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Anatomical brain difference of subthreshold depression in young and middle-aged individuals

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ABSTRACT

Background: Subthreshold depression (StD) is associated with substantial functional impairments due to depressive symptoms that do not fully meet the diagnosis of major depressive disorder (MDD). Its high incidence in the general population and debilitating symptoms has recently put it at the forefront of mood disorder research.
Aim: In this study we investigated common volumetric brain changes in both young and middle-aged StD patients.
Methods: Two cohorts of StD patients, young and middle-aged, ($n = 57$) and matched controls ($n = 76$) underwent voxel-based morphometry (VBM).
Results: VBM analysis found that: 1) compared with healthy controls, StD patients showed decreased gray matter volume (GMV) in the bilateral globus pallidus and precentral gyrus, as well as increased GMV in the left thalamus and right rostral anterior cingulate cortex/medial prefrontal cortex; 2) there is a significant association between Center for Epidemiological Studies Depression Scale scores and the bilateral globus pallidus (negative) and left thalamus (positive); 3) there is no interaction between age (young vs. middle-age) and group (StD vs. controls).
Conclusions: Our findings indicate significant VBM brain changes in both young and middle-aged individuals with StD. Individuals with StD, regardless of age, may share common neural characteristics.

1. Introduction

StD is characterized by avoidant behavior, hyposensitivity to reward, cognitive exhaustion and inattention (Hwang et al., 2015; Takagaki et al., 2014). The heterogeneity of the clinical manifestations of StD patients makes it difficult to discriminate StD from MDD using subjective self-reports and screening of symptoms. Thus, further studies and approaches are needed to help diagnose StD and explore the related neural mechanisms (Hwang et al., 2015).

Current neuroimaging technology allows us to investigate the neural substrates of StD symptoms. Through functional and anatomical analyses, we can identify the pathophysiology of StD (Drevets et al., 2008).

Voxel-based morphometry (VBM) is a neuroanatomical MRI technique which provides great sensitivity for the small scale localization and comparison of regional differences in gray matter (Ashburner and Friston, 2000). It has been widely used in StD studies. For example, Li et al. (2015) found that young women with StD showed significantly decreased gray matter volume in the inferior parietal lobe and increased volume in the amygdala, posterior cingulate cortex and precuneus compared with non-depressed controls. Similarly, Hayakawa (Hayakawa et al., 2013) found decreased volume of the anterior cingulate gyrus in women with StD compared with healthy controls. The gray matter volume of the hippocampus, parahippocampus, ventromedial prefrontal cortex, cingulate cortex and caudate also showed negative correlations with StD severity (Vulser et al., 2015; Zhou et al., 2016).

Despite previous studies on StD, the common neuropathology between different age groups and the specific neurobiological features between and within different age groups has not been extensively studied. The difference in age of onset of MDD is one cause of the heterogeneity of their manifestations (Takahashi et al., 2008). Studies have found that the age of onset could influence the clinical course, symptom severity, cognitive impairment, clinical comorbidity, the number of suicide attempts and treatment response in MDD (Jaworska et al., 2014; Park et al., 2014; Rao et al., 2015). Individuals with early onset MDD (<30 years old) demonstrate higher rates of recurrence, psychiatric

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comorbidities, chronicity, disability and suicidal attempts (Cheng et al., 2014). In contrast, individuals with late onset MDD (>30 years old) have a higher prevalence of cerebrovascular disorders, more severe cognitive impairments, less feelings of sadness, and decreased appetite (Cheng et al., 2014; Lebedeva et al., 2015).

In this study, we investigated the brain volumetric alterations in young and middle-aged StD patients and compared them to age and gender-matched healthy controls. We hypothesized that StD, in both young and middle-aged cohorts, would result in common volumetric changes related to the disease.

2. Materials and methods

2.1. Participants

We screened 981 subjects from three universities (young cohort) and 383 subjects from twelve Beijing community centers (middle-aged cohort) through advertisements and flyers. All participants received a health lecture from investigators followed by a survey containing the Center for Epidemiological Studies Depression Scale (CES-D, Chinese version) (Radloff, 1977). The surveys were evaluated by a trained clinician. Potentially depressed participants were further assessed by a licensed psychiatrist using a 17-item Hamilton rating of depression scale (HAMD).

Inclusion criteria for StD participants included: (1) age between 18 and 60 years; (2) CES-D ≥ 16 (Caracciolo and Giaquinto, 2002; Radloff, 1977); (3) 17-item HAMD score between 7 and 17.

Exclusion criteria included: (1) abnormal or impaired judgment, as indicated by the Wechsler Adult Intelligence Scale (WAIS-R); (2) full diagnosis of severe depression based on ICD-10 (first-episode); (3) prior use of psychiatric medications; (4) any suicidal tendencies posing an immediate threat to the subject's life; (5) history of addiction disorders such as substance abuse and dependence or alcoholism; and (6) any fMRI contraindications including any major medical, neurological or psychological disorders, pregnancy or intent to become pregnant, or a history of head trauma.

Age and gender matched healthy controls (HC) were recruited from the same sources as StD participants. All HC had CES-D scores of <16 and satisfied the same exclusion criteria as StD participants. All participants were given a description of the study and provided with written informed consent forms. All subjects signed the consent forms before the fMRI scans. The study was approved by the Committee on the Use of Human Subjects in Research at Beijing University of Chinese Medicine.

