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ORIGINAL ARTICLE

Resting-state brain alteration after a single dose of SSRI administration predicts 8-week remission of patients with major depressive disorder

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Background. The present study investigated alteration of brain resting-state activity induced by antidepressant treatment and attempted to investigate whether treatment efficacy can be predicted at an early stage of pharmacological treatment.

Method. Forty-eight first-episode medication-free patients diagnosed with major depression received treatment with escitalopram. Resting-state functional magnetic resonance imaging was administered prior to treatment, 5 h after the first dose, during the course of pharmacological treatment (week 4) and at endpoint (week 8). Resting-state activity was evaluated in the course of the 8-week treatment and in relation to clinical improvement.

Results. Escitalopram dynamically modified resting-state activity in depression during the treatment. After 5 h the antidepressant induced a significant decrease in the signal in the occipital cortex and an increase in the dorsolateral and dorsomedial prefrontal cortices and middle cingulate cortex. Furthermore, while remitters demonstrated more obvious changes following treatment, these were more modest in non-responders suggesting possible tonic and dynamic differences in the serotonergic system. Changes after 5 h in the caudate, occipital and temporal cortices were the best predictor of clinical remission at endpoint.

Conclusions. This study revealed the possibility of using the measurement of resting-state neural changes a few hours after acute administration of antidepressant to identify individuals likely to remit after a few weeks of treatment.

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Key words: Escitalopram, first-episode, fractional amplitude of low-frequency fluctuation (fALFF), major depressive disorder, neuroimaging, remission, resting-state fMRI.

Introduction

Remission rates following antidepressant first-line treatment in major depression with agents such as selective serotonin reuptake inhibitors (SSRIs) range between 30–45% (Carvalho *et al.* 2007) and only $\leqslant$50% of patients achieve full remission (Rush *et al.* 2006). There is a well-known delayed onset in response following antidepressant treatment attributed to presynaptic and postsynaptic adaptive mechanisms (Celada *et al.* 2004) which affects the time available to clinicians to make decisions about next step treatments. Hence clinical guidelines often offer pragmatic advice on switching to a different antidepressant (e.g. different class), after 4–8 weeks of continued treatment with a therapeutic dose (APA, 2010; Bauer *et al.* 2013). The possibility of identifying response/remission to a given antidepressant early in treatment history confers the great advantage of reducing disease burden by giving the opportunity to consider alternative treatments sooner if necessary. Clinical research has already indicated that it is possible to detect susceptibility to response to treatment within the first 2 weeks of

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treatment by identifying individuals unlikely to benefit from a given antidepressant regimen (Kim *et al.* 2011). Furthermore, there is evidence that antidepressant response might supervene within a few days of treatment (Taylor *et al.* 2006). It has therefore become increasingly evident that identification of early predictors of antidepressant response at brain level is an essential step to more effectively personalize treatment in major depression.

Traditional antidepressants (i.e. SSRIs), have acute direct effects of augmentation of extracellular 5-HT in serotonergic networks (Artigas, 1993). Preliminary evidence suggests that functional magnetic resonance imaging (fMRI) offers the potential to investigate acute treatment effects at brain level following antidepressant treatment (Kraus *et al.* 2014). A single oral dose of citalopram has been demonstrated to influence task-negative processes during goal-directed behavior in the frontal cortex in healthy controls (Klomp *et al.* 2013). Augmenting serotonin neurotransmission with acute citalopram can modulate emotional expression in healthy male participants (Labuschagne *et al.* 2010). Compared to viewing neutral faces, intravenous citalopram pretreatment also enhanced different blood oxygen-level dependent (BOLD) response of brain regions in subjects with depression, including left anterior cingulate to happy faces, right posterior insula and right lateral orbitofrontal responses to sad faces, and reduced bilateral amygdala responses to fearful faces (Anderson *et al.* 2011). It has also been demonstrated that duration of treatment influences neural responses in the prefrontal cortex (PFC), resulting in decreased activity in the left dorsomedial prefrontal cortex (DMPFC) following 8-week SSRI administration (Wang *et al.* 2014a), and increased activity in the right dorsolateral prefrontal cortex (DLPFC) after 6 months administration (Heller *et al.* 2013). An interesting technical development in functional brain MRI is the possibility to investigate brain networks 'at rest' in the absence of overt stimuli. Biswal and others (Biswal *et al.* 1995) demonstrated that 'at rest' low-frequency fluctuation is equivalent to self-representation of highly synchronous spontaneous neuronal activity (Mantini *et al.* 2007). As the ruminative cognitive style underlying self-generated thoughts in major depression is believed to be important in the generation of symptoms and their maintenance (Perkins *et al.* 2015), resting-state fMRI might be optimally designed to investigate the 'neural predisposition' underlying the neuro-pathology of depressive disorders (Sheline *et al.* 2009). Preliminary evidence suggests that resting-state fMRI can guide treatment response in depressive disorders (Dichter *et al.* 2015). For example, a 10-week treatment study with duloxetine showed an increase in baseline connectivity in the default mode network (DMN) in dysthymic individuals with clinical improvement (Posner *et al.* 2013).

