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An examination of plasma autoantibodies against voltage gated calcium channels in schizophrenia

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ABSTRACT

Autoantibodies targeting the central nervous system have been shown to induce psychiatric symptoms resembling schizophrenia. Concurrently, genetic studies have characterised a number of risk variants associated with schizophrenia although their functional implications are largely unknown. Any biological effects of functional variants on protein function may potentially be replicated by the presence of autoantibodies against such proteins. Recent research has demonstrated that the R1346H variant in the CACNA1I gene coding for the Cav 3.3 protein results in a synaptic reduction of Cav3.3 voltage gated calcium channels and, consequently, sleep spindles, which have been shown to correlate with several symptom domains in patients with schizophrenia. The present study measured plasma levels of IgG against two peptides derived from CACNA1I and CACNA1C, respectively, in patients with schizophrenia and healthy controls. The results demonstrated that increased anti-CACNA1I IgG levels were associated with schizophrenia but not associated with any symptom domain related to the reduction of sleep spindles. In contrast to previously published work indicating that inflammation may be a marker for a depressive phenotype, plasma levels of IgG against either CACNA1I or CACNA1C peptides were not associated with depressive symptoms, suggesting that anti-Cav3.3 autoantibodies may function independently of pro-inflammatory processes.

1. Introduction

Schizophrenia is a complex mental health disorder characterised by a constellation of symptoms including delusions, hallucinations, cognitive deficits, anhedonia and changes in speech affect. These symptoms are organised into several domains including positive, negative, depressive, manic and cognitive symptoms (Keeley and Gaebel, 2017). Although the pathophysiology of schizophrenia remains unknown, alterations in neurotransmitter function and structural changes in the brain suggest that an altered profile of cortical connectivity may underlie at least some of the symptoms of schizophrenia (Abi-Dargham et al., 1998; Baker et al., 2018; Shepherd et al., 2012). Dysfunction of the immune system has long been observed in patients with schizophrenia, with population studies suggesting an increased risk of autoimmune disease in patients with schizophrenia (Benros et al., 2011); convincing evidence suggests that a pro-inflammatory immune profile is associated with negative, particularly depressive, symptoms in schizophrenia (Fernandez-Egea et al., 2016; Goldsmith et al., 2019; Khandaker et al., 2015).

The discovery that IgG antibodies against N-methyl-d-aspartate receptors (NMDAR) are capable of inducing the symptoms of schizophrenia has been hailed as seismic as it demonstrates that IgG antibodies targeting the central nervous system (CNS) are capable of inducing a pathological condition, anti-NMDAR autoimmune encephalitis, which has been occasionally misdiagnosed as schizophrenia (Bartley and Ross, 2020; Dalmau et al., 2011). Since then, a number of autoantibodies targeting proteins in the CNS have been found to be associated with schizophrenia, including antibodies against the muscarinic acetylcholine receptor (mAChR), the gamma-aminobutyric acid (GABA) receptor, synapsin, and tetratricopeptide repeat and ankyrin repeat containing 1 (TRANK1) (Haussleiter et al., 2017; Höltje et al., 2017; Lennox et al., 2017; Whelan et al., 2018). The pathogenic impact of these autoantibodies is currently unclear, although studies of patients with anti-NMDAR encephalitis revealed that, upon binding to the receptor, anti-NMDAR IgG induced the internalisation of NMDAR, reducing its

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Table 1
The median levels of plasma IgG against CACNA1I and CACNA1C peptides.

Antigen	Control (n)		Case (n)		Z	p-value
	Median (344)	IQR	Median (257)	IQR		
CACNA1I	**1.245**	**1.15–1.37**	**1.352**	**1.25–1.47**	**−6.862**	**<0.001**
CACNA1C	1.160	1.10–1.22	1.154	1.09–1.22	−1.122	0.262

The median level of plasma IgG against CACNA1I was significantly higher in individuals with schizophrenia when compared to non-psychiatric controls. The median level of IgG against CACNA1C was not significantly different between the groups. The cut-off for statistical significance was $p < 0.05$. IQR = Interquartile Range.

availability at synapses (Masdeu et al., 2016).

A genome-wide association (GWA) study of schizophrenia confirmed that 108 genetic loci, harbouring >300 genes, were strongly associated with Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Although the functional implications of most loci identified in this study are yet to be elucidated, and an additional GWA study has recently identified more loci of interest (Trubetskoy et al., 2022), studies building on these findings have uncovered novel mechanisms and identified new mutations that may play a role in the development of schizophrenia (Sekar et al., 2016). Exome sequencing of family trios with 105 schizophrenia probands identified two missense mutations in the CACNA1I gene that encodes the α1 subunit of Cav3.3, a member of the Cav3 voltage gated calcium channel family (Gulsuner et al., 2013). This gene was later validated as a locus of interest by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). A subsequent study demonstrated that the expression of one of these mutants, R1346H, in human cell lines was associated with reduced synaptic protein expression of Cav3.3 (Andrade et al., 2016). Recently, the expression of the R1346H variant in a rodent model was shown to result in sleep spindle deficits during non-rapid-eye-movement sleep (Ghoshal et al., 2020).

