Neural oscillatory basis of functional connectivity MRI differences between semantic word tasks

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Introduction: Recently, neuroimaging studies have examined connectivity patterns between brain regions, rather than modulated activity in unimodal regions. Brain networks (implied by connectivity metrics) have been identified using fMRI in both the resting and task positive states. Further, on switching between states, resting state networks (e.g. Default Mode Network (DMN)) have been shown to give way to task-relevant networks. Whilst basic findings are robust, there is a need to determine the neural underpinnings of haemodynamic connections. Various studies making direct neural measurements (MEG, EEG, electrophysiology etc) have shown network changes in specific neural frequency bands [e.g. 1], which may or may not relate to power changes. Here, we compare connectivity patterns measured by fMRI and MEG to examine which aspects of fcMRI changes relate to neural connectivity changes, on a two-condition semantic task designed to elicit functional networks related to interpretation and processing of either abstract (e.g. dream) or concrete (e.g. house) words. We employ novel techniques for computing fMRI and MEG connectivity matrices.

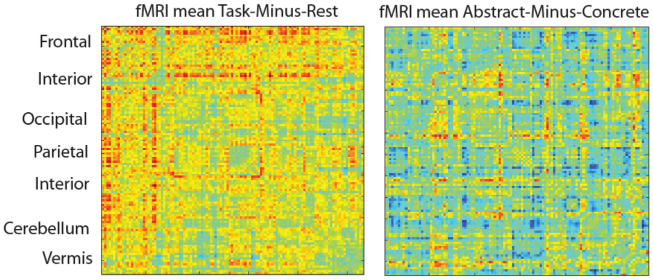

Figure 1: fMRI temporally-weighted 116 AAL region-based connectivity matrices

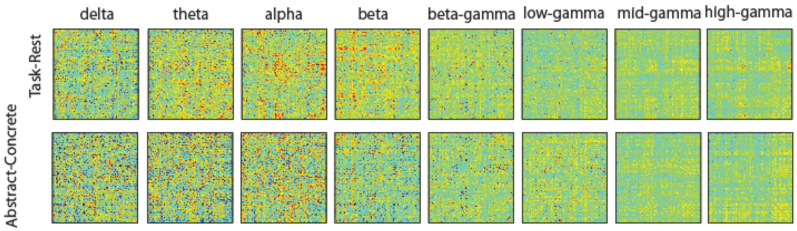

Figure 2: MEG connectivity differences across frequency and 116x116 AAL regions

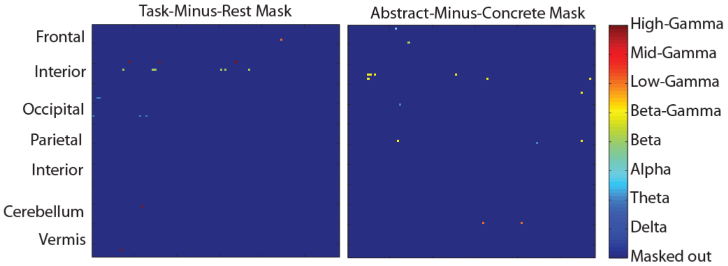

Figure 3: Spatial-spectral mask after dual-threshold (described in text)

Methods: *Paradigm:* Three words appeared for three seconds: the one at the top was the 'test' word and the other two were presented below, side-by-side. The participant had to make a decision as to which of the two bottom words was closer in meaning to the 'test' word. They made a button press (right hand, 2nd or 3rd digit) to indicate either the word on the left or right. The screen showed fixation for 7 seconds after each set of words. The words alternated pseudo-randomly between either abstract or concrete nouns. The three words in each set were similar semantically such that there was no 'correct' answer. *Data Acquisition:* A total of 96 trials was presented in blocks of 16 each with a 90s rest between blocks. Echo-planar images were acquired using a 7T Philips Achieva system (2s TR, 25ms TE, 36slices, 2.4 mm^3 voxels, 80x80 FOV, SENSE factor 2). An anatomical MRI was also collected for coregistration to MNI coordinates. The same paradigm in the same four healthy subjects was used in MEG (275 channel CTF Omega with 3rd order gradient correction). Localising coils were placed on the subjects head to coregister the MEG channels to the subject's anatomical MRI.