Conventional resting-state approaches take advantage of functional connectivity analysis, which examine the inter-regional temporal correlation between predefined seed regions and functionally related brain circuitry. In this work we apply a novel technique named 'amplitude of low-frequency fluctuation (ALFF)' developed by Zang and others (Yu-Feng *et al.* 2007) to explore the amplitude of intra-regional brain activity at rest with fMRI. This technique minimizes the risk of overlooking the functional segregation or regional specialization of the brain functional integrity likely to occur with pre-hypothesized regions of interest (ROI), approaches typical of conventional resting-state techniques (Zhou *et al.* 2010). The validity and reliability of ALFF has already been tested in major depression (Liu *et al.* 2014) suggesting sensitivity to detect differences between cases and controls, correlations with antidepressant treatment response (Yamamura *et al.* 2016), high temporal stability (Küblböck *et al.* 2014), a correlation with conventional functional connectivity methods (Liu *et al.* 2014) and consistent sensitivity and specificity in detecting spontaneous brain activities (Zou *et al.* 2008).

The aim of the present study was to investigate treatment effects in depression measured with fMRI ALFF. We were particularly interested in detecting early neurobiological predictors of treatment efficacy after a single dose of escitalopram by identifying initial changes in resting state especially in brain regions involved in mood regulation, and correlations with treatment effects following a single dose of antidepressant treatment.

Materials and method

Participants and baseline assessment

Seventy-nine first-episode, treatment-naive, right-handed Han Chinese individuals, aged 18–50 years, meeting DSM-IV diagnostic criteria for moderate to severe major depression (First *et al.* 1996) and 78 sex-, age- and handedness-matched healthy controls were recruited from the purpose of this study. Depressed participants, clinically assessed by a board-certified psychiatrist, were outpatients recruited from the Department of Psychiatry, First Affiliated Hospital, Kunming Medical University, China, between 2008 and 2011. The study received approval from the local University ethics committee (Kunming Medical University, Clinical registration no. http//www.ClinicalTrials.gov, NCT00703742) and only participants who were able to consent in writing were included in the research. Recruited patients scored

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⩾17 on the Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960), <28 on the Hamilton Anxiety Scale (HAMA; Hamilton, 1959) and had experienced symptoms of depression for <2 years. Exclusion criteria for both groups included: (1) present or previous history of Axis I and Axis II disorders (including substance misuse and anxiety disorder) aside major depression for patients, neurological and/or significant physical morbidity, (2) previous systemic psychiatric treatment and overt suicidal ideation/behavior for patients, and (4) inability to undergo MRI scans including pregnancy. The MRI examination was performed within 3 days of the clinical evaluation and prior to treatment initiation.

Longitudinal assessment

Patients

A subset of 48 patients participated to the 8-week longitudinal component which included pharmacological treatment and regular clinical reviews at weeks 2 and 4 with a final evaluation at week 8. The highly selective SSRI escitalopram (Owens & Rosenbaum, 2002) was the only treatment administered at a fixed oral dose of 10 mg/day to minimize possible dose-related effects on brain activity. Neuroimaging data were acquired at baseline, 5 h (5H) after the first dose (T_{max} of escitalopram, 5H), and at the end of week 4 (4W) and week 8 (8W). In this study, response was conventionally defined as a reduction of ⩾50% in depression scores at endpoint. In order to measure treatment efficacy, clinical remission at the end of the 8 weeks was used as main clinical outcome and it was conservatively defined as HAMD score of ⩽7.

Controls

A cohort of 16 healthy controls received a single dose of placebo and received the baseline and the 5H MRI scan to control for placebo effects. Additionally 12 healthy controls underwent MRI at baseline and at 8W without any treatment, to control for the time-drift effect on the stability of the resting-state signal.

Imaging acquisition and data processing

All subjects received MRI scans with a 1.5-T clinical GE MRI scanner (Twinspeed, GE, USA) using a birdcage head coil. Obvious structural abnormalities were excluded. Resting-state MRI data were obtained using an echo-planar imaging sequence: repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip angle = 90°, 24 axial slices, thickness/skip = 5/1 mm, matrix = 64 × 64, field of view = 240 × 240 mm^2. Image preprocessing was conducted using the statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of each functional time-series were discarded, and the remaining 150 volumes of fMRI images were employed in subsequent preprocessing for slice timing. Section-timing adjustment and realignment for head motion correction were performed. The group differences in translation and rotation of head motion were evaluated (Qi *et al.* 2012) and no group differences were found comparing the four time points. The data were spatially normalized into MNI space and resampled to 3 × 3 × 3 mm cubic voxels and were spatially smoothed using a 6-mm full-width half-maximum (FWHM) Gaussian kernel. After smoothing, the imaging data were temporally filtered (band pass, 0.01–0.08 Hz) to remove the effects of low-frequency drift and high-frequency noise.

Functional amplitude of low-frequency fluctuation calculation

Functional 'fractional amplitude of low-frequency fluctuation' (fALFF) was calculated using REST software (http://resting-fmri.sourceforge.net) (Supplementary material). To explore the within-group whole-brain fALFF patterns, one-sample *t* tests were performed on the individual fALFF maps in a voxelwise manner for each group. The fALFF difference between patients and controls and the difference between remitted and non-remitted patients were compared using two-sample *t* tests.

Statistical analysis

Using SPM8 software, one-way repeated-measures ANOVA analysis was used to identify overall changes in the fALFF at the four time-points. To reveal fALFF differences between the baseline and three post-treatment time-points separately, paired *t* tests in SPM8 were also used. All results were considered statistically significant at $p < 0.005$ and a cluster size >22 voxels, which corresponded to a corrected $p < 0.05$ (corrected by using the AlphaSim program, http://afni.nih.gov/afni/docpdf/AlphaSim.pdf). Small volume correction was applied by using a gray-matter mask made from the SPM template.

