Molecular, Functional, and Structural Imaging of Major Depressive Disorder

Kai Zhang^{1,2,3,4} · Yunqi Zhu^{1,2,3,4} · Yuankai Zhu^{1,2,3,4} · Shuang Wu^{1,2,3,4} ·
Hao Liu^{1,2,3,4} · Wei Zhang⁵ · Caiyun Xu^{1,2,3,4} · Hong Zhang^{1,2,3,4} · Takuya Hayashi⁶ ·
Mei Tian^{1,2,3,4}

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Abstract Major depressive disorder (MDD) is a significant cause of morbidity and mortality worldwide, correlating with genetic susceptibility and environmental risk factors. Molecular, functional, and structural imaging approaches have been increasingly used to detect neurobiological changes, analyze neurochemical correlates, and parse pathophysiological mechanisms underlying MDD. We reviewed recent neuroimaging publications on MDD in terms of molecular, functional, and structural alterations as detected mainly by magnetic resonance imaging (MRI) and positron emission tomography. Altered structure and function of brain regions involved in the cognitive control of affective state have been demonstrated. An abnormal default mode network, as revealed by resting-state functional MRI, is likely associated with aberrant metabolic

and serotonergic function revealed by radionuclide imaging. Further multi-modal investigations are essential to clarify the characteristics of the cortical network and serotonergic system associated with behavioral and genetic variations in MDD.

Keywords Major depressive disorder · Molecular imaging · Positron emission tomography · Magnetic resonance imaging · Functional connectivity · Serotonin

Introduction

Major depressive disorder (MDD) is one of the most common and costly mental disorders, with a lifetime prevalence of >16% [1] and an annual financial burden of >200 billion dollars in the USA [2]. According to the latest report, MDD has been ranked as the second medical condition with the greatest disease burden worldwide based on years lived with disability [3]. MDD is associated with numerous negative consequences, including health and social issues, among which suicide is the most devastating consequence attempted by as many as 8% of severe MDD patients [4]. Strikingly, only ~50% of MDD patients respond to standard-of-care antidepressants [5], with ~70% failing to achieve complete remission [6]. Thus, it is necessary to understand the potential mechanisms in order to explore more effective diagnostic and therapeutic strategies for MDD.

Over the past several decades, molecular, functional, and structural imaging approaches such as single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI), have been increasingly applied to elucidate the neurobiological mechanisms underlying MDD. Molecular

✉ Takuya Hayashi
takuya.hayashi@riken.jp

✉ Mei Tian
meitian@gmail.com

¹ Department of Nuclear Medicine, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310009, China

² Zhejiang University Medical PET Center, Hangzhou 310009, China

³ Institute of Nuclear Medicine and Molecular Imaging, Zhejiang University, Hangzhou 310009, China

⁴ Key Laboratory of Medical Molecular Imaging of Zhejiang Province, Hangzhou 310009, China

⁵ Department of Orthopedics, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310009, China

⁶ Functional Architecture Imaging Unit, RIKEN Center for Life Science Technologies, Kobe 650-0047, Japan

imaging is defined as the noninvasive, real-time visualization of biological processes at the cellular and molecular levels *in vivo* [7, 8]. SPECT and PET provide information on disease-specific molecular changes in the brain of MDD patients [9], and MRI provides information on brain structure, function and connectivity by using techniques of structural MRI and functional MRI (fMRI).

In this article, we present a selective review of molecular, functional and structural neuroimaging studies published since 2010. We describe the statistics from neuroimaging articles on MDD in the last 10 years, followed by a review of the reports using each neuroimaging modality, particularly structural MRI, resting-state fMRI, and metabolic and neurotransmitter PET and SPECT. Due to space limitations, we do not review papers that measured cerebral blood flow and task-related fMRI in MDD.

Statistics from Recent Neuroimaging Articles on MDD

To capture the trend of recent neuroimaging articles in MDD, we searched the PubMed database and made a publication area chart with the publication date ranging from Jan. 1, 2010 to Dec. 26, 2015. The PubMed database was searched using the retrieving field [Title/Abstract] for neuroimaging articles on MDD and the results were classified into multiple groups based on the type of neuroimaging technique, such as MRI, PET and SPECT, and multi-modal imaging (Fig. 1).

The search criteria were as follows. With regard to publications on MRI, the following search-string was chosen: (major depressive disorder OR major depression OR unipolar depression) AND (magnetic resonance imaging OR MRI); for publications on structural MRI, we added (structural OR structure) to the search-string of publications on MRI; for publications on fMRI, we added (function OR functional) to the search-string of publications on MRI; for resting-state fMRI and task fMRI, we added (rest OR resting) and (task OR tasking), respectively, while for publications on multi-modal fMRI, we added both (rest OR resting) and (task OR tasking). For publications on SPECT or PET, the search-string was as follows: (major depressive disorder OR major depression OR unipolar depression) AND (positron emission tomography OR single photon emission computed tomography OR radionuclide imaging OR PET OR SPECT); for publications on the aberrant serotonergic system in radionuclide imaging, we added (5-HT OR serotonin) to the search string of publications on PET or SPECT; for publications on multi-modal imaging with PET and MRI, we used (major depressive disorder OR major depression OR

Fig. 1 The publication trend of neuroimaging articles using PET, MRI, and/or multi-modal imaging approaches in MDD from 2006 to 2015. **a** Publication trend of articles using PET/SPECT, MRI and multi-modal imaging with PET/SPECT and MRI. **b** Publication trend of studies investigating functional and structural alterations using various MRI approaches. **c** Publication trend of articles using PET or SPECT in investigating serotonergic system or others

unipolar depression) AND (magnetic resonance imaging OR MRI) AND (positron emission tomography OR single photon emission computed tomography OR radionuclide imaging OR PET OR SPECT), and selected each paper using multi-modal imaging approaches in its methods by looking through its abstract.

The results of the PubMed search showed that the number of neuroimaging articles on MDD has increased rapidly in the past decade (Fig. 1a). In particular, the number of MRI studies in 2015 was double that in 2010 (~100 versus ~50), while the number of PET and SPECT

studies remained relatively stable. With regard to the details of MRI studies (Fig. 1b), structural MRI and resting-state MRI are becoming the major imaging methods. While the numbers of structural MRI and task fMRI studies are gradually increasing, the number of resting-state fMRI studies is increasing rapidly. In addition, the numbers of studies exploiting multiple (multi-modal) MRI techniques for understanding MDD have also increased. Among PET or SPECT studies, articles on serotonergic dysfunction seem to occupy the major part (Fig. 1c). Based on these statistics, we focused on reviewing articles using structural MRI, resting-state fMRI and PET or SPECT published since 2010.

