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REVIEW ARTICLE

# Imaging synaptic density in depression

Sophie E. Holmes[1], Chadi Abdallah[2,3] and Irina Esterlis[1,3,4]✉



Major depressive disorder is a prevalent and heterogeneous disorder with treatment resistance in at least 50% of individuals. Most of the initial studies focused on the monoamine system; however, recently other mechanisms have come under investigation. Specific to the current issue, studies show synaptic involvement in depression. Other articles in this issue report on reductions in synaptic density, dendritic spines, boutons and glia associated with stress and depression. Importantly, it appears that some drugs (e.g., ketamine) may lead to rapid synaptic restoration or synaptogenesis. Direct evidence for this comes from preclinical work. However, neuroimaging studies, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), have become useful in assessing these changes in vivo. Here, we describe the use of neuroimaging techniques in the evaluation of synaptic alterations associated with depression in humans, as well as measurement of synaptic restoration after administration of ketamine. Although more research is desired, use of these techniques widen our understanding of depression and move us further along the path to targeted and effective treatment for depression.

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## INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders worldwide, with an estimated 350 million individuals suffering from MDD globally [1]. MDD is characterized by a multitude of symptoms including sadness, anhedonia, and sleep disturbance, and is associated with a high rate of disability and suicide. Individuals with MDD also suffer from specific cognitive deficits, such as poor executive control and reduced learning and memory, which contribute to the poor long-term outcome of this disorder [i.e., higher rates of suicidality than the general population [2], higher rates of unemployment, and higher rates of comorbid substance use [3]] and can be treatment refractory. Although great efforts have been put forth to develop effective treatments via novel mechanisms, we are still not able to provide relief to a large proportion of individuals with MDD [4]. This is likely due to gaps in our understanding of the pathophysiology underlying MDD in living patients with the disorder. Initially, much focus was toward the examination of the monoamine system alterations in MDD due to the available technologies. More recently, we have been able to examine other systems in vivo, including synaptic density alterations, via the use of magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET), albeit via proxy measures. Synaptic plasticity (or synaptogenesis) is involved in every function of the brain including cognitive and emotional processes, sleep, and pain experiences. Alterations in synaptic density and plasticity have also been linked to pathophysiology and treatment of multiple neurobiological disorders, including depression and Alzheimer's disease. The goal of this review is to provide the reader with a limited review of how synaptic alterations can be measured in vivo in the human brain; although the reader must note that depression is a heterogenous disorder, many of the studies below are pilot in nature, and much more work and replication is required to provide definitive answers on the use of these technologies to quantify synaptic density in vivo.

## MAGNETIC RESONANCE TECHNIQUES TO INVESTIGATE SYNAPTIC FUNCTIONING

### Magnetic resonance imaging

Synaptic processes are essential for normal brain functioning and adaptation to new experiences [5]. Many of these processes have been related to psychopathology—especially synaptic fidelity, which is the postsynaptic outcome of a presynaptic signal under normal conditions [6]. Synaptic fidelity, a measure of the accuracy of synaptic signal processing, can be characterized into two response types: immediate and distant. The immediate response is primarily determined by synaptic strength, that is the amount of postsynaptic activation in response to presynaptic action potential. The distant response is the electrically silent synaptic plasticity that will affect future responses to presynaptic signals. This long-term adaptation is accomplished through synaptic scaling and potentiation/depression, often leading to concurrent changes in both synaptic density and strength [6]. Several functional, chemical and structural MRI measures have been related to these immediate and/or distant synaptic responses.

MRI measures of synaptic function are largely based on the fact that cerebral signaling consumes 80% of total brain energy, with the largest proportion of brain energetic needs being for glutamatergic action potentials (71%) and neurotransmitter cycling (9%) [7, 8]. As such, changes in glutamate synaptic density and strength directly affect brain energetics and subsequently the various signals of MR neuroimaging techniques. For example, increasing synaptic density and strength in the PFC will lead to higher energy and oxygen consumptions, as well as changes in

[1]Department of Psychiatry, Yale University, New Haven, CT, USA. [2]Baylor College of Medicine, Houston, TX, USA. [3]National Center for PTSD, Houston, TX, USA. [4]Department of Psychology, Yale University, New Haven, CT, USA. ✉email: irina.esterlis@yale.edu

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regional cerebral blood flow. Therefore, both immediate and distant responses of synaptic fidelity could alter functional MRI (fMRI) using blood-oxygen-level-dependent (BOLD) signal and arterial spin labeling [9, 10]. Similarly, changes in synaptic connectivity are believed to underly alterations in brain circuitry and large-scale networks. Functional connectivity MRI (fcMRI) investigates these brain circuits and networks by assessing the associations of BOLD signal throughout the brain. For example, estimates of functional connectivity strength (a.k.a., global brain connectivity) were found to be positively associated with regional cerebral blow flow [11, 12] and glutamate neurotransmission [13].