Functional fALFF in relation to treatment efficacy and clinical improvement

Functional fALFF differences between measurements at baseline and 5 h after treatment were calculated using the 'ImCalc' function in SPM8, and difference value maps ($Dmap = fALFF_{5H\text{-}map} - fALFF_{base\text{-}map}$) were obtained for each individual. The SSRI treatment efficacy was evaluated using the reducing rate of

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Table 1. *Demographic and clinical data*

	MDD		HC	χ^2/t	p
Total					
N (M/F)	74 (22/52)		74 (22/52)	N.A.	N.A.
Mean age, years (S.D.)	29.41 (8.11)		30.97 (7.11)	−1.239	0.217
Age range, years	18–48		18–49	N.A.	N.A.
Education, years	13.27 (2.87)		13.86 (2.73)	−1.291	0.199
Duration, months	2–24		N.A.	N.A.	N.A.
HAMD base (S.D.)	22.68 (3.85)		1.96 (1.90)	41.185	0.000**
HAMA base (S.D.)	16.66 (5.71)		1.20 (1.63)	22.402	0.000**
Clinical remission	RP	NRP			
N (M/F)	23 (8/15)	15 (2/13)		–	–
Mean age, years (S.D.)	28.35 (8.17)	32.53 (8.45)		−1.523	0.137
Education, years	13.78 (2.52)	13.33 (3.27)		0.478	0.636
Duration, months	13.00 (11.79)	16.73 (8.66)		−1.053	0.299
HAMD baseline (S.D.)	22.43 (2.63)	24.67 (3.66)		−2.192	0.035*
HAMD 4W (S.D.)	9.48 (4.31)	17.00 (6.00)		−4.504	0.000**
HAMD 8W (S.D.)	3.87 (1.99)	13.40 (3.31)		−11.152	0.000**
HAMA baseline (S.D.)	15.61 (3.00)	20.00 (5.63)		−3.135	0.003**
HAMA 4W (S.D.)	8.87 (3.90)	15.27 (5.22)		−4.323	0.000**
HAMA 8W (S.D.)	4.48 (2.04)	11.53 (4.24)		−6.882	0.000**

MDD, Major depressive disorder; HC, healthy controls; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Scale; M, male; F, female; RP, remitted patient; NRP, non-remitted patient; N.A., not applicable.

* $p < 0.01$, ** $p < 0.001$.

HAMD scores:

$$\left(\Delta\text{HAMD} = \frac{(\text{HAMD}_{\text{base}} - \text{HAMD}_{8\text{W}})}{\text{HAMD}_{\text{base}}} \times 100\%\right).$$

Correlation analyses were subsequently performed between the fALFF Dmap and HAMD using SPM8 ($p < 0.05$, FEW-corrected).

As an exploratory analysis we used the subtraction in the fALFF value at 5H and baseline in the ROIs to predict clinical response at 8W. We subsequently calculated sensitivity, specificity, positive and negative predictive values and receiver-operating characteristics for $\text{fALFF}_{5\text{H}}$ (see Supplementary material).

Results

Demographic and clinical data

Seventy-four patients and 74 healthy controls were included in the analyses. Table 1 shows that patients and controls were well matched. Five patients and four controls had to be excluded due to motion artifacts. In the longitudinal component 40 of the 48 patients completed the study and two participants had to be excluded due to motion artifacts ($N = 38$, 79%). Details of the patients and reasons for discontinuation are provided in Supplementary Table S1 and Supplementary Fig. S1. Twenty-three of the 38 patients remitted (61%, mean HAMD score at endpoint: 3.87 ± 1.99), and 15 patients were non-remitters (39%, mean HAMD score at endpoint: 13.40 ± 3.31). The total reduction of HAMD for the remitters was 82.85%, while for the non-remitters it was 44.75% so that responders largely achieved remission (see also Table 1 and Supplementary Fig. S2). There were no significant difference of baseline clinical data between patients who dropped out and completers.

State effects in major depression

Baseline evaluation of the fALFF signal suggested that depressed patients exhibited a decreased signal compared to healthy controls in the DLPFC, DMPFC, precuneus, and right angular gyrus. Conversely an increase in fALFF signal was detected bilaterally in the temporal lobe (see Supplementary Table S2 and Supplementary Fig. S3 for details).

Pharmacological effects and clinical improvement

One-way repeated-measures ANOVA analysis among the four time-points identified a group × time interaction in regions of the DLPFC, anterior cingulate cortex (ACC), and occipital cortex (Table 2 and Fig. 1). Individual *t* tests indicated that following acute (5H) and sub-chronic (4W and 8W) treatment administration

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Table 2. *Brain regions where differences were measured between major depression (MDD) and healthy controls (HC) during the course of treatment and in the placebo experiment*

