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Neural activities during affective processing in people with Alzheimer's disease

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Abstract

This study examined brain activities in people with Alzheimer's disease when viewing happy, sad, and fearful facial expressions of others. A functional magnetic resonance imaging and a voxel-based morphometry methodology together with a passive viewing of emotional faces paradigm were employed to compare the affective processing in 12 people with mild Alzheimer's disease and 12 matched controls. The main finding was that the clinical participants showed reduced activations in regions associated with the motor simulation system (the ventral premotor cortex) and in regions associated with emotional simulation—empathy (the anterior insula and adjacent frontal operculum). This regional decline in blood oxygen level-dependent signals appeared to be lateralized in the left hemisphere and was not related to any structural degeneration in the clinical participants. Furthermore, the regions that showed changes in neural activity differed for the 3 emotional facial expressions studied. Findings of our study indicate that neural changes in regions associated with the motor and emotional simulation systems might play an important role in the development of Alzheimer's disease.

Keywords: Alzheimer's disease; Dementia; Emotional facial expressions; Mirror neuron system

1. Introduction

Alzheimer's disease (AD) is associated with a gradual decline in brain functioning (Buckner, 2004), which eventually affects all cognitive (Bäckman et al., 2004; Buckner, 2004) and affective processing within the brain. While there have been many studies on the cognitive correlates of AD, research on affective processing in individuals with AD has been scarce. Compromised affective processing does have a very significant impact on the quality of social interactions (Phillips et al., 2010; Shimokawa et al., 2001), which then predisposes further cognitive and hence functional decline, adding to the caregiver's burden of care (Ropacki and Jeste, 2005; Scarmeas et al., 2005). Therefore, understanding the changes in affective processing in individuals with AD might be as important for the management of people with AD as the knowledge of cognitive decline that accompanies the illness.

Previous behavioral studies have provided evidence of deficits among individuals with AD in recognizing facial emotions (Guaita et al., 2009; McLellan et al., 2008), specifically in the recognition of happy, sad, and fearful expressions (Kohler et al., 2005). Impairment of facial emotion recognition cannot be explained by impairment of the recognition of faces that are affectively neutral (Hargrave et al., 2002); it appears, rather, to be associated with the

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severity of the illness (Weiss et al., 2008). The study by Wright et al. (2007) on the ability of people with AD to recognize fearful facial expressions found a significant increase in amygdala activity in individuals with AD while viewing neutral and fearful faces. Staff et al. (2011) found that AD patients with impaired emotion perception had decreased blood flow in the medial frontal lobe. Rosen et al. (2006) observed that impaired recognition of negative emotions in patients with dementia (including patients with AD, mild cognitive impairment, or frontotemporal lobar degeneration) was associated with atrophy of the right temporal gyri. Changes of brain activity during normal and pathological aging appear to be quite similar (see St. Jacques et al., 2009).

Over the past decade, a prominent finding has been the realization that observing the facial expressions of others triggers representations of the observer's own motor, somatosensory, and emotional states that are thought to allow the observer to vicariously experience what the observed individual is feeling (Atkinson and Adolphs, 2011; Gallese et al., 2004; Keysers, 2011). The realization that regions involved in motor control are important for social perception has been strongly influenced by the discovery of mirror neurons in the premotor and inferior parietal cortex of monkeys (Gallese et al., 1996; Keysers et al., 2003; Rozzi et al., 2008), which showed that primates transform the actions of others into a vicarious representation of their own corresponding actions. In the case of facial expressions, a number of studies have shown that the ventral premotor cortices (including the precentral and inferior frontal gyrus as well as the inferior frontal operculum) are activated when viewing the dynamic facial expressions of others (Budell et al., 2010; Carr et al., 2003; Grosbras and Paus, 2006; Sato et al., 2004). In light of a monkey's physiology, these results have been interpreted as indicating that the observation of other people's facial expressions triggers a motor simulation in mirror-like neurons necessary for the movement of a person's face in similar ways.

The idea that somatosensory regions are also important for recognizing facial expressions has received strong support from a lesion-mapping study by Adolphs et al. (2000), which found that lesions in the somatosensory cortex (SI) impair the recognition of facial expressions in photographs. A number of functional neuroimaging studies have provided additional evidence by showing that the observation of facial expressions triggers activity in the SI that differentiates between different facial expressions (Germine et al., 2011; Hennenlotter et al., 2005; Keightley et al., 2007; van der Gaag et al., 2007a; Winston et al., 2003). The role of the SI during the observation of facial expressions dovetails well with other mounting evidence for the role of this region in social perception more generally, including the perception of body movement, touch, and pain (Keysers et al., 2010). Together, this suggests that the brain also transforms what others do, facial expressions in particular, into a vicarious representation of what it would feel like to move one's face in that way.

