Research Paper

Recruitment of the left hemispheric emotional attention neural network in risk for and protection from depression

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Background: Family history of major depressive disorder (MDD) increases individuals' vulnerability to depression and alters the way depression manifests itself. Emotion processing and attention shifting are functions altered by MDD and family history of the disease; therefore, it is important to recognize the neural correlates of these functions in association with both factors. **Methods:** Our study determines neural correlates of emotion processing and attention shifting for healthy individuals and patients with MDD with and without family history of depression. We compared the performance and neural activity in a functional magnetic resonance imaging experiment examining emotion processing and attention shifting in all participants. **Results:** Our sample included 4 study groups: healthy controls without family history of depression (n = 25), patients with MDD without family history of the disease (n = 20), unaffected healthy first-degree relatives of patients with MDD (n = 21) and patients with MDD with family history of MDD (n = 30). Compared with healthy controls, unaffected first-degree relatives overactivate the somatosensory cortex and the attention controlling areas during both emotion processing and attention shifting. Patients with family history of MDD have stronger neural activation in subcortical areas during shifting attention from negative stimuli. Patients without family history of MDD have less activation in the paralimbic regions and more activation in core limbic areas, especially during emotion processing. **Limitations:** The conclusions about the intergroup differences in activation can be drawn only about neural areas engaged in the task. **Conclusion:** Unaffected first-degree relatives of patients with MDD overreact to external emotional cues and compensate for the vulnerability with increased involvement of executive control. Patients with a family history of MDD have less executive control over their attentional shifts in the face of negative stimuli. Patients without a family history of MDD process emotional stimuli in a more visceral way than controls.

Introduction

Individuals with a first-degree relative who has major depressive disorder (MDD) are at a 2- to 3-fold greater risk for depression than those without a family history of MDD.[1] Relatives of depressed patients, compared with individuals without family history of psychiatric disorders, are characterized by elevated neuroticism, depressive cognitions and rigidity[2] and by stability of these traits over time.[3] Patients with MDD who had relatives with an affective disorder display greater neuroticism[4] and have an earlier age of onset of MDD.[5] Evidently, family history of MDD alters susceptibility to depression and to an acute MDD episode. The factor is clinically important since it involves mechanisms of elevated risk for MDD (relatives of patients with MDD compared with healthy controls), suggests relative resilience to the disease (relatives of patients with MDD compared with the patients themselves) and points to different endophenotypes of healthy controls and patients with MDD. A good understanding of these mechanisms should not be underestimated if diagnosis, therapy and prevention of the disorder are to be enhanced.

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Certain neural characteristics of individuals with family history of MDD have been explored. These individuals were discovered to have reduced volume of the right hippocampus, the dorsolateral prefrontal cortex and the putamen.[6,7] When a small volume correction was applied in a functional magnetic resonance imaging (fMRI) experiment, healthy adolescents with a family history of MDD displayed altered activation in the amygdala and nucleus accumbens when observing emotional faces.[8] Also, healthy monozygotic twins of patients with MDD showed greater activation in the left inferior frontal gyrus during verbal encoding and retrieval.[9] These neural differences were discovered in spite of the absence of negative bias on a behavioural level, suggesting that susceptibility and associated changes can manifest themselves without behavioural signals. Also, acute tryptophan depletion triggered depressive moods in relatives of patients with MDD, but not in healthy controls.[10] For both groups, severity of depressive mood after acute tryptophan depletion was correlated with an activation in the posterior part of the anterior cingulate cortex (ACC) during the Stroop task.[10] In our recent study, the unaffected healthy first-degree relatives of patients with MDD experienced more activation in the left caudate nucleus and the right middle cingulate cortex (MCC) during inhibition of emotional information; we hypothesized that changes in activation may be the result of a mechanism of compensation.[11] Our findings suggested that areas responsible for executive function and emotional processing may be altered in individuals with family history of MDD.[11]

However, the pathophysiology of the role that family history of MDD plays in the development and diagnosis of MDD is not yet entirely understood. The behavioural data suggest that the key skills impaired in individuals with a family history of MDD are emotion processing[12–14] and attention shifting from emotional content,[15,16] neural correlates of which have been previously verified in healthy individuals.[17–19] These 2 processes are crucial components of emotional regulation[20,21] and represent its 2 basic functions: an ability to explore emotional meaning of the environment and a potential to withdraw from the exploration in accordance with one's goals. The disturbance of emotional regulation is, according to some models,[22–27] a key feature of MDD and involves interplay of cognitive and emotional functions. It has been found that patients with acute depressive episodes are less accurate in classifying emotional content and less effective in inhibiting attention to it than healthy controls.[28,29] These deficits are accompanied by altered functioning of the frontal and cingulate cortex as well as subcortical regions, such as the amygdala and basal ganglia.[30–32]

Family history of MDD may enhance these tendencies. Such impairments could explain elevated levels of neuroticism in relatives of patients with MDD. Emotional regulation, one of the fundamental abilities disturbed in neuroticism,[33] requires efficient emotion processing and effective ability to inhibit it. Interestingly, neural correlates of these 2 abilities, to our knowledge, have not yet been investigated in individuals with a family history of MDD.

No previous study, to our knowledge, has examined whole-brain functional neural correlates of family history of MDD in both healthy controls and patients with MDD. The present study uses this design to investigate processing of emotions and attention shifting from emotional information in individuals with and without family history of MDD. The 4 groups of participants distinguished in the study are

1. patients with MDD with first-degree family history of depression (MDD-FHP),
2. patients with MDD without family history of depression (MDD-FHN),
3. healthy controls with family history of depression (HC-FHP; in our case, unaffected healthy first-degree relatives of patients with MDD), and
4. healthy controls without family history of MDD (HC-FHN).

We applied the factorial analysis with diagnosis and history of MDD as factors and with age and sex as covariates of no interest to verify our hypotheses.