Brain region	Hemisphere	Brodmann area	Cluster size (voxels)	*t*	MNI (x, y, z)		
Escitalopram ANOVA							
Insula_L	L	13	30	4.13	−36	6	−9
Medial frontal gyrus	R, L	8, 9, 10	100	4.02	−9	39	30
					3	45	36
Superior frontal gyrus	R	9	56	3.91	21	54	30
Occipital lobe, lingual gyrus	L	18	64	3.78	−9	−81	6
Cuneus	L	18	36	3.47	−18	−93	21
Supp_motor_area_R	R	6	28	3.55	21	24	57
Supp_motor_area_L	L	6	23	3.51	−6	15	63
Escitalopram paired t test, compared to baseline							
5H							
Increase							
Insula_L	L	13	37	5.73	−36	6	−9
Superior frontal gyrus	R	10	28	4.90	18	48	24
Medial frontal gyrus	R, L	10	60	4.45	0	63	12
Middle frontal gyrus	L	9	28	3.94	−36	33	27
Inferior parietal lobule	L	40	27	4.38	−51	−39	39
Anterior cingulate	L	32	24	4.02	−3	39	12
Cingulum_mid_L	L	24	40	3.94	−9	18	27
Decrease							
Occipital lobe	R, L	18, 19	752	5.32	−18	−69	−6
Middle occipital gyrus	L	19	52	4.66	−42	−78	−6
				3.77	−30	−87	3
Middle occipital gyrus, cuneus	R	18	57	4.08	21	−93	3
Middle temporal gyrus	L	22	27	4.41	−57	−51	3
Superior temporal gyrus	L	41	93	4.07	−57	−27	9
Temporal lobe, fusiform_R	R	37	27	4.20	39	−54	−10
Postcentral gyrus	R	2	34	3.77	48	−30	60
Inferior parietal lobule	R	40	47	4.12	36	−42	66
4W							
Increase							
Superior frontal gyrus anterior cingulate	R, L	10	960	5.19	12	54	33
Cingulum_mid	R	32	32	4.36	12	24	27
Middle frontal gyrus	R	46	62	5.12	51	9	36
Middle frontal gyrus	R	46	65	3.99	36	21	24
Middle frontal gyrus	R	9	23	3.42	42	21	42
Inferior frontal gyrus	L	9	132	5.89	−48	9	33
Precentral lobe	L	6	27	3.55	−39	−3	48
Supp_motor_area	R	32	40	4.64	6	27	51
Parietal lobe, precuneus	R	19	54	4.95	36	−72	36
Parietal lobe, angular gyrus	L	40	57	4.50	−60	−51	33
Inferior parietal lobule	L	40	45	4.09	−48	−48	42
Inferior parietal lobule	R	40	53	3.90	60	−54	39
Decrease							
Occipital lobe, lingual gyrus	R	18	31	4.23	15	−72	−9
Thalamus	R		26	4.22	6	−9	15
Brainstem	R, L		34	4.22	9	−33	−45
Postcentral gyrus	L	3	37	3.84	−36	−30	66
Postcentral gyrus	R	43	22	3.60	60	−15	18
Superior temporal gyrus	L	22	31	3.81	−54	−15	6
8W							
Increase							
Medial frontal gyrus	R.L	9	34	4.50	3	48	39
Superior frontal gyrus	R	8	22	4.31	18	21	57

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Table 2 (*cont.*)

Brain region	Hemisphere	Brodmann area	Cluster size (voxels)	*t*	MNI (x, y, z)		
Superior frontal gyrus	L	6	33	3.74	−21	18	57
Precentral gyrus	L	6	29	4.09	−36	−3	60
Anterior cingulate	R, L	9	36	3.80	6	48	18
Decrease							
Superior temporal gyrus,	L	22	57	4.56	−54	−12	6
Postcentral gyrus		43			−60	−18	21
Placebo, paired t test, compared to baseline							
5H							
Increase							
Fusiform gyrus	L	19	44	7.11	−30	−63	−18
Decrease							
Middle frontal gyrus	L	9	24	4.34	−48	15	30

the fALFF signal decreased in the bilateral post-central gyrus and left superior temporal gyrus (STG) while it increased in a vast area of the PFC incorporating dorsomedial and dorsolateral regions. The acute effect of escitalopram appeared to prominently decrease the activity of the occipital cortex, whereas after 4 weeks of treatment an increase in the activity of the PFC and ACC was evident. We were not able to detect fALFF and resting-state time effects in the cohort of healthy controls during the 8-week period at the corrected significance level ($p < 0.05$), supporting test–retest reliability of the procedures. The alteration of fALFF after a single dose of placebo in the controls demonstrated only a slight effect of increased temporal lobe activity, whereas escitalopram resulted in obvious changes in major depression compared to baseline.

Differences between remitters and non-remitters

Differences were detectable at 5H with decreased activity bilaterally in the orbitofrontal cortex, left STG, right supra-marginal gyrus and post-central gyrus and increased activities in ACC, mid cingulate cortex and right STG in remitters (Fig. 2 and Supplementary Table S3). At 4W changes resulted in increased activities in bilateral PFC [including the DMPFC and ventrolateral prefrontal cortex (VLPFC), mid cingulate cortex, and inferior temporal gyrus] and decreased activity in the midbrain, thalamus and occipital lobe. At 8W increased activity was noted in the left VLPFC and DMPFC and decreased activity in the left STG. However, for the non-remitters, fewer regions with increased activities were identified at all three post-medication time-points (Supplementary Table S3). Only a very small region of the occipital cortex with decreased activity was identified at 4W in the non-remitters. The non-remitters appeared to have a delayed and restricted response to the SSRI at weeks 4 and 8. The comparison between remitters and non-remitters also identified a significantly different resting-state response to escitalopram at different time-points (Supplementary Table S4 and Supplementary Fig. S4). Responders showed higher activity in precuneus, inferior temporal gyrus and occipital cortex, while lower activity in right parahippocampal gyrus, hippocampus and temporal lobe than non-remitters at baseline. At 5H, remitters had higher activity in the ACC, mid cingulate cortex, supplementary motor area, and middle frontal gyrus, but lower activity in occipital cortex, and postcentral gyrus than non-remitters. However, during the sub-chronic treatment, remitters showed lower activity in midbrain (4W) and left parahippocampal gyrus, including amygdala, and hippocampus, than non-remitters (8W) (Fig. 3). Both acute (5H) and sub-chronic (4W) treatment increased more activity on supplementary motor area in remitters than in non-remitters.