Data Analysis: *fMRI:* Data were corrected for motion and slice timing, and normalised. A temporal weighting coefficient was created based on task timing convolved with the canonical haemodynamic response. This served to focus a time-series for either the 'abstract' or 'concrete' condition as well as to reduce artefacts uncorrelated with task-timing [2]. *MEG:* Data were projected from sensors to the brain using a frequency-specific beamformer. Sensor covariance for each band (δ 1.5-4Hz, θ 4-8hz, α 8-12Hz, β 12-20Hz, βγ 20-35Hz, Lγ 35-48hz, Mγ 52-75hz, and Hγ 75-98Hz) was computed over all trials and including both task and rest period. The Hilbert envelope of the projected time-series was computed for each frequency band [3]. *Connectivity Assessment:* Coregistered to MNI space, each subject's data were segmented into 116 regions defined by Automated Ananatomical Labelling (AAL) [4], and voxels within each region averaged together. For fMRI, correlation between the weighted times series for each region was computed, creating a 116x116 connectivity matrix, one for each of abstract and concrete trial types. The connectivity matrix weighted for the rest period was also computed. For MEG, the correlation of the Hilbert envelopes for each AAL region pairing was computed for each trial for (1) abstract words presentation, (2) concrete words presentation, and (3) rest period for both trial types, and then averaged over trials. Matrices of correlation differences were computed for both Task-Minus-Rest (TMR; task is average of abstract and concrete) and Abstract-Minus-Concrete (AMC), for both fMRI (Fig 1) and each MEG frequency band (Fig 2). To find nodes significantly changing in both modalities, two independent masks were created. First, we computed the spatial correlation between a given node's connectivity pattern in fMRI and that same node's connectivity pattern for each MEG frequency band. The first mask was created from nodes with high spatial correlation across subjects (Z-score greater than 2.5 for TMR and 2.0 for AMC). A second independent mask was created based on thresholding the absolute value of the connectivity, keeping only nodes that were above (1.5 and 1.0 times the) mean absolute-value connectivity in three out of four subjects for both fMRI and MEG, respectively. The intersection of these two masks was used to focus on specific spectro-spatial node pairings (Fig 3; colour-coded by frequency band).

Results: *Task-Minus-Rest* connectivity differences in both fMRI and MEG show frequency-specific changes between nodes in task-relevant areas and DMN (*theta*: left (L) hippocampus with superior frontal; *theta*: right (R) cuneus with L motor, superior medial frontal and mid-orbital frontal; *beta*: superior medial frontal with inf. orbital frontal, L/R insula, L inf parietal, and L supramarginal; *low-gamma*: mid-frontal with L inf temporal; *high-gamma*: L supp. motor area with R rolandic operculum, anterior cingulate, and precuneus; *high-gamma*: cerebellum with sup. medial frontal; high-gamma: vermis with R inferior frontal triangularis.) *Abstract-Minus-Concrete* connectivity differences show a different spectral-spatial pattern of changes: (*theta*: R parahippocampal with L middle orbital frontal; *theta*: L superior parietal with L inferior temporal; *alpha*: R motor with sup. med. frontal and vermis; *beta*: L mid-orbital frontal with L insula; *beta-gamma*: L mid-orbital frontal with R mid-orbital frontal, L operculum, L frontal pars triangularis, mid-occipital; *beta-gamma*: L rectus with R mid-orbital frontal, R angular gyrus, and vermis; *beta-gamma*: mid-cingulate with vermis; *beta-gamma*: R somatosensory with sup. med. frontal and vermis; *low-gamma*: cerebellum with R supramarginal and R sup. temporal).

Discussion and Conclusion: By comparing MEG connectivity differences to fcMRI, the underlying neural oscillations of the haemodynamic connectivity changes can be examined. Some results are consistent with previous findings for the task versus rest (e.g. hippocampus-frontal changes in the theta band, presumably related to word-meaning recall, and left SMA - DMN (ACC and precuneus) changes in high-gamma, presumably related to motor preparation). A previous meta-analysis of abstract-versus-concrete word processing [5] found left temporal and operc/tri frontal activity greater for abstract-words and left fusiform, parietal/occipital junction and mid-occipital for concrete-words; this is consistent with the findings here: in theta (SupPar with InfTemp) and in beta-gamma (left orbital frontal with left operc/tri frontal and mid-occipital). Other areas were also found to be different between conditions that were not found in the meta-analysis above; however, this is exciting as the meta-analysis only focussed on unimodal fMRI task-changes, not connectivity changes, nor haemodynamic changes in relation to neural oscillations. This study not only illustrates how multi-imaging-modality whole-brain functional connectivity changes can be used to understand semantic word processing from a spatial-spectral view, but also demonstrates the importance and ability of multimodal fMRI/MEG studies for connectivity.

References: [1] Payne et al. 2009 Brain Res. 1247:126-32 [2] Shinkareva et al. 2009; *NeuroImage*, V 47, Suppl. 1, Page S147 [3] Brookes et al. 2010 Biomag; Dubrovnik [4] Tzourio-Mazoyer et al., 2002. *NeuroImage 15*:273-289 [5] Wang et al. Accepted. HBM.