Finally, there is growing evidence that the regions involved in the feeling of emotions are also vicariously recruited while viewing the feelings of emotions in others (see Bastiaansen et al., 2009 for a review). In particular, the anterior insula and the adjacent frontal operculum (jointly referred to as the insula/frontal operculum [IFO]) have been shown to be activated both when people feel an emotion (disgust or pleasure) and when they see similar emotional (disgust or pleasure) facial expressions of others (Jabbi et al., 2007; Wicker et al., 2003). A number of studies later established that a similar region is recruited when an individual experiences pain or witnesses the pain of others (Lamm et al., 2011). People who have reported to experience more empathy in everyday life have shown stronger vicarious activations in the IFO while witnessing the emotions of others (Jabbi et al., 2007; Lamm et al., 2011). The IFO is functionally connected to the ventral premotor cortex (vPMC), and the IFO seems to receive information from the region of the vPMC that is activated while viewing the facial expressions of others (Jabbi and Keysers, 2008). Therefore, it seems that motor and emotional brain regions act in unison to allow viewers to share the emotional state of others both from a motor and an affective point of view (Keysers, 2011).

From the literature reviewed above, this functional magnetic resonance imaging (fMRI) study was conducted with the aim of understanding whether seeing the emotional facial expressions of others (happiness, sadness, and fear) would trigger brain activation in the motor, somatosensory, and/or emotional simulation systems in people with AD that differed from the brain activation in control participants. Neuroimaging studies on AD-related changes in neural correlates of specific emotions have been scarce. Based on the observation of Kohler et al. (2005) that AD was associated with impaired recognition of happy, sad, fearful, and neutral expressions, in the present study, we aimed to compare patients with AD with normal controls when they were viewing happy, sad, fearful, and neutral facial expressions. We hypothesized that individuals with AD, relative to healthy controls, would show weaker blood oxygen level-dependent (BOLD) signals—when viewing all emotional facial expressions (happy, sad, or fearful faces) in neural regions involved in motor, somatosensory, or emotional simulation. Furthermore, we examined the relationship between the BOLD signals in these simulation systems when viewing emotional faces and the mental as well as the affective states of patients with AD.

2. Methods

2.1. Participants

Altogether, 24 right-handed Chinese women participated in this study approved by the Institutional Review Board of

the University of Hong Kong. Informed written consent was obtained from all of the participants. Women were included if they were younger than 89 years of age, if they were right-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971), and if they had scores on the Mini Mental State Examination (MMSE) of 15 or above (Folstein et al., 1975). People who had a history of traumatic brain injury, or other medical or psychiatric conditions affecting brain functioning, were not included in this study.

Among the 24 participants, 12 were aged from 71 to 88 years (mean ± standard deviation [SD]: 76.7 ± 5.2 years), had a mean of 1.9 years of education (SD: 3.4 years), and were recruited from Queen Mary Hospital in Hong Kong. They were diagnosed as having mild AD according to: (1) the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984), and (2) Clinical Dementia Rating 0.5 or above.

The other 12 women were matched controls recruited from the community. They were aged from 60 to 81 years (mean ± SD: 72.3 ± 6.2 years) and they had a mean of 4.7 years of education (SD: 4.4 years). Their scores on the Clinical Dementia Rating were 0.

2.2. Materials

The visual stimuli employed in this study were validated movie clips containing facial expressions—happy, sad, fearful, and neutral—of 5 men and 5 women (van der Gaag et al., 2007a). We employed this paradigm so that the results acquired in this study can be compared with that of van der Gaag et al. (2007a). The movie clip was adapted to 1.5 seconds in duration for synchronization of the scanning sequence in the fMRI experimental paradigm.

2.3. Procedure

At the beginning of the experiment, participants were interviewed about their affective states using 2 questionnaires. The Affect Grid was used to measure the arousal and pleasure (Russell et al., 1989), and the short version of the Geriatric Depression Scale, which has only 15 questions, was used to measure depression (Sheikh and Yesavage, 1986). To confirm that all participants could view some facial features important for facial emotion recognition (e.g., eyes, eyebrows, and mouth) clearly in the scanner, each of the participants was asked to describe these necessary features of an actor drinking with a straw in a sample movie.

