Abnormal emotional processing in Multiple Sclerosis: an fMRI investigation

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Introduction:
Multiple Sclerosis (MS) is a neurological disorder characterized not only by sensory-motor deficits, but also by cognitive deficits and psychopathological symptoms (1). Previous functional MRI (fMRI) studies in patients with MS have mainly focussed on motor and cognitive disabilities (2,3). Conversely, the psychopathological manifestations associated with MS have been little investigated. There is clinical evidence that MS patients exhibit significantly higher rates of anger, depression, disphoria and pathological laughing and crying (PLC), when compared to healthy individuals (4,5). Two previous fMRI studies in MS have focussed only on negative emotions, and reported controversial results (6,7). Aim of this study was to investigate abnormal emotional processing in MS, with a particular focus on anger and joy.

Methods:
Sixteen patients with relapsing-remitting (RR) MS [F/M ratio=4/12; Mean age(SD)=37.8(9.4) years; median (SD) EDSS score 2.0 (range 1-6)], and 13 healthy controls (HC) [F/M ratio=6/7; Mean age(SD)=34.46(8.59)] were recruited for this study. Each patient underwent neurological and psychological assessments before MR scanning. MRI included the collection of clinical scans (PD and FLAIR sequences), and EPI images with BOLD contrast for fMRI investigation. An event-related design was employed using facial expressions to evoke three basic emotions (anger, sadness and joy), intermixed with neutral faces (control condition). Subjects had to perform, on a trial-by-trial basis, a gender discrimination task by button pressing. This means that the paradigm was designed for the investigation of implicit emotion processing. One-way ANOVA was used to compare between-group fMRI behavioural responses. FMRI data were processed using SPM5 and analyzed with the general linear model for event-related designs. At first level analysis, each single emotion was modelled, for a total of four different conditions plus the control condition (neutral faces). For second level group' comparison a flexible factorial design was employed, including all experimental conditions. Differences were considered as statistically significant at p values cluster level uncorrected < 0.05.

Results:
Psychological measures did not reveal any significant difference between MS patients HC. Behavioural fMRI data showed that RR patients' performed the task (gender discrimination) similarly to HC. fMRI results revealed that RRMS patients had significantly higher brain activation, when compared against HC, in all emotional vs. neutral conditions. More in detail, MS patients compared to HC shoewed the following patterns of increased brain activity: showed: 1) within the middle frontal gyrus (midFG), for emotional expressions of anger; 2) within the right orbitofrontal cortex (OFC) extending to the insular cortex, for expressions of sadness; 3) within the anterior cingulate cortex (ACC), extending to the medial frontal gyrus (medFG), for joy expressions. Finally, when confronted with the happy facial expression, RR patients showed significantly increased activations See figure 1 for details.

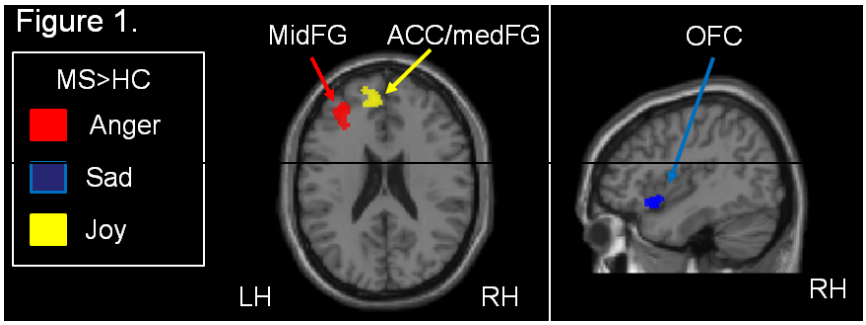

Figure 1. MS patients, compared against HC, showed increased brain activity within the middle frontal gyrus (midFG; Talairach coordinates: x, y, z = -32, 32, 18 Z=3.62), when exposed to anger emotional stimuli (blob in red).
When exposed to sad stimuli, patients showed increased activity in the orbitofrontal cortex (OFC; x, y, z = 42, 18, -12 Z=3.32), extending to the insular cortex (blob in blue).
When processing happy faces, patients showed increased activation in the anterior cingulate cortex (ACC; x, y, z = -14, 48, 42 Z=3.79), extending to the medial frontal gyrus (medFG).

Discussion:
Consistently with previous fMRI studies (6,7), our fMRI findings confirm that an abnormal emotion processing occurs in MS patients. In fact, across all three emotional conditions (i.e. anger, sad and joy) significant increases in brain activity were observed in frontal regions, such as the OFC and the prefrontal cortex (i.e. midFG), which are traditionally implicated in emotional processing (8). These abnormalities might represent the neurobiological substrate for psychopathological symptoms, such as higher anger rates, depression and disphoria, which are recurrent in MS. An alternative explanation, might rely on the hypothesis that, despite task performance' accuracy, patients require an increased neural effort to correctly accomplish task.
Our findings might suggest that increased neural response to emotional stimuli, might explain psychopathological symptoms in MS. Furthermore, our results might confirm the existence of a functional reorganization mechanism, specifically within frontal regions, that are necessary to compensate neuronal damage, within MS patients.
This study supports the assumption of an abnormal emotional processing in MS patients, with specific neural location for each specific emotion. More research is needed to understand what happens within the brain of MS patients, also considering other phenotypes of disorder or different emotion processing paradigms.

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