2.2. Image acquisition

Images were acquired using a 3-axis gradient head coil in a 3-Tesla Siemens Magnetom Trio Tim syngo MR B17 system equipped for echo planar imaging (EPI) at the Research Institute of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University. Magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images were collected with the following parameters: a 12 element T/R head coil, slice orientation = sagittal, slice-thickness = 1.33 mm, number of slices: 128, TR (repetition time) = 2530 ms, TE (echo time) = 3.39 ms, flip angle (FA) = 7°, FOV (field of view) = 256 × 256 mm^2, acquisition matrix = 256 × 192, Magn. preparation = Non-sel.IR, TI (inversion time) = 1100 ms, echo train length = 1, acceleration factor = 1, acquisition time = 8:07 min.

2.2.1. Voxel-based morphometry analysis

All structural data were processed using the VBM method (Ashburner and Friston, 2001) with Statistical Parametric Mapping (SPM12) (Welcome Department of Cognitive Neurology, University College, London, UK) running under a MATLAB suite (Mathworks, Inc., Natick, Massachusetts). The default settings were used unless otherwise specified. First, all images were checked for artifacts, structural abnormalities and pathologies. For better registration, the re-orientation of images was manually set to the anterior commissure. Second, the images were segmented into gray matter (GM), white matter and cerebrospinal fluid, and normalized using the high dimensional DARTEL algorithm (Ashburner, 2007). Then, all participants' gray and white matter images were simultaneously registered to create a study specific template in order to reduce between-participant variability. The template was then used to normalize all images into the standard Montreal Neurological Institute (MNI) space using the "preserve amount" option to retain the volumetric data of the original images in the "DARTEL Normalize to MNI Space" program. Finally, spatial smoothing was performed with an isotropic Gaussian kernel of 10 mm full-width at half maximum (Ashburner and Friston, 2000).

2.3. Statistical analysis

A two-sample *t*-test was used to compare demographic data and total CES-D scores between StD patients and healthy controls with SPSS 18.0 Software (SPSS Inc., Chicago, IL, USA).

We used VBM to compare gray matter volumes between the two groups using a full factorial model in SPM 12, including age and gender as non-interest covariates. To explore the volumetric alteration between StD and matched healthy controls between different age groups (young and middle-aged), a two-sample *t*-test was used to compare the GMV of StD patients and matched healthy controls in both the young and middle-aged group separately, including age and gender as non-interest covariates. We also explored the main volumetric difference between young and middle-aged individuals in the StD cohort using a two-sample *t*-test.

To explore the association between psychiatric measurements and GMV alteration, we used regression analysis between the whole-brain GMV of all subjects and their total CES-D scores, with age and gender included as non-interest covariates.

Similar to a previous study, an absolute threshold for masking of 0.2 was used (Li et al., 2015). A threshold of a voxel-level $p < 0.001$ (uncorrected) and cluster level $p < 0.05$ (family-wise error) was applied for the comparison.

3. Results

A total of 133 participants underwent fMRI scans. A detailed description of the subjects can be seen in our previous publication (Hwang et al., 2016). The demographic and clinical characteristics are shown in Table 1. There were no significant differences in age and gender between StD patients and healthy controls (age: $p = 0.364$; gender: $p = 0.700$). There were no significant differences in CES-D scores between young and middle-aged StD patients ($p = 0.0576$).

Compared with healthy controls, StD patients showed decreased GMV in the left globus pallidus/putamen, right globus pallidus and precentral gyrus, and increased GMV in the left thalamus and right rostral anterior cingulate cortex (rACC)/medial prefrontal cortex (mPFC) (Fig. 1, Table 2).

Table 1
The demographics of subthreshold depression (StD) patients and matched healthy controls. Abbreviation: CES-D, Center for Epidemiological Studies Depression Scale; StD, subthreshold depression.

	Healthy group		StD group	
Items	Young age	Middle-age	Young age	Middle-age
Number (male)	51 (18)	25 (5)	34 (12)	23 (3)
Age in years (mean ± SD)	20.63 ± 1.89	49.2 ± 10.25	20.29 ± 1.40	49.91 ± 8.44
CES-D (mean ± SD)	6.78 ± 4.7	4.40 ± 3.58	24.56 ± 6.66	27.43 ± 4.55