During the fMRI experiment, each participant performed 2 sessions using block-designed passive viewing tasks. Happy, sad, fearful, and neutral movie blocks were each presented twice within a session. Each movie block consisted of ten 1.5-second movie clips of the same type of facial expression. The gender displaying the facial expressions alternated within each block. A fixation was presented at the beginning and at the end of each session, as well as in between 2 contiguous movie blocks (Fig. 1). Participants were asked to watch the movies without generating any overt responses (i.e., passive viewing). The order of movie blocks was balanced across participants within each group. The visual stimuli were displayed using the E-Prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, KS, USA) through a color LCD projector. Because eye-tracking in the scanner was not available, we repeated 1 of the sessions outside the scanner in front of a laptop and monitored participants point-of-regard using a video camera. Participants were instructed to rest their chins comfortably on a foam-made chin rest that had been placed in front of the laptop at a distance of about 20 cm. An experimenter, blind to the neurological status of the participant, then judged whether the participant looked at the movies (e.g., eyes remained open for the whole procedure, except natural blinking, and focused on the central area of the laptop's screen on which the facial stimuli were displayed).

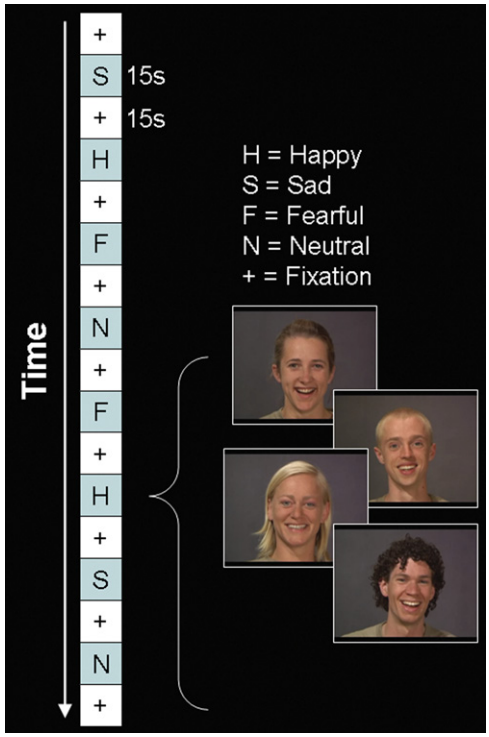

Fig. 1. Schematic diagram of the passive viewing task. Each participant in the scanner carried out 2 sessions of the block-designed passive viewing task. Participants were asked to passively view faces without giving any response during the scanning process. Happy, sad, fearful, and neutral movie blocks were each presented twice within a session. Each movie block consisted of ten 1.5-second movie clips of the same facial expression, and the gender displaying the facial expressions alternated in turn within each block.

2.4. Image acquisition

The experiment was conducted using a 3T Philips Achieva scanner with a SENSE RF head coil with 8 channels. A T1-weighted spin-echo pulse sequence was used to

acquire structural images in a sagittal orientation [repetition time (TR) = 7 msec, echo time (TE) = 3.2 msec, slice thickness = 1 mm], and a T2*-weighted gradient-echo echo-planar imaging pulse sequence (TR = 3000 msec, TE = 30 msec, field of view = 230 × 230 mm, flip angle = 90°, slice thickness = 4 mm, matrix dimension = 128 × 128) was used to acquire functional images parallel to the anterior commissure-posterior commissure (AC-PC) plane with 32 interleaved slices.

2.5. fMRI data analysis

2.5.1. Preprocessing and first-level, single-subject analysis

The fMRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK) in MATLAB 7.7 (MathWorks, Inc., Natick, MA, USA). All echo-planar imaging (EPI) volumes were realigned to the first volume of each participant. Motion parameters for each session were saved and subsequently included as covariates in the generalized linear model in the first-level analyses. First-level, single-subject analyses were conducted using a block-design model, with 4 box-car predictors (1 per block type: happy, sad, fearful, and neutral) convolved with the hemodynamic response function.

2.5.2. Second-level group analysis

The contrasts of the average parameter estimate for all facial emotion blocks (i.e., happy, sad, and fearful facial emotions) were compared against that for the neutral facial expressions using a paired *t* test model for the controls only. This was carried out to enable a comparison of the findings of this study with existing findings to verify the validity of the paradigm in this study. The statistical map (SPM[*t*]) generated was then assigned a threshold at the voxel-level of $p < 0.005$ (uncorrected) with a cluster extent of 25 contiguous voxels. The extent of cluster was determined by the Monte Carlo simulation program implemented in the AlphaSim program in REST software (Release 1.6) (Song et al., 2011). Monte Carlo simulations were carried out 1000 times within a search volume containing 40,592 voxels that covered most of the brain. The Gaussian filter width was 8 mm and the cluster connection radius was set to 4 mm. This ensured a family-wise error inferior of 0.05.