Exploratory correlation of functional fALFF with clinical response

Exploratory correlation analyses identified five clusters where $fALFF_{5H}$ alteration correlated with HAMD (Supplementary Table S5). Negative correlations were measured in two clusters in the bilateral occipital cortices and one cluster in the right temporal lobe. The fALFF alterations of clusters in the left caudate and the right middle temporal gyrus positively correlated with HAMD (Supplementary Fig. S5, A-E).

In all five ROIs, $fALFF_{5H}$ was highly sensitive (70–85%) and moderately specific (60–75%) for the prediction of the later response (Supplementary Table S6). In addition,

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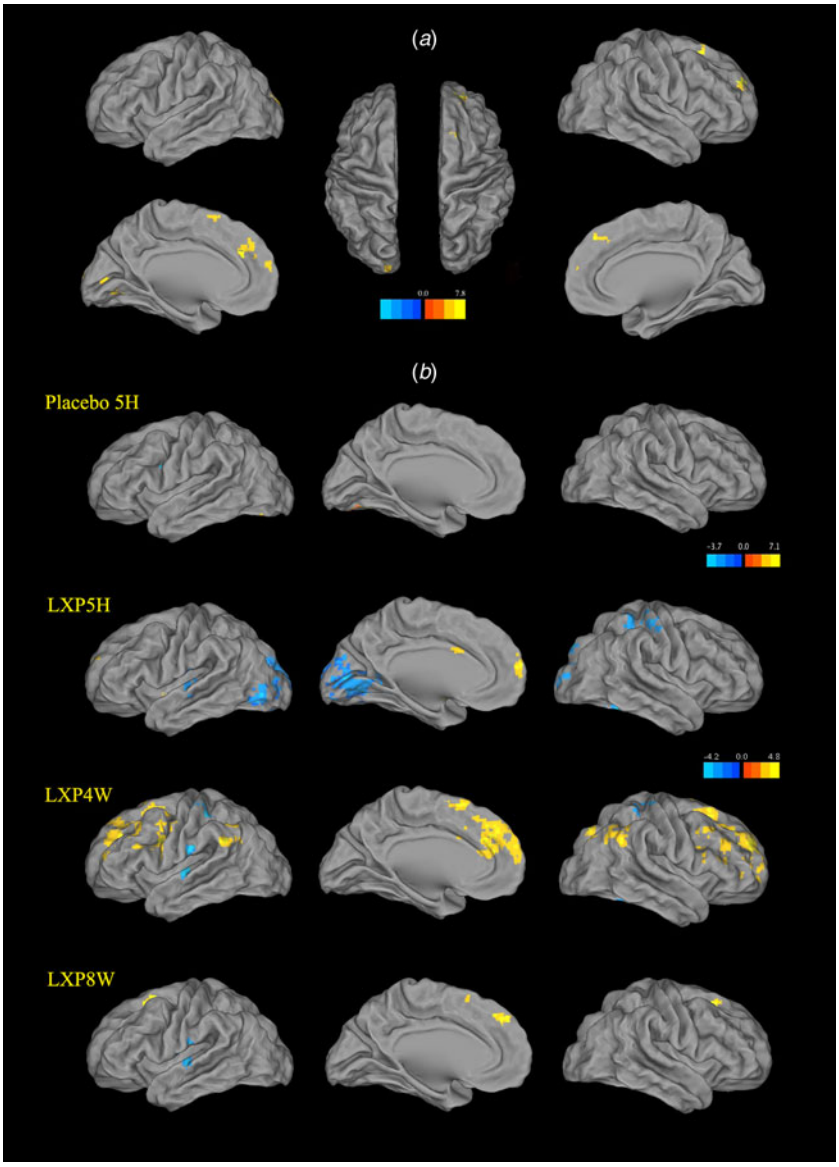

Fig. 1. The figure shows resting-state changes over the course of treatment and in relation to placebo. (*a*) One-way repeated-measures ANOVA analysis among the four time-points of baseline, 5 h (5H), 4 weeks (4W) and 8 weeks (8W). (*b*) Dynamic regulation of fALFF after acute and sub-chronic antidepressant treatment in major depression. The alteration of fALFF after escitalopram treatment at different time-points showed different patterns. LXP, escitalopram.

the positive predictive values for all treatment outcomes (76–82%) were higher than the negative predictive values (59–75%). The area under the curve (AUC) of $fALFF_{5H}$ for all five ROIs was >0.8 (0.80–0.89) (see Supplementary Figs S5F, S6 and Supplementary Table S6 for cut-off values of $fALFF_{5H}$ of each ROI).