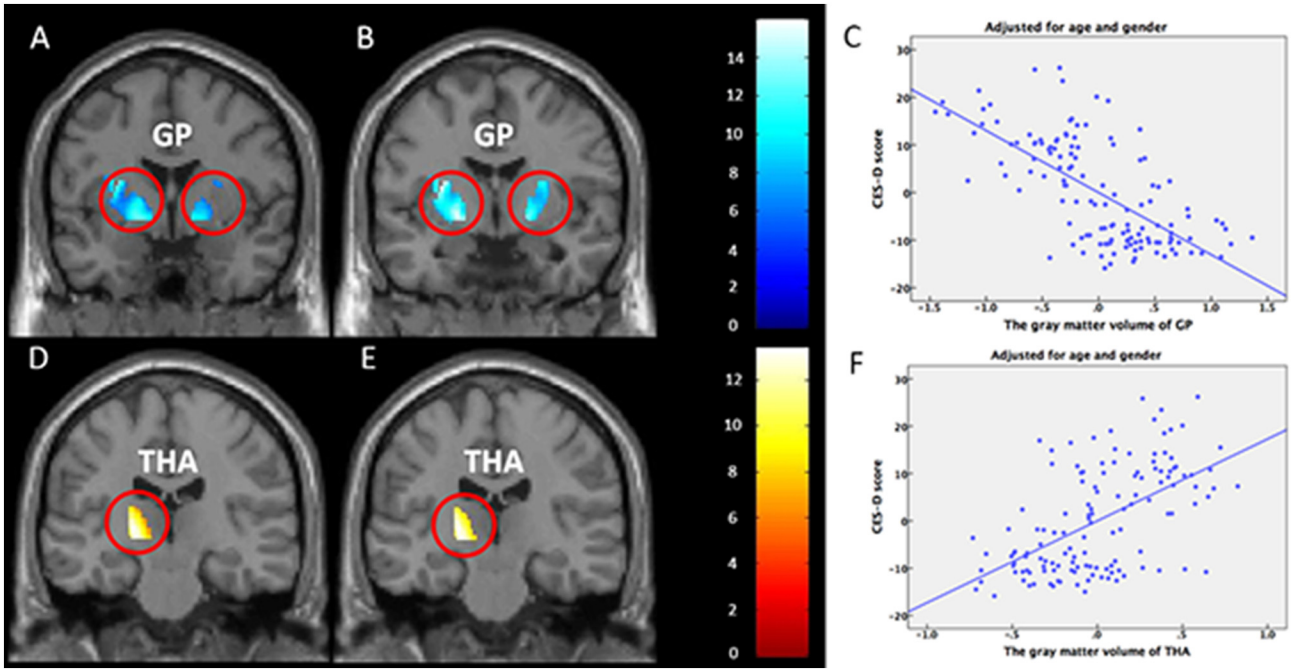

Fig. 1. Brain regions showed a significant difference between StD patients (young and middle-aged) and healthy controls. (A) Significant difference between HC and StD (HC > StD). (B) Negative correlation between CES-D score and whole brain volume. (C) Correlation between CES-D score and the gray matter volume of GP. (D) Significant difference between HC and StD (StD > HC). (E) Positive correlation between CES-D score and whole brain volume. (F) Correlation between CES-D score and the gray matter volume of THA. Abbreviations: HC, healthy controls; StD, subthreshold depression; GP, globus pallidus; THA, thalamus.

Further analysis demonstrated that the middle-aged StD patients showed decreased GMV in the right operculum and bilateral precentral gyrus, and increased GMV in the bilateral inferior frontal gyrus compared to the middle-aged healthy controls (Table 3). With a less conservative threshold of voxel wise $p < 0.005$ and $p < 0.05$ FWE corrected at cluster level was applied, the middle-aged StD patients also showed a significantly decreased GMV in the left globus pallidus (peak coordinates: −44, −45, 22; peak z value: 6.61; 30,319 continuous voxels), and a significantly increased GMV in the left thalamus (peak coordinates: −18, −19, 0; peak z value: 7.40; 7289 continous voxels), the left inferior frontal gyrus (peak coordinates: −60, 20, 28; peak z value: 7.74; 3116 continous voxels) and the right inferior frontal gyrus (peak coordinates: 31, 3, 67; peak z value: 7.30; 9041 continous voxels), when compared to matched healthy controls.

The young StD patients showed decreased GMV in the left globus pallidus/insula, right globus pallidus/putamen, bilateral precentral gyrus, and right fusiform gyrus and increased GMV in the left thalamus compared with young healthy controls (Table 3).

There was no brain region above the threshold we set for the interaction effect between age and StD.

The multiple regression analysis between CES-D scores and whole brain gray matter volume across all StD patients showed a negative association in the left and right lateral globus pallidus and a positive association in the left thalamus (Fig. 1 and Table 2).

4. Discussion

In this study, we used voxel-based morphometry analysis to explore the association between anatomical brain difference in two-cohorts of StD patients (young and middle-aged) compared with age and gender-matched healthy controls. We found remarkable GMV reductions in the bilateral globus pallidus and precentral gyrus, and an increase in the left thalamus and prefrontal cortex (rACC/mPFC, inferior frontal gyrus) in StD patients compared with healthy controls. In addition, we also found a negative association between the gray matter volume of

Table 2
Brain regions showed a significant difference between StD patients (young and middle-aged) and healthy controls. rACC, rostral anterior cingulate cortex; mPFC, medial prefrontal cortex; Inf, infinity.

Conditions	Region	Coordinates (X,Y,Z)			Cluster size	Peak Z
VBM comparison						
HC > StD	Left globus pallidus/putamen	−18	−9	−5	3543	Inf
	Right globus pallidus	15	−3	−6	1718	Inf
	Bilateral precentral gyrus	1	−46	76	1331	7.18
StD > HC	Left thalamus	−18	−21	0	1275	Inf
	Right rACC/mPFC	36	41	−8	1326	7.63
Regression between VBM and CESD						
Negative	Left globus pallidus	−27	−4	15	3366	Inf
	Right globus pallidus	15	−3	−6	1846	Inf
	Bilateral precentral gyrus	1	−46	76	1618	6.97
Positive	Left thalamus	−18	−21	0	1102	Inf

Table 3
Brain regions showed a significant difference between StD patients and healthy controls in both the young and middle-aged cohorts. Inf, infinity.

Conditions	Region	Coordinates (X,Y,Z)			Cluster size	Peak Z
Middle-aged group						
HC > StD	Right operculum	43	−37	24	1524	7.16
	Bilateral precentral gyrus	1	−49	75	1230	6.18
StD > HC	Left inferior frontal gyrus	−60	20	28	1972	7.74
	Right inferior frontal gyrus	57	15	39	1933	7.30
Young group						
HC > StD	Left globus pallidus/insula	−18	−9	−2	3149	Inf
	Right globus pallidus/putamen	16	−6	−2	1490	Inf
	Bilateral precentral gyrus	16	−30	82	1119	6.75
	Right fusiform gyrus	22	−82	−2	1460	6.09
StD > HC	Left thalamus	−18	−21	0	1151	Inf
	Bilateral inferior frontal gyrus	24	59	45	2668	Inf

the bilateral globus pallidus and CES-D scores. In contrast, the left thalamus showed a positive association with CES-D scores.

