RCoA Research, Education & Travel Grants 2013 Award:

The Stanley Rowbotham Fund 2013 Final Report

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Project Title: Gaining insight into the neural correlates underpinning propofol anaesthesia: analysis of data from a functional magnetic resonance (fMRI) and electroencephalography EEG study

Background:

The neural correlates underlying anaesthetic function remain poorly understood [1]. Recent functional magnetic resonance imaging (fMRI) studies have suggested multiple brain regions involved in loss and recovery of awareness in humans[1,2]. The original aims of this project were to reanalyse an existing fMRI and electroencephalography (EEG) dataset to explore the neural correlates related to emergence from anaesthesia. However on evaluating the dataset, it became apparent that although an overall description of deep anaesthetic function had been successfully undertaken[2], exploration and understanding related to a clinically pertinent loss of behavioral responsiveness was outstanding. Therefore it was decided that prior to assessment of emergence a focused analysis assessing loss of behavioral response (LOBR) during induction with propofol anaesthesia would be conducted.

Aims:

To identify the neural correlates underpinning loss of behavioral responsiveness during induction with propofol anaesthesia.

Methods:

This is a reanalysis of the fMRI imaging data collected and reported previously[3]. Following ethical approval, healthy volunteers underwent an experiment during which they received a propofol anaesthetic and underwent a simultaneous FMRI scan and EEG recording. During the experiment the volunteers experienced a resting period with eyes closed and no drug administration for 10 minutes (phase 1), followed by an ultraslow induction to loss of consciousness using propofol sedation (phase 2). A target-controlled intravenous infusion of propofol was used with step increases of 0.2μg ml^{-1} to achieve a maximum effect site concentration (ESC) of 4μg ml^{-1} over 48 minutes. After resting at the peak propofol dose for 10 minutes (phase 3), the propofol sedation was switched off

and subjects were allowed to emerge naturally from unconsciousness over 48 minutes (phase 4).

Noxious laser stimuli, computer generated tones and auditory word tasks were presented to the subjects during the induction and emergence phases (i.e. phases 2 and 4). Loss of appropriate motor response to the auditory word task was used to assess loss of behavioural response (LOBR) in the healthy volunteers. To control for the individualised effect of propofol we truncated fMRI data to centre on each subject's loss LOBR. The data presented here correspond to the stimulus-evoked fMRI responses collected during the induction to loss of consciousness (phase 2) of the fMRI study. Emergence data (phase 4), truncated around the resumption of motor response used to assess regaining of behavioural response (LOBR) is under analysis.

FMRI data were analysed using a two-level general linear model using FEAT version 6.0 to identify brain activity associated with the noxious and auditory stimulation. Six regressors were included at first level to account for each stimulus type pre- and post-LOBR. Further regressors were used to account for each individual's motor responses and any subject motion during the induction. A mixed effects analysis across all subjects (cluster thresholded at Z=2.3, p=0.05) was then performed to identify the main effect of each regressor and any differential processing of these stimuli across the LOBR transition. A conjunction analysis was performed to identify any brain regions, common for all stimuli types that demonstrated significant reductions in stimulus-evoked activity across the LOBR transition.

Results:

FMRI data during induction of propofol anaesthesia are presented from 15 subjects (8 Female) aged 19 to 43 years (mean age 28.7 years). The mean propofol ESC for loss of behavioural response in this group was 1.33 mcg/ml (95% CI 1.1 to 1.56).

By comparing activity in a narrow time-window before with after the loss of behavioral responsiveness (i.e. pre-LOBR > post-LOBR contrast), we found significant localised reductions in FMRI-BOLD stimulus-evoked activity for all external stimuli (mixed effects analysis, cluster thresholded at Z=2.3, p<0.05) (Figure 1). In contrast, no brain regions were found to be more active to any stimulation after LOBR than before (i.e. the post-LOBR > pre-LOBR contrasts). Furthermore we performed a conjunction analysis of the three differential stimulus-evoked contrasts to reveal the regions that were commonly reduced to all stimuli across the LOBR transition. This revealed that activity in the right anterior dorsal insula region was significant reduced to all experimental stimuli after loss of responsiveness under general anaesthesia (Figure 2).