Synaptic density and strength can also be investigated more directly using MR spectroscopy combined with infusion of carbon-13 non-radioactive isotopes ($^{13}$C MRS) [14]. This technique may provide estimates of overall glutamate release and cycling ($V_{Cycle}$), neuronal energetic consumption ($V_{TCAn}$) and energy-per-cycle (EPC, that is $V_{TCAn}/V_{Cycle}$ ratio) [15]. The latter is a putative in vivo measure of overall synaptic fidelity. Higher synaptic density would be predicted to increase both glutamate cycling ($V_{Cycle}$) and energy consumption ($V_{TCAn}$). Higher synaptic strength may increase energy consumption ($V_{TCAn}$) and energy-per-cycle (EPC) [15]. Another MR technique that could assess synaptic function is proton MRS ($^{1}$H MRS), which may provide estimates of regional glutamate and GABA levels. The level of these aminoacids is thought to reflect average synaptic neurotransmission. For example, cortical glutamate level was found to be positively associated with glutamate cycling ($V_{Cycle}$) [16].

Finally, structural MRI (sMRI) estimates of gray matter morphometry are believed to be affected by underlying synaptic plasticity changes. Consistent with this hypothesis, preclinical studies have demonstrated a direct association between the extent of stress-induced reduction of spine density and dendritic length in the anterior cingulate cortex and hippocampus, and their respective volumes estimates by sMRI [17].

## Magnetic resonance findings of synaptic impairment in depression

While a systemic review of MR findings in depression is beyond the scope of the current paper, below we summarize a select set of studies examining the relationship between depression and various MR biomarkers, with focus on findings that illustrate the role of synaptic density and strength in the pathophysiology of chronic stress and depression.

Reduction in hippocampal volumes is one of the earliest and most replicated sMRI evidence of gray matter deficits in MDD and other stress-related disorders [18, 19]. Gray matter deficits were also reported in the PFC [20]. Conversely, preclinical chronic stress paradigms show increased synaptic density and strength in the amygdala and nucleus accumbens. These preclinical findings were paralleled by sMRI studies reporting larger amygdala and nucleus accumbens in patients with MDD [21]. Furthermore, preclinical data show ketamine induced synaptic density increases in hippocampus but reductions in the nucleus accumbens. These findings were also paralleled by increased hippocampal and reduced nucleus accumbens volumes in a pilot study in MDD patients who responded to ketamine treatment [22]. Similarly, other sMRI studies have demonstrated cortical gray matter deficits in MDD that were normalized following ketamine administration [23]. Traditional antidepressants were also found to increase prefrontal cortical thickness in MDD [24]. Together, these findings support the putative relationship between synaptic density and sMRI markers of gray matter. However, it is essential to note that sMRI is not a direct measure of synaptic density and potential confounds may affect the volumetric measures of sMRI.

Reduced global brain connectivity in the PFC is among the most reproducible fMRI finding in MDD [13, 25–29]. These GBC abnormalities in MDD are believed to reflect an underlying PFC reduction in synaptic density and strength [13]. Consistent with this hypothesis, ketamine was found to normalize the PFC GBC deficits in MDD at 24 h post treatment [13, 30, 31]. Notably, the ketamine induced PFC GBC normalization was associated with the antidepressant response [30, 31]. Traditional antidepressants were also found to increase PFC GBC in MDD patients [32]. Moreover, a direct relationship between GBC changes and synaptic glutamate neurotransmission was demonstrated using pharmacoimaging challenges in humans [13]. GBC abnormalities were also reported in several psychiatric disorders that are hypothesized to have alterations in synaptic density and strength [33–37]. Together, these data underscore the relationship between synaptic fidelity and fcMRI measures.

One of the most consistent $^{1}$H MRS findings in MDD is the reported reduction of cortical GABA levels [38], which tend to increase following treatment with antidepressants [39]. Cortical glutamate levels were altered in MDD. However, the results were mixed across studies with reports of increases, decreases or no changes in cortical glutamate levels [40–42]. These alterations in aminoacid neurotransmitters may reflect underlying changes in synaptic functions. A more direct measure of synaptic fidelity could be acquired using $^{13}$C MRS, which shows around 25% reduction in cortical energy production and energy-per-cycle (EPC) in patients with MDD compared to healthy control [16]. Comparable EPC reduction in PFC was also reported in patients with comorbid MDD and PTSD. Importantly, the relationship between EPC and synaptic fidelity was demonstrated using pharmacoimaging challenges in healthy and MDD participants [14].

