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Research report

The relationship between loneliness and working-memory-related frontoparietal network connectivity in people with major depressive disorder

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ABSTRACT

Loneliness affects up to 40 % of middle-aged and older adults, and is closely associated with major depressive disorder (MDD). However, the relationship between loneliness and neural network functioning during executive cognitive processes, such as working memory, in MDD is still unclear. To address this gap, our study recruited 21 medicated MDD patients (mean age = 52.0 ± 5 years) and 24 matched healthy controls (HC) (mean age = 48.7 ± 6 years) who completed an n-back fMRI task. For behavioural performance, we observed no significant moderating effect of MDD or loneliness on the task condition effect. However, loneliness was positively associated, and MDD was negatively associated, with the functional connectivity between the inferior parietal cortex and the rostral dorsomedial prefrontal cortex (DMPFC) during task performance. Furthermore, an interactive effect of loneliness and MDD was observed on the functional connectivity between the supplementary motor area and the caudal DMPFC during the n-back task, with loneliness showing a positive relationship in the HC group but a negative relationship in the MDD group with the connectivity. Our results indicated that loneliness may be associated with altered neural regulatory functioning on self-referential processing and action control, which may further depend on the individual's depressive state. These findings can form the theoretical basis for devising intervention programme aimed at improving the mental wellness of the healthy and depressed lonely individuals.

1. Introduction

Major depressive disorder (MDD) is a common mental disorder and one of the major causes of disability all over the world, resulting in a global socio-economic burden [1]. Loneliness, defined as the perception of insufficiency in one's intimate and social connections, affects up to 40 % of middle-aged and older adults and is associated with altered social and affective processing [2–4]. A large amount of literature demonstrated that loneliness is closely associated with MDD [5–7], and could longitudinally predict depressive symptoms in adolescents, middle-aged adults and older adults over extended periods of time [5,6,8]. The predictive relationship was suggested to be from loneliness to depression rather than the other way round [9]. Accumulating research suggests that MDD patients show altered brain response patterns while performing executive cognitive processes such as working memory (WM) [10,11]. These altered brain cognitive processes may be linked with the reduced affect regulatory functions in MDD individuals [12,13]. However, research on the relationship between loneliness and

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WM is still lacking, particularly among non-elderly populations. Furthermore, the potential joint effect of MDD and loneliness on the brain WM processes is unclear. Delineating the neurocognitive correlates of loneliness and MDD could help us understand how some lonely people may subsequently develop MDD [9], which would then form the crucial basis for devising intervention program targeted on improving the psychological wellness of individuals with affective issues and high perceived loneliness.

Working memory capacity is essential for maintaining daily functioning and affect regulation in both healthy and MDD patients [14,15]. WM is defined as the temporary storage of information during engaging in cognitive tasks [16], and involves maintenance and manipulation of information and switching between inputs and outputs [17]. Patients suffering from MDD demonstrate impairments in WM performance [18,19]. However, there is also evidence that MDD patients and healthy individuals show comparable performance on accuracy and reaction time (RT) in the 1-back and 2-back versions of the WM task [10,20–22]. Neuroimaging studies have compared WM task activities in the prefrontal-parietal networks between MDD patients and healthy individuals [11]. However, the results were mixed with findings of decreased activations [12], no difference [23,24], or increased activations [22,25,26] in the MDD group. Several factors might have contributed to the discrepancy of these results, such as the difficulty level of the WM task (e.g. 1-back vs. 2-back), or the medication that the MDD patients were taking [27].

Notably, MDD patients have been found to show abnormal patterns of functional connectivity in both the cognitive control network (CCN) and the default-mode network (DMN), during WM task performance [13,26,28]. The CCN consists of a frontoparietal network encompassing the lateral prefrontal cortex (LPFC), the superior and inferior parietal cortices, as well as the supplementary motor area (SMA), and is believed to be involved in top-down regulation of cognitive processes in goal-directed WM tasks [29]. MDD patients were found to show reduced functional connectivity within the CCN compared to healthy controls during WM performance [13,26,30]. On the other hand, increased connectivity of DMN was found in MDD patients during resting state and cognitive task performance, compared to healthy controls [13], indicating a lack of suppression in the task-negative DMN. Such DMN hyper-connectivity among MDD patients may indicate failure in controlling self-oriented processes while performing cognitive tasks [31]. The dorsomedial prefrontal cortex (DMPFC), which is typically considered as part of DMN, was also found to show abnormal connectivity in the resting state [31,32] and during WM task performance [13] in MDD patients. The dysfunction of DMPFC was suggested to be one of the key factors that contribute to depression-related impairments, such as reduced cognitive control or enhanced negative self-focus [33]. Recent evidence suggests that the DMPFC consists of heterogeneous subregions with distinct cognitive and affective functions, corresponding respectively to its functional connectivity with the CCN and the DMN [34,35]. Moreover, a recent study suggested that the CCN could be further divided into two functional sub-networks which are connected to the DMN and the dorsal attention network respectively, indicating a functional segregation in regulation of introspective processes and visuospatial perceptual attention [36]. However, the precise nature of the functional interplay between the CCN and the DMPFC during WM performance, and its association with MDD, are still unclear.

Given the close association between MDD and loneliness [9], it might also be expected that lonely individuals would exhibit altered brain network responses during WM performance. The existing evidence on the association between loneliness and WM function is rather limited and inconsistent, and is mostly obtained in elderly samples. One study found that perceived loneliness was negatively associated with WM capacity as assessed by the Digit Span test in older adults [37], while another study reported non-significant association between loneliness and WM as assessed by the Letter-Number Sequencing test [38]. The former study included primarily participants showing minimal levels of depressive symptoms, thus the finding may not generalize to MDD patients [37]. Besides, research is lacking that explores the effect of loneliness on cognitive functions among non-elderly adults with MDD, and it is thus inconclusive whether and how loneliness will affect WM function in younger populations. Moreover, no research has explicitly examined the effect of loneliness on WM-related activations or functional connectivity patterns in the CCN or the DMN, although very limited recent evidence suggests that loneliness showed differential relations with the DMN connectivity during affective processing in elderly MDD patients and in healthy controls [39], and that loneliness was positively associated with resting-state connectivity within the CCN in healthy young adults [40]. These findings offer tentative support for an association between loneliness and functions of the cognitive control (i.e. CCN) and affect-related (i.e. DMN) networks [39,40]. However, no direct evidence exists on the relationship between loneliness and neural network functioning during WM performance.