Discussion

In this study, dynamic changes in resting-state activity after acute/sub-chronic escitalopram administration were found and became manifest after a single dose of oral antidepressant medication. After 5 h the antidepressant induced a significant increase in the DLPFC and DMPFC and middle cingulate cortex. Furthermore, while remitters demonstrated more obvious changes following treatment, these were more modest in non-responders suggesting possible tonic and dynamic differences in the serotonergic system. Changes after 5 h in the caudate, occipital and temporal cortices were the best predictor of clinical remission at endpoint. We also found a significant association between acute responses to antidepressant 5 h after administration and delayed (8W) clinical effects of the SSRI.

Consistent with previous reports (Liu *et al.* 2013), abnormal resting-state activity indexed by fALFF in

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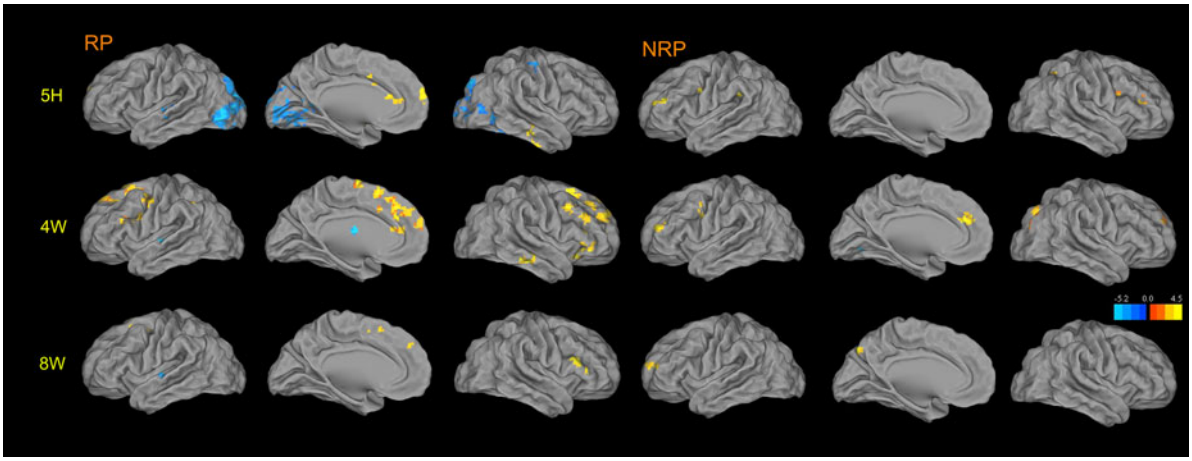

Fig. 2. Brain regions active in remitted patients during the course of the pharmacological study. Compared to baseline, remitted patients (RP) displayed a tendency towards more active responses to the SSRI than non-remitters (NRP), especially at 5 h (5H) and 4 weeks (4W) after treatment. At 5H, significant lower activity was found in the bilateral occipital lobe, left superior temporal gyrus, right supramarginal gyrus and post-central gyrus, while higher activity was found in the ACC, MCC and right superior temporal gyrus in remitters. At 4W, significantly higher activity was found in bilateral prefrontal cortex (including DLPFC, DMPFC and VLPFC), MCC, and inferior temporal gyrus, while lower activity was found in left thalamus in remitters. As for 8 weeks (8W), relatively higher activity was found in the left VLPFC and DMPFC and lower activity in left superior temporal gyrus in remitters. Only fewer regions in the frontal lobe, supramarginal gyrus, ACC and occipital gyrus with higher activity were found in non-remitters at 5H, 4W and 8W. Except for a small region in the occipital gyrus at 4W, there were almost no regions with deceased activity found in non-remitters at all the three time-points compared to baseline. ACC, Anterior cingulate cortex; MCC, mid cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; VLPFC, ventral lateral prefrontal cortex.

depressed patients was detected at baseline, including reduction of fALFF at DLPFC, middle cingulate cortex, posterior cingulate cortex, and right angular gyrus, while increased fALFF was seen in the bilateral temporal lobe. These abnormalities, especially at the DLPFC, were partially reversed by escitalopram after 4 weeks of treatment and might explain adaptive changes which appeared related to the insurgence of a clinical response. Regions where resting-state activity increased over the 4 weeks of treatment included prefrontal and cingulate cortices, and occipital regions, whereas neural activity decreased in the temporal lobe during the same time period. In contrast the acute administration (5H) of an SSRI decreased resting-state neural activity in the occipital cortex. These reversions appeared dampened at the end of the treatment phase (8 weeks), and may be related to a continuous process of synaptic adaption to prolonged pharmacological treatment. Although a single dose of placebo slightly changed resting-state neural activity in healthy controls, these alterations were topographically different from the alterations induced by acute escitalopram in depression. Unfortunately we could not include a placebo arm in the study to investigate placebo effects in major depression because of ethical considerations. Results from a positron imaging study, however, supports independent drug-specific effects induced by 6 weeks' treatment with the SSRI fluoxetine compared to placebo (Mayberg *et al.* 2002).

