Obesity and persistent Inflammation associated with the reduction of hippocampal volume in older patients with schizophrenia

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Objectives: To test the hypotheses that inflammatory processes and obesity might affect hippocampal neurogenesis in schizophrenia.

Background & Aims: Schizophrenia (SCZ) and aging appear to be associated with inflammatory activation and reduced volume of hippocampus. We investigated the relationship among hippocampal volume, peripheral inflammatory markers, and clinical features in older patients with SCZ.

Subjects: We recruited out-patients who met the following criteria: (1) 50 to 75 years old, (2) clinically stable outpatient (in remission) without change in medication within the past 3 months, (3) a final diagnosis of schizophrenic disorder (DSM-IV),and (4) ability and willingness to provide informed consent. The exclusion criteria were: (1) fulfilling criteria for alcohol/substance use disorder, any type of dementia, mental disorders associated with general medical conditions, and any substance/alcohol use disorders, (2) having acute life-threatening/significant disease with intensive treatment, e.g., major stroke, (3) a history of autoimmune or any endocrine disease, a current infection or allergy, or the use of any medication possibly affecting cytokines, blood lipids, or endocrine levels, (4) inability to undergo brain imaging.

Methods: Brain MRI of each patient was performed using a 1.5-T MR scanner (Signa contour, GE-Yokogawa Medical Systems, Tokyo) with three pulse sequences: (1) 124 contiguous, 1.2-mm-thick axial planes of 3-dimensional, T1-weighted images (spoiled gradient recalled acquisition in the steady state, repetition time [TR] = 40 ms, echo time [TE] = 7 ms, flip angle = 90°, and voxel size = 0.86 mm × 0.86 mm × 1.2 mm); (2) 58 contiguous, 3-mm-thick axial planes of proton density images (spin echo [SE], TR = 2860 ms, TE = 15 ms, and voxel size = 0.86 mm × 0.86 mm × 3 mm); and (3) 58 contiguous, 3-mm-thick axial planes of T2-weighted images (SE, TR = 2860 ms, TE = 120 ms, and voxel size = 0.86 mm × 0.86 mm × 3 mm). We measured the plasma levels of soluble interleukin (IL)-2 receptor (sIL-2R), sIL-6R, IL-1β, and IL-1 receptor antagonist. Clinical data were obtained by reviewing medical records and personally interviewing.

Results: There were 29 patients with a mean age of 57.4 years in the study. The **left hippocampal volume** were significantly associated **with the PANNS scores, sIL-6R and partially associated with IL-1β level**. The **right hippocampal volume** was negatively associated **with the body mass index (BMI) and partially associated with age at illness onset**.

Stepwise regression showed that higher sIL-6R level and lower IL-1β level were related to a lower left hippocampal volume, accounting for 23.2% of the variance; higher BMI value and older at illness onset were related to a lower right hippocampal volume, accounting for 22.7% of the variance.

Discussion:

- 1.The results suggest that the reduction in hippocampal volume in people with schizophrenia is exaggerated in those who have high expression of inflammatory cytokines (IL-6 and IL-1β). Further, antipsychotic medication intake does not appear to ameliorate the reduction in hippocampal volume.
2. The circulating IL-6 and leptin levels may reflect the chronic inflammatory state associated with schizophrenia but further evaluation is required. Furthermore, it is important to consider the confounding effects of obesity in any examination of relationships between groups with regard to cytokines, adipokines, and brain volume loss.
- 3.Later illness onset associated with the lower right hippocampal may indicate the importance of considering the possibility of primary brain change with schizophrenia-like manifestation.

Conclusion:.

Persistent inflammation may be associated with reduction of hippocampal volume in older schizophrenic adults. **Neuroinflammation due to obesity and pathophysiology of mental illness may play a role of neuroprogression in SCZ across the life span.**

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Table 1. The relationship between hippocampal volumes and clinical variables

Demographic and clinical variables	Mean	SD	Hippocampus L		Hippocampus R	
			γ	p	γ	p
Age at study interview, yr	61.2	8.3	-0.18	0.33	-0.17	0.35
Education, yr	10.4	4.4	-0.16	0.39	0.05	0.81
BMI at study interview, Kg/m ²	27.09	5.43	-0.27	0.14	-.388*	0.028
Age at SCZ onset, yr	33.4	13.8	-0.28	0.12	-0.32	0.07
Lifetime duration of SCZ, yr	27.7	13.3	0.14	0.45	0.20	0.28
Lifetime all antipsychotics use, yr	7.6	10.2	-0.01	0.95	0.08	0.65
Lifetime FGA antipsychotics use, yr	5.1	9.2	-0.05	0.77	0.04	0.83
Lifetime SGA antipsychotics use, yr	2.5	3.1	-0.04	0.83	0.14	0.46
PANNS scores at study interview	1.2	2.7	-0.360*	0.043	-0.12	0.51
IL-1Ra, pg/mL	680.72	1556.74	0.12	0.57	0.19	0.38
IL-1β, pg/mL	2.73	1.17	0.34	0.07	0.36	0.06
sIL-2R, pg/mL	1172.37	193.94	-0.21	0.28	-0.17	0.37
sIL-6R, pg/mL	47732.20	13025.79	-.437*	0.018	-0.34	0.07
sTNF-R1, pg/mL	797.70	130.74	-0.15	0.45	0.00	1.00