## Magnetic resonance challenges and opportunities

The various findings described above highlight the utility of MRI techniques in investigating synaptic function in vivo in humans. However, these approaches have limitations that should be noted. Importantly, these MR findings are not specific to MDD. In fact, gray matter deficits, such as hippocampal volume reduction, were reported in majority of psychiatric disorders [43]. This lack of specificity represents both a strength and a limitation. It is a strength as it is further evidence relating MRI biomarkers to synaptic density, considering that chronic stress is a major component of these psychiatric disorders. Yet, it does limit their utility as diagnostic biomarkers. Another limitation is that non synaptic variables have large effects on these biomarkers. For example, BOLD signal may be affected by cardiovascular, respiratory and head motion variables. Therefore, it is essential to sufficiently account for these confound variables and mitigate their effects in the study design, data processing and analysis, and interpretation of findings. Multimodal approaches such as concurrent acquisition of EEG may address some of these limitations and has the added benefit of providing enhanced time resolution that could better capture the transient variabilities in synaptic alterations [44].

A main advantage of MRI approaches is the ability to assess the whole brain in vivo in humans. Animal models cannot fully model the complexity of depression or other psychiatric disorders. The preclinical evidence to date is primarily capturing the effects of trauma and chronic stress. In addition, majority of preclinical data have been limited to key brain regions, such as the PFC and hippocampus. While these regions have shown reduction in synaptic density, other brain regions show increases [5]. Furthermore, the human brain is considerably more developed than those investigated in preclinical studies, which are mostly conducted in rodents. It is critical for the field to expand its use of imaging—both mechanistic and challenge studies—to determine the functional and structural correlates of depression and the effects of novel treatments [45]. While synaptic dysconnectivity is common across stress disorders, the premise is the micro variability in synaptic alterations leads to diverging network disturbances and subsequently differing symptom presentations consistent with depression, anxiety or other psychiatric disorders [45, 46].

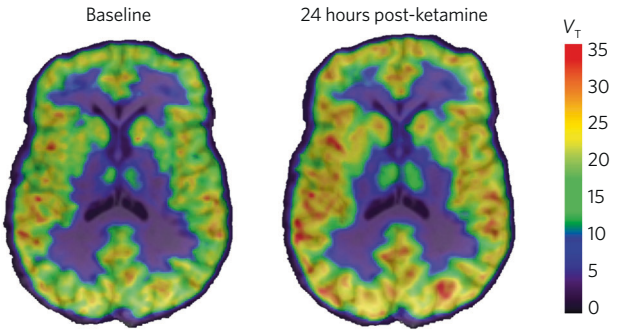


**Fig. 1 Parametric VT images for baseline and 24 hr post-ketamine scans for a representative participant with MDD and low baseline synaptic density levels.** Adapted from (1). VT: tissue-to-plasma concentration ratio at equilibrium and reflects total uptake (specific plus nonspecific binding) of the radioligand.

## HUMAN PET IMAGING

Postmortem and preclinical studies have provided invaluable insight into the neural basis, specifically the synaptic underpinnings, of depression. However, examining the synaptic mechanisms in humans in vivo will be crucial in gaining a complete understanding of depression. In 2016, imaging "synapses" became possible with the development of a radioligand—[$^{11}$C]UCB-J—which enables us to visualize synapses in the living brain. Specifically, [$^{11}$C]UCB-J binds to the protein synaptic vesicle glycoprotein 2 A (SV2A), which is expressed ubiquitously on nerve terminals throughout the brain, providing an indirect measure of synaptic density in humans in vivo. Indeed, our validation work shows that [$^{11}$C]UCB-J binding to SV2A is highly correlated with commonly used synaptic markers in postmortem and in vitro work (synapsin and PSD-95).