This design allows us to address the following questions in our research. The basic interest of the study was the HC-FHP group. When compared with the HC-FHN group, the HC-FHP group represents elevated risk for depression without acute depressive symptoms being present. In comparison with the MDD-FHP group, the HC-FHP group is an example of relative resilience. Therefore, examining neural correlates in these comparison groups is of high clinical relevance and seems to be crucial for targeting vulnerable individuals and developing strategies for prevention of depression. We assumed that the HC-FHP group experienced alterations in neural activation in the areas associated with emotion processing and attention switching in healthy controls (e.g., frontal and cingulate gyri, parietal cortex, insula, premotor cortex, subcortical areas[17–19,34]). We hypothesized that the HC-FHP group had elevated neural activation relative to the MDD-FHP group in frontal, premotor and parietal areas as markers for relative resilience and elevated activation compared with the HC-FHN group in the cingulate cortex and subcortical areas based on our previous study.[11]

Furthermore, it was necessary to verify how emotion processing and attention shifting were altered by an acute depressive episode when the risk caused by family history of MDD was absent. We tested the question by comparing the HC-FHN with the MDD-FHN group. We hypothesized that patients with MDD without family history of the disease had less neural activation in the cortical areas and more activation in the subcortical regions distinguished previously as the ones with reduced activity in general group of patients with depression.[28,29] We hypothesized further that the patients may have less activation in other areas identified previously as the ones associated with the targeted processes in healthy controls (e.g., parietal cortex, insula, premotor cortex[17]).

Finally, we tested how the neural characteristics of emotion processing and attention shifting were changed in an acute depressive episode by the presence of the risk connected with family history of MDD by comparing the MDD-FHP with the MDD-FHN group. We hypothesized that the MDD-FHP participants, as carriers of both the risk and the acute symptoms, were less efficient in behavioural response to the stimuli and that their neural activity was reduced in the areas involved in the 2 targeted processes.

Methods

Participants

We recruited participants for the MDD-FHP and MDD-FHN groups from the psychiatric outpatient clinics of psychiatric services in Dublin South West. The HC-FHP participants were recruited from among the patients' unaffected first-degree relatives. The HC-FHN participants were volunteers recruited through advertisements. Whereas both groups of healthy controls participated in our previous study,[11] this new sample was extended by including patients with MDD, and our data analysis focused on emotion processing and attention shifting.

Participants' health and eligibility were verified by a consultant of psychiatry (Y.F. or T.F.), which involved a psychiatric interview based on the Structured Clinical Interview for DSM-IV,[35] Hamilton Rating Scale for Depression,[36] Montgomery-Åsberg Depression Rating Scale[37] and Beck Depression Inventory.[38] A psychologist (D.L.) then conducted an interview and trained participants for the task. The MDD diagnosis and lack of comorbidities were confirmed by the responsible consultant psychiatrist in all the study groups. We conducted an extensive interview about family history of MDD with each participant to ensure they all were appropriately classified as having or not having a family history of MDD. The exclusion criteria of the study were a previous or current head injury, a current or past psychiatric or neurologic disease (apart from MDD in the case of the patients), a current medical disease influencing the central nervous system, alcohol or drug dependency and inability to read or see content presented on the screen.

After an extensive description of the study, we obtained written informed consent from all participants. The study protocol was approved by the local ethics committee of Trinity College Dublin, the University of Dublin, Ireland, and was prepared in accordance with the ethical standards in the Declaration of Helsinki.

Design

The study was a 4-sample design with the MDD-FHP, the MDD-FHN, the HC-FHP and the HC-FHN as comparison groups. After the ascertainment procedure presented previously, participants were assigned to 1 of the 4 groups. A task involving processing of emotions and shifting attention from emotional information was adapted from Northoff and colleagues[17] to record participants' brain activity during an event-related fMRI experiment.

Task

The task was adapted from a previous work of Northoff and colleagues,[17] who established its neural correlates in healthy controls. In our study, the aim of the task was to examine emotion processing and attention shifting, the 2 skills altered in individuals with a family history of MDD. The task consisted of 2 conditions and a baseline. The first condition involved an act of emotion recognition, whereas the second required participants to shift their attention from emotion processing to processing of nonemotional information. Both conditions involved observing visual stimuli with established emotional valence taken from the International Affective Picture System[39] (IAPS) database and making judgments about emotional or nonemotional features of the stimuli.

The experiment was an fMRI event-related design with 180 trials. Each trial consisted of a viewing stage during which participants looked at a picture, and a response stage wherein they answered a question concerning the picture (Appendix 1, Fig. S1, available at cma.ca/jpn). Participants answered "yes" or "no" to all the questions depending on whether they believed the question stated truth or falsehood by pressing 1 of 2 buttons on a response box from Current Design Inc. with the right hand. The trials were alternated with a picture of a fixation cross, which served as a baseline for the analysis. This procedure was validated in previous fMRI studies as well as in the study from which the task was adapted to probe nonrelative signal variability caused by group differences.[17,40,41]

Of the 180 trials, 90 belonged to the emotion processing condition (emotional trials) and 90 to the attention shifting condition (nonemotional trials). Participants started each trial by observing a picture taken from the IAPS database. Subsequently, in emotional trials after observing the picture, participants answered a question referring to its emotional content (Was it positive? Was it negative? Was it neutral?). In nonemotional trials after observing the picture, participants answered a question about its shape (Was it horizontal? Was it vertical?) and suppressed processing of emotional information. The 2 conditions were pseudorandomly distributed in the experiment. Participants did not know before the start of each trial and during the picture viewing which of the 2 types of questions would be asked. To answer correctly they had to process information about both the emotional valence and the shape of the picture until the question was asked, after which the whole attention would focus on 1 type of information. Therefore, the nonemotional trials involved shifting attention away from the processing of emotional information. Each trial lasted 4 seconds.

