Temporal dynamics of distributed brain networks in schizophrenia

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Background: One of the most important contributions of fMRI to systems neuroscience has been the identification of a small number of remarkably robust spatially distributed networks that are modulated under many circumstances. The nodes of these networks exhibit coordinated BOLD fluctuations during rest and performance of diverse tasks[1]. Some networks are involved in sensory processing; others link nodes involved in cognition or attention. Most importantly, evidence is emerging that these networks are disrupted in a variety of disorders (e.g. schizophrenia[2]). Although fMRI has excellent spatial resolution, it is limited by providing only an indirect haemodynamic response to neural activity which has poor temporal specificity. However, recent developments in magnetoencephalography (MEG) have yielded functional networks from electrophysiological data that resemble closely the networks obtained by fMRI[3], facilitating investigation of the electrophysiological processes underlying the haemodynamic networks observed in fMRI, as well as measurement of network dynamics on the millisecond timescale at which the brain operates. In this study, we investigate network dynamics using MEG in patients with schizophrenia and healthy controls. We aim to elucidate the time-frequency evolution of oscillatory effects in networks previously well characterised by fMRI, and delineate any group differences in these effects.

Methods: 12 patients and 14 controls (group matched for age, gender and parental socioeconomic status) undertook 8 blocks of a "relevance modulation" target-detection task. Alternating images of butterflies and images of ladybirds were presented. Within a given block, only one type of stimulus was relevant to the task. In "butterfly-relevant" blocks, the participant had to respond (right-hand button press) only if the butterfly matched a previously memorised example. In "ladybird-relevant" blocks, the participant had to respond only if the numbers of red and yellow ladybirds displayed were equal. Targets were rare, and discarded from the analysis. Relevant non-targets were compared with irrelevant non-targets.

MEG data were collected using the 3rd order gradiometer configuration of a CTF 275 channel MEG system. Data were hardware filtered to 1-150Hz. Source localisation was achieved using a beamformer approach[5] in which electrical source activity was estimated for each vertex of an 8mm^3 isotropic grid spanning the entire brain. Beamformed data were frequency filtered into 17 overlapping frequency bands and the Hilbert envelope computed within each band yielding oscillatory power timecourses. 8 networks that matched closely fMRI networks that had previously been shown to have functional significance[1], were selected. Hilbert envelope timecourses were collapsed spatially across voxels within these networks, and averaged across relevant and irrelevant trials. The mean resting state amplitude of each timecourse, within each frequency band, was subtracted on a subject by subject basis, yielding time-frequency difference spectrograms which were averaged across subjects.

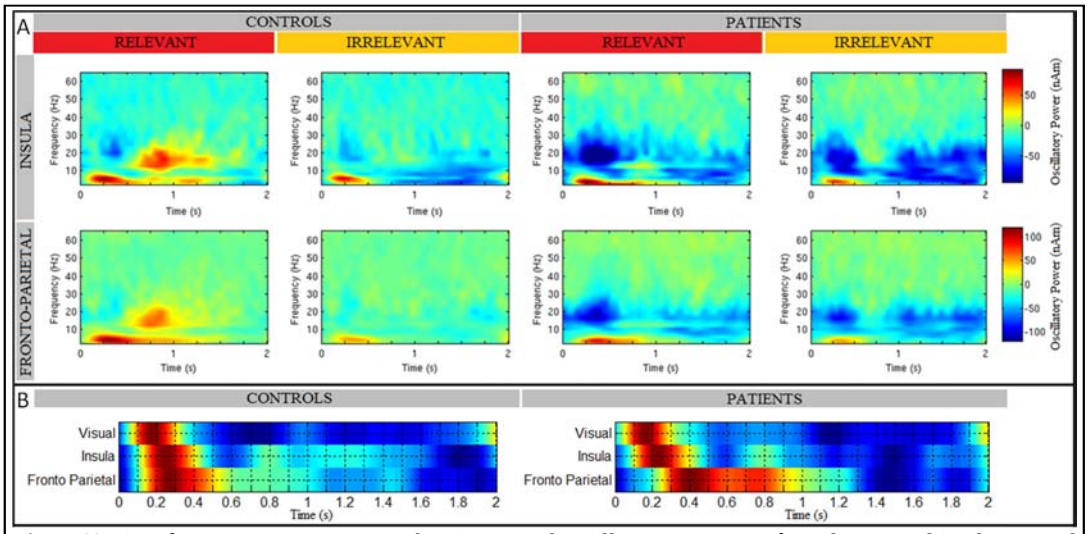

Fig 1. A*) Time frequency spectrograms showing neural oscillatory responses for relevant and irrelevant task conditions in the insula and fronto-parietal networks.* ***B****) Group mean post stimulus induced theta responses in controls and patients for visual, insula and fronto-parietal networks. (Relevant condition only)*

Results: Figure 1A presents time frequency difference spectrograms, showing evolution of neural oscillatory power in the bilateral insula and fronto-parietal networks. Time zero corresponds to the presentation of the stimulus. The differences between relevant and irrelevant stimuli are more marked for controls, particularly in the beta band (13-30Hz). Controls and patients also differ within conditions: unlike controls, patients exhibit a drop in beta amplitude at 0.2s with no rebound at ~1s. Figure 1B shows the timing of the peak theta (4-8Hz) response from 3 networks. In both groups, timing information is apparent across the three networks, with visual activity being followed by activity in insula and fronto-parietal networks. Note that in patients, responses are later than controls; this difference is significant in the fronto-parietal network ($p<0.05$).

Discussion and Conclusions: We have demonstrated the suitability of MEG for investigating electrophysiological aspects of brain networks, and that these effects can yield time-frequency signatures with functional and clinical meaning. We have shown that not only do patients exhibit reduced modulation of brain activity by task-relevance, but also a slower build-up of activity in executive networks. Thus we have shown that patients with schizophrenia exhibit significant differences in both the amplitude and timing of task-induced neuronal responses. These results add to a growing body of evidence suggesting that large scale distributed networks are of significant clinical importance. Furthermore, our results emphasize the advantages afforded by a multi-modal approach to network characterisation; by showing the importance of neural oscillations and elucidating subtle timing differences which are not accessible to fMRI.

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