MRI

MRI has the ability to characterize a wide range of imaging contrasts in living tissues, and visualizes tissue morphology and function *in vivo* with the use of magnetic field and radiofrequency [10]. The predominant superiority of MRI as a molecular imaging modality is its high spatial resolution (micrometers). Thus, morphological study of the brain has been a major interest in the field of MRI studies of MDD. Imaging techniques for morphological MRI include not only conventional structural MRI for evaluating regional gray matter volume but also the recent method of diffusion tensor MRI that captures microstructural changes in white matter. In addition, fMRI has emerged as a noninvasive approach that enables the monitoring neural activity changes based on the blood-oxygen-level-dependent signal [11]. In particular, resting-state fMRI is easy to perform and does not require any task performance. Structural MRI and resting-state fMRI are the major MRI modalities (Fig. 1b).

MR Imaging of Brain Morphology and Structure

A number of structural MRI studies of MDD have shown morphological abnormalities, mainly cortical thickness, gray matter volume, and white matter integrity [12–17], particularly in the frontal areas.

Voxel-based morphometry (VBM) is a powerful and objective approach that allows whole-brain assessment of anatomical abnormalities (for methodology, see [18]). Due to its simplicity of use, VBM has motivated many neuroscientists to characterize the specific abnormalities of gray-matter volume throughout the brain in MDD [15, 19, 20]. Recent meta-analysis of VBM in MDD has shown strong evidence of gray-matter volume reduction in the anterior cingulate cortex (ACC) [21–23]. The ACC is involved in multiple cognitive and affective functions, such as

decision-making [24], empathy [25], conflict-monitoring [26], working memory, attention, and information-processing [27]. Thus, structural alterations in the ACC may be associated with the affective and cognitive dysfunctions in MDD. Some studies have focused on the early morphological changes in first-episode, medication-naïve MDD patients [28–30]. A recent study in untreated, first-episode, mid-life MDD patients showed a modestly negative correlation between cortical thickness in the rostral middle frontal cortex and depression severity based on the Hamilton Depression Rating Scale (HDRS) [31] (Fig. 2), indicating that increased thickness might be present in milder cases or that it might represent a compensation for inflammatory factors or other aspects of the pathophysiology of MDD. Similarly, a recent, prospective, longitudinal study demonstrated that a thicker right caudal ACC at baseline is associated with greater symptom improvement over follow-up [32]. Besides, it has been reported that cortical thickness changes in the opposite direction over follow-up in MDD patients. Specifically, remitters showed increased while non-remitters showed decreased cortical thickness in several regions, indicating that structural recovery might occur only if patients respond to treatment. Interestingly, among the entire sample who received pharmacotherapy, only remitters showed increased hippocampal volume and cortical thickness in the rostral middle frontal gyrus, orbitofrontal cortex, and inferior temporal gyrus, whereas a previous study documented increased orbitofrontal cortical thickness in both remitters and non-remitters after antidepressant treatment [33]. Thus, it has been suggested that the reversible alterations in some frontal regions might be associated with remission itself or with antidepressant effects. The antidepressant-induced structural changes may be attributable to increased neuronal turnover, enhanced axonal and dendritic sprouting, synaptogenesis, increased numbers of glial cells, and a larger neuropil volume stimulated by antidepressants [32, 34]. But these conclusions need to be clarified in future studies.

Other VBM studies have also found structural abnormalities in regions including the insula, thalamus, and hippocampus in MDD patients [28, 35–43]. The anterior insula connects to the inferior frontal cortex and to the ACC [44]. It is thought to be involved in social-emotional and cognitive networks [45], and thus may play a crucial role in the neurobiology of MDD [42]. Similarly, given that the thalamus is connected to the cortex and to negative emotion-generating limbic structures such as the amygdala [38], the anomalous thalamic structure may account for deficits in the top-down regulation of negative affect in individuals with MDD. Moreover, the hippocampus is involved in memory function [46, 47]. MDD patients have a reduced hippocampal volume specific to the cornu

Fig. 2 Left regions with cortical thickness differences between MDD patients and healthy controls; significant cortical thickening in right rostral middle frontal gyrus and right supramarginal gyrus (red). Right scatterplots showing a negative correlation between cortical thickness

in the right rostral middle frontal gyrus and HDRS scores (right) [31]. (reprint permission was obtained from both the publisher and the corresponding author)

ammonis and dentate gyrus subfields [35]; this is probably due to stress-related or/and repeated neurotoxic processes associated with cumulative exposure to stress and depressive symptomatology [36, 37, 42].

It is critical to note that, in addition to gray-matter changes, altered white-matter integrity has also been reported in MDD using diffusion tensor imaging (DTI). DTI is a unique MRI approach that allows for noninvasive detection of the orientation and integrity of white-matter tracts *in vivo* by evaluating the diffusion of water molecules in neural tissue (for methodology, see [48]). One study reported reduced white-matter integrity, as measured by fractional anisotropy (FA), in the prefrontal white matter of MDD patients [49]. Another study reported decreased white-matter integrity in the right solitary fasciculus—a “bottom up” afferent pathway connecting the brainstem to the amygdala; this supports the hypothesis that brainstem-amygdala disconnection might be a potential mechanism of MDD [50]. Decreased white-matter integrity has also been identified in the corpus callosum, inferior fronto-occipital fasciculus, and left superior longitudinal fasciculus in MDD patients with melancholic and atypical features [51]. Intriguingly, one study showed that the FA value for anterior cingulate-limbic white matter is a predictor of the antidepressant treatment effect in MDD, i.e., patients with a higher FA in the cingulate and a lower FA in the stria terminalis are more likely to achieve remission [52].

Taken together, structural MRI studies using VBM and DTI have shown alterations in cortical thickness, gray-matter volume, and white-matter integrity in frontal and fronto-subcortical areas in MDD patients, which may explain some of the executive, behavioral, and emotional deficits. Furthermore, several specific abnormalities in certain areas, such as cortical thickness in the rostral middle frontal cortex and right caudal ACC, and white-matter integrity in the anterior cingulate-limbic system, may be applied to predict status severity, symptom improvement, and treatment effect.

