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RESEARCH ARTICLE

Abnormal Neural Responses to Facial Expression Images in Major Depressive Patients

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To differentiate the perception and identification processes between different affective categories can aid the understanding of neuropathology in major depressive disorder (MDD). The present study proposed a novel technique by utilizing independent component analysis and cortical source imaging to investigate the different impaired neural substrates of emotional responses to negative and positive facial images in MDD. Nineteen MDD patients and nineteen age- and gender-matched normal controls (NC) were recruited and performed a gender discrimination task with facial expression images. The event-related magnetoencephalographic signals were recorded and processed through independent component analysis, beamforming source imaging analysis, and clustering methods. Four time components were specified for further statistical analysis. We found that the MDD patients had significantly increased cortical activity of the inferior frontal, thalamus, and occipital regions evoked by angry faces, compared with happy faces, at all time components. Compared with the NC group, the MDD patients showed hypo-activation of the cingulate cortex and anterior frontal pole in angry emotion and hippocampus and lingual region in happy emotion. Only at the third component (NC at 140 ms, MDD at 125 ms) the MDD patients showed hyper-activation of the temporal cortex in negative emotion. Our results revealed the significantly different neuronal circuitries between MDD and NC groups corresponding to different facial expression stimuli. These findings suggest the dysfunction of perceptual responses to emotional salient information in the MDD patients during early visual processing.

KEYWORDS: Major Depressive Disorder, Magnetoencephalography, Independent Component Analysis, Source Imaging, Emotion Perception.

INTRODUCTION

Affective facial expressions are important signals to interpersonal social communications. Abnormalities both in recognition of emotion in facial expression images and generation of adequate emotional responses are generally displayed in patients with major depressive disorder (MDD) [17, 28]. Depressive patients showed negative emotional bias which tended to interpret neutral face as sad expression [7] and absent of excessive negative affect [24].

One of the neuropathological models for depression indicated imbalanced interactions between the ventral and dorsal systems [4, 14, 22], which were characterized by increased activation in the ventrolateral prefrontal as well as orbitofrontal cortices and decreased activation in the dorsolateral prefrontal and medial frontal cortices. The ventral system is associated with identification of emotional stimulus and generation of emotional experiences, whereas the dorsal system is associated with regulation of emotional responses.

Recently, numerous functional neuroimaging studies have reported disrupted neural responses to different affects in MDD patients. In response to negative emotional stimuli, depressed patients showed decreased activity in the ventromedial prefrontal cortex [15], right hippocampus, and right insula [19] whereas increased activity in the right fusiform gyrus, left putamen, left parahippicampal gyrus extending to left amygdala [28]. As to positive emotional stimuli, depressed patients revealed decreased activity in the right anterior cingulated cortex, left insula [18], basal ganglia, and limbic regions [6], and increased activity in the ventromedial prefrontal

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cortex [15], bilateral fusiform gyri and right putamen [28]. However, seldom studies investigate how emotional information modulates early visual processing for depressive patients.

Magnetoencephalography (MEG) provides excellent temporal resolution which is beneficial to characterize dynamic neural responses to distinct emotional stimuli. The present study aimed at distinguishing the different brain activation patterns during early emotion perception for MDD patients and healthy subjects in response to negative and positive emotional facial images by MEG. Angry and happy face images, which induced similar arousal levels, were used as negative and positive valenced visual stimuli, respectively, in an implicit emotional task. To discern the temporal dynamics of neural responses, independent component analysis (ICA) was applied to decompose neuronal network into several sub-networks with independent temporal courses. The maximum contrast beamformer method was then employed to image cortical source distribution for each sub-network. We hypothesized that depressed patients were more sensitive to negative emotion than to positive emotion in both visual and emotion-related regions within the early 200 milliseconds post-stimulus onset.