The most impressive changes induced by escitalopram in our study are the increased activity in prefrontal networks including DMPFC, DLPFC and cingulate cortex at week 4 accompanied by decreased activity in the occipital cortex at 5H. A recent study reported that an acute administration of ketamine leads to reductions in the resting-state functional connectivity of subgenual ACC (sgACC) with other regions (Wong *et al.* 2016). Other studies found the fMRI change of PFC and cingulate cortex following antidepressant treatment at a task condition. For example, a single dose of mirtazapine can attenuate responses to self-referential processing task in the medial PFC and the ACC (Komulainen *et al.* 2016). Another study also found a different effect of agomelatine on brain activities after short-term and long-term use. Seven days agomelatine treatment significantly deactivated the VLPFC during an emotional self-referential task, while significantly increasing the activation of the ventral ACC after 7 weeks in major depression (Delaveau *et al.* 2016). The occipital cortex is part of resting-state networks (Beckmann *et al.* 2005; Fransson *et al.* 2007) and visual recognition circuits (i.e. containing the lingual gyrus, middle occipital gyrus, fusiform gyrus and cuneus) were also

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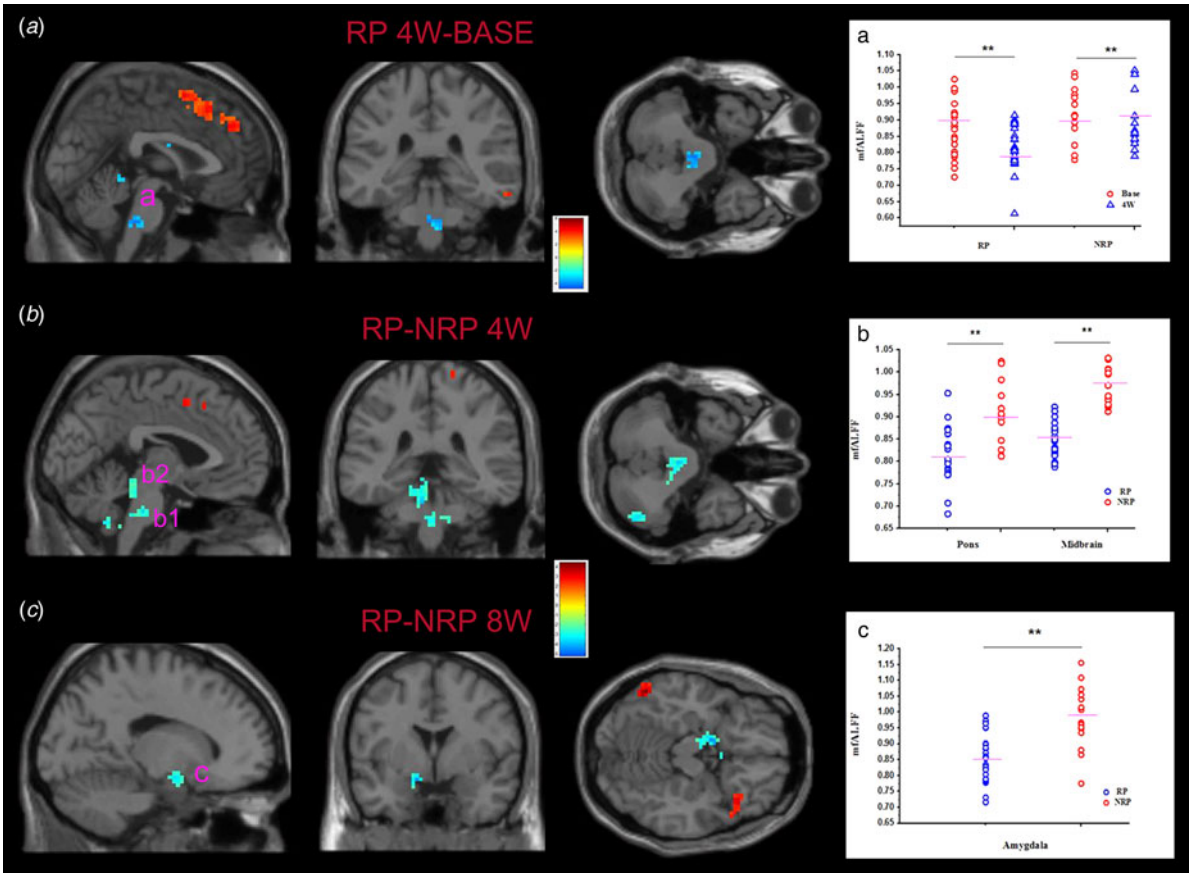

Fig. 3. Escitalopram elicited more prominent responses in remitted patients (RP) than non-remitted patients (NRP) in midbrain and amygdala at 4 (4W) and 8 (8W) weeks. (*a*) fALFF reduction of RP in pons (*a*) at 4W compared to baseline; (*b*) fALFF of pons (b1) and midbrain (b2) decreased in RP *v*. NRP at 4W; (*c*) fALFF of amygdala (*c*, cluster of left amygdala) decreased in RP *v*. NRP at 8W (** $p < 0.001$).

implicated in two studies of early SSRI response (Wang *et al.* 2014*a*, *b*). A growing body of evidence indicates the importance of the PFC in the pathogenesis of mood disorders (Price & Drevets, 2010; Wise *et al.* in press) including neuropsychological homeostasis and cognitive control. PFC and cingulate cortex are particular relevant in exercising cognitive control (Rive *et al.* 2013), including the tendency often seen in depression to generate negative valenced cognitions (Quirk & Beer, 2006). Gray-matter reduction shown in the PFC (Arnone *et al.* 2016) might relate to the decreased baseline activities revealed in this study. A recent study found that sensory experience within the occipital cortex can modulate visual cortical circuitry by modifying neurotransmission and synaptic connectivity (Larsen *et al.* 2014). Increased activity in the PFC and decreased activity in the occipital cortex suggest that SSRI treatment might play a role in dynamically regulating these regions by setting a different balance in the resting-state network potentially linked with clinical response.