For group comparisons, we performed 3 separate analyses of variance, 1 per emotion to allow for separate group differences for each emotion. For happy expressions, we performed a 2 group (AD vs. control) × 2 type of emotion (happy vs. neutral) analysis of variance, and then repeated the procedure twice; once for sad and once for fearful stimuli. The variables age, years of education, and affective states (i.e., arousal, pleasure, and depression) were all included as covariates. The statistical maps (SPM[*F*]) generated respectively were then assigned a threshold at the voxel-level of $p < 0.001$ (uncorrected) with a cluster extent of 20 contiguous voxels. The extent of cluster was also determined by the Monte Carlo simulation program implemented in the AlphaSim program in REST software. Higher voxel-level and smaller cluster-level thresholds compared with previous analyses were set to focus our findings in the most prominent regions. The automated anatomical labeling toolbox (Tzourio-Mazoyer et al., 2002) was employed to label the suprathreshold clusters.

2.5.3. Region-of-interest (ROI) analysis

To further explore the underlying pattern of neural activity underlying significant interaction effects, we also investigated the mean percent signal change within each of these suprathreshold clusters. The percent signal changes were extracted using the MarsBar toolbox (Release 0.42) (Brett et al., 2002). The mean percent signal change was produced by averaging the percent signal change within the functional ROI mask for the corresponding condition for each participant. We then used these values to examine if BOLD activity in the ROI can predict the mental (as assessed using the MMSE score) and/or affective states (as assessed using the scores of arousal, pleasure, and depression) of our participants with AD. The correlation analyses were performed with a statistical software package (SPSS 13.0 software, SPSS, Inc.).

2.5.4. Voxel-based morphometry analysis

To explore if differences in BOLD signals in the ROI could be due to structural changes in the regions concerned, we performed a voxel-based morphometry analysis on these clusters using a small volume correction at $p < 0.05$. The magnetic resonance images were processed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) using the VBM8 toolbox (Christian Gaser; dbm.neuro.uni-jena.de/vbm/download/). All magnetic resonance images were first screened for artifacts or gross anatomical abnormalities. Then the orientation of each image was adjusted to match the brain template by setting the image origin to the anterior commissure. High-dimensional Dartel normalization was used during spatial normalization for better intersubject alignment (Ashburner, 2007). The East Asian brain template was selected. Modulated gray matter segments were generated using the nonlinear components derived from the normalization matrix to preserve the actual gray matter values locally and adjust for individual differences in total brain size. Finally, a Gaussian kernel of 8-mm full-width half-maximum (FWHM) was used to smooth the modulated images.

Statistical analyses were performed on the smoothed modulated gray matter images with SPM8. Two-sample independent *t* tests were used to test for brain differences between the patients with AD and the healthy controls on a whole-brain voxel-by-voxel basis. The absolute threshold masking was set to 0.1. Small volume correction was performed on the 3 resultant regions (IFO, medial prefrontal

Table 1
Demographic data of both the control and AD groups

	Control, mean (SD)	AD, mean (SD)	*t*	*df*	*p*
MMSE	26.8 (2.9)	18.3 (3.4)	6.566	22	<0.001
Age (y)	72.3 (6.2)	76.7 (5.2)	−1.859	22	0.076
Education (y)	4.7 (4.4)	1.9 (3.4)	1.715	22	0.100
Arousal	6.5 (2.1)	6.8 (1.8)	−0.416	22	0.681
Pleasure	6.7 (1.9)	6.1 (1.8)	0.761	22	0.455
Depression	3.3 (3.0)	3.8 (2.6)	−0.433	22	0.670

Arousal and pleasure were measured with the Affect Grid (Russell et al., 1989), and depression was measured with the Geriatric Depression Scale (Sheikh and Yesavage, 1986) before scanning.
Key: AD, Alzheimer's disease; Control, healthy controls; MMSE, Mini Mental State Examination (Folstein et al., 1975).

cortex [mPFC], and vPMC) using the functional ROI masks generated for extracting BOLD signals.

3. Results

The scores on the MMSE for participants with AD (mean ± SD, 18.3 ± 3.4) were significantly lower ($t(22) = 6.566$, $p < 0.001$) than those for the control participants (26.8 ± 2.9). Apart from this, the AD and the control groups were matched on ages, years of education, and affective states (i.e., arousal, pleasure, and depression; see Table 1).

