Synaptic dysfunction

Synaptic dysfunction results from alterations in cell-intrinsic molecular mechanisms or from changes in biochemical processes occurring in the surrounding environment.

Synaptic dysfunction is involved in schizophrenia pathophysiology. However, whether in vivo synaptic density is reduced in early stages of psychosis, including its high-risk states, remains unclear.

Objective: To investigate whether synaptic density (synaptic vesicle glycoprotein 2A [SV2A] binding potential) is reduced in first-episode psychosis (FEP) and clinical high-risk (CHR) and investigate the effect of cannabis use on synaptic density and examine its relationship with psychotic symptoms and gray matter microstructure across groups.

Design, setting, and participants: This cross-sectional study was performed in a tertiary care psychiatric hospital from July 2021 to October 2023. Participants were patients with antipsychotic-free or minimally exposed FEP or CHR and healthy controls with a clean urine drug screen (except cannabis).

Main outcomes and measures: Synaptic density was quantified with dynamic 90-minute [18F]SynVesT-1 positron emission tomography (PET) scans across prioritized brain regions of interest (ROIs) delineated in individual magnetic resonance images (MRIs). Cannabis use was confirmed with urine drug screens. Gray matter microstructure was assessed using diffusion-weighted MRI to estimate neurite density.

Results: A total of 49 participants were included, including 16 patients with FEP (mean [SD] age, 26.1 [4.6] years; 9 males and 7 females), 17 patients at CHR (mean [SD] age, 21.2 [3.5] years; 8 males and 9 females), and 16 healthy controls (mean [SD] age, 23.4 [3.6] years; 7 males and 9 females). Synaptic density was significantly different between groups ($F_{2,273} = 4.02$, $P = .02$, Cohen $F = 0.17$; ROI: $F_{5,273} = 360.18$, $P < .01$, Cohen $F = 2.55$) with a group × ROI interaction ($F_{10,273} = 2.67$, $P < .01$, Cohen $F = 0.32$). Synaptic density was lower in cannabis users ($F_{1,272} = 5.31$, $P = .02$, Cohen $F = 0.14$). Lower synaptic density across groups was associated with more negative symptoms (Positive and Negative Syndrome Scale negative scores: $F_{1,81} = 4.31$, $P = .04$, Cohen $F = 0.23$; Scale of Psychosis-Risk Symptoms negative scores: $F_{1,90} = 4.12$, $P = .04$, Cohen $F = 0.21$). SV2A binding potential was significantly associated with neurite density index ($F_{1,138} = 6.76$, $P = .01$, Cohen $F = 0.22$).

Conclusions and Relevance: This study found that synaptic density reductions were present during the early stages of psychosis and its risk states and associated with negative symptoms. The implications of SV2A for negative symptoms in psychosis and CHR warrant further investigation. Future studies should investigate the impact of cannabis use on synaptic density in CHR longitudinally [1)]

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Blasco MB, Nisha Aji K, Ramos-Jiménez C, Leppert IR, Tardif CL, Cohen J, Rusjan PM, Mizrahi R. Synaptic Density in Early Stages of Psychosis and Clinical High Risk. JAMA Psychiatry. 2024 Nov 13. doi: 10.1001/jamapsychiatry.2024.3608. Epub ahead of print. PMID: 39535765.