Functional Imaging of Magnetic Field Therapy

John A. Robertson[(1)], *Jean Théberge*[(2)], *Julie Weller*[(3)],
Dick J. Drost[(4)], *Frank S. Prato*[(5)], *Alex W. Thomas*[(6)]

1. Bioelectromagnetics, Imaging, Lawson Health Research Institute,
St. Joseph's Health Care, 268 Grosvenor St., N6A 4V2, London, Ontario, Canada
And
Dept. of Medical Biophysics, University of Western Ontario, London, Ontario
Phone: 519.646.6000x64682 email: jroberts@lawonimaging.ca

2. Same as (1) *plus* Diagnostic Imaging, St. Joseph's Health Care, London, Ontario
email: jtheberg@lawsonimaging.ca

3. Dept. of Psychology, University of Western Ontario, London, Ontario
email: jweller@uwo.ca

4. Same as (2) email: drost@lawsonimaging.ca

5. Same as (2) email: prato@lawsonimaging.ca

6. Same as (2) email: athomas@lawsonimaging.ca

1.0 Introduction

There is a growing interest in how magnetic fields can affect biological systems. Previous research in our laboratory has indicated that a specific pulsed magnetic field known as the "complex neuroelectromagnetic pulse" (CNP) [1,2] can have analgesic effects in snails, rodents, and humans, and affect other behaviours such as standing balance. Moreover, in humans the effect is specific to nociception, and does not affect thermal sensory thresholds [2]. This effect appears to be due to the magnetic field exposure of the central nervous system, as seen by the effectiveness of localized head-only exposures [3,4]. There are also reports of pulsed magnetic field exposures affecting EEG, further indicating that an effect on neural processing is present[6].

With the increasingly widespread use of magnetic resonance imaging (MRI), which involves the use of strong static and time-varying magnetic fields, there is further curiosity about what sort of effects these fields could have on human behaviour. A paper by Rohan *et al.* [5] describes the temporary effects of a particular MRI pulsed gradient magnetic field sequence on participants with bipolar disorder. The research was largely serendipitous, following patient reports after an MRI scan. Building upon our earlier work with a specifically designed pulsed magnetic field, we chose to deliver the CNP within an MRI system. Our objectives were to test the MRI environment as a novel way of producing the pulseform as well as to determine whether, and how, the CNP could influence neural processing of pain.

2.0 Methods

Right-handed healthy adult subjects aged 18-60 were recruited to participate in a functional magnetic resonance imaging study. Exclusion criteria included claustrophobia, nerve damage to the hand, analgesic use on the day of the study, alcohol use on the day of the study, and the inability to lie still for an hour, as well as any other MRI exclusion criteria (e.g.: cardiac pacemakers). Subjects were blinded to their condition of sham vs pulsed magnetic field exposed.

Subjects were given acute thermal pain with a Medoc TSA-II (Medoc, Israel). A 1.6 x 1.6 cm Peltier thermode probe was attached to the hypothenar region of the right hand and heated under computer control (heat stayed on for 21 seconds, off for 24 seconds, with 3 second ramps in between). Each subject underwent a test prior to the fMRI to determine their individual pain tolerance. The target temperature was adjusted individually to attain a subjective

pain rating of at least 7/10 on a verbal analog scale (1-10). Actual temperatures varied between 48 and 51°C, depending on the subject.

After informed consent and thermal pain pre testing, subjects were placed in the Siemens Avanto 1.5 T MRI system, told to hold still and keep their eyes closed during the functional imaging, and that they would have a 50-50 chance of receiving a pulsed magnetic field exposure that may have analgesic effects. Single-shot echo-planar BOLD fMRI images were acquired (16 oblique slices, 64 x 64 resolution, 192 mm FOV, 3 s TR) while the thermal pain cycled on and off, 10 times for each round of functional imaging. Immediately after each round the subjects were asked to rate their subjective pain verbally over the intercom. The subjects then had a 15 minute "rest" period within the MRI system during which time they were instructed not to move, and were exposed to the CNP pulsed magnetic field, or a sham condition. The functional imaging and pain process was then repeated to obtain "post-exposure" data, following which T1-weighted anatomical images were obtained (3D MPRAGE sequence, T_1-weighted, 1 mm isovoxels, saggital acquisition).

The analgesic pulsed magnetic field exposure was done within the MRI system by programming the Z-gradient coils (the gradient lying along the bore of the magnet). The peak gradient strength was 2 mT/m, and the table was offset 10 cm cranially from the isocentre so that the field at the brow level was set to be 200 μT, the same field strength used in whole-body exposures (non-MRI) within our lab in the past with Helmholtz coils [2].