3.1. Validation of the paradigm

All participants were able to correctly identify the valence of all the emotional facial expressions presented. Higher BOLD signals were found in the left precentral gyrus and the right superior and middle temporal gyrus when viewing emotional facial expressions (i.e., happy, sad, and fearful expressions) than when viewing neutral facial expressions (Table 2). These results are consistent with previous findings on the neural activity associated with the processing of facial expressions (Lee et al., 2002, 2005; Sabatinelli et al., 2011; van der Gaag et al., 2007a), and hence, this finding supports the validity of the paradigm employed in this study.

3.2. Processing of emotional facial expressions

Between-group comparison of BOLD signals for the contrast of viewing emotional (the average BOLD signal of viewing happy, sad, and fearful faces) versus neutral faces revealed no significant findings. We hence proceeded with examining the between-group BOLD signals differences for each of the emotions studied, i.e., happy, sad, and fearful faces.

The whole brain voxel-based analysis showed a significant interaction effect between the groups and the type of emotion in the left anterior IFO when viewing happy facial expressions compared with neutral facial expressions (Table 3, Fig. 2); in the left mPFC when viewing sad facial expressions compared with neutral facial expressions (see Table 3, Fig. 3); and in the left vPMC (Brodmann area [BA] 6) when viewing fearful facial expressions compared with neutral facial expressions (see Table 3, Fig. 4). Furthermore, relative to BOLD signals associated with viewing neutral facial expressions, those for viewing emotional facial expressions were weaker in patients than the normal controls in the above reported brain regions.

To examine if the activations observed in our participants would predict their mental or affective state, we correlated the BOLD values (the percent signal changes extracted from each functional ROI) of the contrast that led to the detection of the cluster with the MMSE and pleasure scores of affective states in the AD group. The percent signal changes in the left IFO ($r = 0.692$, $p = 0.013$) and the left vPMC ($r = 0.644$, $p = 0.024$) were positively correlated with the pleasure scores. No other significant correlations were found ($-0.468 < r < 0.371$, $p > 0.125$).

3.3. Voxel-based morphometry analysis

Finally, to assess whether changes in gray matter volume might account for the reductions in BOLD activity in the 3 clusters reported above, we conducted a voxel-based mor-

Table 2
The brain regions of the control group where emotional facial expressions (i.e., happy, sad, and fearful) showed higher BOLD activity than the neutral facial expressions

Regions	BA	Side	MNI coordinates			Cluster	*t*
			x	y	z		
Premotor cortex	6	L	−45	13	52	43	6.016
Superior and middle temporal gyrus	21, 22	R	45	−28	−2	128	5.023

All of the listed brain regions were cluster-corrected at 25 contiguous voxels and survived the threshold of $p < 0.005$. Cluster is the number of significant voxels in the regional cluster; *t* is the *t*-value of the significant peak voxel.
Key: BA, Brodmann area; BOLD, blood oxygen level-dependent; L, left; MNI, Montreal Neurological Institute; R, right.

Table 3
Brain regions showed a significant interaction effect in the 2 (i.e., control group vs. AD group) × 2 (i.e., emotional movie displays vs. neutral movie displays) ANOVA for happy, sad, and fearful facial expressions, respectively

	Regions	BA	Side	MNI coordinates			Cluster	*F*
				x	y	z		
Happy	Anterior IFO	13/47	L	−36	23	−2	33	17.939
Sad	Medial prefrontal cortex	8	L	−21	11	40	20	12.091
Fearful	Ventral premotor cortex	6	L	−45	−10	28	24	26.831

All of the listed brain regions were cluster-corrected at 20 contiguous voxels and survived the threshold of $p < 0.001$ (for happy and fearful expressions) or $p < 0.005$ (for sad). Cluster is the number of significant voxels in the regional cluster; *F* is the *F*-value of the significant peak voxel.
Key: ANOVA, analysis of variance; BA, Brodmann area; IFO, insula/frontal operculum; L, left; MNI, Montreal Neurological Institute.

phometry analysis on the modulated gray matter images. Small volume correlation analyses on these 3 regions showed that the 2 groups did not differ in gray matter volume in any of these 3 regions (corrected $p > 0.05$).