METHODS

Participants

Nineteen MDD patients (8 males; ages between 22–65 years, mean $= 34 \pm 10.3$) were recruited from the outpatients of the Psychiatric Department at Taipei Veterans General Hospital and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) by two independent psychiatrists. All patients without past history of neurological trauma, current neurological disorder, drug abuse, and other Axis I disorder. The depressive levels of the patients were assessed using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The mean HDRS score of all enrolled patients was 8.68 ± 7.92 and all patients were on a range of medications, including lithium, anticonvulsants, antidepressant, and antipsychotics. Nineteen age-matched normal controls (NC) (7 males; ages between 22–65 years, mean $= 34 \pm 11.6$) without past history of psychiatric or neurological illness were recruited from the local community and assessed by Mini International Neuropsychiatric Interview to exclude possible morbidity of major psychiatric illness. All participants signed informed consent statements approved by the local institutional review boards before experiments.

Paradigm

Face-only gray-colored images, consisting of neutral, angry, happy, and sad expressions, were presented in a pseudorandom order by STIM2 (Neuroscan Inc.; VA, USA), with seventy-two images for each expression. Each image was displayed for 1500 milliseconds, followed by a fixation image around 1000 milliseconds, and then a response visual cue, a question mark, was exhibited for 500 milliseconds. Subjects were asked to identify the gender of the face image by lifting their left-index finger for male or right- index finger for female upon an optical pad, immediately when the subject saw the response cue. Only responses to angry and happy faces were analyzed in the present study because of controlling confounding of arousal levels of different emotions.

Data Acquisition

Event-related MEG signals were measured by a whole-head 306-channel magnetometer system (Vectorview, Elekta Neuromag, Finland) at a sampling rate of 1000 Hz with online band-pass filtering between 0.03 and 300 Hz. The electrooculograms (EOG) for detecting eye blinks and/or movements were recorded to obtain EOG-free trials. For each subject, a high-resolution anatomical magnetic resonance image was acquired by a 1.5 Tesla system (GE Signa EXCITE) using a T1-weighted sequence (3D-FSPGR; echo time $= 1.836$ ms; repetition time $= 8.548$ ms; flip angle $= 15°$; field of view $= 260 \times 260 \times 192$ mm^3; matrix size $= 256 \times 256 \times 124$ mm^3). To co-register the anatomical and functional images of each individual, the nasion and the bilateral pre-auricular points were determined with a 3D-digitizer (Isotrak, Polhemus Navigation Sciences, Colchester, VT) before the MEG experiment.

Data Analysis

In this study, ICA was first applied for noise removal. ICA is a useful method to extract the statistically independent sources from mixtures of data blindly [12], which can be described as follows:

$$X = A \times S$$

where X is the mixed observation data matrix, A is the unknown mixing matrix, and S represents independent component sources. Many variations of ICA technique have been proposed in the literature. Here we adopted the FastICA algorithm [11] for its simplicity and computational efficiency. Noise components were determined based on kurtosis index, which estimates the degree of nongaussianity:

$$kurt(x) = \frac{E[(x-\mu)^4]}{\sigma^4} - 3$$

where μ is the mean of x, σ is its standard deviation, and E is the expectation. The components with larger or smaller kurtosis based on linear quartile thresholding as

well as statistical-based methods [1] were selected as noise components. Then the noise-free signals X' were reconstructed by multiplying the noise-free components S' and their corresponding mixing matrices A' as following

$$X' = A' \times S'$$

These noise-free signals were thus re-analyzed by ICA to obtain temporal independent components of evoked neuronal responses. A potential problem of ICA technique is the instability of the obtained ICs because of its inappropriate initial condition resulting in local extremum. To deal with this problem for each data set, we repeated ICA many times (twenty in this study) with random initial conditions [10] and applied an average-linkage hierarchical clustering method to group similar components resolved from all runs together [25].

For each obtained cluster, the neuromagnetic responses were reconstructed and the maximum contrast beamformer [3] was employed for source localization and estimation of the temporal brain activity. The beamforming method, a spatial filtering technique for source imaging, is becoming increasingly popular in recent years. It yielded a spatial filter designed, under a forward model constraint, for each targeted brain location to minimize the variance of filtered activities over a time interval of interest. The F-statistics at a particular location was the ratio of the activation power of an active state over that of a control state and expressed as the activation index,

$$F_\theta = \frac{w_\theta^T C_\alpha w_\theta}{w_\theta^T w_\theta}$$

The cortical source distribution for each cluster was then obtained by iteratively scanning through the brain volume using the same procedure.

