Investigating Task-Based Activation and Functional Connectivity in the White Matter using fMRI at 3 Tesla

Don Marciel Ragot[1,2], Erin Mazerolle[3], and J. Jean Chen[1,4]

[1]Rotman Research Institute, Baycrest, Toronto, Ontario, Canada, [2]Engineering Science, University of Toronto, Ontario, Canada, [3]University of Calgary, Ontario, Canada, [4]Medical Biophysics, University of Toronto, Ontario, Canada

Target Audience: This work is intended for those interested in spin-echo-based fMRI and in performing fMRI in cerebral white matter.

Purpose: A large number of studies have utilized fMRI to study the mechanisms of healthy brain function as well as neurological diseases and mental disorders [1]. However, most of these fMRI studies are limited to the cerebral gray matter (GM), despite that GM only account for approximately 50% of total brain matter [2]. White matter (WM) connectivity is critical for maintaining healthy brain function [3]. Nonetheless, any fMRI signals in the WM are often dismissed as artifacts [4], as WM is known to have lower BOLD signal sensitivity [5]. Thus, while neuronal signals undoubtedly exist in WM, its limited signal-to-noise ratio (SNR) makes BOLD imaging challenging. Recent studies have used BOLD to detect WM functional activation in the largest white matter structures in the brain while subjects are performing Interhemispheric Tasks (IT), tasks that stimulate both left and right brain hemispheres [6]. While these studies lay the foundation for white-matter fMRI, they also used custom acquisition pulse sequences unavailable on conventional fMRI scanners. In addition, they report focal brain activity, but do not assess functional connectivity in the WM. In this work, we investigate **(1)** the feasibility of detecting WM activation using conventional fMRI acquisitions and **(2)** task-related functional connectivity in the WM.

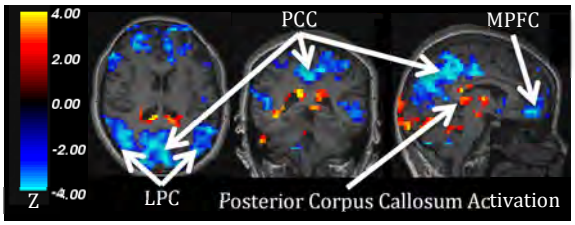

Fig. 1. In a sample subject: task-related corpus callosal activation and default-mode network deactivation. **LPC**: lateral parietal cortex, **PCC**: posterior cingulate cortex, **MPFC**: medial prefrontal cortex

Methods: 4 subjects were scanned on a 3T Siemens Tim Trio scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. We used a block-design IT task (8 blocks, 6 min/scan) using the Sperry Task Functionally Lateralized Stimulation [6], *i.e.* lateralized word and face stimuli briefly presented to the left and right eye fields separately. We ran both gradient-echo and spin-echo EPI scans with different TEs on one of the subjects and assessed which scan provided the most consistent activation in the corpus callosum. We used FSL-FEAT to analyzed task-related activation. Physiological noise was removed first using RETROICOR. Then, slice timing and motion correction, spatial smoothing (7.5 mm FWHM), and high pass filtering (>0.0125Hz) were performed. Lastly, fMRI images were registered to anatomical images and MNI152 space. To analyze WM functional connectivity, we created WM masks from individual anatomical scans, which were also registered to MNI152 space. We chose seeds to trace WM connections relevant for the task activations in the bilateral visual regions as well deactivations in the Default Mode Network (DMN). Therefore, the WM networks of interest were **(1)** the optic radiations and **(2)** the genu of the corpus callosum (connects bilateral MPFC of the DMN). We ensured that the seeds we chose were restricted to regions where WM masks overlapped across subjects and would not overlap with task-activated and task-deactivated regions. Lastly, connectivity maps were averaged across all subjects and thresholded at r > 0.5.