To address a broad range of different emotional values, pictures used in the experiment were either positive, negative or neutral in emotional valence and either horizontal or vertical in shape, with 60 unrepeated pictures in each valence category (30 for each condition). As the valence of IAPS pictures is described on a scale from 1 to 9, where 1 represents very negative and 9 very positive, in our study, pictures in the 1–3 interval were classified as negative, 4–6 neutral and 7–9 positive. To ensure that the chosen pictures would have a consistent appraisal in the healthy population, we selected the ones with minimal standard deviation (SD) in emotional valence and the ones judged similarly by men and women. Since the examined group consisted of emotionally vulnerable participants, negative pictures presenting highly disturbing content, such as death or mutilation, were excluded after consultation with a psychiatrist. Ultimately, the respective mean (and SD) valence values for the negative, positive and neutral categories were 2.54 (0.34), 7.64 (0.34) and 4.97 (0.23), respectively.

Before entering the scanner, participants were instructed

and trained by a psychologist to perform the task. The training involved practice sessions of the task, with and without a computer. The training was designed to account for different levels of computer expertise among participants.

Behavioural data acquisition and analysis

We used the stimulus-delivery Presentation software (Neuro-Behavioural Systems) to program the task and record participants' answers and reaction times. Accuracy was defined as a percentage of correct answers in nonemotional trials and as a percentage of answers in accordance with standardized appraisals of emotional valence in emotional trials. We conducted a 4-way analysis of variance (ANOVA) to verify whether the 4 groups differed in terms of reaction times and accuracy measures separately for the 2 conditions. Age and sex were used as covariates. Subsequently, post hoc analysis between each pair of groups was performed to assess participants' reaction times and accuracy. We considered results to be significant at $p < 0.05$. All the calculations were performed in SPSS version 16.0.

Image acquisition

The MRI protocol consisted of acquiring a high-resolution 3-dimentional T_1-weighted structural data set (spoiled gradient recalled acquisition sequence with repetition time [TR] 8.5 ms, echo time [TE] 3.9 ms, spatial resolution 1 mm^3), followed by an fMRI experiment (spin echo–echo planar image sequence with TR 2000 ms, TE 35 ms, in-place resolution 3×3 mm^2, slice thickness 4.8 mm, 550 dynamic scans of 2 seconds duration each). All the MRIs were obtained with a 3 T Philips Achieva scanner.

Image data analysis

We performed the entire image data analysis using Statistical Parametric Mapping version 8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/).

Preprocessing

We realigned the echo planar images to the first volume to correct for motion. Realignment parameters were inspected visually to identify any potential excessive head movement (in accordance with previous studies, the thickness of 1 slice and more; in the case of our study, 4.8 mm was considered as excessive movement). Each participant's structural image was coregistered to the mean of the motion-corrected functional images using a 12-parameter affine transformation. The image slice time was corrected to TR/2. The structural images were segmented according to the standard procedure.[42] Spatial normalization to standard $3 \times 3 \times 3$ mm Montreal Neurological Institute (MNI) space was then applied to the functional images to allow for intersubject analysis. Finally, the images were smoothed using an 8 mm full-width at half-maximum Gaussian kernel.

First level analysis

For each individual, each condition was contrasted separately with null events (t test). In addition, the trials for each condition were separated into neutral, negative and positive categories. As such, we acquired 6 t contrasts for every participant:

- neutral emotional trials > null events,
- negative emotional trials > null events,
- positive emotional trials > null events,
- neutral non-emotional trials > null events,
- negative non-emotional trials > null events, and
- positive non-emotional trials > null events.

Motion correction values were taken into account in the model as a covariate of no interest.

Second-level analysis

A $2 \times 2 \times 6$ factorial analysis was performed on the calculated contrasts, with the diagnosis of MDD (patients with MDD v. healthy controls) as the first factor, family history of MDD (positive v. negative) as the second factor and the type of trial (neutral emotional v. negative emotional v. positive emotional v. neutral nonemotional v. negative nonemotional v. positive nonemotional trials) as the third factor. Participants' age and sex were added as covariates of no interest. The differences between patients and controls and between individuals with and without a family history of MDD were established. We performed a post hoc analysis to verify the differences between HC-FHP and HC-FHN, HC-FHP and MDD-FHP, HC-FHN and MDD-FHN, and MDD-FHP and MDD-FHN. We calculated contrasts between all groups separately for the emotion-processing condition and attention-shifting condition. Since the HC-FHP group was the main group of interest in our analysis, comparisons with that group were also performed separately for each type of emotional valence of the stimuli in each of the conditions.

The whole-brain family-wise error (FWE) cluster correction ($p < 0.05$) was used to correct for multiple comparisons. Only areas surviving the correction were reported and taken into account in the final conclusions. We used automated anatomic labelling to localize the significant results in a standard stereotactic space (MNI template).

We performed an additional analysis for patients with MDD to verify whether different treatments were associated with variance in neural activation during the task and whether the treatment method could interfere with family history in the group of patients with MDD. A 3×6 factorial analysis was carried out with type of medication as the first factor (selective serotonin reuptake inhibitors [SSRIs], dual action, no medication), type of processing as the second factor and age and sex as covariates of no interest. The methods of verifying statistical significance and labelling the results were the same as those for the analysis of diagnosis and family history of MDD.

Results

Participants

In all, 96 participants took part in the study and were assigned to the 4 study groups as follows: 30 to MDD-FHP, 20 MDD-FHN, 21 HC-FHP and 25 HC-FHN. All patients were nonpsychotic. The 2 groups of patients with MDD did

not differ in terms of the age at onset of illness, illness duration (cumulative and present) or number of admissions to medical facilities. Depressed individuals and healthy controls differed significantly in all applied depression ratings (all $p < 0.05$). There was no significant difference in the ratings between the 2 groups of healthy controls and between the 2 groups of patients with MDD. None of the patients had psychotic depression. They all were in treatment in our outpatient services. The 4 groups discerned were balanced in relation to age, sex and handedness (Table 1).