To address this research gap, the present study focused on investigating how loneliness affected the task performance and brain connectivity in MDD patients and matched healthy controls while completing a WM task (1- versus 0-back), which measures information maintenance and manipulation capacities [16]. We applied generalized psycho-physiological interaction (gPPI) analysis to capture the functional connectivity within and across brain networks in different task condition [41]. Based on the limited existing literature, we tentatively hypothesized that MDD patients would show decreased connectivity within and between the CCN and the DMPFC relative to controls during the WM task. Also, loneliness levels would be associated with the functional connectivity strengths within and between the CCN and the DMPFC during WM performance, and the association may be different in the MDD and control groups. In view of the inconclusive evidence on the effect of MDD and loneliness on working memory performance, we did not form explicit hypothesis on the behavioural results.

2. Material and methods

2.1. Participants

Twenty-seven middle-aged participants (mean age = 51.8 ± 5.0 years, 19 females) formally diagnosed of major depressive disorder (MDD) as determined by the DSM-IV criteria, and 27 matched healthy controls (HC) (mean age = 48.9 ± 5.7 years, 21 females) participated in the current study. All participants were right-handed and had normal or corrected-to-normal vision. The MDD patients were recruited from the Chang Gung Memorial hospital in Taiwan, and the HC individuals were recruited from local communities. All participants scored 24 or above on the Chinese version of the Mini-Mental State Examination (MMSE) [42] that assesses general cognitive function, indicating an absence of dementia in the current samples. All healthy participants reported no past or current neurological diseases or psychological illnesses. The MDD patients reported no comorbidity. For the patients, antidepressants were maintained during the time of study due to ethical reasons. The medications for all patients had been unchanged for at least two weeks prior to the study day. All participants gave written informed consent. This study was approved by the research ethics committee of the Chang Gung Memorial Hospital.

All participants completed the Chinese version of the 17-item Hamilton Rating Scale for depression (HAMD) [43], the Chinese version of the 20-item UCLA Loneliness Scale that measures perceived loneliness [44], and the MMSE. For the behavioural analysis, in total 9 participants were excluded: incomplete psychometric or behavioural data (3 participants), > 7 HAMD scores in the HC group (2 participants), and abnormal task performance (4 participants: 3 MDD patients and 1 HC). The 4 participants with abnormal task performance all showed very low accuracy in the 0-back task (all below 61 %, or < 4 SD

Table 1
Demographics, psychological measurements, clinical characteristics and working memory task performance, and the effect of MDD and loneliness, and their interactive effect on these variables.

	MDD (N = 21)	HC (N = 24)	MDD effect	Loneliness effect	Group × Loneliness effect
Sex[a] (Male/Female)	6/15	5/19	t = .06, p = .90	t= −.63, p = .44	t= −.02, p = .59
Age (mean ± SD)	52.0 ± 5.0	48.7 ± 6.0	t= −.77, p = .44	t = 1.00, p = .31	t = .68, p = .48
HAMD score (mean ± SD)	13.0 ± 5.3	2.3 ± 2.0	**t= −5.58, p < .01**	t = 1.40, p = .20	t = .89, p = .40
UCLA score (mean ± SD)	50.2 ± 11.2	33.2 ± 7.4	**t= −6.03, p < .01**	—	—
MMSE (mean ± SD)	27.2 ± 1.4	27.0 ± 1.1	t = .63, p = .52	t = 1.53, p = .13	t= −.48, p = .63
MDD characteristics					
Age of onset (years)	41.1 ± 8.7		—	t= −1.37, p = .20	—
No. of episode[b]	1.8 ± 0.7		—	$\|ts\|$ < 2.8, ps > .27	—
Illness duration (years)	11.1 ± 8.3		—	t = 1.36, p = .22	—
Antidepressant load	2.3 ± 1.5		—	t = 1.02, p = .32	—
Total medication load	3.7 ± 1.6		—	t = 1.00, p = .34	—
WM performance					
0-back					
Accuracy (in %; mean ± SD)	91.5 ± 8.0	92.3 ± 6.8	t = 1.20, p = .25	t = 1.36, p = .13	t= −1.60, p = .06
RT (in ms; mean ± SD)	565.9 ± 97.2	483.6 ± 46.2	**t= −3.01, p = .03**	t= −.47, p = .67	t = .29, p=.73
1-back					
Accuracy (in %; mean ± SD)	91.8 ± 8.0	90.3 ± 8.7	t= −.61, p = .59	t= −.21, p = .82	t= −1.59, p = .10
RT (in ms; mean ± SD)	638.4 ± 122.1	532.8 ± 109.0	t= −2.05, p = .13	t = .25, p = .84	t = 1.01, p = .38

[a] Binary logistic regression was used.
[b] Multinomial logistic regression was used; Statistically significant effects (5000 times bootstrapping, p < 0.05) are marked in bold. MDD: major depressive disorder; HC: healthy controls; Total medication included antidepressants and hypnotics.

below the sample mean), while their performance on the 1-back task was relatively normal (all above 83 %, or within 1.5 SD from the sample mean). Thus, the data of those participants were discarded since their performance deviated substantially from the other individuals. In total, 21 MDD patients (mean age = 52.0 ± 5.0 years, 15 females) and 24 matched HCs (mean age = 48.7 ± 6.0 years, 19 females) remained in the behavioural data analyses. One participant was further excluded in our imaging analysis due to incomplete MRI scanning. Participants' demographic and psychometric data, and patients' clinical information, are included in Table 1.