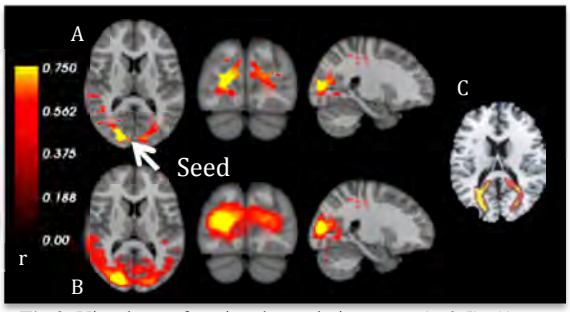

Fig 2. Visual tract functional correlation maps (r>0.5): A) After applying WM Mask; B) Without Masking; C) Structural reference: visual tract WM structure [7]

Results: As seen in **Fig. 1**, corpus callosal activation (red-yellow) and default-mode network deactivation (shown in blue) were detected (Z>2.3, p <0.05) using spin-echo EPI with TE=45ms. . Since WM activation was detected using the aforementioned scan, we used the parameters of this scan for the subsequent WM functional connectivity analysis. In visual WM network, WM functional connectivity clusters were seen bilaterally, mostly localized to the visual network, with the highest correlation values appearing on the WM tract (**Fig. 2**). **Fig. 3** shows that WM connectivity was also localized to the anterior corpus callosum. However, a cluster of connectivity can be seen in WM tract in the bilateral temporal lobes.

Discussion: Based on our findings, conventional gradient-echo EPI, which is widely used for GM fMRI studies, performed poorly for detecting WM activation**.** On the other hand**,** corpus callosal activation was detectable using a conventional spin-echo EPI scan at 3 Tesla. However, activation detection was inconsistent across subjects, due to the relatively low WM signal-to-noise ratio. Despite the inconsistent detection of WM activation, we found consistent WM functional connectivity across all subjects. While this connectivity might be the result of partial-volume effects from GM activity, functional connectivity to WM seeds appear to be strongest in WM despite physical proximity to neighbouring GM. Furthermore, the connectivity maps match with WM structures that connect task-related GM areas. Analyzing WM functional connectivity has been difficult due to a high degree of variability in WM structures across different subjects. To get around this problem, only voxels within WM regions overlapping across subjects were chosen as seeds for connectivity analysis. For more robust group analysis, better white-matter coregistration is needed.

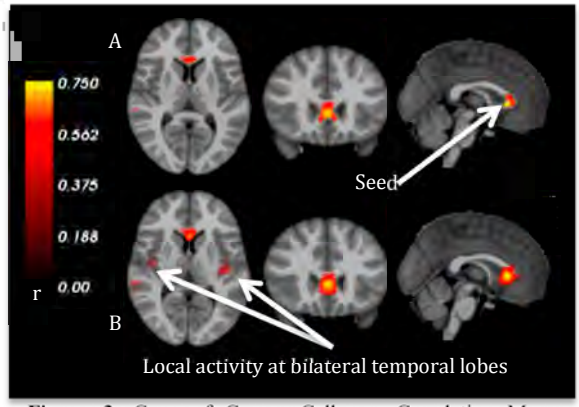

Figure 3. Genu of Corpus Callosum Correlation Maps (r>0.5): A) After applying WM Mask; B) Without Masking [8]

Conclusion: For the first time, we demonstrate the use of a conventional spin-echo EPI sequence to detect functional activation in white matter; this sequence is commercially available on all major scanner models. We also detected localized task-related functional connectivity in several WM networks, corresponding well to the WM tracts connecting task-relevant GM areas (in this case, bilateral visual cortex and the default-mode network). Our results suggest the possibility of studying functional health in white matter using easily accessible fMRI methods. Further experiments with more subjects will be needed to further establish the robustness of white matter activation.

References: [1] D. Zhang et al. Nat. Rev. Neurol. 2010; 6:15–28. [2]S. E. Black. Brain Cogn. 2007; 63:192–193. [3] M. Catani et al. Brain J. Neurol. 2005; 128: 2224–2239. [4] N. K. Logothetis et al. Annu. Rev. Physiol. 2004; 66: 735–769, 2004. [5] J. R. Gawryluk et al. Front. Neurosci. 2014; 8. [6] Mazerolle EL et al. BMC Neurosci 2008; 9:84. [7] Loenneker T et al. Human Brain Mapping 2011; 32:935-947. [8] Tang YY et al. PNAS 2010; 107:15648-15652.