4. Discussion

The main finding was that our clinical participants showed reduced activations in regions associated with the classical mirror neuron system (MNS), the motor simulation system—the vPMC—and in regions associated with emotional simulation—empathy (the anterior insula and adjacent frontal operculum). Changes in BOLD activation observed cannot be explained by any observable structural degeneration in our clinical participants. Furthermore, the regions that showed changes in neural activity differed for the 3 emotional facial expressions studied. Specifically, we observed declined neural activity in the left IFO (BA 13/47) when processing happy facial expressions; in the left mPFC (BA 8), a region associated with the MNS when processing sad facial expressions; and in the left vPMC (BA 6), also associated with the MNS, when processing fearful facial expressions. Changes appeared to lateralize in the left hemisphere. Importantly, levels of brain activation in the left IFO

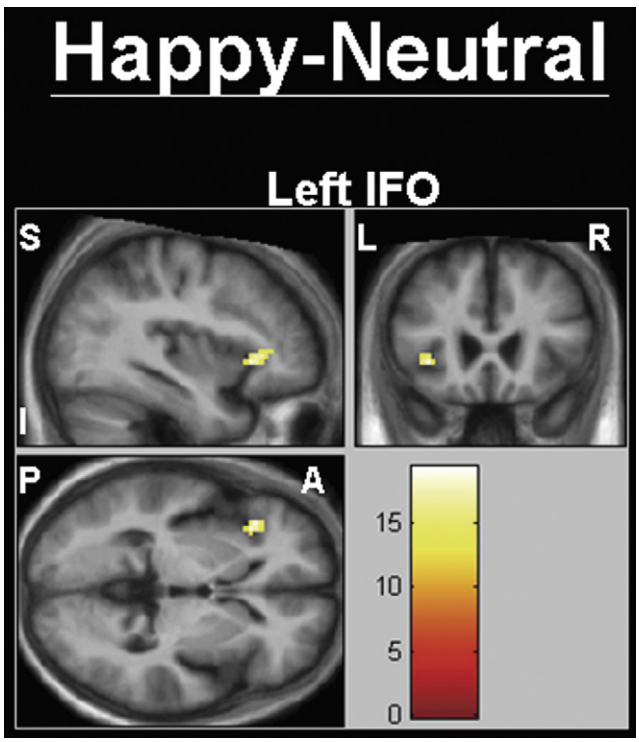

Fig. 2. Happy-neutral. A significant interaction effect between group and type of emotion for the happy facial expressions was found at the left anterior insula/frontal operculum. The SPM *F* map overlaid on the average of the normalized, bias-corrected, anatomical images from all participants. Abbreviations: A, anterior; I, inferior;IFO, anterior insula/frontal operculum; L, left; P, posterior; R, right; S, superior.

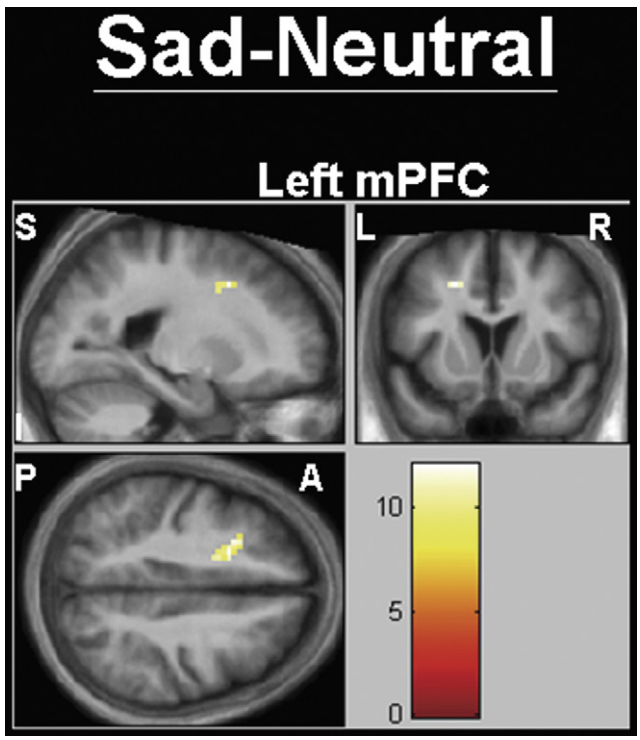

Fig. 3. Sad-neutral. A significant interaction effect between group and type of emotion for the sad facial expressions was found at the left mPFC. The SPM *F* map overlaid on the average of the normalized, bias-corrected, anatomical images from all participants. Abbreviations: A, anterior; I, inferior; L, left; mPFC, medial prefrontal cortex; P, posterior; R, right; S, superior.