MR Imaging of Resting-State Functional Connectivity

The last six years have witnessed a rapid increase in the number of resting-state fMRI studies on functional connectivity. Increased interest in this field has emerged from the hypothesis that the intrinsic and spontaneous activity is the essence of ‘default-mode’ brain function [53]. Advanced methods for analyzing functional connectivity using MRI (for review, see [54]), such as seed-based correlation analysis, independent component analysis, regional homogeneity, and amplitude of low-frequency fluctuations, have been increasingly used. Through these techniques, aberrant functional connectivity has been identified in MDD, such as in the salience network (SN) [55, 56], default mode network (DMN) [57–60], cognitive control

network (CCN) [59, 61], and affective network (AN) [60, 62]. The SN, predominantly consisting of the anterior insular cortex and dorsal ACC, serves to assess the correlation of internal and external stimuli to produce appropriate responses and direct behaviors [63]. Dysfunction of this network might account for the negative interpretation bias common in MDD [64]. The DMN, consisting of the posterior cingulate cortex and medial prefrontal cortex (PFC) as its core areas [65, 66] and the precuneus and temporo-parietal cortices, underlies the psychological process of introspection—the mind turning internally as it moves away from externally-concentrated thoughts [67–69]. A majority of studies have demonstrated that the DMN is hyperactive in MDD [70, 71], and this may account for the rumination states in MDD [72]. The CCN, consisting of the dorsolateral PFC and pregenual ACC [73, 74], is thought to be involved in the top-down modulation of attention and the regulation of emotional responses [75, 76]. Dysfunction of this network may explain the attention deficits and anhedonia in MDD. The AN, consisting of the amygdala and the subgenual and pregenual cingulate, has been implicated in appetite, libido, and sleep, so hyperactivity of this network may explain the vegetative disturbances in MDD patients [71].

Using resting-state fMRI, one study investigated the DMN, CNN, and AN simultaneously [71], and showed that all three networks had higher functional connectivity in MDD patients than in healthy controls. In addition, these networks had higher functional connectivity to the bilateral dorsal medial PFC (an area termed the dorsal nexus) in MDD patients than healthy controls, indicating that the dorsal nexus might explain the compromised concurrent and synergistic behaviors in MDD patients, like rumination and emotional and vegetative dysregulation. Intriguingly, it revealed that the PFC, ACC, and precuneus regions had significantly increased connectivity to the dorsal nexus in MDD patients *versus* controls (Fig. 3). Besides the above networks, other important functional connections exist. To explore the pattern of inter-hemispheric functional connectivity in MDD, Lai *et al.* [77] carried out an investigation in first-episode, medication-naïve patients with MDD using resting-state fMRI. They reported that patients presented lower inter-hemispheric connectivity in the anterior sub-network of the DMN (bilateral medial frontal cortex and ACC) and the cerebellar posterior lobe than healthy controls, and demonstrated that the strength of inter-hemispheric connectivity was inversely correlated with depression severity. This study indicated that the cerebellum might play a role in the DMN alterations, and this was further confirmed by a later investigation by Guo *et al.* [78].

Hence, it is supposed that MDD is a disorder with dysfunctional neural networks in numerous areas rather

than a disease of a single impaired region. Furthermore, the aberrant networks are capable of explaining at least part of the clinical symptoms. Interestingly, networks may show abnormal functional connectivity to the same brain nodes, which further adds our understanding of the concomitant symptoms of MDD patients. Meanwhile, altered functional connectivity values detected by resting-state fMRI have been used to evaluate the therapeutic effect of a diversity of treatments on MDD, such as specific pharmacological treatments, psychological treatment, transcranial magnetic stimulation, and electroconvulsive shock therapy [79–86]. To date, pharmacotherapy is still the dominant method for patients with MDD. Escitalopram, a selective serotonin reuptake inhibitor (SSRI), is one of the most common drugs for the treatment of MDD patients. One investigation explored the treatment effect of escitalopram in MDD using resting-state fMRI [87]. It presented a group-by-time interaction on functional connectivity strength (FCS) in the bilateral dorsomedial PFC and bilateral hippocampus, and that hyperconnectivity of the bilateral dorsomedial PFC occurred in MDD patients at baseline and subsequently decreased after treatment; on the contrary, the hypoconnectivity of the bilateral hippocampus at baseline in MDD patients subsequently increased after treatment. Moreover, FCS reduction in the dorsomedial PFC was significantly associated with symptom improvement. However, since the treatment outcomes of the SSRI class of antidepressants cannot be extrapolated to norepinephrine reuptake inhibitors [88–91], another study focused on the treatment effect of duloxetine—a dual serotonin-norepinephrine reuptake inhibitor—in MDD using MRI [92]. This study showed a group-by-time interaction in the anterior DMN in which MDD patients presented increased functional connectivity with treatment, and that reduced baseline resting-state connectivity in the orbitofrontal component of the anterior DMN is a predictor of greater clinical response.

Taken together, these findings suggest that antidepressants can modulate the disrupted intrinsic network connectivity in MDD patients, thus significantly adding to our understanding of the antidepressant effect at the circuit level and revealing feasible imaging-based biomarkers for the assessment of treatments for MDD. Hence, MRI has potential for aiding in predicting therapeutic effects and exploring prognostic biomarkers to accelerate the progress of treatment for MDD patients.

PET and SPECT

Radionuclide imaging approaches, including SPECT and PET, are molecular imaging modalities that utilize radio-labeled molecules to image the molecular interactions of biological processes *in vivo* [93]. They have the advantages

Fig. 3 Left connectivity maps from dorsal nexus to all the regions in the brain. Pictured are the lateral and medial surface functional connectivity of the left hemisphere for both healthy controls (a, b) and MDD patients (c, d). Significantly increased functional connectivity for MDD is evident. Right comparison of MDD and

control groups for mean resting-state connectivity between the dorsal nexus and the combined regions in dorsal lateral prefrontal cortex, precuneus, and subgenual anterior cingulate cortex ($P < 0.01$) [71]. (reprint permission was obtained from both the publisher and the corresponding author)

of high sensitivity and specificity to molecular targets in living subjects [94], and thus are capable of providing insight into molecular events *in vivo*, such as blood flow, glucose and oxygen metabolism [95], and neurotransmitters [96]. Compared with SPECT, PET has a higher sensitivity and relatively faster acquisition of dynamic data, along with the potential to quantify observations.

PET Imaging of Brain Metabolism

Using ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET, emerging evidence has shown that MDD patients undergo metabolic changes in the brain during the clinical course and therapeutic process. A recent voxel-based meta-analysis of neuroimaging studies using ^{18}F -FDG PET compared the cerebral metabolism in MDD patients with healthy controls [97]. The results showed that MDD patients had significantly lower regional cerebral glucose metabolism in the right caudate and cingulate cortex, left lentiform nucleus, putamen, and extra-nuclear (BA 13), and bilateral insula, whereas higher metabolism was detected in the right thalamus, pulvinar, declive of the posterior lobe, and left culmen of the vermis. It has been suggested that these dysfunctional regions might be associated with the pathophysiology of MDD. Moreover, the decreased metabolism in the basal ganglia, limbic system, and insula might be compensated by increased metabolism in the thalamus and cerebellum, in line with the hypothesis proposed in a previous study [98]. However, it is notable that the metabolic alterations in these regions have been reported in other mental illnesses such as schizophrenia [99], autism [100], and bipolar disorder [101]. Therefore, further studies are

required to investigate the specific dysfunctional regions involved in MDD.