Out of the patients group, 17 individuals were taking SSRIs, 19 were taking dual-action substances and 13 were not medicated. Patients treated with different medications did not differ in age, sex, handedness and scores in the depression rating scales (all $p > 0.05$).

Behavioural results

Patients with MDD differed significantly from healthy controls in accuracy and reaction times in each condition (all $p < 0.05$). Depressed patients were always slower and less accurate. Individuals with family history of MDD did not differ significantly from individuals without family history of MDD in accuracy and reaction times. There were no significant interactions between diagnosis and family history.

In the post hoc analysis, we observed significant differences (all $p < 0.05$) between the HC-FHP and the MDD-FHP participants in accuracy and reaction times in the attention shifting condition (Table 2). The MDD-FHP participants were significantly slower and less accurate than the healthy controls. The comparison between the MDD-FHN and the HC-FHN participants produced a trend reaching statistical significance in the accuracy of emotional trials; the MDD-FHN participants were less accurate in judging emotional valence than HC-FHN participants. Comparisons between the HC-FHP and the HC-FHN groups and between the MDD-FHP and the MDD-FHN groups did not produce significant behavioural differences (Table 2).

Functional MRI results

Patients with MDD versus healthy controls

During emotional processing, healthy controls displayed greater activation than patients with MDD in the following regions: the right precuneus/posterior cingulate cortex, right rolandic operculum, right insula, left angular gyrus, left supramarginal gyrus and left rolandic operculum. Patients with MDD did not show any increase in neural activity in this condition (Table 3 and Appendix 1, Table S1).

During attention shifting from emotional processing, healthy controls displayed greater activation than patients with MDD in the following regions: the right superior frontal gyrus, bilateral supplementary motor area/MCC, right precuneus, right rolandic operculum and left inferior parietal gyrus. There were no areas with increased activation for patients with MDD (Table 3).

Individuals with and without family history of MDD

There were no differences between the 2 groups in either condition.

Interactions between diagnosis and family history

The ANOVA revealed a statistically significant negative interaction between diagnosis and family history of MDD in the left middle occipital gyrus (MOG), supramarginal gyrus (SuMG), inferior triangular frontal gyrus, inferior parietal gyrus (IPG), postcentral gyrus (PoCG), precentral gyrus and the bilateral superior occipital gyrus (SOG) and cuneus.

Post hoc analysis

MDD-FHN versus HC-FHN

While processing emotional valence of the stimuli, the HC-FHN group showed greater activation than the MDD-FHN group in the right insula, right rolandic operculum and right precuneus/PCC. The MDD-FHN group experienced an increase of neural activation during emotion processing compared with the HC-FHN group in the vermis 3 and the left caudate nucleus (Table 3).

During attention shifting, the HC-FHN group showed greater activation than the MDD-FHN group in the right SuMG, right insula and right rolandic operculum gyrus. There was no increase of neural activity in the MDD-FHN group (Table 3).

MDD-FHP versus HC-FHP

In emotion processing, the HC-FHP group displayed greater

Table 1: Demographic and clinical characteristics of the study groups and statistical significance of group differences

Group	No.	Age, mean (SD) [range] yr	Sex, no. female:male	Test, mean (SD) score			Age at onset, mean (SD) yr	Cumulative illness duration, mean (SD) yr	No. admissions to hospital, mean (SD)
				HAM-D	MADRS	BDI II			
MDD-FHP	30	40.7 (9.0) [24–57]	19:11	29.0 (6.5)	30.7 (6.6)	34.7 (11.9)	23.6 (10.6)	9.4 (9.3)	0.4 (0.7)
MDD-FHN	20	45.7 (12.5) [23–64]	14:6	28.1 (6.6)	28.5 (7.3)	30.3 (11.7)	27.4 (15.3)	9.6 (13.4)	1.3 (4.9)
HC-FHP	21	38.6 (14.5) [21–65]	11:10	3.7 (3.1)	3.1 (4)	3.7 (5.7)	—	—	—
HC-FHN	25	36.3 (11.9) [21–65]	13:12	1.8 (1.9)	0.5 (1.7)	2.04 (2.5)	—	—	—
p value of the intergroup difference		0.07	0.55	< 0.001*	< 0.001*	< 0.001*	0.33	0.93	0.31

BDI II = Beck Depression Inventory II;[38] HAM-D = Hamilton Rating Scale for Depression;[36] HC-FHN = healthy controls without family history of MDD; HC-FHP = healthy controls with a family history of MDD; MADRS = Montgomery-Åsberg Depression Rating Scale;[37] MDD = major depressive disorder; MDD-FHN = patients with MDD without family history of MD; MDD-FHP = patients with MDD with a family history of MDD; SD = standard deviation.
*Significant differences between patients with major depressive disorder (MDD-FHN, MDD-FHP) and healthy controls (HC-FHP, HC-FHN); 4-group factorial analysis of variance was used for age and depression ratings; χ^2 was applied for sex.

activation in the left cuneus, left SuMG and left SOG than the MDD-FHP group. The MDD-FHP group did not display elevated neural activity (Table 3, Fig. 1A).

While shifting attention from emotional processing, the HC-FHP group displayed greater activation in the bilateral SOG and left IPG than the MDD-FHP group. There was no increase of activation in the MDD-FHP group (Table 3, Fig. 1B).

HC-FHP versus HC-FHN

During processing of emotional valence, the HC-FHP group displayed greater neural activation than the HC-FHN group in the left SuMG, left IPG and left PoCG. There was no increase of activation in the HC-FHN group (Table 3, Fig. 2A).