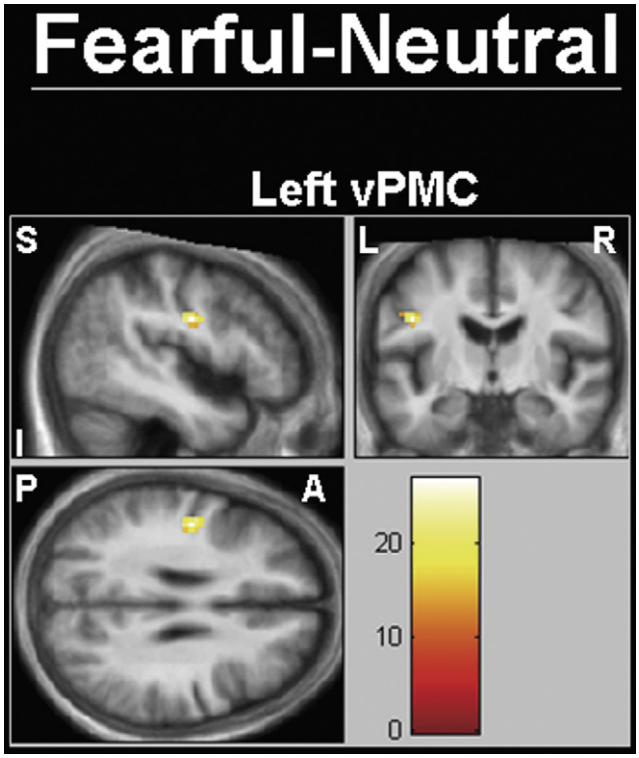

Fig. 4. Fearful-neutral. Significant interaction effect between group and type of emotion for the fearful facial expressions was found at the left vPMC. The SPM *F* map overlaid on the average of the normalized, bias-corrected, anatomical images from all participants. Abbreviations: A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior; vPMC, ventral premotor cortex.

and the left vPMC predicted the level of affect (pleasure scale) in the AD group. These findings indicate that neural changes in regions associated with motor and emotional simulation might play an important role in the development of AD and that they are associated with affective functioning.

4.1. Level of BOLD signals

The reduced activation levels observed in our clinical participants might reflect an acceleration of the normal aging process in the MNS (Bastiaansen et al., 2011). Behavioral ratings of the participants' capacity to focus their eyes on the stimuli showed no evidence of differences in eye-gazing patterns between the participants with AD and the healthy controls. Accordingly, it seems that, despite similar initial visual input, the brains of our participants with AD were less engaged by the emotions of others than those of our matched controls.

The fact that the changes in BOLD activation in the left IFO and in the vPMC of the AD group correlated only with affective functioning (as measured using the pleasure scale) suggests that these regions might play an important role in determining the affective burden associated with AD. Future longitudinal studies will be helpful for understanding how changes in BOLD signals along the temporal courses of AD pathology covary with affective decline and hence providing more insights into the pathophysiology of AD.

4.2. Regional differences

The IFO is a region with complex pattern of connectivity that integrates motor signals from premotor and inferior parietal regions with affective information from the rest of the insula and the limbic system (Cerliani et al., 2011). Functionally, it is most often associated with emotional empathy (Bastiaansen et al., 2009; Lamm et al., 2011), and it has been shown to integrate information from the motor and affective system during a person's observation of other people's emotions (Adolphs et al., 2000; Jabbi and Keysers, 2008). Activation of the IFO has been reported mainly for emotions such as pleasure, disgust, and pain (Chen et al., 2009; Jabbi et al., 2007; Lamm et al., 2011), but not so much with regard to sadness or fear. The fact that we found the IFO to differ between our AD and control groups during the observation of happy facial expressions dovetails well with this aforementioned literature.

The vPMC is a complex region that is most strongly associated with the MNS (Gallese et al., 2004), and the disruption of the vPMC is associated with impairments in perceiving the goal-directed actions (Pobric and Hamilton, 2006) and the communicative signals (Meister et al., 2007) of others. Levels of activation in this region predict how empathic participants are when processing facial expressions (Gazzola et al., 2006). The vPMC is also an important source of input into the IFO (Cerliani et al., 2011; Jabbi and Keysers, 2008), and it has been associated with the processing of fearful stimuli (Sagaspe et al., 2011; Schutter et al., 2008). The fact that BOLD signals in this region predicted affective decline in our AD group suggests that changes in neural activity in the left vPMC may play an important role in the symptoms associated with AD.

Activation of the mPFC has been consistently observed in the majority of imaging studies on emotion, and it likely plays a general role in emotional processing (Northoff et al., 2004; Phan et al., 2002). Furthermore, this region has been thought to play a role in the theory of mind and empathy (Völlm et al., 2006). Hence, activity in this region may facilitate regulation by altering the perceived mental states of the people in the emotional pictures.