In addition, several studies have focused on discovering the neural predictors of various therapies for MDD with ^{18}F -FDG PET imaging [102, 103]. Recently, Roffman *et al.* [102] investigated the neural correlates of short-term psychodynamic psychotherapy in MDD for the first time using this approach. They reported that the pretreatment glucose metabolism in the right posterior insula was markedly and positively correlated with depression severity (Fig. 4a). Moreover, among patients who completed treatment, a reduced depression score was associated with a pre- to post-treatment reduction in glucose metabolism in the right insula, which in turn was associated with a higher insight rating. These results indicated that the insula, a region paramount in regulating self-monitoring, is prominently implicated in the metabolic process underlying MDD. On the other hand, the pretreatment metabolism in the right precuneus was significantly higher in completers *versus* non-completers (Fig. 4b) and positively associated with psychological mindedness (Fig. 4c), suggesting that precuneus metabolism can be used to predict the therapeutic response with high sensitivity. Hence, all these findings showed that pretreatment glucose metabolism in specific regions such as the insula and precuneus may be of great value in predicting the response to diverse therapeutic methods.

PET and SPECT Imaging of Neurotransmitters

Emerging evidence has shown that the serotonergic system is involved in MDD [104, 105], mainly based on the

Fig. 4 Resting ^{18}F -FDG PET imaging in MDD patients with psychodynamic psychotherapy. **a** A significant positive correlation between pretreatment HDRS and regional cerebral glucose metabolism was identified in three clusters in and adjacent to the right posterior insula (yellow; $P < 0.05$, corrected for whole-brain volume). **b** Pretreatment regional cerebral glucose metabolism in the right precuneus was significantly higher in completers compared with non-completers (yellow; $P < 0.05$, corrected for whole-brain volume). **c** In all patients, pretreatment glucose metabolism in the right precuneus significantly and positively correlated with psychological mindedness ($\rho = 0.70$; $P = 0.002$) [102]. (reprint permission was obtained from both the publisher and the corresponding author)

antidepressant effect of SSRIs. Also, most antidepressant medications either directly or indirectly elevate serotonin (5-HT) transmission [106].

Among the various classes of 5-HT receptors, the 5-HT_{1A} receptor is most common in the brain and was the first to be successfully cloned. ^{11}C -WAY-100635 is an antagonist radioligand that binds equally to low- and high-

affinity 5-HT_{1A} receptors [107]. Using ^{11}C -WAY-100635 PET, Miller *et al.* [108] investigated changes in 5-HT_{1A} receptor binding, as well as its association with the standardized treatment effect of escitalopram in MDD patients. The authors demonstrated higher 5-HT_{1A} receptor binding in patients with MDD than controls in various regions such as the ACC, amygdala, dorsolateral PFC, and hippocampus,

consistent with previous studies in humans [109, 110] and animals [111, 112]. In addition, remitters to escitalopram had higher baseline 5-HT_{1A} receptor binding in the raphe nuclei than non-remitters. The 5-HT_{1A} receptor is an autoinhibitory autoreceptor located somatodendritically on serotonergic neurons in the raphe nuclei, as well as on target neurons throughout most brain regions. Thus, these findings suggest that higher 5-HT_{1A} receptor levels in the raphe nuclei lead to lower basal firing rates of serotonergic neurons, and thus lower 5-HT release. After several weeks of SSRI treatment, these raphe autoreceptors become desensitized, resulting in a progressive increase in the firing rates of serotonergic neurons and then increased 5-HT release. The increased 5-HT release united with the elevated serotonergic neurotransmission due to SSRIs demonstrates remission. Nevertheless, others have assumed that SSRIs cause downregulation, rather than desensitization, of the 5-HT_{1A} receptor [107]. Thus, to differentiate desensitization from downregulation, novel PET agonist radioligands that specifically bind to high-affinity 5-HT_{1A} receptors are required. The increase in 5-HT_{1A} receptors in MDD patients has been supported by Lemonde *et al.* [113] who explored the C(-1019)G 5-HT_{1A} promoter polymorphism in patients with MDD. They reported that the G allele was twofold enriched in depressed patients *versus* controls and fourfold enriched in suicide completers of whom 52% met the criteria for MDD. This was confirmed in later investigations [110, 114]. The higher-expressing G allele is considered to contribute to the overexpression of autoinhibitory somatodendritic 5-HT_{1A} receptors, resulting in reduced serotonergic neurotransmission.

The serotonin transporter (SERT), located on serotonergic neurons mainly in the dorsal raphe nuclei, is responsible for the modulation of released 5-HT via its reuptake from the extracellular space into presynaptic neurons [115]. Altered SERT has been reported in MDD patients [116–118], and has been considered to be involved in the pathophysiology of depression [119] and suicide [115]. Recently, a study by Yeh *et al.* [120] used N,N-dimethyl-2-(2-amino-4-[¹⁸F]fluorophenylthio) benzylamine (4-[¹⁸F]-ADAM) PET to investigate the association of SERT with suicide attempts in MDD patients. 4-[¹⁸F]-ADAM is a highly-selective radiotracer for assessing SERT availability [121]. The authors demonstrated that SERT availability in the midbrain, thalamus, and striatum was notably lower in the MDD group, and especially in the depressed suicidal group, than in the control group and assumed that these regions might be involved in the neuropathology of depression and subsequent suicidal behaviors in MDD patients. In addition, midbrain SERT availability was inversely correlated with depression severity on HDRS in the MDD group (Fig. 5), indicating that more severe symptoms of depression are associated

with lower SERT availability. These findings are similar but not identical to previous results [116–118, 122], probably due to heterogeneous demographic and clinical characteristics, different radioligands, and methodological differences. More importantly, they also reported that the depressed suicidal group had a higher PFC/midbrain SERT binding ratio than both the depressed non-suicidal and control groups (Fig. 6). These results suggest that an incongruent reduction of PFC SERT binding in the midbrain might distinguish depressed suicide-attempters from non-attempters among MDD patients and might be related to the pathophysiology of suicide behaviors. Taken together, these investigations elucidated that MDD is associated with abnormalities of the serotonergic system, and emphasized the vital role of the striatum and cortico-basal ganglia pathway in the neuropathology of affective disorders and subsequent suicide behaviors in patients with MDD [123].