Sleep spindle deficits have been reported to be associated with schizophrenia in both medicated and antipsychotic-naïve patients, and therefore may be an endophenotype of schizophrenia (Manoach et al., 2014; Wamsley et al., 2012). Disruptions of sleep are very common in patients with schizophrenia and sleep deprivation is well known to induce hallucinations in non-psychiatric individuals (Waite et al., 2020; Waters et al., 2018). Finally, reduced sleep spindle formation has been found to be correlated with measures of positive symptoms, executive function and measures of IQ in patients with schizophrenia (Manoach et al., 2014).

Causative risk alleles have proven difficult to isolate from genetic studies of schizophrenia, but if the identified gene variants are able to influence protein function, as with the R1346H identified in the CACNA1I locus, an antibody directed against the protein of interest may be able to replicate such functional alterations, meaning that the autoantibody against that protein may potentially contribute to disease development in a similar manner to the genetic variant. As such, examining IgG against known schizophrenia risk variants identified may be a promising approach for the discovery of disease-related autoantibodies. The present study examined the levels of circulating IgG antibodies against the peptide antigens derived from CACNA1I and CACNA1C proteins in plasma samples from patients with schizophrenia and healthy controls using an enzyme-linked immunosorbent assay (ELISA) developed in-house. Additionally, due to symptom associations with sleep spindle deficits, plasma levels of IgG against these peptides were examined for their association with positive symptoms, cognitive symptoms, sleep deficits as well as depressive symptoms in individuals with schizophrenia.

2. Materials and methods

2.1. Study samples

All the samples used for this study were collected through the University of Aberdeen and NHS Grampian, Aberdeen, UK, in the period between 2002 and 2008, and stored at the Grampian Biorepository. Plasma samples were separated from whole blood by centrifugation using a routine protocol and then aliquoted before storage at −80 °C until use. This study used the plasma samples from 247 patients with schizophrenia (mean aged 40 ± 13 years) and 344 non-psychiatric controls (aged 44 ± 12 years). The case subjects were identified through psychiatric hospitals or outpatient facilities, and the control subjects, recruited from local communities. were screened for psychiatric disorders. A family history of mental illness was obtained by a self-reporting questionnaire. All case samples met the DSM-IV criteria for a diagnosis of schizophrenia and all participants were of British Caucasian origin. All participants gave written consent to donating their blood samples for genetic and serological analyses. The study was approved by local ethics committees (NREC references: 13/13/NS/0125 and 21/PR/0858) and conformed to the Declaration of Helsinki and its amendments.

Supplementary Table 1 lists the available demographic data for the samples used in this study. The case group was more female and older than the control group ($p < 0.05$). Information on the medication status was not available for all participants in this study but the available medication information is given in Supplementary Table 2. Similarly, the patient database contains symptom information in the form of the Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT) (McGuffin, 1991), although a full checklist of symptom information was not available for all patients.

2.2. Peptide antigens

CACNA1I and CACNA1C were selected from the list of genes proximal to schizophrenia-associated loci confirmed by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Sequences for Cav3.3 and Cav1.2, encoded by CACNA1I and CACNA1C genes, respectively, were retrieved from the NCBI database (https://www.ncbi.nlm.nih.gov/). The amino-acid sequences were analysed through computational prediction for HLA-II restricted and B-cell epitopes (http://www.iedb.org). Twelve HLA-DRB1 alleles, the most common alleles in a European-derived Caucasian population, were used for the HLA-II epitope prediction (de Bakker et al., 2006). Two resulting peptides derived from CACNA1I (RYYNVCRTGSA**N**PHKGAINFDNIGY) and CACNA1C (QNGTVCKPGWDGPKHGITNFDNFAFA) were respectively synthesised by solid phase chemistry to a purity >95% (Mimotopes, Australia).

2.3. In-house ELISA

In order to measure plasma levels of IgG against the peptides antigens derived from CACNA1I and CACNA1C proteins, an in-house ELISA was developed, as previously detailed (McLean et al., 2017). Briefly, the synthetic peptides were coated to a sulfhydryl 96-well plate (Corning, USA) at 20 μg/mL and incubated for 1.5 h at room temperature. Following wash in triplicate, unbound sulfhydryl groups were blocked using 10 μg/mL of freshly reconstituted L-cysteine (VWR, USA), and the peptide-coated plates were then dried at 40 °C and stored at 4 °C until use within six months. 50 μl plasma diluted 1:150 in assay buffer was

added to each well on the plate. Following a 1.5-h incubation period and washing steps, 50 μl HRP-conjugated anti-human IgG antibody (Abcam, UK), diluted 1:50,000 in assay buffer, was added to each well followed by 1 h incubation. A colour change was visualised using 50 μl of 3, 3′,5, 5′-Tetramethylbenzidine (TMB) (Sigma-Aldrich, USA) with incubation for 20 min, followed by adding 25 μl of commercial stop solution (Sigma-Aldrich, USA). The optical density (OD) was then measured using a Varioskan Lux plate reader (Thermofisher, USA). Each sample was tested in duplicate; a peptide derived from a maize protein was used as the control antigen for non-specific binding background and assay buffer was used as negative control (NC). A specific binding index (SBI) was used as a measure of relative IgG levels to present the data and was calculated according to the following formula:

$$SBI = \left[OD_{Antigen} - OD_{NC}\right] / \left[OD_{maize} - OD_{NC}\right]$$