Before statistical analysis, the average-linkage hierarchical clustering method was applied again to the above-obtained cortical source distributions of all clusters in order to prevent over-estimated statistics due to spatial dependency between clusters. Finally, re-calculated cortical source distribution of each individual was normalized into a stereotaxic space. At each specified time component, a voxel-wise pair t-test was performed to compare the difference between emotions within group and a two-sample t-test was conducted to compare the difference of

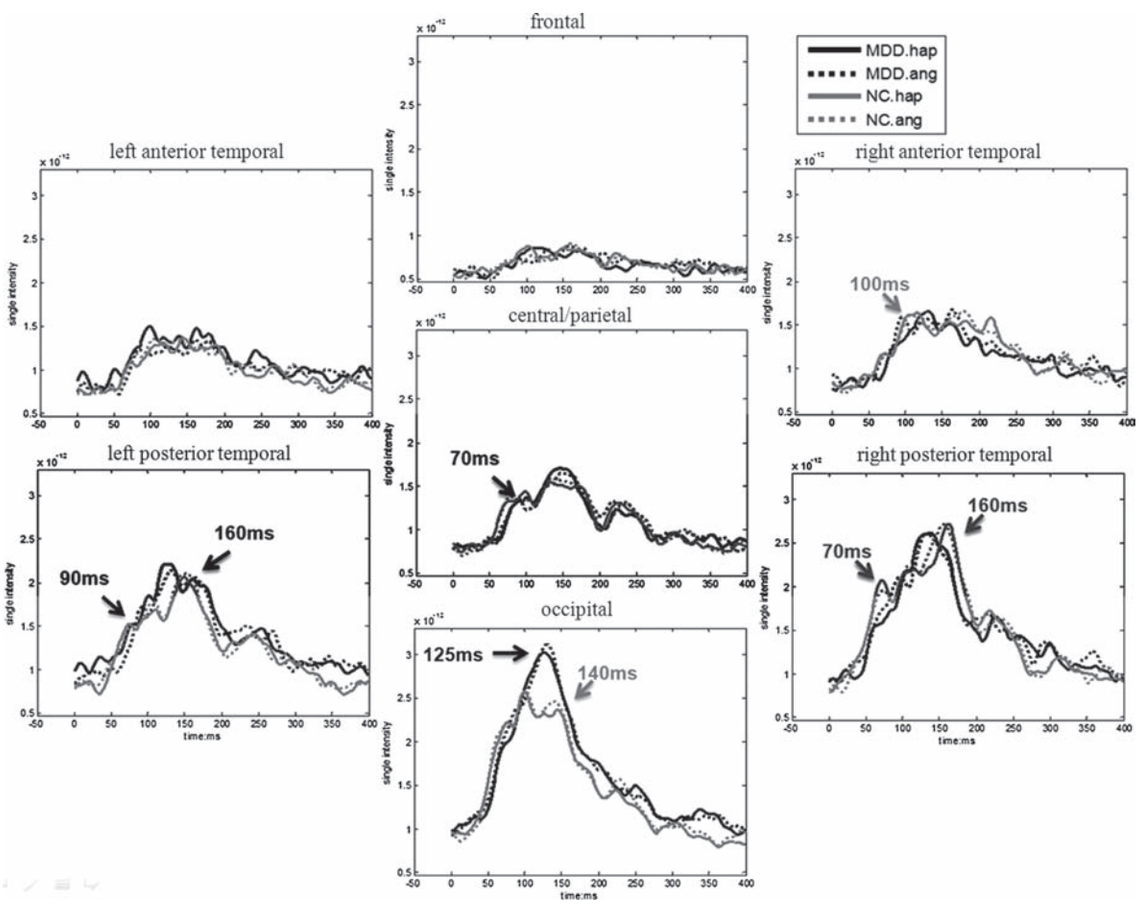

Fig. 1. Illustration of grand-averaged MEG time-series signals in response to happy (hap) faces and angry (ang) faces for patients with major depressive disorder (MDD) and normal controls (NC) and the corresponding specified time components, respectively.

affective responses between groups using SPM2 software (Wellcome Trust Centre for Neuroimaging, London, UK).