4.1. VBM changes in both young and middle-aged individuals with StD

At the threshold we set, we found different VBM change patterns in young and middle-aged StD patients. Specifically, the young StD patients showed a significant GMV increase in the left thalamus and a significant GMV decrease in the bilateral globus pallidus, left insula, right putamen, and bilateral precentral gyrus compared to young healthy controls. Middle-aged StD patients showed increased GMV in the bilateral inferior frontal gyrus, and decreased GMV in the right operculum and bilateral precentral gyrus compared to middle-aged healthy controls. The only overlapping region between the young and middle-aged groups was the bilateral precentral gyrus, which showed significant VBM decrease in StD patients.

However, when a less conservative threshold of voxel wise $p < 0.005$ and $p < 0.05$ FWE corrected at cluster level was applied, the middle-aged StD patients also showed a significantly decreased GMV in the left globus pallidus and bilateral precentral gyrus and a significantly increased GMV in the left thalamus when compared to matched healthy controls. This finding is very similar to those observed in young StD patients. In addition, we did not find a significant interaction between age (young vs. middle-aged) and group (StD vs. control). Thus, our results indicate common VBM changes across the two cohorts of StD patients (young vs. middle-aged) at the globus pallidus, precentral gyrus and thalamus.

In previous studies, Zhou et al. (2016) found that elderly StD patients (mean age, 66.5 year old) showed reduced VBM in the hippocampus and parahippocampus. Li et al. (2015) found that young women (mean age, 20.26 years old) with StD showed significantly decreased GMV in the right inferior parietal lobule and significantly increased GMV in the amygdala, posterior cingulate cortex, and precuneus. Taki et al. (2005) found that elderly, male StD patients showed decreased GMV in the medial part of the bilateral frontal lobes and the right precentral gyrus. Our results are partly consistent with these findings.

One common finding across the two cohorts was the VBM decrease at the precentral gyrus. The precentral gyrus consists of the primary motor cortex and is the cortical area responsible for voluntary movement (Exner et al., 2002; Nitsche et al., 2003). It is also involved in cognitive processing and emotion regulation (Seo et al., 2014). Specifically, previous studies found that the precentral gyrus along with amygdala, insula, striatum, and thalamus were activated when presented with avoidance cues (Schlund et al., 2010). Active avoidance in depressed individuals refers to cognitively denying or minimizing a stressful situation while deciding that nothing can be done to change it (Carvalho, 2011). Increased levels of avoidance motivation is one of the most important traits in depression (Spielberg, 2011). Investigators found a positive correlation between the volume of both the precentral gyrus and the anterior cingulate cortex with higher levels of anxiety and the corresponding avoidant motivational set in neurodegenerative disease (Shinagawa et al., 2015). We speculate that the decreased precentral VBM may be associated with avoidance motivation in MDD and StD. Further studies are needed to test this hypothesis.

In our study, we found significantly decreased GMV in the globus pallidus (GP) in StD patients compared to healthy controls. As part of the basal ganglia, GP is involved in behavioral motor control, reward, motivation and affective processing (Caligiuri et al., 2006; Howell et al., 2016). A previous study found that the increased response to incentive cues in the globus pallidus was correlated with anhedonia (Chung and Barch, 2015), which is also a core symptom of depression (Pizzagalli, 2014). Consistent with our results, Kempton and colleagues found that compared with healthy controls, MDD patients showed reduced volume in the bilateral globus pallidus (Kempton et al., 2011). Previous studies suggest that the volumetric reduction in the globus pallidus in depressed individuals is associated with reduced awareness of the causal efficacy of goal-directed actions (Griffiths et al., 2015); our results further endorse these findings.

4.2. VBM changes in young StD patients

Young StD patients also showed decreased volumetric gray matter in the right putamen, left insula and right fusiform gyrus compared with matched healthy controls. The insula, thought to be a key neural correlate of the core symptoms of MDD (Stratmann et al., 2014), is engaged in the perception of emotion and can monitor the body's ongoing internal emotional state (Harvey et al., 2007). Foland-Ross and colleagues followed 33 never-depressed adolescent (10–15 years old) for five years and found that the decreased cortical thickness of bilateral insula could predict the subsequent onset of depression in adolescent (Foland-Ross et al., 2015).

The putamen is a key region in the reward network and is also involved in the pathology of MDD and StD (Macoveanu et al., 2014; Mori et al., 2016). A prospective longitudinal study spanning six years (ages 12 to 18) found that the putamen GMV reduction from early to mid-adolescence was related to the onset of depression (Whittle et al., 2014). Previous studies also found decreased GMV in the right fusiform in early onset depression in adults (age 18–29) compared with healthy controls (Shen et al., 2016; Truong et al., 2013; Zhang et al., 2012). Many previous studies have demonstrated the abnormal functional and structural changes of occipital areas in MDD (Chen et al., 2016; Shen et al., 2016). In a previous study, we found that acupuncture treatment can increase resting-state functional connectivity in the dorsal putamen and fusiform gyrus in patients with depression (Wang et al., 2017). Our results are consistent with the above findings.

4.3. VBM changes in middle-aged StD patients

Middle-aged StD patients showed a reduction in GMV at the operculum. As part of the premotor network, the operculum participates in the voluntary control of emotional facial expression, hedonic processing, observation, self-focus, and rumination and is active when one feels sad and is ruminating about other people's intentions (Caruana et al., 2016; Young et al., 2013). An anatomical study also revealed a link between the operculum and the emotion network (Jezzini et al., 2015). Additionally, individuals with late onset MDD have been found to experience less sadness (Korten et al., 2012), which may help explain the reduced operculum volume in our study.