2.2. Working memory task and procedure

Participants completed the n-back (0- and 1-back) WM task inside the fMRI scanner (Fig. 1). The WM stimuli were digits from 1 to 10. The total task consisted of 6 blocks of 12 trials, with each of the 0-back and 1-back conditions being delivered over 3 sequential blocks (Fig. 1) in a separate run. In the 0-back condition, participants were asked to judge whether the current stimulus matched a target number (i.e. 5). This condition had no WM component and served as a baseline control for task-general attention and perceptual processes. In the 1-back condition, participants were asked to judge whether the current stimulus matched the number presented in the immediately previous trial. Blocks of trials were separated by 36-second resting periods. In each trial, the stimulus was presented centrally for 0.5 s, followed by a black fixation cross for 2 s. Participants were required to respond before the disappearance of the fixation cross (i.e. within 2.5 s after the beginning of each trial), via pressing one of two buttons. The allocation of buttons to 'yes' and 'no' responses was counterbalanced across participants. The total task lasted for 6 min and 36 s.

2.3. Demographic, clinical and behavioural data analysis

The effects of MDD, loneliness and the interactive effect of MDD × loneliness on the demographic, clinical characteristics and psychological measurements were investigated utilizing a series of linear or logistic regression models implemented in SPSS v. 24 (IBM Corp., Armonk, NY) (Table 1).

For WM task performance, we tested the main and interactive effects using linear regression models. A bootstrapping procedure (5000

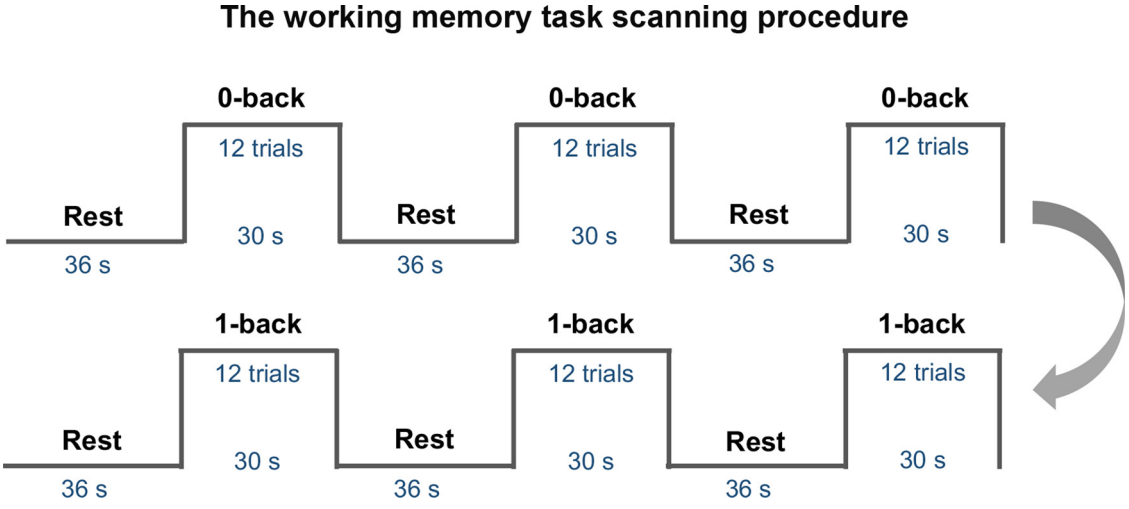

Fig. 1. The WM task scanning procedure. Participants completed 3 blocks of the WM task under each of the 0-back and 1-back conditions. In-between blocks were 36-second resting periods.

times) was employed to correct for any potential data non-normality and/or heteroscedasticity [45]. The main effect analysis incorporated variables of interest including WM load (0-back versus 1-back), group (MDD versus HC), and loneliness, while also controlling for the condition-specific mean RT (for accuracy) or condition-specific mean accuracy (for RT). We then tested the 2-way and 3-way interactive effects of the variables of interest. Statistical thresholds were set at $p < 0.05$, two-tailed.

2.4. MRI data acquisition

The imaging data were acquired using a clinical 3 T GE MRI scanner equipped with an 8-channel head coil. The fMRI data were acquired using echo-planar imaging (EPI) pulse sequence (voxel size = 3.44 × 3.44 × 4 mm^3; slice number = 36; TR = 3000 ms; TE = 30 ms; flip angle = 90°; FOV = 220 × 220 mm^2; matrix = 64 × 64). The structural MRI data were acquired using T1-weighed BRAVO sequence (voxel size = 0.98 × 0.98 × 1 mm^3; 160 sagittal slices; TR = 8.2 ms; TE = 3.2 ms; flip angle = 12°; FOV = 250 × 250 mm^2; matrix size = 256 × 256).

2.5. FMRI data analysis

The fMRI data were pre-processed using DPARSFA v. 4.3 [46] and SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/). The WM fMRI data were corrected for slice timing, realigned and normalized to the MNI standard space using the DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra) method [47]. The normalized images were then resampled to a 3-mm isotropic spatial resolution and smoothed using a Gaussian kernel with full-width half-maximum of 6 mm. No participant showed head motion that exceeded one voxel size in any direction.

The pre-processed data were then entered into the first-level general linear model (GLM) voxelwise analysis. A design matrix was constructed for each participant with one regressor representing each task condition (0-back or 1-back), six regressors of motion parameters and a mean regressor (i.e. the intercept of the timeseries). The whole duration of each block (30 s) (including all trials) were convolved using a canonical hemodynamic response function (HRF). Contrast images of the two conditions (*0-back > 1-back*, *1-back > 0-back*) were estimated for each participant and entered into the group-level analysis.