The exact mechanism of how escitalopram affects resting-state activity remains unclear. A recent study demonstrated that escitalopram decreased intrinsic DMN regional connectivity, including ACC, posterior cingulate cortex, hippocampal complex and lateral parietal regions, suggesting that the serotonergic system plays an important role in default mode connectivity and its contribution to cognition (van de Ven *et al.* 2013). There are reports that the neurophysiological basis of the fMRI signal may originate more extensively from synaptic activity (Logothetis *et al.* 2001) or be driven by neurotransmitter-related signaling (Rauch *et al.* 2008). In the central nervous system, of all the serotonergic (5-HT) receptors, the 5-HT_{1A} receptor is the most extensively distributed (Pytliak *et al.* 2011), present in high density in the cortex, hippocampus, septum, and raphe nuclei, and in low density in the basal ganglia and thalamus (el Mestikawy *et al.* 1991). The 5-HT_{1A} receptors in the raphe nuclei are largely somatodendritic autoreceptors, whereas those in other areas are postsynaptic receptors. The acute response for SSRI decreases the serotonergic output via the negative feedback of autoreceptors in the raphe nuclei. It is believed that chronic use of SSRI can induce

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the increase of serotonergic output following 5-HT_{1A} autoreceptor desensitization. The desensitization of 5-HT_{1A} autoreceptor and increased postsynaptic activation via a general increase in serotonin levels has been shown to be a major mediator in the therapeutic benefits of SSRIs. Reduced resting-state activity at 5 h with increased activity at 4 and 8 weeks in our results were consistent with putative receptor-level alterations.

Receptor mapping studies in rodents have demonstrated that serotonergic afferents project to multiple regions of the limbic system, including the anterior and posterior cingulate cortices (Bozkurt *et al.* 2005). Serotonergic projection may inhibit the 'aversive amplification' circuit, including the 'prefrontal-amygdala circuit', and might contribute to the negative affective bias shown in mood disorders (Robinson *et al.* 2013). Neurophysiological studies in animals support the notion that functional results emerging from neuroimaging studies might result from changes in metabolic demands as a consequence of altered serotonin levels (McBean *et al.* 1999; Schwarz *et al.* 2007). Thus, the global component of the fMRI fluctuations measured during resting-state appears tightly coupled with underlying neural activities (Schölvinck *et al.* 2010).

Remitters to treatment showed a significant tendency to modify resting-state activity in the occipital cortex where the signal decreased while neural activity increased in regions such as the cingulate cortex and furthermore decreased in areas such as the post-central gyrus at week 4 of treatment. Conversely, non-remitters showed much lower levels of significant changes. This would support the notion that a relatively silent network might reflect the persistence of pathological mechanisms and unchanged cognitive function. We also noted that the remitters had increased activities in pre- and post-central gyri but decreased activity levels in the midbrain at week 4 and in the hippocampal gyrus, amygdala and subgenual ACC after 8 weeks of treatment compared to non-responders. Speculatively it might be postulated that increased neural activity in the midbrain, being located in proximity of the dorsal raphe nuclei might indicate a higher responsiveness of the serotonin system in remitters. The limbic system is vital to affective regulation circuits in depression, and increased connectivity has been demonstrated in limbic regions such as the insula, amygdala (Connolly *et al.* 2013), and PFC (Späti *et al.* 2015). Furthermore, abnormalities in functional connectivity between limbic and brain areas such as the subgenual cingulate cortex have also been found in both emotionally triggered and resting conditions (Palmer *et al.* 2015). A possible interpretation of the lower activity detected at endpoint in non-responders in this study might reflect a delayed clinical response in some individuals or indicate a lower sensitivity to serotonin reuptake inhibition in the brain areas where neural activity was measured in this experiment (van de Ven *et al.* 2013).

The finding of resting-state activity correlating with later remission to escitalopram treatment is of interest. The observation of decreased reactivity at 5H in the occipital lobe combined with increased activity in the caudate and medium temporal gyrus in response to a single dose of escitalopram suggested a better clinical outcome. The caudate and temporal lobe are important in the emotion pathway (Mayberg, 1997; Phillips *et al.* 2003).

Although explorative in nature, the $fALFF_{5H}$ for all five ROIs was significantly sensitive and specific in predicting the later response based on the change of the resting-state activity at 5H. If confirmed, these data suggest that acute neural changes in specific brain regions might provide potentially useful biomarker data for the identification of patients favorably responding to SSRIs at week 8.

Limitations of this study include the relatively small sample size, the use of a fixed-dose regimen for the antidepressant of choice, which although in the therapeutic range might have restricted remission rate in some clinical cases where higher doses were required, and the relatively milder severity of depression. Future studies could confirm the generalizability of the findings in a larger sample (1) with more severe depressive features, (2) with/without co-morbid anxiety symptoms, (3) clinically treated with variable doses of antidepressant medication and (4) with confirmatory blood levels for efficacy. Furthermore, subjective responses to the acute effects of antidepressants could be better assessed in future studies with rating scales evaluating state effects. Alternative methods to model nonlinear data may be better suited than the technics used in this work.

In conclusion this work identified resting-state dynamic alterations in major depression following pharmacological treatment and in relation to clinical improvement. Our results may provide potentially useful information to further understand the neurobiological basis of treatment and clinical response which might help clinicians to make decisions in relation to medication.

Supplementary material

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0033291716002440

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Declaration of Interest

Danilo Arnone has received travel grants from Servier and Jannsen.

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