On the other hand, genetic heritability is thought to play a paramount role in the occurrence of MDD, so a relevant family history is a potential risk factor for MDD. To explore whether differences in SERT availability exist between healthy individuals with and without familial risk, Hsieh *et al.* [124] initiated an investigation using ¹²³I-2-((dimethylamino) methyl) phenyl)thio)-5-iodophenylamine SPECT. They found that SERT availability in the midbrain was evidently lower in individuals with a first-degree family history of MDD than in healthy controls and hypothesized that midbrain SERT availability could be a promising marker for vulnerability to MDD. Whether the

Fig. 5 Inverse correlation between HDRS score and midbrain SERT BP_{ND}. It manifested an inverse correlation between HDRS and midbrain SERT BP_{ND}. SERT, serotonin transporter; BP_{ND}, binding potential of non-displaceable region [120]. (reprint permission was obtained from both the publisher and the corresponding author)

Fig. 6 The SERT BP_{ND} ratio between PFC and midbrain in depressed suicide, depressed non-suicide patients, and healthy controls. The ratio was significantly higher in the depressed suicide group than in both the depressed non-suicide patients and healthy controls ($P < 0.01$). Bars represent mean values. SERT, serotonin transporter; BP_{ND}, binding potential of non-displaceable region; PFC, prefrontal cortex [120]. (reprint permission was obtained from both the publisher and the corresponding author)

midbrain SERT availability is an endophenotype for MDD, however, remains to be further elucidated.

Based on these findings, it appears that an impaired serotonergic system is critically involved in the onset and progression of MDD. However, similar changes in the serotonergic system have also been reported in other neuropsychiatric disorders, such as schizophrenia [125]. Thus, the specificity of the changes remain an issue. In addition, besides involvement of the serotonergic system, abnormal neurotrophin signaling [4], aberrant expression of inflammatory cytokines [126, 127], and the dopaminergic system [128–130] are thought to contribute to the genesis of depression as well. Therefore, the occurrence and development of the disorder is a complex process involving multiple mechanisms. It is imperative to understand the specific mechanisms underlying MDD in order to precisely diagnose and develop targeted and effective treatment approaches.

Conclusions and Future Perspectives

Emerging evidence has revealed that brain structure and activity are significantly altered in MDD, particularly in regions involved in affective and behavioral control. Furthermore, monoamine-deficiency and abnormal networks may underlie MDD. Interestingly, there seems to be a

potential association between a dysfunctional serotonergic system and an abnormal DMN. These two major systems may play reciprocal and mutual roles in the cognitive control of affective state and dysfunctions in both may underlie the onset and progression of MDD. However, the mechanisms by which the serotonergic system is related to the DMN, or to other structural and functional network changes, need further clarification. In addition, more research is needed, particularly on exploring how potential imaging biomarkers are associated with behavioral and genetic variations, as well as with therapeutic effects.

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References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of dsm-iv disorders in the national comorbidity survey replication. *Archives of General Psychiatry* 2005, 62: 593–602.
2. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 2015, 76: 155–162.
3. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015, 386: 743–800.
4. Thompson SM, Kallarackal AJ, Kvarta MD, Van Dyke AM, LeGates TA, Cai X. An excitatory synapse hypothesis of depression. *Trends Neurosci* 2015, 38: 279–294.
5. Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Van Noord M, *et al.* Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med* 2011, 155: 772–785.
6. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv* 2009, 60: 1439–1445.
7. Fowler AM. A molecular approach to breast imaging. *J Nucl Med* 2014, 55: 177–180.
8. Weissleder R, Mahmood U. Molecular imaging. *Radiology* 2001, 219: 316–333.
9. James ML, Gambhir SS. A molecular imaging primer: modalities, imaging agents, and applications. *Physiol Rev* 2012, 92: 897–965.
10. Blamire AM. The technology of MRI—the next 10 years? *Br J Radiol* 2008, 81: 601–617.
11. Logothetis NK. The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc Lond B Biol Sci* 2002, 357: 1003–1037.
12. Tu PC, Chen LF, Hsieh JC, Bai YM, Li CT, Su TP. Regional cortical thinning in patients with major depressive disorder: a surface-based morphometry study. *Psychiatry Res* 2012, 202: 206–213.