While shifting attention from emotional processing, the HC-FHP group displayed greater neural activation in the left SOG, left IPG and left SuMG than the HC-FHN group. There was no increase of activation in the HC-FHN group (Table 3, Fig. 2B).

MDD-FHP versus MDD-FHN

There were no differences between the 2 groups of patients with MDD in the neural correlates of emotion processing and attention shifting.

The HC-FHP group as a representation of risk and relative resilience: different types of stimuli

HC-FHP versus MDD-FHP

During emotion processing, when the valence categories were considered separately, the HC-FHP group showed an increased activation in comparison to the MDD-FHP group during processing of positive stimuli. The increase was observed in the left SOG, left MOG and left angular gyrus. The difference was not noted during processing of negative and neutral stimuli.

During attention shifting, when the valence categories

Table 2: Behavioural differences between the study groups: patients versus healthy controls; family history of major depressive disorder versus no family history of major depressive disorder; post hoc analysis of differences between individual pairs of groups

Group; contrast	Group, mean (SD)		*p* value, intergroup difference
	Group 1	Group 2	
MDD (n = 50) v. healthy controls (n = 46)			
Emotion processing condition accuracy	74.8 (12.8)	82.9 (9.4)	0.001
Emotion processing condition reaction time	1.51 (0.44)	1.33 (0.31)	0.020
Attention shifting condition accuracy	77.6 (16.6)	88.7 (11.1)	< 0.001
Attention shifting condition reaction time	1.65 (0.43)	1.3 (0.27)	< 0.001
Family history of MDD (n = 51) v. no family history of MDD (n = 45)			
Emotion processing condition accuracy	78.5 (12.6)	79.1 (11.2)	0.82
Emotion processing condition reaction time	1.41 (0.44)	1.44 (0.33)	0.73
Attention shifting condition accuracy	81.9 (15.8)	84.3 (14.4)	0.44
Attention shifting condition reaction time	1.53 (0.45)	1.42 (0.34)	0.18
HC-FHP (n = 21) v. HC-FHN (n = 25)			
Emotion processing condition accuracy	82.9 (11.6)	82.9 (7.3)	> 0.99
Emotion processing condition reaction time	1.27 (0.26)	1.37 (0.35)	0.84
Attention shifting condition accuracy	89.9 (11.5)	87.6 (10.8)	0.94
Attention shifting condition reaction time	1.28 (0.22)	1.32 (0.32)	> 0.99
HC-FHP (n = 21) v. MDD-FHP (n = 30)			
Emotion processing condition accuracy	82.9 (11.6)	75.4 (12.6)	0.11
Emotion processing condition reaction time	1.27 (0.26)	1.5 (0.51)	0.17
Attention shifting condition accuracy	89.9 (11.5)	76.3 (16.1)	0.006
Attention shifting condition reaction time	1.28 (0.22)	1.71 (0.48)	< 0.001
HC-FHN (n = 25) v. MDD-FHN (n = 20)			
Emotion processing condition accuracy	82.9 (7.3)	73.8 (13.5)	0.05
Emotion processing condition reaction time	1.37 (0.35)	1.53 (0.29)	0.50
Attention shifting condition accuracy	87.6 (10.8)	79.8 (17.6)	0.29
Attention shifting condition reaction time	1.32 (0.32)	1.56 (0.32)	0.15
MDD-FHP (n = 30) v. MDD-FHN (n = 20)			
Emotion processing condition accuracy	75.4 (12.6)	73.8 (13.5)	0.96
Emotion processing condition reaction time	1.5 (0.51)	1.53 (0.29)	0.99
Attention shifting condition accuracy	76.3 (16.1)	79.8 (17.6)	0.84
Attention shifting condition reaction time	1.71 (0.48)	1.56 (0.32)	0.51
4-way analysis of variance			
Emotion processing condition accuracy	4	3	0.010
Emotion processing condition reaction time	2.1	3	0.11
Attention shifting condition accuracy	5.1	3	0.003
Attention shifting condition reaction time	8.1	3	< 0.001

Accuracy = percentage of correct answers; HC-FHN = healthy controls without family history of MDD; HC-FHP = healthy controls with a family history of MDD; MDD = major depressive disorder; MDD-FHN = patients with MDD without family history of MD; MDD-FHP = patients with MDD with a family history of MDD; SD = standard deviation.

were considered separately, the HC-FHP group showed increased activation in comparison to the MDD-FHP group in shifting attention from negative and neutral stimuli. The increase of neural activation in shifting attention from negative stimuli was observed in the left MCC/ACC and left SOG. The increase characteristic of attention-shifting from neutral stimuli was noted in the left PoCG, left IPG, bilateral SMA and right superior frontal gyrus.

When the valence categories were considered separately, the MDD-FHP group also showed increased neural activation compared with the HC-FHP group in shifting attention from negative stimuli. The increased in neural activation was observed in the left cerebellum 4–5, left fusiform/parahippocampal gyrus and right cerebellum 6.

HC-FHP versus HC-FHN

During emotion processing, when the valence categories were considered separately, the HC-FHP group compared with the HC-FHN group displayed increased neural activation during the processing of negative stimuli in the left IPG and left PoCG. The increase was not noted during processing of positive and neutral stimuli.