In the first in vivo study to investigate synaptic density in depression, we evaluated the relationship between [$^{11}$C]UCB-J binding and depression severity in a transdiagnostic sample of 26 individuals with MDD and/or PTSD, and compared to 21 healthy comparison (HC) subjects [47]. When the clinical groups were divided into high and low depression severity, it was apparent that those with the high severity of depression had most significant alterations in synaptic density. In fact, we observed a significant correlation between synaptic (SV2A) density and depression such that in the full sample, lower synaptic density was associated with higher depression severity in dlPFC, anterior cingulate cortex (ACC) and hippocampus—key regions associated with emotional regulation and cognitive control. Furthermore, all individuals participated in MRI and fMRI and our findings suggest that lower synaptic density in the dlPFC is associated with downstream network dysfunction (between dlPFC and PCC—key nodes of the central executive and default mode networks). This suggests that deficits in synaptic density in the clinical group could subserve some of the cognitive alterations observed in depression. These novel in vivo findings add to the literature implicating synaptic deficit as a substrate for depression in stress-related disorders and further incentivize the discovery and evaluation of interventions that target synaptic loss. It is important to know that while the density and spatial organization of synaptic connections is likely to have downstream effects on the functional reorganization of the brain, direct studies evaluating (and manipulating) synaptic density vs. function are warranted.

Of course, replication of pre-clinical and postmortem findings in vivo is important; however, determining whether the mechanism in question is actually implicated in symptom relief is crucial. As stated earlier, perhaps the most promising pharmacological treatment for depression in recent decades is ketamine, which exhibits synaptogenic properties in animal models of stress. Using [$^{11}$C]UCB-J PET, for the first time in vivo, we examined whether a single dose of ketamine resulted in an increase in synaptic density 24 h after administration in individuals with MDD and/or PTSD or HCs, as well as in non-human primates [48]. Overall, we found no detectible effect of ketamine on synaptic density, in MDD, PTSD, HCs or in non-human primates. However, an exploratory analysis showed that those individuals with MDD and/or PTSD who had the lowest synaptic (SV2A) density at baseline exhibited significantly increased synaptic density post-ketamine (Fig. 1). Further, this increase in synaptic density was associated with a reduction in depression severity, suggesting that synaptogenesis could underlie ketamine's therapeutic effects in humans. Our findings raise the question of whether the cytoarchitectural changes associated with ketamine are occurring primarily post-synaptically. Further work is needed to establish ketamine's likely nuanced effects on both pre- and post-synaptic mechanisms. Also important would be determining the *type* of synapses affected in depression. Studies combining [$^{11}$C]UCB-J PET with glutamatergic/GABAergic ligands or with MRS may shed light on the type of synapses affected. Determining how interventions such as ketamine target synapses, and which neurotransmitter systems are affected, will be crucial in the effective treatment of depression.

PET imaging has also been used to elucidate other markers of synaptic function in relation to depression. The metabotropic glutamate receptor 5 (mGluR5)—located primarily post-synaptically—plays a key role in synaptic plasticity and is thought to be associated with depression. Using [$^{18}$F]FPEB PET and MRS, we found no differences between control and MDD groups in mGluR5 availability [42]. Although this is not consistent with a smaller in vivo study previous to ours [49]. Importantly, for the first time in vivo, we observed a negative association between mGluR5 availability and tissue glutamate in the ACC [42], providing first evidence in vivo in human for the hypothesized excitotoxicity of receptors under conditions of elevated glutamate levels. We also showed that mGluR5 availability is reduced after a single dose of ketamine, likely due to rapid glutamate surge which leads to receptor internalization. Importantly, ketamine-induced mGluR5 downregulation was associated with an antidepressant response after a single dose [50] suggesting that mGluR5 is an important target for symptom changes.

[$^{18}$]FDG studies measuring glucose metabolism in MDD have generally shown dysfunction in regions of the limbic system and frontal lobes [51]. A coupling between glucose metabolism and synaptic density has been observed in cognitively normal and Alzheimer's disease (AD) participants [52]. Exploring the interplay between synaptic density and glucose metabolism in MDD would provide important information on the relationship between synaptic structure and function, and a more comprehensive understanding of synaptic dysfunction in depression.

## CONCLUSION

Although this review is limited in its focus on human neuroimaging work related to synaptic density in depression, it is clear from both preclinical and clinical research that multiple synaptic mechanisms underlie depression—and could therefore act as targets for new interventions. We are hopeful that through using translational research to guide clinical imaging studies—and by utilizing our imaging tools—that further critically-needed advances will be made in the effective treatment of depression. For example, combining PET imaging (ideally with multiple radioligands) with MR measures such as MRS and fMRI, will result in a more complete understanding of the synaptic and network-level underpinnings of depression. The goal is that this in turn will help in identifying the mechanisms of action of new interventions, and ultimately in guiding more targeted and effective treatments for depression.

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## AUTHOR CONTRIBUTIONS

SH prepared PET imaging portions of the manuscript and contributed to the overall flow. CA prepared the MR imaging portions of the manuscript and contributed to the overall flow. IE designed the project and oversaw manuscript preparation.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Irina Esterlis.