13. Han KM, Choi S, Jung J, Na KS, Yoon HK, Lee MS, *et al.* Cortical thickness, cortical and subcortical volume, and white matter integrity in patients with their first episode of major depression. *J Affect Disord* 2014, 155: 42–48.
14. Reynolds S, Carrey N, Jaworska N, Langevin LM, Yang XR, Macmaster FP. Cortical thickness in youth with major depressive disorder. *BMC Psychiatry* 2014, 14: 83.
15. Grieve SM, Korgaonkar MS, Koslow SH, Gordon E, Williams LM. Widespread reductions in gray matter volume in depression. *Neuroimage Clin* 2013, 3: 332–339.
16. Nakano M, Matsuo K, Nakashima M, Matsubara T, Harada K, Egashira K, *et al.* Gray matter volume and rapid decision-making in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2014, 48: 51–56.
17. Qi H, Ning Y, Li J, Guo S, Chi M, Gao M, *et al.* Gray matter volume abnormalities in depressive patients with and without anxiety disorders. *Medicine (Baltimore)* 2014, 93: e345.
18. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *Neuroimage* 2000, 11: 805–821.
19. Machino A, Kunisato Y, Matsumoto T, Yoshimura S, Ueda K, Yamawaki Y, *et al.* Possible involvement of rumination in gray matter abnormalities in persistent symptoms of major depression: an exploratory magnetic resonance imaging voxel-based morphometry study. *J Affect Disord* 2014, 168: 229–235.
20. Depping MS, Wolf ND, Vasic N, Sambataro F, Thomann PA, Christian Wolf R. Specificity of abnormal brain volume in major depressive disorder: a comparison with borderline personality disorder. *J Affect Disord* 2015, 174: 650–657.
21. Bora E, Fornito A, Pantelis C, Yucel M. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord* 2012, 138: 9–18.
22. Lai CH. Gray matter volume in major depressive disorder: a meta-analysis of voxel-based morphometry studies. *Psychiatry Res* 2013, 211: 37–46.
23. Du MY, Wu QZ, Yue Q, Li J, Liao Y, Kuang WH, *et al.* Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2012, 36: 11–16.
24. Botvinick MM. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Behav Neurosci* 2007, 7: 356–366.
25. Decety J, Moriguchi Y. The empathic brain and its dysfunction in psychiatric populations: implications for intervention across different clinical conditions. *Biopsychosoc Med* 2007, 1: 22.
26. Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR, *et al.* fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *J Affect Disord* 2009, 118: 69–78.
27. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 1998, 280: 747–749.
28. Lai CH, Wu YT. Frontal-insula gray matter deficits in first-episode medication-naïve patients with major depressive disorder. *J Affect Disord* 2014, 160: 74–79.
29. Lai CH, Wu YT. The gray matter alterations in major depressive disorder and panic disorder: Putative differences in the pathogenesis. *J Affect Disord* 2015, 186: 1–6.
30. Zhao YJ, Du MY, Huang XQ, Lui S, Chen ZQ, Liu J, *et al.* Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. *Psychol Med* 2014, 44: 2927–2937.
31. Qiu L, Lui S, Kuang W, Huang X, Li J, Li J, *et al.* Regional increases of cortical thickness in untreated, first-episode major depressive disorder. *Transl Psychiatry* 2014, 4: e378.
32. Phillips JL, Batten LA, Tremblay P, Aldosary F, Blier P. A prospective, longitudinal study of the effect of remission on cortical thickness and hippocampal volume in patients with treatment-resistant depression. *Int J Neuropsychopharmacol* 2015, 18: pyv037.
33. Jarnum H, Eskildsen SF, Steffensen EG, Lundbye-Christensen S, Simonsen CW, Thomsen IS, *et al.* Longitudinal MRI study of cortical thickness, perfusion, and metabolite levels in major depressive disorder. *Acta Psychiatr Scand* 2011, 124: 435–446.
34. Leistedt SJ, Linkowski P. Brain, networks, depression, and more. *Eur Neuropsychopharmacol* 2013, 23: 55–62.
35. Malykhin NV, Coupland NJ. Hippocampal neuroplasticity in major depressive disorder. *Neuroscience* 2015, 309: 200–213.
36. MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, *et al.* Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc Natl Acad Sci U S A* 2003, 100: 1387–1392.
37. Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 2006, 16: 239–249.
38. Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology* 2010, 35: 192–216.
39. Jung J, Kang J, Won E, Nam K, Lee MS, Tae WS, *et al.* Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in Major Depressive Disorder: a voxel-based morphometry study. *J Affect Disord* 2014, 169: 179–187.
40. Liu CH, Jing B, Ma X, Xu PF, Zhang Y, Li F, *et al.* Voxel-based morphometry study of the insular cortex in female patients with current and remitted depression. *Neuroscience* 2014, 262: 190–199.
41. Opel N, Redlich R, Zwanzger P, Grotegerd D, Arolt V, Heindel W, *et al.* Hippocampal atrophy in major depression: a function of childhood maltreatment rather than diagnosis? *Neuropsychopharmacology* 2014, 39: 2723–2731.
42. Stratmann M, Konrad C, Kugel H, Krug A, Schoning S, Ohrmann P, *et al.* Insular and hippocampal gray matter volume reductions in patients with major depressive disorder. *PLoS One* 2014, 9: e102692.
43. Hagan CC, Graham JM, Tait R, Widmer B, van Nieuwenhuizen AO, Ooi C, *et al.* Adolescents with current major depressive disorder show dissimilar patterns of age-related differences in ACC and thalamus. *Neuroimage Clin* 2015, 7: 391–399.
44. Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. *Neuroimage* 2011, 55: 8–23.
45. Stephani C, Fernandez-Baca Vaca G, Maciunas R, Koubeissi M, Luders HO. Functional neuroanatomy of the insular lobe. *Brain Struct Funct* 2011, 216: 137–149.
46. Turner AD, Furey ML, Drevets WC, Zarate C, Jr., Nugent AC. Association between subcortical volumes and verbal memory in unmedicated depressed patients and healthy controls. *Neuropsychologia* 2012, 50: 2348–2355.
47. Kaymak SU, Demir B, Senturk S, Tatar I, Aldur MM, Ulug B. Hippocampus, glucocorticoids and neurocognitive functions in patients with first-episode major depressive disorders. *Eur Arch Psychiatry Clin Neurosci* 2010, 260: 217–223.
48. Sexton CE, Mackay CE, Ebmeier KP. A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry* 2009, 66: 814–823.
49. Li L, Ma N, Li Z, Tan L, Liu J, Gong G, *et al.* Prefrontal white matter abnormalities in young adult with major depressive disorder: a diffusion tensor imaging study. *Brain Res* 2007, 1168: 124–128.
50. Song YJ, Korgaonkar MS, Armstrong LV, Eagles S, Williams LM, Grieve SM. Tractography of the brainstem in major depressive disorder using diffusion tensor imaging. *PLoS One* 2014, 9: e84825.
51. Ota M, Noda T, Sato N, Hattori K, Hori H, Sasayama D, *et al.* White matter abnormalities in major depressive disorder with