At the group level, we tested the main effects of MDD and loneliness, and their interactive effect. The analysis was carried out in 3 steps. First, we examined the main effect of WM load (0-back versus 1-back) across all participants by adopting a one-sample *t*-test design, with loneliness score as a covariate. Then, we examined the main effects of MDD and loneliness by adopting a two-sample *t*-test design (i.e. the model included two columns representing MDD and control groups and one column representing loneliness scores across all participants). Finally, we examined the interactive effect of MDD and loneliness by adopting a two-sample *t*-test design with the loneliness variable split for the patient and HC groups (i.e. the model included two columns representing MDD and control groups, as well as two columns representing loneliness scores of the two groups separately). All analyses additionally controlled for the mean task accuracy difference between the 0-back and 1-back conditions. Whole-brain and region-of-interest (ROI) statistical thresholds were determined using the threshold-free cluster enhancement (TFCE) method [48], adopting a family-wise-error (I)-corrected $p < 0.05$. The TFCE procedure was performed using the TFCE toolbox of SPM12, with 5000 permutations run for each analysis.

We selected four ROIs for the small volume correction (SVC) analyses. The SVC analyses were based on anatomical masks of the LPFC, parietal cortices, SMA and the DMPFC, which were created using WFU PickAtlas [49] (Supplementary Fig. S1). The LPFC mask included bilateral superior, middle and inferior frontal gyri (BA8, 9, 44, 45, 46, 47). The parietal cortices mask included bilateral superior and inferior parietal lobule (BA7, 39, 40). The SMA mask included bilateral supplemental motor area (BA6, 8, 32). The DMPFC mask included bilateral medial superior frontal gyri (BA8, 9). To correct for the number of masks, false discovery rate (FDR) procedure was further applied on the I-corrected *p* values for significant ROI results.

To further characterize the effects of MDD, loneliness and MDD × loneliness on the significant signals, parameter estimates (betas) were extracted from the significant clusters and subjected to linear regression analyses with bootstrapping (5000 times) using SPSS v. 24, controlling for between-participant accuracy difference (*1-back > 0-back*). Furthermore, to explore the relationship between task activation and behaviour, we performed a series of linear regression analyses with individual participants' between-condition accuracy difference as the dependent variable, and brain signals as the predictor, while controlling for participants' between-condition RT difference (*1-back > 0-back*). Similar linear regression analyses were conducted with participants' between-condition RT difference as the dependent variable, while controlling for participants' between-condition accuracy difference. We further conducted additional linear regression analyses assessing the effects of MDD illness-related characteristics on the significant brain signals for the patients. FDR correction was applied on the number of ROIs. Statistical significance was considered as $p < 0.05$, two-tailed.

2.6. GPPI analysis

We adopted the generalized PPI (gPPI) approach [41] to examine the effects of MDD and loneliness on the brain network function during WM task performance. Seed regions were constructed as 6-mm spheres centred at the peak coordinates of the significantly activated clusters in the WM task (*1-back > 0-back*). Separate gPPI analyses were performed for each seed region. In the first-level model, we extracted the first eigenvariate of the BOLD signals from the seed region. The signals were adjusted for nuisance covariates (i.e., motion regressors) and were mean-corrected, and formed the physiological term of the gPPI analysis. Then, each of the main analysis task regressors was separately convolved with the hemodynamic response function (HRF) to form the psychological term. Lastly, the extracted BOLD signals were deconvolved to get an estimated neural activity, and multiplied by each of the task regressors separately before being convolved to form the gPPI terms. In the second-level design, the design models were identical to those of the regional analyses as outlined above. The gPPI results were also evaluated using the TFCE approach to derive I-corrected *p* values, at both whole-brain and ROI levels. Again, FDR procedure was applied to correct for the number of ROIs. Of note, as we were primarily interested in the functional connectivity between different seed regions, we only tested the between-seed connectivity patterns. As in the regional analyses, parameter estimates were extracted from the significant clusters and further analysed using linear regression models with bootstrapping (5000 times), to examine the relationship between functional connectivity and task behavioural measures.

3. Results

3.1. Demographic and behavioural results

As expected, the MDD group showed significantly higher HAMD scores and loneliness scores than the HC group (*ps* < 0.01) (Table 1). No other variable showed significant MDD, loneliness or MDD × loneliness effect (*ps* > 0.05). The WM performance of the two groups are shown in Table 1.

For the analysis of accuracy, we found a significant MDD × loneliness effect (β = -.004, t = -2.33, p = 0.013), as loneliness was positively associated with overall task accuracy in the MDD group (β = .002, t = 1.98, p = 0.029) but not in the HC group (β = -.002, t = -1.40, p = 0.11). No other significant main effect (*ps* > 0.4), two-way interactive effect (*ps* > 0.2) or three-way interactive effect was

Table 2
Task activation (*1-back > 0-back*) and gPPI results.

Contrasts	*ROIs* / Brain regions	BA	MNI coordinates (mm)			Cluster size (mm^3)	TFCE value	*p*-FWE	*p*-FDR
			x	*y*	*z*				
Task activation: *1-back* > *0-back*									
	whole brain								
	Frontal_Mid_L	6/9	−45	24	24	1131	1200.66	0.001	0.002
	Frontal_Mid_R	6/8/9	27	9	51	1075	820.25	0.007	0.011
	Frontal_Sup_Medial_L	8/32	0	24	45	184	771.15	0.009	0.013
	Parietal_Inf_L	40	−30	−57	45	337	714.72	0.013	0.017
	Parietal_Inf_R	40	54	−48	51	176	572.35	0.026	0.028
	Precuneus_L	7	−12	−69	57	22	493.66	0.040	0.040
	LPFC								
	Frontal_Mid _L	9/6/8	−45	24	24	1175	910.71	< 0.001	0.002
	Frontal_Mid_R	8/9/6	33	6	51	1127	622.25	< 0.001	0.002
	Parietal cortices								
	Parietal_Inf_L	40	−30	−57	45	553	518.67	0.001	0.002
	Parietal_Inf_R	40	48	−54	54	653	416.15	0.002	0.004
	SMA								
	Supp_Motor_Area_L	8/32	−3	21	45	193	419.91	< 0.001	0.002
	Supp_Motor_Area_R	6	15	9	63	26	128.02	0.023	0.027
	DMPFC								
	Frontal_Sup_Medial_L	8	0	24	45	82	309.06	0.001	0.002
GPPI results									
MDD effect: HC > MDD parietal seed [-30 −57 45]									
	DMPFC								
	Frontal_Sup_Medial_R	9	12	57	0	10	153.25	0.020	0.06
MDD × Loneliness effect: HC > MDD SMA seed [-3 21 45]									
	DMPFC								
	Frontal_Sup_Medial_R	8	6	33	45	16	137.84	0.022	0.066