RESULTS

Figure 1 showed the grand average of MEG time-series signals within each region, seven in total. Four time components for the normal and patient groups were specified manually, including 70/100/140/160 ms and 70/90/125/140 ms, respectively, for early emotion perception processing. The statistical contrast results between positive and negative emotions for each group were listed in Table I. In overall, the depressed patients showed significantly increased activation of negative emotion, compared to positive emotion, in the right visual cortex, thalamus, ventrolateral prefrontal cortex, and left dorsolateral prefrontal cortex at all time components. The normal group exhibited higher activations of the right visual cortex and superior temporal cortex at both 100 and 140 ms in response to happy faces, which were diminished in the patient group.

Table II listed the statistical results of group differences for each emotion. In angry faces, the patient group revealed decreased activations in the regions of the right posterior cingulated (BA23) and left anterior frontal cortices at all the first, second and fourth time components, compared to the normal group. Notably only at the third component (125 ms), the patient group showed higher activations at the left inferior temporal gyrus and right superior temporal gyrus in response to negative emotion. As to happy face condition, the patients groups exhibited decreased activations in the right hippocampus and right lingual gyrus at all time components. Figures 2(A) and (B) illustrated the corresponding statistical imaging results for Tables I and II, respectively.

DISCUSSION

The present study proposed a novel approach by utilizing advanced neuroimaging techniques to delineate the different pattern of neuronal dynamics between the NC and MDD groups in response to positive and negative facial emotions, respectively. We found that compared to the NC group, the MDD patients showed less neuronal activations in both emotions. Only at 125 ms, MDD patients showed lager activation of temporal cortex than NC group in negative emotion. Furthermore, the depressed patients had significantly increased neuronal activations in negative emotion relative to positive emotion at all time components during early visual processing of emotion perception.

The contrast results between emotions showed that the MDD patients exhibited increased activation in the right thalamus and visual cortex in negative emotion. The finding of the thalamus in this study was consistent with the previous report [17]. The thalamus acted as a relay station where receiving sensory inputs from peripherals and sending information to cortical regions [27] and also involved in a rapid processing with the perception of potentially dangerous events [20]. Furthermore, previous studies indicated that the angry faces enhance rapid

Table I. Comparison results between negative and positive emotions for each group.

Group	Time (ms)	Emotion	BA	Region	MNI coordinates (mm)			*P* value	Cluster size
					X	Y	Z		
NC	70	Ang > Hap	6	Precentral_L	−48	10	40	0.008	154
	100	Ang < Hap	18	Occipital_mid_L	−28	−96	19	0.005	1013
			21	Temporal_mid_R	54	−20	−5		492
	140	Ang > Hap	46	DLPFC_L	−32	40	26	0.002	4066
			9	DLPFC_L	−24	46	38		
	160	Ang < Hap	21	Temporal_sup_R	54	−20	−4	0.008	567
MDD	70	Ang > Hap	45	IFC_L	−36	44	17	0.001	3113
			18	Occipital_inf_R/	34	−90	−14		20585
				Thalamus_R	2	−24	−4		20585
			20	Temporal_mid_L	−54	−20	−12		2505
	90	Ang > Hap	18	Occipital_inf_R	34	−90	−14	0.008	110
	125	Ang > Hap	46	VLPFC_L	−40	52	10	<0.001	3232
			45	IFC_R	54	44	16		120
			18	Occipital_inf_R	32	−85	−14		4199
			21	Temporal_mid_L	−70	−20	−12		686
				Thalamus_R	4	−20	−2		24010
	160	Ang > Hap	18	Lingual_R	30	−90	−18	0.03	1636
			7	Pariental_sup_R	28	−53	70		2586
				Thalamus_R	5	−15	17		127
		Ang < Hap	43	Postcentral_L	−60	−4	20	0.03	1042

Notes: NC, normal controls; MDD, patients with major depressive disorder; Ang, angry; Hap, happy; L, left; R, right; ant, anterior, inf, inferior, mid, middle; sup, superior; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; IFC, inferior frontal cortex; BA, Brodmann area.

