EXPLORING THE WHITE MATTER MICROSTRUCTURE UNDERPINNING ELECTROPHYSIOLOGICAL DYNAMICS: A COMBINED DT-MRI AND MEG STUDY

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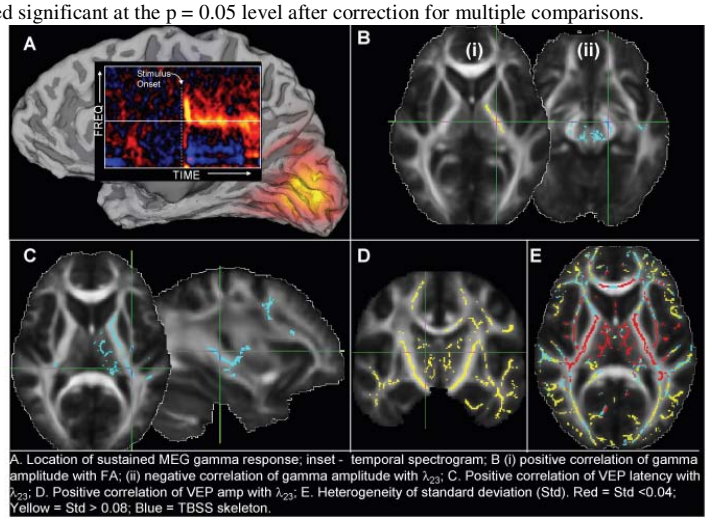
INTRODUCTION: The presence and modulation of neuronal oscillations at specific frequencies appear to be fundamental to the implementation of perception and cognition within the brain. Gamma oscillations (30-100 Hz) have been proposed as a temporal coding scheme through which distributed neuronal groups are able to become synchronous – allowing communication between these areas and underlying the "binding" of stimulus features[1]. It is not known whether stimulus-driven gamma oscillations arise from purely cortico-cortical interactions or whether there is a role for a thalamo-cortical mechanism. If the latter were true, we would expect properties of gamma oscillations to be modulated by the microstructure of the pathways comprising the thalamo-cortical circuits (e.g., it is possible that the 'stronger' the thalamo-cortical connection, the more synchronous the signals - and hence the larger the gamma response). Here we explored this hypothesis directly – that amplitude of the gamma response in response to a visual stimulus is correlated with white matter microstructure. We also examined the correlation between: (i) latency of the onset of the visual (LOV); and (ii) the amplitude of the visually evoked potential amplitude (VEP-Amp) with measures of white matter microstructure, predicting *a priori* that latency and amplitude would be negatively and positively correlated with FA respectively (with flipped correlations with λ_{23}) in visual pathways.

METHODS: Subjects: Twenty healthy subjects (15 M / 5 F; Age 33 +/-6.2 yrs) were recruited under informed consent. **Diffusion MRI Acquisition:** Diffusion-MRI data were acquired on a GE 3T HDx system with an 8 channel receive coil using a peripherally gated twice-refocussed EPI sequence with 6 b=0 images and 60 isotropically-distributed gradients[2].; **MEG Data Acquisition:** Data were acquired on a CTF-Omega 275-channel radial gradiometer system sampled at 1200 Hz with 0-300 Hz bandpass. Participants were presented 200 trials of a fixation cross followed by a 3 cycle/degree, high-contrast single quadrant square wave grating stimulus (size 4 x 4 degrees, lower left visual field, 0.5 degrees from fixation, stimulus presentation time was 2-2.5 seconds); **Analysis of MEG Data**: Synthetic aperture magnetometry (SAM[3]) was used to create differential 3D images of source power for periods of fixation versus visual stimulation. From these images, peak gamma oscillation locations were found to be located in primary visual cortex and virtual SAM sensors were constructed at these locations. Peak latency and peak amplitude measures of evoked activity were extracted from the virtual sensors by averaging in the time-domain. Gamma amplitude and frequency information was obtained by time-frequency decomposition of the virtual sensors using the Hilbert transformation. **Analysis of Diffusion MRI Data:** After motion / distortion correction, DW-data were analysed using both the tensor model (fitted using nonlinear least squares), and super-resolved constrained spherical harmonic deconvolution[4]. Scalar maps of fractional anisotropy (FA), generalized fractional anisotropy[5] (GFA), principal eigenvalue (λ_1) and the average of the remaining two eigenvalues (λ_{23}). The scalar maps were then analysed using Tract-Based Spatial Statistics[6] (TBSS) – using threshold-free cluster enhancement for statistical inferences. For each scalar diffusion parameter (FA, GFA, λ_1 and λ_{23}), the following explanatory variables (EVs) were entered into a General Linear Model: Group Mean, Gamma Amplitude, VEP-Amp and LOV, with positive and negative contrasts for all EVs. All inferences were deemed significant at the p = 0.05 level after correction for multiple comparisons.