The brain regions are reported using xjView9.6 (http://www.alivelearn.net/xjview8/). Peak coordinates in bold served as the centre of the seed regions used in the gPPI analysis. BA: Broadman area; Frontal_Mid: middle frontal gyrus; Supp_Motor_Area: supplementary motor area; Parietal_Inf: inferior parietal (supramarginal and angular gyri); Frontal_Sup_Medial: superior medial frontal gyrus; LPFC: lateral prefrontal cortex; SMA: supplementary motor area; DMPFC: dorsomedial prefrontal cortex; MDD: major depressive disorder; HC: healthy controls; R: right hemisphere; L: left hemisphere.

observed (β = -.001, t = -0.23, p = 0.796).

For the analysis of RT, our results showed that the main effects of MDD (β = -95.22, t = -3.38, p = 0.008) and WM load (β = 60.76, t = 2.95, p = 0.007) were significant. MDD patients demonstrated longer overall RTs compared to the HC group, and RTs in the 1-back condition were longer compared to those in the 0-back condition. However, no significant two-way or three-way interactive effect was observed ($|ts| < 1.16$, $ps > 0.3$).

3.2. Working memory fMRI regional analysis

The whole-brain analysis showed that, compared to the 0-back condition, the 1-back condition elicited greater activations in the prefrontal and parietal areas in the total participant sample (Table 2, Supplementary Fig. S2). Further SVC analyses showed that the LPFC, parietal cortices, SMA and DMPFC all showed significant activations in the 1-back condition compared to the 0-back condition (all $p_{corr} < 0.05$) (Table 2). The reverse comparison elicited no significant activation. No significant main effect of MDD or loneliness, and no interactive effect of MDD × loneliness, were found on activations to the *1-back > 0-back* contrast.

We further tested the effects of MDD and loneliness on the parameter estimates of the significant clusters within the *a priori* ROIs for the *1-back > 0-back* contrast, using linear regression analyses controlling for accuracy difference between the conditions. Again, no significant main effect of MDD, loneliness or their interactive effect was found (all $p_{corr} > 0.8$).

The brain-behaviour analyses revealed that activations in the LPFC (t_{43} = -2.60, p_{corr} = 0.042) and the DMPFC (t_{43} = -2.91, p_{corr} = 0.042) showed significant negative correlations with accuracy difference of the *1-back > 0-back* contrast (Fig. 2). These relationships were not modulated by group (all $p_{corr} > 0.2$). However, the SMA and DMPFC activations did not show significant correlations with accuracy difference ($p_{corr} > 0.14$). No significant correlation between the task activations and RT difference was found (all $p_{corr} > 0.9$). No significant effect of HAMD or illness-related characteristics was observed on the task activations in the MDD group (all $p_{corr} > 0.5$).

3.3. GPPI analysis

Our gPPI analysis adopted four 6-mm-sphere seed regions centred at the local maxima of LPFC, parietal (inferior), SMA and caudal DMPFC that were significantly activated in the WM task (*1-back > 0-back*). Whole-brain analysis revealed no significant effect for the *1-back > 0-back* contrast on the functional connectivity. ROI analyses revealed that HC showed significant more positive connectivity between the inferior parietal cortex (IPC) and a rostral and relatively ventral part of the DMPFC (rostral DMPFC) compared to the MDD group for the *1-back > 0-back* contrast (maxima = 12, 57, 0, voxels = 10, TFCE = 153.25, p = 0.02). There was also a significant MDD × loneliness effect on the functional connectivity between the SMA and a caudal and dorsal portion of the DMPFC (caudal DMPFC) for the *1-back > 0-back* contrast (maxima = 6, 33, 45, voxels = 16, TFCE = 137.84, p = 0.022), characterized by loneliness having a more positive effect on the connectivity in the HC group compared to in the MDD group. However, these effects were only marginally significant after FDR correction (p_{corr} = 0.06 for the IPC-rostral DMPFC connectivity and p_{corr} = 0.066 for the SMA-caudal DMPFC connectivity) (Table 2).

Further linear regression analyses on the significant functional connectivities revealed significant main effect of MDD (t_{43} = 4.83, p_{corr} = 0.002) and loneliness (t_{43} = 3.14, p_{corr} = 0.01) on the IPC-rostral DMPFC connectivity (Fig. 3). Specifically, the MDD group showed less positive IPC-rostral DMPFC connectivity compared to the HC group, and perceived loneliness score was associated with more positive IPC-rostral DMPFC connectivity. No significant interactive effect of MDD × loneliness was found (p_{corr} = 0.681). Analyses of the SMA-caudal