- melancholic and atypical features: A diffusion tensor imaging study. *Psychiatry Clin Neurosci* 2015, 69: 360–368.
52. Korgaonkar MS, Williams LM, Song YJ, Usherwood T, Grieve SM. Diffusion tensor imaging predictors of treatment outcomes in major depressive disorder. *Br J Psychiatry* 2014, 205: 321–328.
 53. Raichle ME. The restless brain: how intrinsic activity organizes brain function. *Philos Trans R Soc Lond B Biol Sci* 2015, 370.
 54. Smith SM, Vidaurre D, Beckmann CF, Glasser MF, Jenkinson M, Miller KL, *et al.* Functional connectomics from resting-state fMRI. *Trends Cogn Sci* 2013, 17: 666–682.
 55. Liu CH, Ma X, Song LP, Tang LR, Jing B, Zhang Y, *et al.* Alteration of spontaneous neuronal activity within the salience network in partially remitted depression. *Brain Res* 2015, 1599: 93–102.
 56. Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, *et al.* Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Front Hum Neurosci* 2013, 7: 930.
 57. Sambataro F, Wolf ND, Pennuto M, Vasic N, Wolf RC. Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity. *Psychol Med* 2014, 44: 2041–2051.
 58. Chen Y, Wang C, Zhu X, Tan Y, Zhong Y. Aberrant connectivity within the default mode network in first-episode, treatment-naïve major depressive disorder. *J Affect Disord* 2015, 183: 49–56.
 59. Alexopoulos GS, Hoptman MJ, Kanellopoulos D, Murphy CF, Lim KO, Gunning FM. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J Affect Disord* 2012, 139: 56–65.
 60. Zeng LL, Shen H, Liu L, Wang L, Li B, Fang P, *et al.* Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain* 2012, 135: 1498–1507.
 61. Shen T, Li C, Wang B, Yang WM, Zhang C, Wu Z, *et al.* Increased cognition connectivity network in major depression disorder: a FMRI study. *Psychiatry Investig* 2015, 12: 227–234.
 62. Zhang X, Zhu X, Wang X, Zhu X, Zhong M, Yi J, *et al.* First-episode medication-naïve major depressive disorder is associated with altered resting brain function in the affective network. *PLoS One* 2014, 9: e85241.
 63. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 2007, 27: 2349–2356.
 64. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. *The American journal of psychiatry* 2012, 169: 693–703.
 65. Campbell KL, Grigg O, Saverino C, Churchill N, Grady CL. Age differences in the intrinsic functional connectivity of default network subsystems. *Front Aging Neurosci* 2013, 5: 73.
 66. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 2005, 102: 9673–9678.
 67. Posner J, Hellerstein DJ, Gat I, Mechling A, Klahr K, Wang Z, *et al.* Antidepressants normalize the default mode network in patients with dysthymia. *JAMA Psychiatry* 2013, 70: 373–382.
 68. Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biol Psychiatry* 2007, 61: 198–209.
 69. Fitzgerald PB, Oxley TJ, Laird AR, Kulkarni J, Egan GF, Daskalakis ZJ. An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. *Psychiatry Res* 2006, 148: 33–45.
 70. Nejad AB, Fossati P, Lemogne C. Self-referential processing, rumination, and cortical midline structures in major depression. *Front Hum Neurosci* 2013, 7: 666.
 71. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A* 2010, 107: 11020–11025.
 72. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev* 2009, 33: 279–296.
 73. Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, *et al.* Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neurosci Res* 2004, 50: 1–11.
 74. MacDonald AW, 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 2000, 288: 1835–1838.
 75. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 2002, 3: 201–215.
 76. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 2003, 54: 504–514.
 77. Lai CH, Wu YT. Decreased inter-hemispheric connectivity in anterior sub-network of default mode network and cerebellum: significant findings in major depressive disorder. *Int J Neuropsychopharmacol* 2014, 17: 1935–1942.
 78. Guo W, Liu F, Liu J, Yu M, Zhang Z, Liu G, *et al.* Increased cerebellar-default-mode-network connectivity in drug-naïve major depressive disorder at rest. *Medicine (Baltimore)* 2015, 94: e560.
 79. Fava M, Kendler KS. Major depressive disorder. *Neuron* 2000, 28: 335–341.
 80. Dichter GS, Gibbs D, Smoski MJ. A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *J Affect Disord* 2014, 172c: 8–17.
 81. Shen Y, Yao J, Jiang X, Zhang L, Xu L, Feng R, *et al.* Sub-hubs of baseline functional brain networks are related to early improvement following two-week pharmacological therapy for major depressive disorder. *Hum Brain Mapp* 2015, 36: 2915–2927.
 82. Oltedal L, Kessler U, Ersland L, Gruner R, Andreassen OA, Haavik J, *et al.* Effects of ECT in treatment of depression: study protocol for a prospective neuroradiological study of acute and longitudinal effects on brain structure and function. *BMC Psychiatry* 2015, 15: 94.
 83. Wang LJ, Kuang WH, Xu JJ, Lei D, Yang YC. Resting-state brain activation correlates with short-time antidepressant treatment outcome in drug-naïve patients with major depressive disorder. *J Int Med Res* 2014, 42: 966–975.
 84. Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe P, *et al.* Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder. *Neuropsychopharmacology* 2014, 39: 488–498.
 85. Crowther A, Smoski MJ, Minkel J, Moore T, Gibbs D, Petty C, *et al.* Resting-state connectivity predictors of response to psychotherapy in major depressive disorder. *Neuropsychopharmacology* 2015, 40: 1659–1673.

