MIDAZOLAM SEDATION DISRUPTSTS THE CORTICOLIMBIC NETWORK CONNECTION: An fcMRI study

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Purpose

Functional neuroimaging modalities are increasingly applied to study functional connectivity defined as synchronisation of spatially remote neurophysiological events(1). Spontaneous low frequency fluctuations of the BOLD (blood oxygenation level dependent) fMRI signal have been successfully used to study functional connectivity (fc) in the brain 'at rest'(2) Advanced processing controlling for spurious correlations allowed in recent years to characterise disease-specific alterations including the dysregulation of the cortical-limbic circuitry in major depression(3). Moreover, cortico-limbic dysregulation as assessed by fc BOLD fMRI were found to be reversible after chronic antidepressant treatment(4). This suggests that fc analysis may be a suitable tool for in vivo human studies of psychopharmacological effects on co-ordinated network activity. Recent electrophysiological studies directly corroborate the notion that alterations of coordinated interactions of the cortical-limbic circuitry as assessed by fc analysis may underly drug induced anxiety and mood changes (5). It remains unclear if and how acute pharmacological manipulations affect the functional connectivity between cortical-limbic networks in humans.This study investigated the effects of the anxiolytic and sedative drug midazolam on fc in the cortico-limbic circuit in healthy volunteers.

Method

Resting state data from healthy male volunteers undergoing midazolam challenge study were used (6). All subjects gave written informed consent and the study was approved by the University of Nottingham Research Review board. Volunteers were scanned at baseline and after i.v. midazolam (0.05mg/kg body weight) application outside the scanner (details as described in 6). Sedation was scored using the Ramsay scale. Scanning was done at 3T (Philips Achieva) using an 8-channel head coil and a standard EPI sequence with TR/TE = 2100/35 ms, 64x64 matrix, 35 axial slices and voxel dimensions 3.25x3.25x3 mm. Resting state fMRI scans lasted 15minutes. Image analysis was carried out by FSL4.0 software (FMRIB Oxford, UK). Images were preprocessed using high and low pass filtering, spatial smoothing and motion correction in the FSL 4.0 environment. After carrying out Melodic ICA component analysis, independent components were visually inspected for noise and selected noise components were removed. Image registration was achieved by FLIRT function of FSL4.0 software. ROIs were drawn by using FSLview and Jim4 software. A circle with a radius of 4mm was chosen for Amygdala, 6mm for the medial Thalamus, hippocampus and anterior cingulate and ellipsoids with largest diameter of 6.5mm for subgenual cortex (Fig1). Further ROI include the motor and visual cortex and precuneus manually drawn by using FLSview. The position of ROIs were defined based on anatomical landmarks and the position was controlled using the FSL atlas database and MNI coordinate. The derived time series were then further corrected for spurious correlations using white matter and CSF time series as regressors of no interest. Correlation analysis was performed between ROI time series using ACC as a reference to all other ROIs time series. The correlation coefficients were transformed to t-scores. T-scores of pre and post midazolam conditions were calculated for each combination and statistical significance was tested by using Wilcoxon test. The significance level was set at $p<0.05$. There were no multiple test correction was performed.

Results

Correlations between ACC and limbic structures were similar to those previously reported (4). During baseline, the ACC was showed strongest connections to the amygdala and subgenual cortex (Fig2). Midazolam induced sedation was associated with significant reductions of cortico-limbic functional connectivity (Fig2). Functional connectivity disruption was strongest between anterior cingulate and hippocampus, followed by amygdala and subgenual cortex.

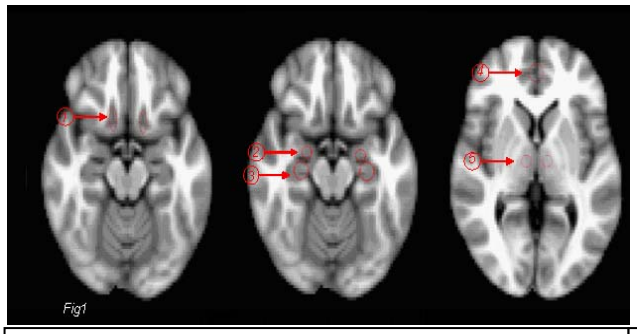

Fig1. Region of interest(ROI) placement for connectivity analysis. 1:subgenual(SBG);2: amygdala(Amyg);3: hippocampus(Hippo); 4:anterior cingulate cortex(ACC); 5:medial thalamus(mThal)

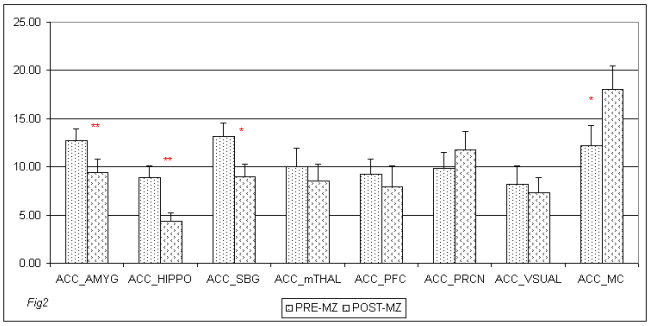

Fig2. Resting state cortico-limbic LFBF correlations (mean+SEM) in 12 healthy volunteers before and after midazolam sedation. Pre-MZ before sedation Post-MZ after sedation. ** $p<0.05$; * $p<0.1$

There was no effect on non limbic cortex (visual, precuneus), but a tendancy for increased connectivity with the motor cortex. Similar effects were seen for cortico-limbic connectivity reduction when using PFC and subgenual cortex as input regressor. It is tempting to speculate that decreased cortico-limbic connectivity may reflect a decreased regulatory effect of ACC over the limbic system. Our study deployed a sedative drug dose, but it will be interesting to study lower doses to assess whether the drug's anxiolytic effect leads to similar cortico-limbic decoupling. The study is further limited by lack of multiple test correction.

Conclusion

This is to our knowledge the first human study showing altered functional connectivity after acute pharmacological manipulation. Midazolam administration resulting in deep sedation (Ramsay score 3 level) decreased the functional connectivity in cortico-limbic circuits that may reflect its specific psychotropic action.

References:

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