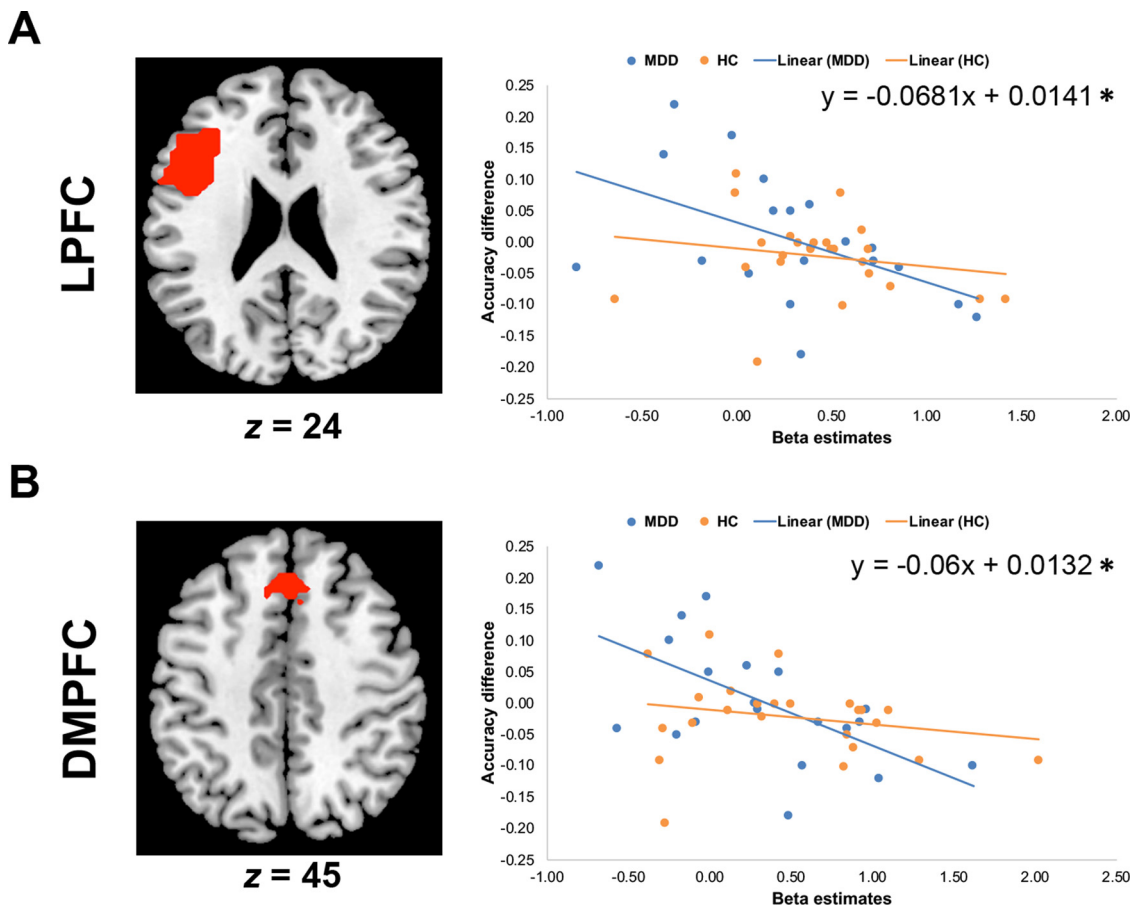

Fig. 2. The relationship between activations of 2 clusters showing significant WM load effect (*1-back > 0-back*) and between-condition accuracy difference (*1-back > 0-back*). Activations in the LPFC (A) and DMPFC (B) were significantly and negatively associated with accuracy difference in the total participant sample (p_{corr} = 0.042). LPFC: lateral prefrontal cortex; DMPFC: dorsomedial prefrontal cortex. *: $p < .05$.

DMPFC connectivity confirmed the significant interactive effect of MDD × loneliness (t_{43} = 4.61, p_{corr} = 0.002) (Fig. 3). Follow-up analyses revealed that loneliness had a positive effect on the connectivity in the HC group (t_{23} = 4.40, p_{corr} = 0.002), while it had a negative effect in the MDD group (t_{19} = -2.97, p_{corr} = 0.018). No significant correlation was found between the two connectivities and RT or accuracy difference (all $p_{corr} > 0.1$). No significant effect of HAMD or illness-related characteristics were observed on the connectivities in the MDD group (all $p_{corr} > 0.2$).

4. Discussion

This study was targeted on examining the separate as well as interacting effects of MDD and loneliness on the functions of CCN and DMN during WM processing. The most important finding was that loneliness moderated the functional connectivity between the CCN and the DMPFC during WM performance. Specifically, for the IPC-rostral DMPFC connectivity, loneliness showed a positive relationship with the connectivity in both the MDD and the HC groups, whereas for the SMA-caudal DMPFC connectivity, loneliness demonstrated an interactive effect with MDD, exhibiting a positive association in the HC group but a negative association in the MDD group. Moreover, compared to the MDD group, the HC exhibited significantly higher IPC-rostral DMPFC connectivity. These results provide novel evidence supporting the joint influences of MDD and loneliness on core network functioning during fundamental cognitive processing. However, the GPPI results were only marginally significant after FDR correction. Therefore, these findings should be interpreted with caution.

4.1. The effects of loneliness on WM performance

As expected, participants showed longer RT in the 1-back compared to the 0-back condition [50]. It is considered that higher WM load requires additional cognitive processing such as attention, maintenance of information and inhibition of task-irrelevant information, accounting for the relative increase in RT [51]. However, no significant difference in accuracy or RT was observed between the MDD and HC groups while performing the 1-back versus 0-back task, in accordance with some previous studies [10,52,53]. Several factors may contribute to the lack of behavioural difference between the patients and controls in our study, such as that the patients were on medication at the time of study, and that we only included a relatively easy WM task (i.e. 1-back task, as opposed to 2- or 3-back tasks) [54–56]. Future studies can test drug-naïve MDD patients on more difficult n-back tasks to more finely characterize any working memory deficits associated with MDD.