During attention shifting, when the valence categories were taken into account separately, the HC-FHP group displayed

Table 3: Differences in neural activation between the study groups during emotion processing and attention shifting

Comparison; brain region	Cluster size, no. voxels	MNI coordinate			Cluster-corrected *p* value
		x	*y*	*z*	
Control > MDD: emotion processing					
Right precuneus/posterior cingulate cortex	500	27	–43	25	< 0.001
Right rolandic operculum		45	–25	25	
Right insula		36	–22	25	
Left angular gyrus	283	–33	–55	22	< 0.001
Left supramarginal gyrus		–48	–25	25	
Left rolandic operculum		–33	–43	22	
Control > MDD: attention shifting					
Right superior frontal gyrus	149	15	17	46	0.006
Left supplementary motor area/middle cingulate cortex		–9	8	46	
Right supplementary motor area/middle cingulate cortex		6	5	46	
Right precuneus	961	27	–46	25	< 0.001
Right rolandic operculum		42	–40	19	
Left inferior parietal gyrus		–33	–28	34	
HC-FHN > MDD-FHN: emotion processing					
Right insula	338	36	–22	25	< 0.001
Right rolandic operculum		45	–25	25	
Right precuneus/posterior cingulate cortex		27	–43	25	
MDD-FHN > HC-FHN: emotion processing					
Vermis 3	108	–3	–34	–5	0.021
Left caudate nucleus	82	–3	5	10	0.045
HC-FHN > MDD-FHN: attention shifting					
Right supramarginal gyrus	539	45	–22	25	< 0.001
Right insula		27	–31	22	
Right rolandic operculum		36	–19	22	
HC-FHP > MDD-FHP: emotion processing					
Left cuneus	828	–12	–85	28	< 0.001
Left supramarginal gyrus		–57	–52	28	
Left superior occipital gyrus		–21	–82	28	
HC-FHP > MDD-FHP: attention shifting					
Left superior occipital gyrus	443	–15	–85	25	< 0.001
Right superior occipital gyrus		24	–73	25	
Left inferior parietal gyrus		–24	–40	37	
HC-FHP > HC-FHN: emotion processing					
Left supramarginal gyrus	539	–57	–49	31	< 0.001
Left inferior parietal gyrus		–51	–49	43	
Left postcentral gyrus		–39	–43	40	
HC-FHP > HC-FHN: attention shifting					
Left superior occipital gyrus	594	–24	–79	28	< 0.001
Left inferior parietal gyrus		–45	–46	37	
Left supramarginal gyrus		–57	–22	40	

HC-FHN = healthy controls without family history of MDD; HC-FHP = healthy controls with a family history of MDD; MDD = major depressive disorder; MDD-FHN = patients with MDD without family history of MD; MDD-FHP = patients with MDD with a family history of MDD; MNI = Montreal Neurological Institute.

greater neural activation than the HC-FHN group in shifting attention from all types of stimuli. The increase of neural activation during attention shifting from negative stimuli was observed in the bilateral MCC and left PoCG. The increase representative for attention shifting from positive stimuli was noted in the left MOG, left SOG and left cuneus. The increase characteristic of attention shifting from neutral stimuli was observed in the left IPG.

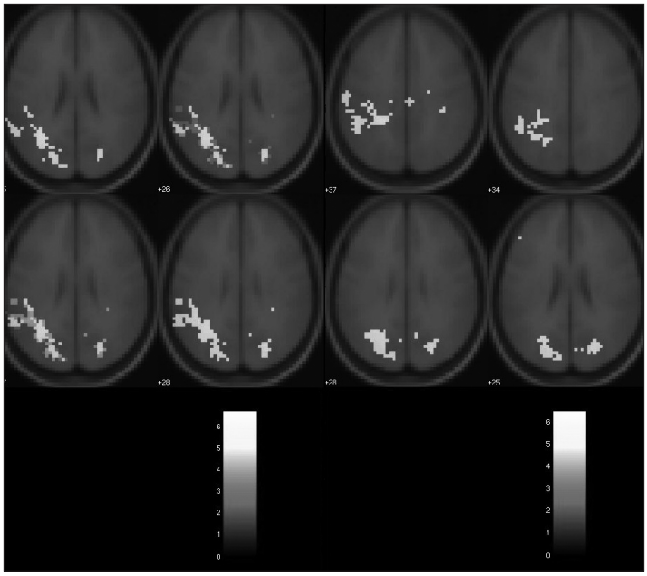

Fig. 1: Increased activation in the healthy controls with a family history of major depressive disorder compared with patients with major depressive disorder with a family history of the disease during (**A**) emotion processing and (**B**) attention shifting (family-wise error, whole-brain cluster correction, $p < 0.05$); the scale expresses *t* values.

Different types of treatment

Patients with MDD treated with different types of medication and untreated individuals with MDD did not differ in neural correlates of emotion processing and attention shifting (all $p < 0.05$, FWE-corrected for the whole brain).

Discussion

To our knowledge, our study is the first to confirm that the difference in cerebral functions between patients with MDD and healthy controls is modulated by an individual's family history of MDD. This discovery is in agreement with previous findings about the importance of a family history of depression in diagnosis[1–4,43] and neuroimaging[6,8,9] of individuals with MDD. As predicted, neural mechanisms of emotion processing and attention shifting from the said processing are affected by the aforementioned modulation.

On the basis of neural alterations observed in emotion processing and attention shifting, we propose an explanation of the relative resilience and risk for depression in individuals with a family history of MDD. Our results show that family history in healthy individuals, which might be a trait associated with both risk and relative resilience, is distinguished by an increase of activation in vast regions of the left hemisphere during both emotion processing and attention shifting. In contrast, acute depression without family risk of MDD is characterized by deactivations in the right insula and right rolandic operculum during both emotion processing and attention shifting and by increased activation in the subcortical regions during emotion processing.