We found significantly increased GMV in the thalamus in young StD patients compared with matched healthy controls, and an increase in middle-aged StD (with a less conservative threshold) compared to healthy controls. The thalamus is the central component of the limbic-cortical-basal ganglia-thalamic circuits and projects to the basal ganglia and returns feedback information to the cortex (Haber and Calzavara, 2009). It is involved in the mediating of motivation, emotional drive, and planning of goal-directed behavior (Haber and Calzavara, 2009; Taber et al., 2004) and is regarded as one of the centrally disrupted regions in mood disorders (Li et al., 2014; Price and Drevets, 2010).

Recently, a meta-analysis found that medication-naïve MDD patients showed increased volume in his/her right thalamus following the first depressive episode compared with medication-free and medicated MDD patients (Zhao et al., 2014). A previous postmortem study found that MDD patients showed elevated neuron numbers in the limbic thalamus compared to patients with bipolar disorder or schizophrenia (Young et al., 2004). We previously found that there is increased functional connectivity between the default mode network and the thalamus in StD patients compared with healthy controls (Hwang et al., 2016). A study from another group found that spontaneous activity in the thalamus correlates with antidepressant treatment (Yamamura et al., 2016). Our results demonstrate volumetric change in the thalamus even before the onset of MDD.

4.4. VBM changes between HC and StD

Additionally, increased GMV was found in the inferior frontal gyrus (IFG) and rACC/mPFC, which is consistent with prior studies (Arnone et al., 2012; Bora et al., 2012). The inferior frontal gyrus is regarded as the inhibitory component of the prefrontal-limbic system (Cha et al., 2016). Studies suggest that the IFG is involved in the regulation of emotion and attention by inhibiting the negative feedback loop and interpreting emotional states (Cha et al., 2016; Vasic et al., 2014).

Previous studies have found that the rACC/mPFC are key regions involved in automatic attention control (Phillips et al., 2008) and the modulation of visceral activity to affective stimuli (Ongür and Price, 2000). We found that the resting state functional connectivity between the subgenual ACC and the default mode network was significantly associated with symptom severity in StD patients (Hwang et al., 2016). The abnormal function and structure of the ACC/mPFC has been regarded as a biomarker in MDD (Phillips et al., 2015). In one of our previous studies, we found that repeated acupuncture treatment increased the resting-state functional connectivity between the rACC and amygdala, which was positively associated with clinical improvement (Wang et al., 2016).

In this study, we found similar volumetric changes in young and middle-aged StD patients. In a previous study, Botteron et al. (2002) compared the GMV of the subgenual prefrontal cortex between adolescents and middle-aged females with depression and found that the magnitude of the difference between depressed and control groups was similar in younger and older women. Consistent with these findings, our results indicate a common pathophysiology underlying young and middle-aged individuals with StD.

In summary, we found significant volumetric reductions in the globus pallidus and bilateral precentral gyrus, and increased GMV in the thalamus and prefrontal cortex across two cohorts of StD patients (young and middle-aged). Our findings indicate a common neural pathophysiology in StD patients across different ages. The identification of structural changes in StD patients may be critical in identifying appropriate therapies for the illness.

Conflict of interest

The authors declare no conflict of interest.

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References

Arnone, D., Mcintosh, A.M., Ebmeier, K.P., Munafò, M.R., Anderson, I.M., 2012. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur. Neuropsychopharmacol. 22 (1):1–16. http://dx.doi.org/10.1016/j.euroneuro.2011.05.003.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38 (1), 95–113.

Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—the methods. NeuroImage 11 (6 Pt 1):805–821. http://dx.doi.org/10.1006/nimg.2000.0582.

Ashburner, J., Friston, K.J., 2001. Why voxel-based morphometry should be used. NeuroImage 14 (6):1238–1243. http://dx.doi.org/10.1006/nimg.2001.0961.

Bora, E., Harrison, B.J., Davey, C.G., Yucel, M., Pantelis, C., 2012. Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. Psychol. Med. 42 (4):671–681. http://dx.doi.org/10.1017/s0033291711001668.

Botteron, K.N., Raichle, M.E., Drevets, W.C., Heath, A.C., Todd, R.D., 2002. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biol. Psychiatry 51 (4):342–344. http://dx.doi.org/10.1016/S0006-3223(01)01280-X.

Caligiuri, M.P., Brown, G.G., Meloy, M.J., Eberson, S., Niculescu, A.B., Lohr, J.B., 2006. Striatopallidal regulation of affect in bipolar disorder. J. Affect. Disord. 91 (2–3): 235–242. http://dx.doi.org/10.1016/j.jad.2006.01.014.

Caracciolo, B., Giaquinto, S., 2002. Criterion validity of the Center for Epidemiological Studies Depression (CES-D) scale in a sample of rehabilitation inpatients. J. Rehabil. Med. 34 (5), 221–225.

Caruana, F., Gozzo, F., Pelliccia, V., Cossu, M., Avanzini, P., 2016. Smile and laughter elicited by electrical stimulation of the frontal operculum. Neuropsychologia 89:364–370. http://dx.doi.org/10.1016/j.neuropsychologia.2016.07.001.

Carvalho, J.P., 2011. Avoidance and Depression: Evidence for Reinforcement as a Mediating Factor. (PhD diss.). University of Tennessee http://trace.tennessee.edu/utk_graddiss/1172.