Similarly, loneliness had no effect on participants' accuracy or RT during performing the 1-back versus 0-back task. This result agreed with that of a former study which also found no significant effect of loneliness on the WM index of the Letter-Number Sequencing test [38], but contrasted with the finding of a previous study that employed the Digit Span test to test the loneliness effect on WM performance [37]. Several factors might contribute to the inconsistent results. First, the n-back WM task adopted in the current study was distinct from the Digit Span test, such that performance on those tasks may not show correlation [57]. Specifically, the Digit Span test measure loaded on a non-speeded WM factor [58], and thus might not be as sensitive as the n-back task for testing WM performance. Second, the participants recruited in our study were middle-aged (50.1 ± 5.8 years) while the

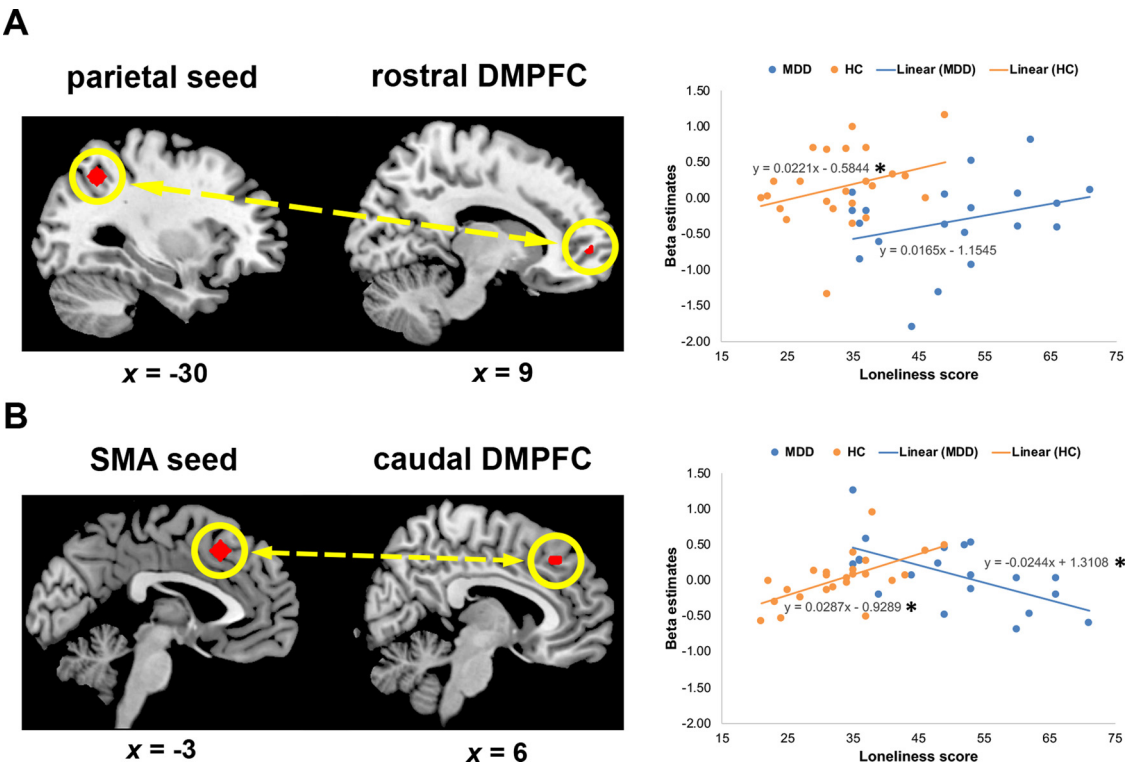

Fig. 3. The effects of MDD and loneliness on functional connectivity between the IPC and the rostral DMPFC, and between the SMA and caudal DMPFC, for the *1-back* > *0-back* contrast. (A) HC showed significantly more positive IPC-rostral DMPFC connectivity compared to the MDD group. The same connectivity also showed significant positive association with loneliness. (B) The interactive effect of MDD × loneliness on the SMA-caudal DMPFC connectivity was characterized by loneliness having a significant positive association with the connectivity in the HC group, but a significant negative association in the MDD group. *: $p < .05$.

former study recruited older adults (80.7 ± 7.1 years) (Wilson et al., 2007). It is possible that loneliness may have differential effects on cognitive function among samples of different ages, given the older population may manifest more pronounced cognitive decline [59]. Furthermore, while the former study included primarily non-depressed individuals [37], our study explicitly involved both MDD patients and healthy controls. Overall, our results suggest that behavioural measures of WM function may not be sensitive to MDD diagnosis or self-reported loneliness levels.

4.2. Relationship between WM task activation and performance

Brain activations during 1-back versus 0-back performance were identified in the CCN including the LPFC, IPC and SMA, as well as in the DMPFC, consistent with a large body of previous research findings [60–64]. Furthermore, the brain activations in the LPFC and the DMPFC showed negative correlations with accuracy difference between the 1- and 0-back tasks (*1-back* > *0-back*). It could be that participants who recruited those brain regions to lesser extent were able to engage in more efficient WM processing [21,53]. Also, the observed brain-behavioural relationship across the total participant sample indicated considerable individual variations in both WM performance and the associated brain signals, in both the patient and control groups [65]. Such inter-participant heterogeneity might have contributed to the lack of main effect of MDD or loneliness, as discussed above. On the other hand, we did not observe significant correlation between brain activations and performance RT, consistent with previous studies [24]. This could be partly due to the nature of our n-back task which required participants to respond within a 2.5-second interval. It remains to be tested whether significant brain-RT relationship might be uncovered for tasks that do not impose time limits on response.

4.3. The effects of loneliness on functional connectivity between the DMPFC and CCN

Loneliness exhibited distinct associations with the IPC-rostral DMPFC and SMA-caudal DMPFC connectivity during WM performance. There is existing evidence indicating that the rostral and caudal parts of the DMPFC may be involved in non-overlapping functions. Specifically, during rest, the rostral DMPFC was found to be functionally connected to the DMN while the caudal DMPFC was connected to the CCN, indicating that the former might be more involved in the self-reflective processes while the latter might be more involved in attentional and cognitive control [35]. We found that loneliness was positively associated with the IPC-rostral DMPFC connectivity in both the MDD and HC groups. Given the same inferior parietal region was found to be activated during WM processing, this structure is likely to be part of the CCN, which is typically activated when attention is focused on external stimuli in cognitive tasks [66,67]. Recent evidence also identified the IPC as part of a CCN subnetwork, which is functionally connected to the DMN, possibly for regulatory functions on self-referential processing and social reasoning [36]. As part of the DMN [68], the rostral DMPFC (BA9/10) has been suggested to be involved in self-referential mental inspection [69] and social cognition [70,71]. Furthermore, previous studies showed that the DMN including the medial frontal areas was more deactivated in tasks that demand greater cognitive resource (e.g. 1-back and 2-back) compared to the simple letter detection task (0-back) [72], and the DMN and the CCN showed the highest response correlation during the most difficult 3-back condition [73], indicating an increased regulation of self-referential processes by the high-level executive control system during demanding cognitive tasks [74].