Functional image processing was done with Brain Voyager (Brain Innovation B.V., the Netherlands) v1.9.9. Individual datasets were preprocessed with mean intensity adjustments, temporal filtering (with a high pass filter that had a cut-off frequency of 3 cycles/scan) and 3D motion correction, and then converted to Talairach models to be combined for a General Linear Model (GLM) group analysis. For the sake of analysis, “pain” was taken to be when the heat was on at target temperature, all other images (baseline and the ramps) were taken to be part of the “rest” condition. Default hemodynamic response curves were used. An average of all Talairach anatomicals was created to display the results of the GLM analysis. The default False Discovery Rate (FDR) method was used to balance images to $q<0.05$. The FDR is an algorithm that accounts for multiple comparisons within fMRI analysis that is less stringent than a Bonferroni correction.

All procedures were approved by the University of Western Ontario Human Ethics Review Board (protocol #10059).

3.0 Results

Thirty-one subjects have been included in the analysis (17 sham, 14 CNP). There were no significant differences between groups with respect to age or gender representation. There was no significant group by time interaction with respect to subjective pain scores; that is to say, in this experiment there was no observed effect of the CNP pulsed magnetic field on reported pain scores.

From analysis with Brain Voyager, several differences in pain processing were observed within groups over time, as well as between groups. In the anterior cingulate region, a decrease in activity was observed following CNP exposure compared to before exposure, whereas an increase in activity was seen in the sham group when comparing the post- and pre-exposure pain-related activity. An increase in activity was also seen in the posterior cingulate for the CNP post-exposed group. In this case, the relative increase is due to less deactivation, as this area of the brain is normally deactivated during the painful stimulus.

4.0 Conclusions

These results indicate that there is an effect of the CNP on the functional processing of pain, even when there is no significant effect of the pulseform on subjective pain ratings. The anterior cingulate is a region of the brain commonly associated with pain processing, and the different response of the CNP-exposed group over time indicates that the pulseform has some effect on processing within this region. The increase in activation in the posterior cingulate can be potentially be explained by an analgesic effect (although none was observed in the subjective scores), as this region is associated with the so-called "default brain". If there is some analgesic effect

present, then the heat stimulus may cause less of a disruption to the "default processing", leading to the relative increase in activity observed (i.e.: less deactivation).

The subjective pain ratings did not show any effect of the CNP, with both sham and CNP exposed groups having a slight, non-significant decrease in pain scores following exposure. This may be due to the short duration of the CNP (15 minutes), since previous experiments with the CNP in our lab have focused on longer exposure durations (generally 30 minutes or more). A recent study [4] on repeated exposures with chronic pain patients indicates that there is a cumulative effect of multiple CNP exposures over several days, with 40 minutes of exposure each time. Despite this lack of subjective effectiveness, the pulsed magnetic field exposure did induce significant changes in functional activity. It is also possible that the effect of the CNP on neural processing is altered by the interactions of the strong static field (1.5 Tesla) and the time-varying fields associated with the imaging procedures [7].

The present work demonstrates some of the functional changes that the CNP induces in the brains of healthy volunteers. To the best of our knowledge, this is the first use of functional magnetic resonance imaging to demonstrate the effect of a weak pulsed magnetic field on neural functioning and/or brain blood flow. In the course of our study, the MRI scanner was used both as a detection tool for imaging as well as an active therapy system, using pulsed magnetic fields with the specific aim of inducing analgesia. Behavioural effects of MRI gradient sequences have been reported previously [6], but those magnetic field exposures were not specifically designed with biological effect in mind. In the future, the interaction between the magnetic fields within an MRI and neural processing may become medically important.

5.0 References

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6.0 Acknowledgements

The authors would like to thank Dr. Derek Mitchell, Dr. Dwight Moulin, Dr. Alexandre Legros, Dr. Keith St. Lawrence, and Mr. Lynn Keenliside for their assistance with this project. This project was funded by a grant from the Canadian Natural Sciences and Engineering Research Council, the Canadian Institutes of Health Research (CIHR), Ontario Research and Development Challenge Fund (ORF), and Fralex Therapeutics Inc (FTI).

Statement of Conflict of Interest: Drs Alex Thomas and Frank Prato are co-founders of and shareholders in FTI. Dr. Thomas is V-P Research for FTI. Mr. John Robertson receives a student stipend and research support from FTI. FTI is a publicly traded company on the Toronto Stock Exchange [TSX:FXI]. See (www.fralex.com) for details.