Cha, J., DeDora, D., Nedic, S., Ide, J., Greenberg, T., Hajcak, G., Mujica-Parodi, L.R., 2016. Clinically anxious individuals show disrupted feedback between inferior frontal gyrus and prefrontal-limbic control circuit. J. Neurosci. 36 (17):4708–4718. http://dx.doi.org/10.1523/JNEUROSCI.1092-15.2016.

Chen, Z., Peng, W., Sun, H., Kuang, W., Li, W., Jia, Z., Gong, Q., 2016. High-field magnetic resonance imaging of structural alterations in first-episode, drug-naive patients with major depressive disorder. Transl. Psychiatry 6 (11), e942. http://dx.doi.org/10.1038/tp.2016.209.

Cheng, Y., Xu, J., Yu, H., Nie, B., Li, N., Luo, C., ... Xu, X., 2014. Delineation of early and later adult onset depression by diffusion tensor imaging. PLoS One 9 (11), e112307. http://dx.doi.org/10.1371/journal.pone.0112307.

Chung, Y.S., Barch, D., 2015. Anhedonia is associated with reduced incentive cue related activation in the basal ganglia. Cogn. Affect. Behav. Neurosci. 15 (4):749–767. http://dx.doi.org/10.3758/s13415-015-0366-3.

Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213 (1–2):93–118. http://dx.doi.org/10.1007/s00429-008-0189-x.

Exner, C., Koschack, J., Irle, E., 2002. The differential role of premotor frontal cortex and basal ganglia in motor sequence learning: evidence from focal basal ganglia lesions. Learn. Mem. 9 (6):376–386. http://dx.doi.org/10.1101/lm.48402.

Foland-Ross, L.C., Sacchet, M.D., Prasad, G., Gilbert, B., Thompson, P.M., Gotlib, I.H., 2015. Cortical thickness predicts the first onset of major depression in adolescence. Int. J. Dev. Neurosci. 46:125–131. http://dx.doi.org/10.1016/j.ijdevneu.2015.07.007.

Griffiths, K.R., Lagopoulos, J., Hermens, D.F., Hickie, I.B., Balleine, B.W., 2015. Right external globus pallidus changes are associated with altered causal awareness in youth with depression. Transl. Psychiatry 5, e653. http://dx.doi.org/10.1038/tp.2015.148.

Haber, S.N., Calzavara, R., 2009. The cortico-basal ganglia integrative network: the role of the thalamus. Brain Res. Bull. 78 (2–3):69–74. http://dx.doi.org/10.1016/j.brainresbull.2008.09.013.

Harvey, P.O., Pruessner, J., Czechowska, Y., Lepage, M., 2007. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol. Psychiatry 12 (8):767–775. http://dx.doi.org/10.1038/sj.mp.4002021.

Hayakawa, Y.K., Sasaki, H., Takao, H., Mori, H., Hayashi, N., Kunimatsu, A., ... Ohtomo, K., 2013. Structural brain abnormalities in women with subclinical depression, as revealed by voxel-based morphometry and diffusion tensor imaging. J. Affect. Disord. 144 (3):263–268. http://dx.doi.org/10.1016/j.jad.2012.10.023.

Howell, N.A., Prescott, I.A., Lozano, A.M., Hodaie, M., Voon, V., Hutchison, W.D., 2016. Preliminary evidence for human globus pallidus pars interna neurons signaling reward and sensory stimuli. Neuroscience 328:30–39. http://dx.doi.org/10.1016/j.neuroscience.2016.04.020.

Hwang, J.W., Egorova, N., Yang, X.Q., Zhang, W.Y., Chen, J., Yang, X.Y., ... Kong, J., 2015. Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. Transl. Psychiatry 5, e683. http://dx.doi.org/10.1038/tp.2015.174.

Hwang, J.W., Xin, S.C., Ou, Y.M., Zhang, W.Y., Liang, Y.L., Chen, J., ... Kong, J., 2016. Enhanced default mode network connectivity with ventral striatum in subthreshold depression individuals. J. Psychiatr. Res. 76:111–120. http://dx.doi.org/10.1016/j.jpsychires.2016.02.005.

Jaworska, N., MacMaster, F.P., Yang, X.R., Courtright, A., Pradhan, S., Gaxiola, I., ... Ramasubbu, R., 2014. Influence of age of onset on limbic and paralimbic structures in depression. Psychiatry Clin. Neurosci. 68 (12):812–820. http://dx.doi.org/10.1111/pcn.12197.

Jezzini, A., Rozzi, S., Borra, E., Gallese, V., Caruana, F., Gerbella, M., 2015. A shared neural network for emotional expression and perception: an anatomical study in the macaque monkey. Front. Behav. Neurosci. 9:243. http://dx.doi.org/10.3389/fnbeh.2015.00243.

Kempton, M.J., Salvador, Z., Munafo, M.R., Geddes, J.R., Simmons, A., Frangou, S., Williams, S.C., 2011. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch. Gen. Psychiatry 68 (7):675–690. http://dx.doi.org/10.1001/archgenpsychiatry.2011.60.

Korten, N.C., Comijs, H.C., Lamers, F., Penninx, B.W., 2012. Early and late onset depression in young and middle aged adults: differential symptomatology, characteristics and risk factors? J. Affect. Disord. 138 (3):259–267. http://dx.doi.org/10.1016/j.jad.2012.01.042.

Lebedeva, A., Borza, T., Haberg, A.K., Idland, A.V., Dalaker, T.O., Aarsland, D., ... Beyer, M.K., 2015. Neuroanatomical correlates of late-life depression and associated cognitive changes. Neurobiol. Aging 36 (11):3090–3099. http://dx.doi.org/10.1016/j.neurobiolaging.2015.04.020.