Table II. Comparison results between groups in positive and negative emotions.

Time (ms)	Group	Emotion	BA	Region	MNI coordinates (mm) X	Y	Z	*P* value	Cluster size
1st component									
(NC:70; MDD:70)	NC > MDD	Ang	23	Cingulum_mid_R	10	−26	46	0.005	3435
			10	Frontal_sup_L	−26	63	15		5150
			7	Pariental_sup_L	−25	−56	58		1029
				Precuneus_R	10	−54	40		3435
		Hap	10	Frontal_sup_L	−18	67	8	< 0.0003	1505
				Hippocampus_R	26	−10	−10		2299
			18	Lingual_R	12	−68	−4		7289
2nd component									
(NC:100; MDD:90)	NC > MDD	Ang	23	Cingulum_mid_R	10	−26	46	0.03	617
			4	Paracentral_lobule_R	12	−30	58		617
		Hap		Hippocampus_R	26	−10	−12	0.0005	493
			18	Lingual_R	10	−68	−2		754
3rd component									
(NC:140; MDD:125)	NC < MDD	Ang	21	Temporal_inf_L	−60	−8	−28	< 0.0003	4053
			42	Temporal_sup_R	61	−28	18		4430
	NC > MDD	Hap		Hippocampus_R	26	−10	−10	0.005	168
			19	Occipital_sup_L	−16	−87	19		3031
4th component									
(NC:160; MDD:160)	NC > MDD	Ang	27	Calcarine_L	−18	−40	4	0.05	446
			23	Cingulum_mid_R	10	−34	32		3184
			10	Frontal_sup_L	−16	64	12		1995
		Hap		Hippocampus_R	26	−10	−12	0.0003	500
			18	Lingual_R	8	−66	−2		449

Notes: NC: normal controls, MDD: patients with major depressive disorder; Ang: angry, Hap: happy; L: left, R: right; ant: anterior, inf: inferior, sup: superior, post: posterior; BA: Brodmann area.

top-down control [29] and benefit visual short-term memory which encodes and maintains the information of face identity and emotion processing [13]. The findings of the persistent increased thalamic and visual cortical activity of negative emotion in the depressed patients may implicate over-gating of negative valenced stimuli and thus enhance the visual encoding and working memory processing of emotional content.

We also found that MDD patients demonstrated increased activation in the left ventrolateral prefrontal cortex (VLPFC; BA45) and dorsolateral prefrontal cortex (DLPFC; BA46) to angry faces in comparison with responses to happy faces. Numerous studies indicated that the abnormal activation in the prefrontal cortex may be a state marker to mood disorders [4, 14, 23]. The VLPFC is involved in generation of relevant behavior and experiences in the response to emotionally salient material [22] and the DLPFC is involved in the regulation of emotional experiences and behavior [21] and suppression of emotional responses [5]. In this study, the enhanced left VLPFC and DLPFC activations of angry faces in the depressed patients may imply their facilitation of selective attention to negative stimuli and engagement more in suppression of emotional responses.

Compared with the normal group, the MDD patients exhibited increased activation of the left inferior temporal gyrus and right superior temporal gyrus in negative emotion at 125 ms. The superior temporal sulcus is an important region to extract the facial emotional information [13] and elicits a strong response to selective attention to the perception of dynamic feature information [8, 9]. The inferior temporal cortex is involved more in perceiving facial identity [8, 9]. The findings of the higher activations in these regions for the depressed patients reflected their over-activation of the bottom-up reappraisal function by negative information during early visual processing stage.

As to happy stimuli, the MDD patients had decreased activation of the hippocampus, compared with NC subjects, that was in line with the reports in [18, 6]. The hippocampus is a critical part of the human limbic system involving in encoding context [4], memory recollection [2], and retrieval of both facial identity and affective facial expressions [6]. Previous studies have reported that the hippocampus may have decreased metabolism and volume in depressive patients, which were associated with impairments in execution function, learning, emotion-mediated memory formation, and regulation of the affective processing [16, 26].