The vulnerability to the disease among unaffected first-degree relatives of patients with MDD is observed when the group is compared with the healthy controls without family

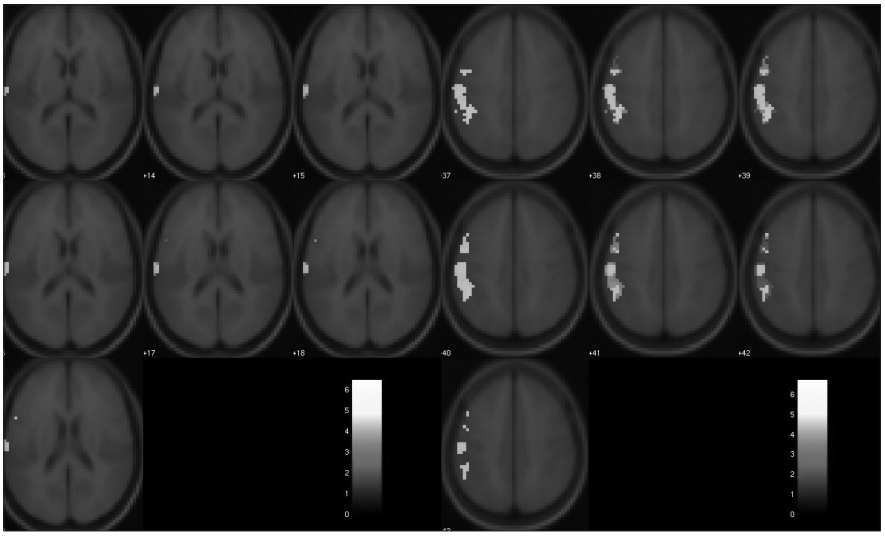

Fig. 2: Increased activation in the healthy controls with a family history of major depressive disorder compared with healthy controls without a family history of the disease during (**A**) emotion processing and (**B**) attention shifting (family-wise error, whole-brain cluster correction, $p < 0.05$); the scale expresses *t* values.

history of MDD. It has to be mentioned that family risk represents genetic and environmental factors. During emotion processing, an increase of activation characteristic of the HC-FHP group compared with the HC-FHN group was noted in the left PoCG, the region associating emotional and somatosensory sensations.[44–46] This suggests that vulnerability to MDD associated with family history of the disease is characterized by stronger somatosensory reaction to visually processed emotional information. The increased activation of the area suggests greater reactivity to emotional stimuli in the HC-FHP compared with the HC-FHN group.[47,48] During attention shifting, an increase of activation characteristic of the HC-FHP compared with the HC-FHN group was noted in the visual cortex. In healthy controls, increased activation in the visual cortex during processing of stimuli with emotional valence is attributed to allocation of greater attention resources to emotional cues.[49–52] Increased activation of this area in the HC-FHP group in the course of attention shifting suggests that the group pays more attention to emotional valence of the stimuli, even when this is not required. An increase characteristic of the HC-FHP group was also observed during both emotion processing and attention shifting in an area commonly associated with executive control, the left IPG,[53–57] and in a region involved in language operations, the left SuMG.[58–60] Both regions participate in managing emotional arousal either through focusing attention on and off the affective cues or through naming emotional states and organizing them.[61–63] It can be concluded that vulnerability to MDD is characterized by increased sensory reactivity to emotional cues, both when attention is focused on them and when it is not. Our results suggest that heightened sensory reactivity may be compensated by increased activation in areas responsible for managing emotional arousal. This may explain why the behavioural changes are not observed in the HC-FHP group, even if the vulnerability is present. Such was also the case in previous studies of behavioural and functional correlates of family vulnerability to the disease.[9]

With regards to the neural correlates of relative resilience, when compared with the MDD-FHP group, the HC-FHP group displayed greater activation during emotion processing in the visual cortex and the left SuMG, which is involved in associating somatosensory information with verbal categories and lexical knowledge.[59] One can conclude that in the resilient HC-FHP group, greater attention resources are devoted to observing external emotional stimuli than in the MDD-FHP group. Increased activation in the somatosensory-lingual cortex during emotional decision-making is connected in healthy controls with an individual's awareness of his or her emotional state and with the control that the language system has over perceiving of one's emotions.[59,60] Thus, we can conclude that relative to the MDD-FHP group, the HC-FHP group has more potential for paying attention to external emotional cues and to their own emotional reactions to these cues.

During attention shifting, the HC-FHP group experiences greater activation than the MDD-FHP group in the visual cortex and left IPG, a region required in attention switches.[18,48,53–55,64–70] Observed overactivation suggests the aforementioned mechanism of compensation, which characterizes the HC-FHP group. Having strong sensory reactions to external emotional cues when there is a requirement to focus on external nonemotional information puts more demand on the attention control system. In turn, this can be stabilized by increased activation in the areas managing attention. Some of the areas of the attention control network have been previously reported as having smaller volumes in the HC-FHP group.[6] That may put an additional strain on the attention network.

When one considers emotional valence of stimuli, stronger reaction of sensory neural areas[44–46] to positive stimuli is characteristic of relative resilience. In the course of shifting attention from negative stimuli, relative resilience is characterized by greater activation in areas managing attention[18,48,53–55,64–70] and decreased activation in regions of emotional arousal.[34] These changes suggest that relative resilience to MDD is associated with better reactivity to positive emotional cues and stronger control of attention in the face of negative information.

In contrast, vulnerability to MDD is characterized by a stronger activation in sensory and attention managing areas[18,44–46,48,53–55,64–70] during evaluation of negative stimuli. A similar pattern is observed in the course of attention shifting from negative information with a more notable increase in the attention network. The vulnerability is also connected with an increase in activation in the visual cortex[49–52] in the course of attention shifting from positive emotional cues and in attention areas[18,48,53–55,64–70] during attention shifting from neutral stimuli. These alterations suggest that family vulnerability to MDD is associated with stronger reaction to negative stimuli, which is counterbalanced by stronger control of attention in the face of negative stimuli. Attention shifting from negative information engages the attention network more in individuals with family history vulnerability to MDD than in healthy controls.

In our study, the patients without family history of the disease epitomized the mechanism for acute symptoms of depression without a connected family history risk. During evaluation of emotional valence of the stimuli, they experienced decreased activity in the right insula and rolandic operculum, regions that, in healthy controls, participate in the recognition of emotional valence and in motivation.[34] This suggests that, compared with the HC-FHN group, patients with acute symptoms of MDD may have difficulties focusing on external affective information while assessing the emotional value of stimuli. Our behavioural results confirm this hypothesis to a certain extent. Therefore, we can hypothesize that impairments in focusing on external emotional information while there is a need to do so seem to be inherent to the acute symptoms of MDD.

