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HOT TOPICS

First in vivo evaluations of synaptic density alterations in the brain

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We have been aware of structural (neuronal, glial, etc.) changes associated with mental disorders; however, this knowledge stemmed from postmortem examinations, indirect neuroimaging measurements, or preclinical studies. The technological advancements that now allow us to quantify synaptic density in vivo in humans have sped our understanding of the neuropathophysiology of mental disorders. We are able to assess synaptic density alterations in vivo and relate to functionality via positron emission tomography (PET) and the radioligand [^{11}C]UCB-J, which binds to synaptic vesicle glycoprotein (SV2A), a marker of synaptic density [1].

Several groups have now published findings using this novel technology and report quantifications of in vivo alterations in synaptic density including in individuals with epilepsy [1], schizophrenia [2], cannabis use disorder [3], and Alzheimer's disease [4], in line with some of the previous postmortem findings (direct comparisons are difficult given the variability in regional assessments, medication use, and comorbidities). Our group focuses on mood and trauma disorders, which are thought to be underpinned in part by a loss of synaptic connections. We conducted the first in vivo examination of synaptic density across major depressive (MDD) and post-traumatic stress (PTSD) disorders [5]. Using PET, functional MRI, and cognitive and mood assessments in individuals with MDD and/or PTSD ($n = 26$) or healthy comparison ($n = 21$), we showed that deficits in synaptic density in the dlPFC, ACC, and hippocampus are a function of depression severity specifically (corrected for multiple comparisons). Unlike some other disorders, such as Alzheimer's disease, the synaptic density alterations detected in individuals with depression were widespread in the brain, which may contribute to the heterogenous symptomatology observed in MDD. Functionally relevant, we detected that synaptic density deficits in the dlPFC were associated with alterations in cognitive functioning and functional connectivity (secondary analyses, not corrected for multiple comparisons). These were the first in vivo findings directly relating synaptic deficits to functional disturbances in mood disorders.

Although these results are very exciting, the real test to the technological advancements is whether we can use these tools to help individuals suffering from disorders of the brain. Preclinical work conducted by the late Ronald Duman's group and others shows that a single dose of the NMDA receptor antagonist ketamine induces synaptogenesis in rats [6] (quantified via electron microscopy and synaptic density protein analyses, including SV2A). Whether this can be measured in vivo with PET and [^{11}C]UCB-J is yet to be determined; however, translating preclinical work to humans is crucial and would bring significant implications for precision medicine—if we can develop biomarkers of lower synaptic density and synaptogenesis to be used in the clinic, we can use tools such as PET to accelerate treatment for some disorders of the brain. Specific to the current topic, we might be able to predict which individuals with MDD may respond to rapid synaptogenic treatments like ketamine vs. other medicines that may have smaller and/or slower effects at the synapse or other targets. Although a lot more work needs to be done to efficaciously identify individuals who could benefit from certain therapies, the above studies provide hope.

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COMPETING INTERESTS

The authors have no competing interests.

ADDITIONAL INFORMATION

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