The observed differences in the regional BOLD signals appeared to lateralize in the left hemisphere and are consistent with previous behavioral as well as neuroimaging findings (Filley et al., 1986). The intraneuronal filamentous deposits disrupting axonal transport induced widespread metabolic decline, at a faster rate in the left hemisphere than in the right hemisphere (Thompson et al., 2003). Hence, it becomes apparent why the differences in regional BOLD signals observed in this study appeared to lateralize in the left hemisphere.

We did not achieve any significant results for the amygdala that were reported in the study by Carr et al.

(2003). However, the significant result in Carr et al. (2003) was derived from contrasting emotional expressions with a baseline of fixation. A more stringent analysis of contrasting emotional expressions with a neutral expression by van der Gaag et al. (2007b) did not find significant results in bilateral amygdala. As we have adopted the research materials and method for data analysis from van der Gaag et al. (2007a), this may explain the lack of findings for the amygdala. Nonetheless, previous studies have shown that the level of activity in the amygdala differed between AD patients and the normal controls (e.g., Wright et al., 2007). Changes of amygdala activity associated with viewing affective stimuli were also observed during normal aging (St. Jacques et al., 2009). Taken these observations together, future neuroimaging studies should consider employing task paradigms and methodologies sensitive to amygdala activity; findings of which will provide significant insight into the potential of amygdala activity for differentiating AD patients from normal controls.

Phillips et al. (2003) proposed that there were 2 neural systems for affective processing: a ventral system for the identification of the emotional significance of stimuli, the production of affective states and autonomic response regulation; and a dorsal system critical for the regulation of the affective states. The ventral system includes the amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and prefrontal cortex; whereas the dorsal system consists of the hippocampus, dorsal regions of anterior cingulate gyrus, and prefrontal cortex. In the present study, the significant between-group BOLD difference in the left IFO (a neural region of the ventral system) for viewing happy faces was observed. On the contrary, between-group BOLD differences in the left mPFC and vPMC (regions in the dorsal system) while viewing sad and fearful faces respectively were detected. These observations suggest that the dorsal and ventral affective processing systems were differentially affected in AD; and the effect appears to be emotion-specific.

St. Jacques et al. (2009) reported that the most consistent finding in neuroimaging studies on aging and emotion was that older adults, relative to their younger counterparts, seemed to require more frontal activity for processing affective stimuli. In this study, the BOLD differences between patients with AD and the normal controls were found in the frontal regions, which is consistent with that of St. Jacques et al. (2009). It seems that changes of affective processing in AD may relate to neurodegeneration of the frontal functional status.

4.3. Limitations

There are a couple of limitations that should be acknowledged. First, with much deliberation, in order to control for the confounding variance introduced by the requirement of our participants with AD to remember task instructions, we decided to adopt a passive viewing experimental paradigm. As a matter of fact, the MMSE scores (18.3 ± 3.4) of the participants with AD were much lower than those (24.6 ± 2.8) reported in the study by Wright et al. (2007) on the processing of emotional stimuli in patients with AD. We fully acknowledge that explicit emotion recognition tasks (Grady et al., 2003; Wright et al., 2007), can provide results that differ from those of passive viewing: the former investigates the MNS's capacity to process emotions; the latter investigates the MNS's propensity to represent emotions without any incentive to do so. The distinction between spontaneous and deliberate processing of social stimuli merits more explicit investigation in future AD research. Second, the cohort design does not allow for an understanding of the longitudinal neural change associated with the processing of emotional facial expressions. For example, it is worth exploring when and under what risk factors the neural changes would spread to other regions associated with the MNS and affective empathy. Also, previous studies have provided evidence that an impaired ability to discriminate facial expressions might have in fact begun at the mild cognitive impairment stage (Weiss et al., 2008). Further studies comparing emotional processing in people with AD and in people with mild cognitive impairment would be worthwhile.

4.4. Conclusions

People with AD present with reduced neural activity in the MNS and regions associated with affective empathy when viewing happy, sad, or fearful facial expressions. These changes lateralize in the left hemisphere. Reduced BOLD signals associated with the viewing of emotional facial expressions may be an alert for the possible degeneration of socioaffective functioning in people with AD, which further erodes their cognitive status and their eventual functional independence.

Disclosure statement

The authors declare no conflict of interest.

This study was approved by the Institutional Review Board of The University of Hong Kong. Informed written consent was obtained from all of the participants.

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