In contrast, MDD-FHN individuals experience increased activation in the core limbic group of the central nervous system regions. The overactivated area is known to participate in various stages of producing a strong emotional arousal.[34] The striatum is associated with the emotional integration and with transferring emotional signals to the peripheral nervous system.[34] This indicates that the visceral, rather than the informative, component dominates an emotional display in the MDD-FHN group.[71]

When attention shifting from emotion processing, in comparison with the HC-FHN group, the MDD-FHN group experience reduced activation in the right SuMG, an area participating in attentional shifts[72] and inhibition[73] in healthy controls. Reductions of activation in this area have been previously reported in elderly patients with MDD when they were asked to focus their observation on a particular target.[74] Hence, changes noted in neural correlates of both targeted processes suggest that, relative to HC-FHN individuals, patients with MDD may be less in control of focusing their attention on the external environment.

Since there was no difference in neural activation between patients treated with different types of antidepressants, we concluded that, in our task, treatment method was a factor of no interest and did not influence the link between the diagnosis and family history of MDD. The neural correlates of emotion processing and attention shifting evoked by our task were localized in areas that are usually not connected with response to antidepressant treatment in patients with MDD.[75–77] Owing to variability in the duration of treatment, it is also possible that some of the patients may not have responded to treatment yet.

An advantage of our study is the large number of participants in each subgroup. It allows for a thorough examination of the differences between individuals with and without a family history of MDD in connection with the diagnosis of the disorder. Also, the whole-brain analysis permits the exploration of changes occurring in the entire network involved in emotion processing and attention shifting.

To our knowledge, our study is the first to show the mechanism of risk and resilience connected with a family history of MDD where neural changes in emotion processing and attention shifting are the basis of the observed alterations. Emotional processing and attention shifting are of great importance in emotional regulation; therefore, their changes may lead to an increase in the risk for MDD, which, according to some models,[22,24] is a disorder of the representation and regulation of emotions and mood. In our study, both groups of healthy controls experienced greater neural activation than patients with MDD in regions responsible for higher cognitive functions. This is in accordance with these models' assumptions. Also, both groups of patients with MDD experienced increased activation in the subcortical regions, which further confirms assumptions of the models. The HC-FHP participants seemed to react in a more sensory way to emotional valence of stimuli, yet their elevated activation in the areas responsible for attentional control appeared to compensate for any potential impairment in information flow. Therefore, the behavioural differences between the groups of healthy controls were not observed.

Limitations

As a limitation of our study, we have to mention that the conclusions about the intergroup differences in activation can be drawn only about neural areas engaged in the task and processes of emotion recognition and attention shifting. As such, we cannot be sure if these are the only neural differences between the groups. Since several post hoc tests were conducted, we used strong statistical thresholds, with a threshold of $p < 0.05$, FWE-corrected, for the whole brain to minimize type I errors. In contrast, given the number of participants, the behavioural results are difficult to interpret, but they provide interesting additional information on the task performance. Some of the patients participating in the study were medicated. The additional analysis showed that there was no difference between unmedicated patients and patients treated with various types of substances. This suggests that the kind of therapy the participants received was a factor of no interest in our study. Since this was not a primary objective of the study and the statistical power was lower compared with the main diagnosis and family history differences, this result needs confirmation in a further study.

Conclusion

Family history of MDD increases the risk for the disease in healthy individuals and accelerates its onset in patients with MDD. Our study shows a potential neuropsychological mechanism of these alterations. Family history of MDD influences neural correlates of emotion processing and attention shifting in patients with MDD and healthy controls. The 2 processes are responsible for self-regulation and, when altered, may lead to affective and cognitive dysfunctions.

The HC-FHP individuals share the family risk with MDD-FHP individuals, but are also characterized by relative resilience to the disease. They experience increased neural activity during emotion processing in the left somatosensory cortex and the left attention area in comparison to healthy controls. In addition, they have greater neural activation in the left visual and somatosensory–lingual cortices relative MDD-FHP individuals. This suggests that HC-FHP individuals have stronger sensory reactions to emotional stimuli than the general population, but they can control reactions with increased attentional focus. Also, they pay more attention to external emotional cues than patients with MDD. During attention shifting, HC-FHP individuals compensate for the greater activation in the somatosensory system by engaging cortical areas responsible for particularly difficult attentional shifts. If the system of attentional control fails, HC-FHP individuals may be more prone to acute symptoms of MDD. Such a change is observed in MDD-FHP individuals, who, as previously stated, experience reductions of activation in the attention control system and are less effective in attention shifting than healthy controls.

The MDD-FHN group represents acute symptoms of MDD without increased vulnerability to the disease associated with family history. They experience reduced activation in the right insula and right rolandic operculum during emotion processing and in the right SuMG during attention shifting. They also show increased activation in the subcortical areas responsible for arousal management during emotion processing. These reactions are characteristic of acute depressive symptoms without the prior risk associated with a family history of the disorder. They seem to imply that patients with MDD pay less attention to informative aspects of emotional

experience, but display stronger visceral reactions to these experiences.

Family history of MDD seems to be associated with an increase of somatosensory reaction to emotion processing. In emotional self-regulation, this increase is balanced by greater involvement of attentional control. If the control fails, symptoms of MDD may appear.

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Contributors: D.M. Lisiecka, A. Carballedo, J. Meaney and T. Frodl designed the study. D.M. Lisiecka, A. Carballedo, A.J. Fagan, Y. Ferguson and T. Frodl acquired the data. D.M. Lisiecka and T. Frodl analyzed the data. D.M. Lisiecka and T. Frodl wrote the article. All authors reviewed the article and approved its publication.

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