Therefore, our results might indicate that lonelier individuals generally show increased regulation of self-referential processing, as reflected by the more positive functional connectivity between the IPC and the rostral DMPFC, during WM processing. This could be due to the

greater negative self and social cognitive bias in lonely individuals [4,75], which require greater regulatory effort during performing cognitive tasks. We also identified that MDD patients showed decreased connectivity between the IPC and the rostral DMPFC, compared to the HC group. Past evidence indicates that MDD patients show reduced efficiency in suppressing the DMN during goal-directed task activity [13]. It could be that MDD-related hyperactivity in the DMN may be associated with its reduced functional connectivity with the CCN, possibly indicating reduction of top-down regulation of introspective processes in MDD patients when performing WM task [76]. Our results suggested that the DMPFC might be a vital target for devising intervention programme targeted at enhancing the mental health of the lonely and depressed individuals, supported by the findings showing that applying transcranial magnetic stimulation (TMS) on the DMPFC in MDD patients could reduce MDD symptoms [77], and improve cognitive task performance [78].

On the other hand, loneliness showed differential relationships with the SMA-caudal DMPFC connectivity in the MDD and HC groups. Specifically, loneliness was positively associated with the SMA-caudal DMPFC connectivity in the HC group but negatively associated with the same connectivity in MDD patients. The SMA region found in our study (centred at [-3, 21, 45]) falls largely in the anterior portion of the structure (i.e. pre-SMA) [79], and is proposed to be implicated in action control and inhibition [79,80]. Lesions in this area can generate automatic execution of actions contingent on environmental stimuli [80–83] and cause deficits in WM performance [83]. A meta-analysis on 24 studies found that the SMA (BA6, 8) and caudal DMPFC (BA8) were activated robustly during performing the n-back task [84]. This finding was later confirmed by a number of independent studies [73,85–87]. In addition, the connectivity directed from the frontoparietal network to the pre-SMA in an n-back task might reflect the processes of selecting action, preparing upcoming response and monitoring outcome, supporting the central role of the pre-SMA in implementing response control mechanisms during WM processes [88]. In view of the proposed function of the caudal DMPFC in cognitive control [35], its stronger connectivity with the pre-SMA in lonely HC individuals may indicate enhanced top-down control of voluntary actions [89–91]. We speculate that similar enhanced action inhibition mechanism may be employed in lonely individuals during social contexts, where enhanced negative social bias may prevent them from engaging in interactions with others [92–94].

On the other hand, the SMA-caudal DMPFC connectivity was negatively associated with loneliness in MDD patients. It could be that due to impaired top-down control function in MDD individuals, the patients had become less capable of controlling their actions when performing goal-directed tasks [76], as reflected by the reduced connectivity strength. In other words, the increased action control associated with high loneliness was no longer operative in MDD due to deteriorated cognitive resource that progressed with illness course [95]. These speculations remain to be tested by future longitudinal studies that involve following up lonely individuals through the course of MDD development. However, the interpretation of the interactive effect of MDD and loneliness on SMA-caudal DMPFC connectivity should be cautious. As the loneliness scores in the MDD and HC groups showed considerable non-overlapping, we could not be entirely certain whether the differential associations between loneliness and the functional connectivity were due to the moderating effect of MDD, or to the different ranges of loneliness levels. Future study could recruit larger sample sizes of MDD patients and healthy controls and try to include wider range of loneliness levels in both groups to resolve this issue.

4.4. Limitations

Some limitations of the current study need to be acknowledged. MDD is a very heterogenous disease and our patients were in different episodes, which might influence their cognitive processes. However, we observed no significant effect of MDD episode or other illness-related variables on the behavioural or neural measures. Future studies may replicate our findings in more homogeneous MDD samples. In addition, our MDD patients were on medication due to ethical reasons, and alterations in serotonin levels may affect emotional processing [96]. Future studies may recruit non-medicated MDD patients. Furthermore, our sample size is relatively modest, which might limit the generalizability of the current findings. Moreover, the UCLA loneliness scale adopted in our study primarily assesses perceived subjective loneliness, while we had no measure of the individuals' objective social isolation. In order to systematically delineate the effects of subjective and objective loneliness, future studies should additionally include measures of objective social status [e.g. 97]. Finally, since this is a cross-sectional study, we cannot ascertain the directionality of the associations between MDD, loneliness and brain functional connectivity.

5. Conclusions

Taken together, the present study contributes to the existing knowledge on the neurobiological mechanism of loneliness, by providing important insights into the associations between loneliness and the functional interplay between the CCN and DMPFC during WM processing, in MDD and healthy individuals. Our results indicate that in contrast to MDD, loneliness may be associated with increased regulation of self-referential processing by the cognitive control networks. Further, loneliness levels may interact with the onset of MDD, providing a joint effect on the neural system of action control. Our preliminary findings carry clinical implications for the functional changes in cognitive and affective regulations in high loneliness individuals, and provide novel insights on how these changes may transform as the individual develops MDD. These insights can serve as the theoretical basis for devising intervention programme targeted at improving the mental wellness of healthy and depressed lonely individuals.

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CRediT authorship contribution statement

Mengxia Gao: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Robin Shao:** Conceptualization, Data curation, Methodology, Writing - review & editing. **Chih-Mao Huang:** Data curation, Writing - review & editing. **Ho-Ling Liu:** Project administration, Writing - review & editing. **Yao-Liang Chen:** Project administration, Writing - review & editing. **Shwu-Hua Lee:** Project administration, Writing - review & editing. **Chemin Lin:** Funding acquisition, Writing - review & editing. **Tatia M.C. Lee:** Funding acquisition, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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