Effective connectivity analysis of emotional processing in remitted depression

N. Goulden[1], S. McKie[1], E. Pegg[1], D. Downey[2], R. Elliott[1], S. R. Williams[2], I. M. Anderson[1], and J. F. Deakin[1]

[1]Neuroscience and Psychiatry Unit, University of Manchester, Manchester, United Kingdom, [2]Imaging Science and Biomedical Engineering, University of Manchester, Manchester, United Kingdom

Introduction

Depression is an illness characterised by low mood and lack of motivation with other symptoms including feelings of worthlessness or guilt. Patients may also be socially withdrawn and agitated (DSM-IV). Differences in emotional face processing have been observed in depression compared with healthy control volunteers. Elevated amygdala activation has been reported, which normalises with antidepressant treatment (Sheline et al., 2001). Studying depressed volunteers is confounded by mood and motivation, and also any medication the patients may have been prescribed. One approach to avoiding these confounds is to study remitted patients, as some of the abnormalities associated with depression persist into remission (Bhagwagar and Cowen, 2008). By studying this group it may be possible to identify trait risk factors for depression. We therefore studied a group of healthy control and remitted depressed volunteers performing an fMRI emotional face processing paradigm in order to identify whether the abnormal amygdala response persists into remission. In order to identify risk factors in regional coupling we also applied an effective connectivity analysis, using Dynamic Causal Modelling (DCM).

Methods

37 right-handed healthy volunteers (12 males) aged 19-52 were recruited. Volunteers had no personal or family history of psychiatric illness and no contraindications to MR scanning. 30 right-handed remitted depressed volunteers (8 males) aged 19-54 were recruited. These volunteers were required to meet major depression in full remission criteria from SCID interview, to have been remitted from depression for a minimum of 3 months and also to satisfy a diagnostic interview supporting classification to remitted depressed group.

A series of faces were presented to the volunteer while they were in the scanner. Each face was presented for 3 seconds with a 1 second gap. There were four conditions: neutral faces (N), happy faces (H), sad faces (S), fearful faces (F) and rest (R) where a fixation cross was displayed. Each block was 21 seconds long and we had an NHNSNFNRSNHNFNRFNSNHNR order in a session that lasted 462 seconds in total. Subjects were asked to distinguish whether the face was male or female via a button box.

Images were acquired on a 1.5T Philips Intera scanner using a single-shot echo-planar (EPI) pulse sequence. Each volume comprised 29 contiguous axial slices (TR/TE=2100/40ms, 3.5mm by 3.5mm in-plane resolution, slice thickness 4.5mm with a 0.5mm gap). A T1-weighted structural image was also collected for each volunteer.

Having carried out a first level fixed effects analysis for each individual, we carried out a second level random effects analysis. For the DCM analysis maxima were found in each region of interest in the random effects analysis. In our sample 21 healthy control and 22 remitted depressed volunteers exhibited amygdala activation and were included in the analysis. The areas chosen were the primary visual cortex (V1), the fusiform gyrus (F), the amygdala (A) and the orbitofrontal cortex (OFC). Local maxima within 14mm of the group activation were located for each individual and data extracted from a 6mm radius sphere region of interest. We then specified the DCM models using the toolbox in SPM5, using the slice timing correction tool. Only the right hemisphere was modelled with all faces as input, all connections present and all connections apart from the input connection modulated by viewing each type of emotional face (Fig 1). We therefore specified three models, one with happy faces modulating all connections, one with sad faces and one with fearful faces. In order to test for differences between groups we carried out t-tests on the data for all parameters. We also carried out two repeated measures ANOVAs separately for connections and modulations. The factors were parameter (connections/modulation), emotion, direction (feed-forward or feed-back) and group (healthy control or remitted depressed – an independent factor). We also carried out ANOVAs for each emotion individually and for each direction of connection individually.

Results

fMRI

Unlike currently depressed individuals, remitted depressed volunteers exhibited lower amygdala activation in response to viewing faces than healthy control volunteers ($t=3.29$, $p<0.001$). In all other regions of interest, activation was higher in healthy control volunteers than in remitted depressed volunteers.

DCM-ANOVAs

The first 4 factor ANOVA on the connections revealed a main effect of direction ($F=36.597$, $p<0.001$) and a parameter*direction interaction ($F=16.683$, $p<0.001$). The same was found when restricting to happy and sad emotions. When restricting to the fear condition an additional main effect of connection was revealed ($F=2.703$, $p=0.048$). When restricting the directions to both feed-forward and feed-back a main effect of connection was revealed ($F=7.189$, $p<0.001$ and $F=5.298$, $p=0.002$).

The first 4 factor ANOVA for the modulations revealed a main effect of direction ($F=5.008$, $p=0.031$) and a parameter*direction interaction ($F=6.34$, $p=0.003$). No significant main effects or interactions were found when restricting emotions to happy and sad. A main effect of direction was observed when the fear data were analysed ($F=5.23$, $p=0.027$) separately. No significant main effects or interactions were observed in the ANOVA restricted to feed-forward parameters. The ANOVA restricted to feed-back parameters revealed a main effect of connection ($F=3.745$, $p=0.028$) and a main effect of emotion ($F=4.198$, $p=0.018$).

DCM-T-tests

In the happy model, a significant difference was observed in the connection from the fusiform gyrus to the amygdala ($p=0.0384$). In the sad model a significant difference was observed in the same connection ($p=0.0317$) with a significant difference in the modulation of this connection also observed ($p=0.0317$). The sad model also resulted in a significant difference in the modulation from the orbitofrontal cortex to the fusiform gyrus ($p=0.0445$). In the fear model no significant differences between the groups were observed.

Discussion

These results demonstrate a difference in feed-forward and feed-back processing of emotional faces in healthy control and remitted depressed individuals. There were no abnormalities in effective connectivity associated with fearful faces in remitted patients, however for happy and sad faces a difference was found in the connection from the fusiform gyrus to amygdala. This may indicate a difference in the way that visual information is projected to the amygdala for a response to be generated. Abnormal responses to happy and sad stimuli are consistent with a hypothesis of disrupted emotional processing in depression. Our findings in a remitted group suggest either that these abnormalities persist after clinical recovery, potentially representing a trait vulnerability, or that they represent a compensatory mechanism in previously depressed patients in order to maintain remission. The additional modulations observed during sad face processing may also reflect this persistent emotional abnormalities. These results indicate that effective connectivity is a valuable tool for exploring subtle abnormalties within neural circuitry in psychiatric disorders.

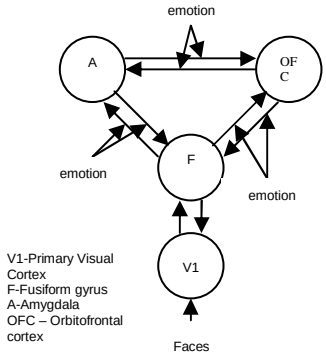

Figure 1: The model tested

References

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