Cingulate cortex functional connectivity increase predicts relapse of major depression.

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Introduction: Recent functional imaging studies suggest alterations in cortico-limbic circuit connectivity in depression. Moreover, these functional connectivity (fc) changes were found to correlate with symptom severity and normalised upon antidepressant treatment (1). The direction of these fc changes is however debated with one group showing increased default network connectivity and another showing decreased cortico-limbic connectivity (2). Nonetheless, more and more studies implicate cingulate gyrus as a focus of dysfunction (3, 4). In this study, we aimed to compare fc of the rostral anterior cingulate between patients with history of remitted recurrent depression and healthy controls.

Methods: Twenty patients with remitted recurrent depression and twenty one healthy volunteers underwent 6min lexical task

activation fMRI. All participants had the Structured Clinical Interview for DSM administered by a senior psychiatrist. Recruited patients had at least 2 episodes of major depression before inclusion but were now recovered (Hamilton score < 8) and did not have evidence of any other psychiatric disorder, personality disorder, serious drug/alcohol problems or other untreated medical disorder. Scanning was done at 3T (Philips Achieva) using an 8-channel head coil and a standard EPI sequence with TR/TE = 2300/40 ms, 64x64 matrix, 35 axial slices and voxel dimensions 3.25x3.25x3 mm. Image analysis was carried out by FSL4.0 software (FMRIB Oxford, UK). Images were preprocessed using high and low pass filtering, spatial smoothing, motion correction and the physiology related artifacts were further removed using Melodic ICA de-noising function. All the images were registered to the MNI template. Region-of-interest rostral anterior cingulate (rACC) was

Figure 1. Region-of-interest used in seed based analysis. Rostral anterior cingulate (rACC) as shown in green.

drawn on the MNI template using Jim4 software (Fig1). Time series of rACC was used as input regressor for subsequent seed-based correlation analysis. Lexical task related activity, CSF, WM time series and motion parameters were used as regressors of no interest. Group analysis compared patients, controls and patient subgroups (relapse and non-relapse patient group). Group analysis was performed using cluster corrected mixed effect modeling (FLAME) with p<0.05.

Results: One year follow-up resulted in 7 subsequent relapsed patients and 2 patients did not attend follow – up clinics. Demographic analysis including age, gender, and handedness did not show any significant difference between groups. rACC connectivity with other

brain areas did not differ between remitted recurrent depression patients and healthy control subjects. However, rACC (BA 24) connectivity with the cingulate cortex (BA 32) was significantly increased in patients who subsequently relapsed (n=7) in comparison with the non-relapse patient group (n=11) (Fig 2).

Discussion: This study showed that the pattern of connectivity in the remitted patient group as a whole was similar to that in healthy controls, but a subgroup of seven subjects that relapsed during one year follow–up demonstrated increased cingulate functional connectivity during remitted state. The increased cingulate functional connectivity has been previously shown in depressed state in Greicius *et al* study (5). Thus, this study further highlights the possibility of the functional connectivity as a potential marker of states in major depression. Main limitation of this study was this study utilised task-related fMRI data. Although task-related fMRI has been used for functional connectivity studies (6), it should be noted that tasks can modulate within and between network connectivity.

Conclusion:

Here we show increased anterior cingulate functional connectivity in remitted state patients with recurrent depression relapsed within one year follow-up. Anterior cingulate functional connectivity may be a potential marker to predict individuals prone to relapse in major depression.

Figure 2. rACC connectivity map - fc increase in relapse subjects. a) Relapsed subjects b) Non – relapsed subjects c) above 2 groups contrast map. Maximum Z-score of primary peak is 3.19 and primary peak location -2, 30, 26 (MNI coordinate).

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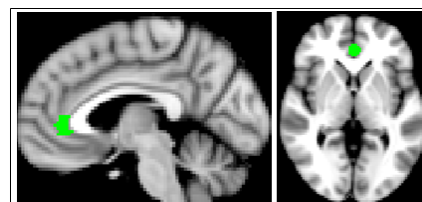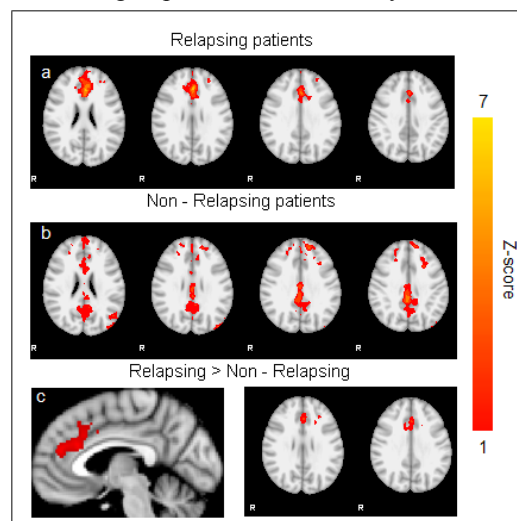**6.** Fair DA, et al. Neuroimage 2007;35(1):396-405.