Complement opsonin C1q protein and mRNA expression in prefrontal cortex in schizophrenia and bipolar disorder

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BACKGROUND

Schizophrenia (SCZ) and bipolar disorder (BD) are severe mental illnesses; SCZ is characterized by psychotic, negative, and cognitive symptoms, whereas BD is associated with mania and depression, leading to dramatic changes to one's mood that can impact a person' s ability to carry out simple everyday tasks.[1]

Both illnesses present with heterogenous symptoms among individuals, making diagnosis and treatment difficult. Research looking to elucidate pathophysiology among patients could lead to improved treatments.

GOALS

The complement system is a major player in the immune system and also plays a vital role in normal brain development and homeostasis[2], including regulation of neurogenesis, neuronal migration, synaptic pruning, and plasticity.[3] C1q is the initiating protein of complement's classical pathway and has been shown to tag vulnerable synaptic elements for microglial engulfment.[4] The complement system has been implicated in the pathophysiology of SCZ[5], leading to the hypothesis that levels of complement opsonins, including C1q, are increased in the disorder, contributing to synaptic dysfunction.

AIM: To determine whether C1q protein and mRNA expression is altered in the brain in SCZ and BD.

METHODS

Sample: Frozen tissue comprising prefrontal cortex from control (n=35), SCZ (n=35) and BD (n=34) subjects. Demographics are listed in **Table 1.**

Procedures: Western blotting was utilized to determine C1q protein levels (single chain), with values normalized against total protein. qPCR with SYBR green detection was utilized to quantify C1qB mRNA expression. Normalization was performed by geometric averaging of internal controls GAPDH and TBP.

Statistics: Normality tests were performed in SPSS, followed by univariate ANCOVA to examine differences in expression levels between groups. Planned contrasts were utilized to compare control to SCZ and control to BD. Associations with potential confounders were evaluated with Spearman's Rank correlations.

TABLE 1. DEMOGRAPHICS

Group	N	Sex#	Mean Age (years)	Mean PMI (hours)	Mean BMI	Mean pH	Mean RIN	Mean Age of Onset (years)	Mean Illness Duration (months)	Antipsychotics (mean lifetime dose, cpze)	Smoker (y/n)
SCZ	35	9F 26M	42.6	31.4	31.5	6.5	7.4	21.3	21.3	85004	23/4
CON	35	9F 26M	44.2	29.4	30.9	6.6	7.2	N/A	N/A	N/A	9/9
BD	34	18F 16M	45.4	37.9	28.9	6.4	7.3	25.3	20.1	10212	15/6

#Female (F), Male (M)

RESULTS

The C1q protein is made of 16 polypeptide chains (6A, 6B, 6C), arranged as 3 subunits of 6 chains, with molecular weight ~460kDa (**Figure 1**). Western blots (**Figure 2**) resolve the individual chains at ~25kDa, dimers at ~50kDa, trimer ~75kDa, and the full subunit (ABC-CBA doublet) at ~150kDa.

FIGURE 1. C1q DIAGRAM

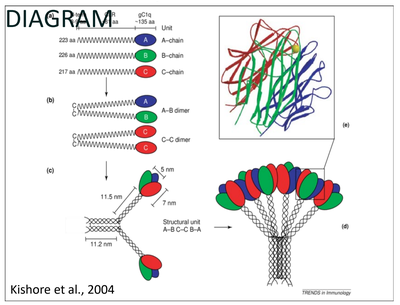
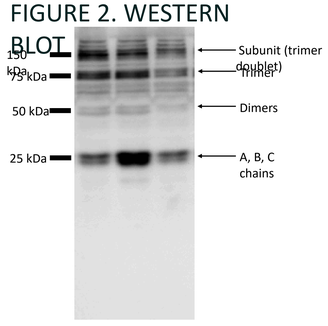


FIGURE 2. WESTERN BLOT



RESULTS

C1qB mRNA Expression (**Figure 3**): In comparing C1qB mRNA, both the ANCOVA and the planned contrasts showed that the difference between groups was not significant (p>0.05).

C1q Protein Expression (**Figure 4**): ANCOVA showed that differences between groups were not significant (p=0.11). However, planned contrasts showed that C1q protein was significantly higher in the SCZ group compared to the controls (p=0.043).

FIGURE 3. C1qB mRNA EXPRESSION

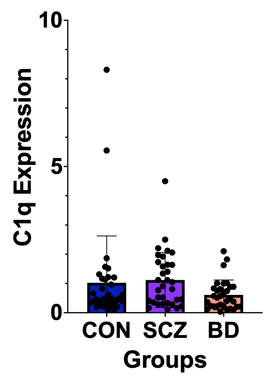
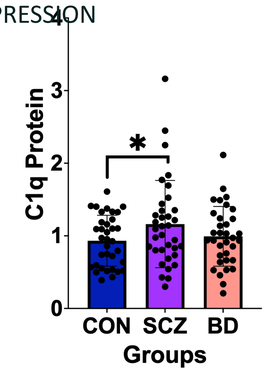


FIGURE 4. C1q PROTEIN EXPRESSION



Potential Confounders: C1qB mRNA was correlated with PMI (p<0.01) C1q protein was significantly correlated with serum C-reactive protein (CRP) (p<0.01). Neither C1qB mRNA nor protein were correlated with age, BMI, pH, age of onset, illness duration, or RIN (p>0.05). No impacts of sex, suicide, or smoking were found.

SNAP-25: C1q protein was significantly correlated with SNAP-25 (p=0.005), a synaptic SNARE protein used as a marker of pre-synaptic density.

RESULTS

Medication: The majority of SCZ and BD subjects were prescribed mood stabilizers (SCZ=11/35, BD=23/34) and/or antidepressants (SCZ=9/35, BD=19/34) at the time of death, while all SCZ subjects and 23/34 BD subjects had a history of antipsychotic use. Neither C1q mRNA nor protein were correlated with lifetime antipsychotic dose (p>0.05). No impacts of mood stabilizer or antidepressant prescription were found.

CONCLUSIONS

C1q protein was significantly higher in the SCZ group compared to controls. C1qB mRNA did not differ between groups.

A significant relationship between C1q protein and serum CRP levels, a marker of peripheral inflammation, was observed. Further, a significant correlation between C1q and SNAP-25, a synaptic SNARE protein was observed.

Further studies are required to fully elucidate the role of neuroinflammation and complement opsonins in SCZ, and their impacts on synaptic density.

REFERENCES

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