RESULTS: MEG RESULTS: VEPs and sustained gamma responses were obtained in all 20 individuals (Fig A); **TBSS Results:** (N.B. Unless otherwise stated, all other contrasts revealed nothing significant) *Age*: As expected, there were significant negative correlations between FA and GFA with age throughout much of the white matter, and a trend for age to be associated with λ_1 (negative) and λ_{23} (positive); *Gamma Amplitude:* Strong positive correlations with FA were found predominantly in left posterior limb of internal capsule (PLIC) and bilateral cerebral peduncle (CP) and habenulo-peduncular tract (HPT) (Fig B). These patterns largely mirrored in location, but reversed in sign, by λ_{23}. Notably, regions of significant correlation were more extensive with λ_{23} than FA. (GFA and λ_1 showed no correlation); *VEP-Onset Latency:* Positive correlations with λ_{23} were found predominantly in left PLIC, but additional regions were found in anterior limb and in thalamic regions (Fig. C). Again, although less extensive, FA showed reverse correlation (i.e., the higher the FA, the shorter the latency), but there was no correlation with GFA and λ_1 *VEP Amplitude*: Negative correlations with FA were seen bilaterally in internal capsule, and more extensive positive correlations with λ_{23} were found including internal capsules bilaterally, thalamus bilaterally and genu of corpus callosum. (Fig. D). Finally, $\lambda_1$showed positive correlations in the thalamus, while GFA did not correlate with VEP amplitude at all.



A. Location of sustained MEG gamma response; inset - temporal spectrogram; B (i) positive correlation of gamma amplitude with FA; (ii) negative correlation of gamma amplitude with λ_{23}; C. Positive correlation of VEP latency with λ_{23}; D. Positive correlation of VEP amp with λ_{23}; E. Heterogeneity of standard deviation (Std). Red = Std <0.04; Yellow = Std > 0.08; Blue = TBSS skeleton.

DISCUSSION: While there have been prior attempts to correlate MEG-derived latencies with diffusion metrics[7], this is the first ever attempt to correlate aspects of gamma oscillations with white matter microstructure. Given the extremely conservative nature of the TBSS approach the correlations that we found demand careful consideration. However, there are some important observations to be made: Signs of the Correlations: The *signs* of the correlations of (i) gamma amplitude; and (ii) VEP onset latency with FA and λ_{23} are exactly as we hypothesized. The greater spatial extent of significant correlations seen with λ_{23} over FA suggests that looking at hindrance to diffusion across the equator of the fitted tensor is a more sensitive and specific marker in these forms of investigation, raising the *possibility* that myelination may play an important role in modulating the electrophysiological response. The signs of the VEP amplitude *versus* FA and λ_{12} correlations, however, were not at all expected. Rather than invoking *ad hoc* / *post hoc* hypotheses involving complexity of brain (especially on the eve of the ISMRM deadline), we will continue to investigate this particular correlation to provide a carefully considered and satisfying explanation. Locations of the Correlations: We had hypothesized visual pathways to be involved – particularly between LGN and occipital lobe. However, these regions did not show up in the analysis. Digging deeper into the data, we computed the inter-subject standard deviation of scalar values projected onto the TBSS skeleton (Fig E). The results are illuminating. Importantly, we find that the standard deviation is extremely heterogenous – even on the skeleton. In particular, the lowest variance is found in the posterior limb of internal capsule, cerebral peduncles and habenulo-interpeduncular regions - where we found our correlations. In contrast, the standard deviation in the visual pathways of interest (optic radiations and in white matter adjacent to LGN) is *at least twice* that in the internal capsule / peduncles. This means that either: (a) there is truly more variance in the data in these regions – but this is does correlate with the electrophysiological data; *or* (b) the TBSS skeletonisation approach does not perform as well in these regions – and thus the projected value onto the skeleton may not always come from the desired structure / be the desired value. This observation raises the possibility that what we are looking at is a general global between diffusion / electrophysiological correlation. However, the heterogeneity in inter-subject variance in the TBSS-skeleton values, introduces spatial dependence in our power to detect significant. This is partly substantiated by increasing the statistical threshold - which results in the expected correlations, of the correct sign, appearing in the optic radiations. For subsequent analyses, a more robust approach might involve a tailored approach to extracting tract-specific values[9] (e.g. integrating metrics along the optic radiations between LGN and cortex).

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