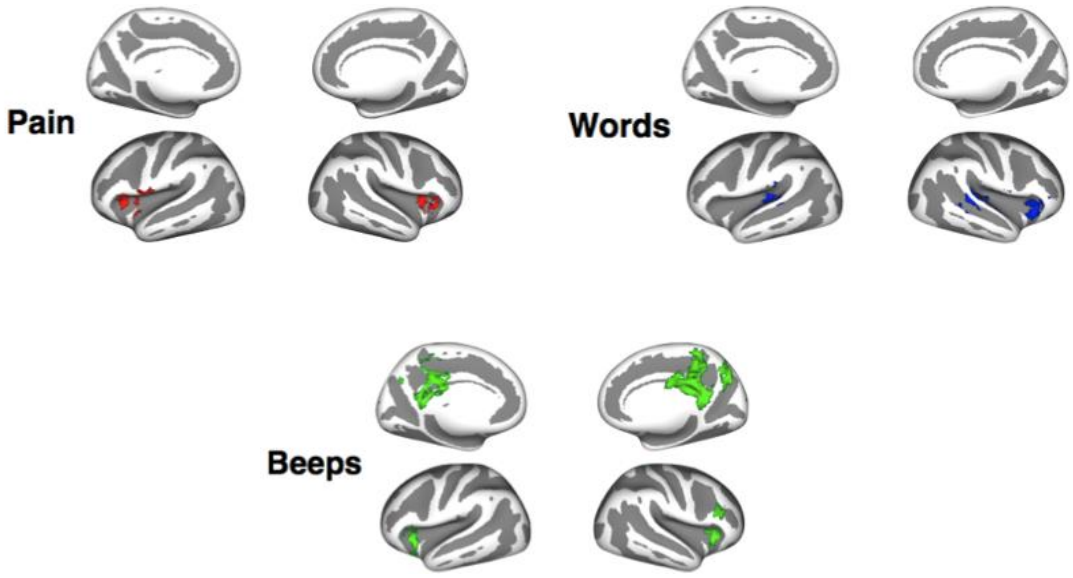

Fig 1: Results of pre LOBR> post LOBR contrast analysis for experimental stimuli.

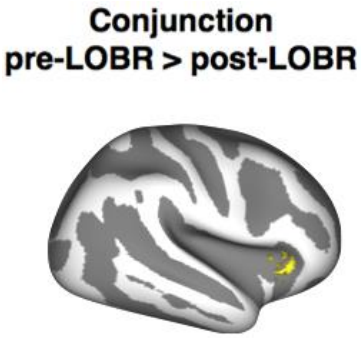

Fig 2: Results of conjunction analysis showing anterior insula activity prior to LOBR.

Conclusions:

Our data adds to the growing body of evidence, which upholds the anterior insula cortex as an important neural correlate of human consciousness[4]. It also gives insight into how the anaesthetic agent propofol can effectively be used in functional magnetic imaging experiments aimed at understanding human awareness. From the anaesthetic point of view, our results give insight into the stepwise mechanism by which propofol induces loss of awareness at clinically pertinent LOBR. The approach used in this analysis is currently being applied to the emergence data from the same dataset.

Dissemination:

Dr Warnaby has presented the results of this work at the Anaesthetic Research Society Meeting in Manchester in April 2014 and the Edinburgh Anaesthesia Festival in August 2014. An abstract of this data has ben accepted for the World Pain Congress in Buenos Aires due to be held in October 2014. A paper is currently being prepared for submission to a high-impact peer-reviewed journal.

Future Research:

Following the publication of these results we plan to complete the emergence data analysis, which is currently in progress. Specifically, we aim to assess whether the anterior insula is also a key area involved in emergence from anaesthesia.

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References:

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