Li, R., Ma, Z., Yu, J., He, Y., Li, J., 2014. Altered local activity and functional connectivity of the anterior cingulate cortex in elderly individuals with subthreshold depression. Psychiatry Res. 222 (1–2):29–36. http://dx.doi.org/10.1016/j.pscychresns.2014.02.013.

Li, H., Wei, D., Sun, J., Chen, Q., Zhang, Q., Qiu, J., 2015. Brain structural alterations associated with young women with subthreshold depression. Sci. Rep. 5:9707. http://dx.doi.org/10.1038/srep09707.

Macoveanu, J., Knorr, U., Skimminge, A., Sondergaard, M.G., Jorgensen, A., Fauerholdt-Jepsen, M., ... Kessing, L.V., 2014. Altered reward processing in the orbitofrontal cortex and hippocampus in healthy first-degree relatives of patients with depression. Psychol. Med. 44 (6):1183–1195. http://dx.doi.org/10.1017/S0033291713001815.

Mori, A., Okamoto, Y., Okada, G., Takagaki, K., Jinnin, R., Takamura, M., ... Yamawaki, S., 2016. Behavioral activation can normalize neural hypoactivation in subthreshold depression during a monetary incentive delay task. J. Affect. Disord. 208:670. http://dx.doi.org/10.1016/j.jad.2015.12.023.

Nitsche, M.A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., Tergau, F., 2003. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J. Cogn. Neurosci. 15 (4):619–626. http://dx.doi.org/10.1162/089892903321662994.

Ongür, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10 (3):206–219. http://dx.doi.org/10.1093/cercor/10.3.206.

Park, S.C., Hahn, S.W., Hwang, T.Y., Kim, J.M., Jun, T.Y., Lee, M.S., ... Park, Y.C., 2014. Does age at onset of first major depressive episode indicate the subtype of major depressive disorder?: the clinical research center for depression study. Yonsei Med. J. 55 (6):1712–1720. http://dx.doi.org/10.3349/ymj.2014.55.6.1712.

Phillips, M.L., Ladouceur, C.D., Drevets, W.C., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol. Psychiatry 13:833–857. http://dx.doi.org/10.1038/mp.2008.65.

Phillips, M.L., Chase, H.W., Sheline, Y.I., Etkin, A., Almeida, J.R., Deckersbach, T., Trivedi, M.H., 2015. Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches. Am. J. Psychiatry 172 (2):124–138. http://dx.doi.org/10.1176/appi.ajp.2014.14010076.

Pizzagalli, D.A., 2014. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annu. Rev. Clin. Psychol. 10:393–423. http://dx.doi.org/10.1146/annurev-clinpsy-050212-185606.

Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. Neuropsychopharmacology 35:192–216. http://dx.doi.org/10.1038/npp.2009.104.

Radloff, L.S., 1977. The CES-D scale a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1 (3):385–401. http://dx.doi.org/10.1177/014662167700100306.

Rao, J.A., Kassel, M.T., Weldon, A.L., Avery, E.T., Briceno, E.M., Mann, M., ... Weisenbach, S.L., 2015. The double burden of age and major depressive disorder on the cognitive control network. Psychol. Aging 30 (2):475–485. http://dx.doi.org/10.1037/pag0000027.

Schlund, M.W., Siegle, G.J., Ladouceur, C.D., Silk, J.S., Cataldo, M.F., Forbes, E.E., ... Ryan, N.D., 2010. Nothing to fear? Neural systems supporting avoidance behavior in healthy youths. NeuroImage 52 (2):710–719. http://dx.doi.org/10.1016/j.neuroimage.2010.04.244.

Seo, D., Olman, C.A., Haut, K.M., Sinha, R., MacDonald 3rd, A.W., Patrick, C.J., 2014. Neural correlates of preparatory and regulatory control over positive and negative emotion. Soc. Cogn. Affect. Neurosci. 9 (4):494–504. http://dx.doi.org/10.1093/scan/nst115.

Shen, Z., Cheng, Y., Yang, S., Dai, N., Ye, J., Liu, X., ... Xu, X., 2016. Changes of grey matter volume in first-episode drug-naive adult major depressive disorder patients with different age-onset. Neuroimage Clin 12:492–498. http://dx.doi.org/10.1016/j.nicl.2016.08.016.

Shinagawa, S., Babu, A., Sturm, V., Shany-Ur, T., Ross, P.T., Zackey, D., ... Rankin, K.P., 2015. Neural basis of motivational approach and withdrawal behaviors in neurodegenerative disease. Brain Behav. 5 (9), e00350. http://dx.doi.org/10.1002/brb3.350.

Spielberg, J.M., 2011. Moderation by Depression and Anxiety of Connectivity Among Brain Areas Associated With Motivation. (PhD diss). University of Illinois at Urbana-Champaign https://www.ideals.illinois.edu/handle/2142/26407.

Stratmann, M., Konrad, C., Kugel, H., Krug, A., Schoning, S., Ohrmann, P., ... Dannlowski, U., 2014. Insular and hippocampal gray matter volume reductions in patients with major depressive disorder. PLoS One 9 (7), e102692. http://dx.doi.org/10.1371/journal.pone.0102692.

Taber, K.H., Wen, C., Khan, A., Hurley, R.A., 2004. The limbic thalamus. J. Neuropsychiatr. Clin. Neurosci. 16 (2):127–132. http://dx.doi.org/10.1176/jnp.16.2.127.

