central control of autonomic responses.

These results provide the first convergent fMRI evidence to confirm indications from animal, stimulation and lesion studies that the hippocampus, anterior cingulate and ventromedial prefrontal cortex are associated with the generation of the OR [4,6–10].

Future studies might seek to replicate these findings using different paradigms, and across different modalities. The findings might also be extended to elucidate more fine grained aspects of the networks underlying the OR, including models that propose possible lateralisation of some of these networks. Our findings concerning orienting networks provide a frame of reference that has implications for the array of applications of orienting and habituation in learning theory, models of emotion and neuropsychiatric research.

REFERENCES


Acknowledgements: The development of this new integrated fMRI-SCR system was supported by Wellcome Trust Collaborative Biomedical Research Travel funding (L.M.W., E.G., M.J.B.). We also acknowledge the support of the Rebecca Cooper Medical Research Foundation, The Neuroscience Institute of Schizophrenia and Allied Disorders (NISAD), and the facilitatory efforts of Dr Brian Hutton.

Table 1. Talairach coordinates and approximate Brodmann areas with OR brain activity.

<table>
<thead>
<tr>
<th>Region (approx. Brodmann area)</th>
<th>Side</th>
<th>x°</th>
<th>y°</th>
<th>z°</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate (24)</td>
<td>R</td>
<td>7</td>
<td>32</td>
<td>–3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Lingual gyrus (17)</td>
<td>L</td>
<td>–4</td>
<td>–80</td>
<td>–6</td>
<td>0.00008</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>–4</td>
<td>–70</td>
<td>–24</td>
<td>0.00008</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>18</td>
<td>–56</td>
<td>–15</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fusiform gyrus (18)</td>
<td>R</td>
<td>25</td>
<td>80</td>
<td>–15</td>
<td>0.0002</td>
</tr>
<tr>
<td>Superior temporal gyrus (22)</td>
<td>R</td>
<td>51</td>
<td>–4</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>L</td>
<td>–29</td>
<td>–35</td>
<td>–3</td>
<td>0.002</td>
</tr>
<tr>
<td>Medial prefrontal gyrus (32)</td>
<td>R</td>
<td>4</td>
<td>46</td>
<td>–6</td>
<td>0.001</td>
</tr>
<tr>
<td>Medial temporal gyrus (39)</td>
<td>L</td>
<td>–36</td>
<td>–63</td>
<td>21</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*The cluster with the largest number of voxels within each region is reported. Talairach coordinates (x, y, z, in mm) refer to the voxel with the maximum FPK in each cluster (with a minimum of 4 voxels per cluster).