86. Weiduschat N, Dubin MJ. Prefrontal cortical blood flow predicts response of depression to rTMS. *J Affect Disord* 2013, 150: 699–702.
87. Wang L, Xia M, Li K, Zeng Y, Su Y, Dai W, *et al.* The effects of antidepressant treatment on resting-state functional brain networks in patients with major depressive disorder. *Hum Brain Mapp* 2015, 36: 768–778.
88. Lisiecka D, Meisenzahl E, Scheuerecker J, Schoepf V, Whitty P, Chaney A, *et al.* Neural correlates of treatment outcome in major depression. *Int J Neuropsychopharmacol* 2011, 14: 521–534.
89. Frodl T, Scheuerecker J, Schoepf V, Linn J, Koutsouleris N, Bokde AL, *et al.* Different effects of mirtazapine and venlafaxine on brain activation: an open randomized controlled fMRI study. *J Clin Psychiatry* 2011, 72: 448–457.
90. Outhred T, Hawkshad BE, Wager TD, Das P, Malhi GS, Kemp AH. Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: Implications for differential treatment efficacy. *Neurosci Biobehav Rev* 2013, 37: 1786–1800.
91. Wagner G, Koch K, Schachtzabel C, Sobanski T, Reichenbach JR, Sauer H, *et al.* Differential effects of serotonergic and noradrenergic antidepressants on brain activity during a cognitive control task and neurofunctional prediction of treatment outcome in patients with depression. *J Psychiatry Neurosci* 2010, 35: 247–257.
92. Fu CH, Costafreda SG, Sankar A, Adams TM, Rasenick MM, Liu P, *et al.* Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine. *BMC Psychiatry* 2015, 15: 82.
93. Phelps ME. PET: the merging of biology and imaging into molecular imaging. *J Nucl Med* 2000, 41: 661–681.
94. Jones T, Rabiner EA, Company PETRA. The development, past achievements, and future directions of brain PET. *J Cereb Blood Flow Metab* 2012, 32: 1426–1454.
95. Phelps ME. Positron emission tomography provides molecular imaging of biological processes. *Proc Natl Acad Sci U S A* 2000, 97: 9226–9233.
96. Laruelle M. Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. *J Cereb Blood Flow Metab* 2000, 20: 423–451.
97. Su L, Cai Y, Xu Y, Dutt A, Shi S, Bramon E. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. *BMC Psychiatry* 2014, 14: 321.
98. Sacher J, Neumann J, Funfstuck T, Soliman A, Villringer A, Schroeter ML. Mapping the depressed brain: a meta-analysis of structural and functional alterations in major depressive disorder. *J Affect Disord* 2012, 140: 142–148.
99. Baldacara L, Borgio JG, Lacerda AL, Jackowski AP. Cerebellum and psychiatric disorders. *Rev Bras Psiquiatr* 2008, 30: 281–289.
100. Luna B, Minshew NJ, Garver KE, Lazar NA, Thulborn KR, Eddy WF, *et al.* Neocortical system abnormalities in autism: an fMRI study of spatial working memory. *Neurology* 2002, 59: 834–840.
101. Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET. A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disord* 2011, 13: 1–15.
102. Roffman JL, Witte JM, Tanner AS, Ghaznavi S, Abernethy RS, Crain LD, *et al.* Neural predictors of successful brief psychodynamic psychotherapy for persistent depression. *Psychother Psychosom* 2014, 83: 364–370.
103. Conway CR, Chibnall JT, Gangwani S, Mintun MA, Price JL, Hershey T, *et al.* Pretreatment cerebral metabolic activity correlates with antidepressant efficacy of vagus nerve stimulation in treatment-resistant major depression: a potential marker for response? *J Affect Disord* 2012, 139: 283–290.
104. Elhwuegi AS. Central monoamines and their role in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2004, 28: 435–451.
105. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new ‘5-HT’ hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2011, 35: 702–721.
106. Neumeister A, Nugent AC, Waldeck T, Geraci M, Schwarz M, Bonne O, *et al.* Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. *Arch Gen Psychiatry* 2004, 61: 765–773.
107. Gray NA, Milak MS, DeLorenzo C, Ogden RT, Huang YY, Mann JJ, *et al.* Antidepressant treatment reduces serotonin-1A autoreceptor binding in major depressive disorder. *Biol Psychiatry* 2013, 74: 26–31.
108. Miller JM, Hesselgrave N, Ogden RT, Zanderigo F, Oquendo MA, Mann JJ, *et al.* Brain serotonin 1A receptor binding as a predictor of treatment outcome in major depressive disorder. *Biol Psychiatry* 2013, 74: 760–767.
109. Miller JM, Brennan KG, Ogden TR, Oquendo MA, Sullivan GM, Mann JJ, *et al.* Elevated serotonin 1A binding in remitted major depressive disorder: evidence for a trait biological abnormality. *Neuropsychopharmacology* 2009, 34: 2275–2284.
110. Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, *et al.* Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. *Biol Psychiatry* 2006, 59: 106–113.
111. Naudon L, El Yacoubi M, Vaugeois JM, Leroux-Nicollet I, Costentin J. A chronic treatment with fluoxetine decreases 5-HT(1A) receptors labeling in mice selected as a genetic model of helplessness. *Brain Res* 2002, 936: 68–75.
112. Shishkina GT, Kalinina TS, Dygalo NN. Serotonergic changes produced by repeated exposure to forced swimming: correlation with behavior. *Ann N Y Acad Sci* 2008, 1148: 148–153.
113. Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, *et al.* Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosci* 2003, 23: 8788–8799.
114. Neff CD, Abkevich V, Packer JC, Chen Y, Potter J, Riley R, *et al.* Evidence for HTR1A and LHPP as interacting genetic risk factors in major depression. *Mol Psychiatry* 2009, 14: 621–630.
115. Purselle DC, Nemeroff CB. Serotonin transporter: a potential substrate in the biology of suicide. *Neuropsychopharmacology* 2003, 28: 613–619.
116. Ho PS, Ho KK, Huang WS, Yen CH, Shih MC, Shen LH, *et al.* Association study of serotonin transporter availability and SLC6A4 gene polymorphisms in patients with major depression. *Psychiatry Res* 2013, 212: 216–222.
117. Miller JM, Hesselgrave N, Ogden RT, Sullivan GM, Oquendo MA, Mann JJ, *et al.* Positron emission tomography quantification of serotonin transporter in suicide attempters with major depressive disorder. *Biol Psychiatry* 2013, 74: 287–295.
118. Selvaraj S, Murthy NV, Bhagwagar Z, Bose SK, Hinz R, Grasby PM, *et al.* Diminished brain 5-HT transporter binding in major depression: a positron emission tomography study with [11C]DASB. *Psychopharmacology (Berl)* 2011, 213: 555–562.
119. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem* 1994, 40: 288–295.

120. Yeh YW, Ho PS, Chen CY, Kuo SC, Liang CS, Ma KH, *et al.* Incongruent reduction of serotonin transporter associated with suicide attempts in patients with major depressive disorder: a positron emission tomography study with 4-[18F]-ADAM. *Int J Neuropsychopharmacol* 2014, 18: pyu065.
121. Huang WS, Huang SY, Ho PS, Ma KH, Huang YY, Yeh CB, *et al.* PET imaging of the brain serotonin transporters (SERT) with N,N-dimethyl-2-(2-amino-4-[18F]fluorophenylthio)benzylamine (4-[18F]-ADAM) in humans: a preliminary study. *Eur J Nucl Med Mol Imaging* 2013, 40: 115–124.
122. Nye JA, Purselle D, Plisson C, Voll RJ, Stehouwer JS, Votaw JR, *et al.* Decreased brainstem and putamen SERT binding potential in depressed suicide attempters using [11C]-zient PET imaging. *Depress Anxiety* 2013, 30: 902–907.
123. Marchand WR, Lee JN, Johnson S, Thatcher J, Gale P, Wood N, *et al.* Striatal and cortical midline circuits in major depression: implications for suicide and symptom expression. *Prog Neuropsychopharmacol Biol Psychiatry* 2012, 36: 290–299.
124. Hsieh PC, Chen KC, Yeh TL, Lee IH, Chen PS, Yao WJ, *et al.* Lower availability of midbrain serotonin transporter between healthy subjects with and without a family history of major depressive disorder—a preliminary two-ligand SPECT study. *Eur Psychiatry* 2014, 29: 414–418.
125. Selvaraj S, Arnone D, Cappai A, Howes O. Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. *Neurosci Biobehav Rev* 2014, 45: 233–245.
126. Audet MC, Anisman H. Interplay between pro-inflammatory cytokines and growth factors in depressive illnesses. *Front Cell Neurosci* 2013, 7: 68.
127. Catena-Dell’Osso M, Rotella F, Dell’Osso A, Fagiolini A, Marazziti D. Inflammation, serotonin and major depression. *Curr Drug Targets* 2013, 14: 571–577.
128. Brunswick DJ, Amsterdam JD, Mozley PD, Newberg A. Greater availability of brain dopamine transporters in major depression shown by [99m Tc]TRODAT-1 SPECT imaging. *Am J Psychiatry* 2003, 160: 1836–1841.
129. Neumeister A, Willeit M, Praschak-Rieder N, Asenbaum S, Stastny J, Hilger E, *et al.* Dopamine transporter availability in symptomatic depressed patients with seasonal affective disorder and healthy controls. *Psychol Med* 2001, 31: 1467–1473.
130. Yang YK, Yeh TL, Yao WJ, Lee IH, Chen PS, Chiu NT, *et al.* Greater availability of dopamine transporters in patients with major depression—a dual-isotope SPECT study. *Psychiatry Res* 2008, 162: 230–235.