Takagaki, K., Okamoto, Y., Jinnin, R., Mori, A., Nishiyama, Y., Yamamura, T., ... Yamawaki, S., 2014. Behavioral characteristics of subthreshold depression. J. Affect. Disord. 168: 472–475. http://dx.doi.org/10.1016/j.jad.2014.07.018.

Takahashi, K., Oshima, A., Ida, I., Kumano, H., Yuuki, N., Fukuda, M., ... Mikuni, M., 2008. Relationship between age at onset and magnetic resonance image-defined hyperintensities in mood disorders. J. Psychiatr. Res. 42 (6):443–450. http://dx.doi.org/10.1016/j.jpsychires.2007.05.003.

Taki, Y., Kinomura, S., Awata, S., Inoue, K., Sato, K., Ito, H., ... Fukuda, H., 2005. Male elderly subthreshold depression patients have smaller volume of medial part of prefrontal cortex and precentral gyrus compared with age-matched normal subjects: a voxel-based morphometry. J. Affect. Disord. 88 (3):313–320. http://dx.doi.org/10.1016/j.jad.2005.08.003.

Truong, W., Minuzzi, L., Soares, C.N., Frey, B.N., Evans, A.C., MacQueen, G.M., Hall, G.B., 2013. Changes in cortical thickness across the lifespan in major depressive disorder. Psychiatry Res. 214 (3):204–211. http://dx.doi.org/10.1016/j.pscychresns.2013.09.003.

Vasic, N., Plichta, M.M., Wolf, R.C., Fallgatter, A.J., Sosic-Vasic, Z., Gron, G., 2014. Reduced neural error signaling in left inferior prefrontal cortex in young adults with ADHD. J. Atten. Disord. 18 (8):659–670. http://dx.doi.org/10.1177/1087054712446172.

Vulser, H., Lemaitre, H., Artiges, E., Miranda, R., Penttilä, J., Struve, M., Fadai, T., Kappel, V., Grimmer, Y., Goodman, R., Stringaris, A., Poustka, L., Conrod, P., Frouin, V., Banaschewski, T., Barker, G.J., Bokde, A.L.W., Bromberg, U., Büchel, C., Flor, H., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Lawrence, C., Loth, E., Mann, K., Nees, F., Paus, T., Pausova, Z., Rietschel, M., Robbins, T.W., Smolka, M.N., Schumann, G., Martinot, J.-L., Paillère-Martinot, M.-L., 2015. for the IMAGEN Consortium, Subthreshold depression and regional brain volumes in young community adolescents. J. Am. Acad. Child Adolesc. Psychiatry 54 (10):832–840. http://dx.doi.org/10.1016/j.jaac.2015.07.006.

Wang, X., Wang, Z., Jian, L., Chen, J., Xian, L., Nie, G., ... Huang, R., 2016. Repeated acupuncture treatments modulate amygdala resting state functional connectivity of depressive patients. Neuroimage. Clin. 12:746–752. http://dx.doi.org/10.1016/j.nicl.2016.07.011.

Wang, Z., Wang, X., Liu, J., Chen, J., Liu, X., Nie, G., ... Liu, M., 2017. Acupuncture treatment modulates the corticostriatal reward circuitry in major depressive disorder. J. Psychiatr. Res. (16):30837–30838 pii: S0022-3956. 10.1016/j.jpsychires.2016.12.017.

Whittle, S., Lichter, R., Dennison, M., Vijayakumar, N., Schwartz, O., Byrne, M.L., ... Allen, N.B., 2014. Structural brain development and depression onset during adolescence: a prospective longitudinal study. Am. J. Psychiatry 171 (5):564–571. http://dx.doi.org/10.1176/appi.ajp.2013.13070920.

Yamamura, T., Okamoto, Y., Okada, G., Takaishi, Y., Takamura, M., Mantani, A., ... Yamawaki, S., 2016. Association of thalamic hyperactivity with treatment-resistant depression and poor response in early treatment for major depression: a resting-state fMRI study using fractional amplitude of low-frequency fluctuations. Transl. Psychiatry 6, e754. http://dx.doi.org/10.1038/tp.2016.18.

Young, K.A., Holcomb, L.A., Yazdani, U., Hicks, P.B., German, D.C., 2004. Elevated neuron number in the limbic thalamus in major depression. Am. J. Psychiatry 161 (7): 1270–1277. http://dx.doi.org/10.1176/appi.ajp.161.7.1270.

Young, K.D., Bellgowan, P.S., Bodurka, J., Drevets, W.C., 2013. Behavioral and neurophysiological correlates of autobiographical memory deficits in patients with depression and individuals at high risk for depression. JAMA Psychiat. 70 (7):698–708. http://dx.doi.org/10.1001/jamapsychiatry.2013.1189.

Zhang, X., Yao, S., Zhu, X., Wang, X., Zhu, X., Zhong, M., 2012. Gray matter volume abnormalities in individuals with cognitive vulnerability to depression: a voxel-based morphometry study. J. Affect. Disord. 136 (3):443–452. http://dx.doi.org/10.1016/j.jad.2011.11.005.

Zhao, Y.J., Du, M.Y., Huang, X.Q., Lui, S., Chen, Z.Q., Liu, J., ... Gong, Q.Y., 2014. Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. Psychol. Med. 44 (14):2927–2937. http://dx.doi.org/10.1017/S0033291714000518.

Zhou, H., Li, R., Ma, Z., Rossi, S., Zhu, X., Li, J., 2016. Smaller gray matter volume of hippocampus/parahippocampus in elderly people with subthreshold depression: a cross-sectional study. BMC Psychiatry 16:219. http://dx.doi.org/10.1186/s12888-016-0928-0.