The limitation of this study would be the drug effect. Our MDD patients were receiving a wide range of medications, including lithium, anticonvulsants, antidepressant, and antipsychotics. This confounding factor may influence

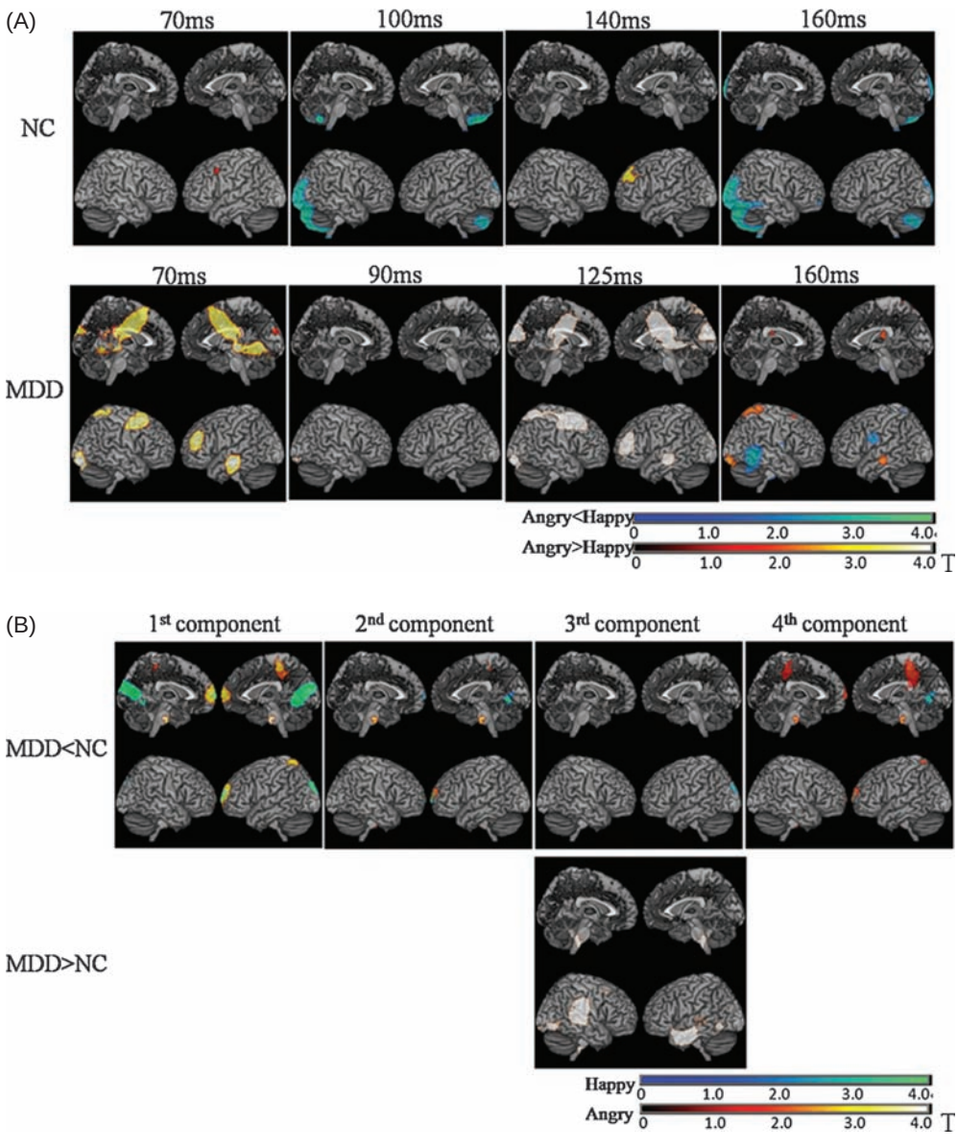

Fig. 2. Comparison results of source images between emotions (A) within group and (B) between groups in response to happy and angry faces.

the effects on emotional responsiveness. Further studies should be needed to distinguish the treatment efficiency of patients with different affective disorders in processing emotional facial expressions.

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