2.4. Data analysis

Due to the non-normal distribution of plasma IgG antibodies against CACNA1I and CACNA1C observed in this study (Supplementary Table 3), the differences in the median IgG levels in plasma between case and control samples were analysed using the Mann-Whitney *U* test. Linear regression was used to examine the impact of age and sex on plasma IgG levels. Data on drug and alcohol use were available only for cases instead of controls, so the association of plasma IgG levels with excessive drug and alcohol use in the year prior to sample collection was examined only in the case group. In order to examine the impact of medication on plasma IgG levels, antipsychotic doses were converted into chlorpromazine (CPZ) equivalent daily doses according to Bazire's Psychotropic Drug Directory (Bazire, 2007). Linear regression was used to examine the impact of CPZ equivalent doses on plasma IgG levels that were assigned as the dependent variable and the CPZ equivalent dose as the independent variable.

Available symptom data from schizophrenia patients in this study cohort were used in the form of Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT) categories to examine symptom association with plasma IgG levels by the presence or absence of positive symptoms, sleep disturbances, cognitive deficits, and depressive symptoms. Individual symptoms were classified under these headings and the Mann-Whitney *U* Test was applied to compare plasma IgG levels between cases who experienced the specific symptom and those who did not. In order to examine the overall association between plasma IgG levels and positive symptoms, depressive symptoms, sleep disturbances or cognitive deficits, the resulting p-values from each Mann-Whitney *U* test were used to calculate a combined p-value using Fisher's Combined Probability.

3. Results

3.1. Increased levels of plasma IgG against CACNA1I peptide in schizophrenia

Plasma levels of IgG against the peptide antigens derived from CACNA1I and CACNA1C proteins were not significantly associated with sex and age (Supplementary Table 3); the median IgG levels in plasma were not significantly different in patients with schizophrenia who had experienced excessive drug or alcohol use in the year prior to sample collection from those who had not (Supplementary Table 5). Additionally, there was no relationship between plasma IgG levels and CPZ equivalent daily doses (Supplementary Table 6).

As shown in Table 1, the median level of plasma IgG against the CACNA1I-derived peptide was significantly higher in patients with schizophrenia than non-psychiatric controls ($Z = -6.82$, $p < 0.001$), but there was no significant difference in the median level of plasma IgG against the CACNA1C peptide between the patient group and the control group ($Z = -1.122$, $p = 0.262$). The inter-assay deviation of the two IgG assays used in this study was calculated using the SBI of quality control (QC) plasma sample pooled from >20 individual samples; the coefficient of variation (CV) was 13.88% for the anti-CACNA1I IgG assay and 9.78% for the anti-CACNA1C assay, respectively, based on the QC sample tested over 43 plates.

3.2. Association between IgG levels and schizophrenia symptoms

Disruption of voltage gated calcium channels has been found to be linked to a reduction in sleep spindles (Ghoshal et al., 2020), which is in turn correlated with measures of positive symptoms, sleep disturbances and cognitive dysfunction in schizophrenia (Manoach et al., 2014). In this study, plasma levels of IgG against voltage gated calcium channel derived peptides were examined by the presence of positive symptoms (Table 2), sleep disturbances (Table 3) and cognitive deficits (Table 4). Plasma IgG levels for the two peptides were not significantly associated with any symptom domain ($p > 0.05$). In examining a difference in plasma IgG levels between the presence and absence of specific symptoms, anti-CACNA1I IgG levels were significantly higher in schizophrenia patients who experienced the positive symptom of thought insertion than those patients who did not experience such a symptom ($Z = -3.057$, $p = 0.0022$) (Supplementary Table 7), although plasma IgG levels were not associated with positive symptoms as a class (Table 2), specific cognitive symptoms ($p > 0.017$) or specific sleep abnormalities ($p > 0.008$) (Supplementary Tables 8 and 9).

Due to associations between the immune system and negative symptoms, particularly depression, plasma IgG levels were examined for association with depressive symptoms. However, the median levels of plasma IgG against the peptide antigens derived from CACNA1I and CACNA1C proteins were not associated with depressive symptoms ($p > 0.05$) (Table 5) and there was no difference observed in plasma IgG levels between individuals who experienced any specific depressive symptom and those who did not experience that symptom ($p > 0.007$) (Supplementary Table 10).

4. Discussion

The expression of R1346H-containing CACNAI1 protein has been shown to reduce the surface expression of Cav3.3, to induce electroencephalogram changes and to interfere with sleep spindle formation in a transgenic animal model (Gulsuner et al., 2013; Andrade et al., 2016; Ghoshal et al., 2020). The finding that the R1346H mutation reduces the surface availability of Cav3.3 is of particular relevance for the potential role of anti-CACNA1I IgG in schizophrenia as studies of anti-NMDAR encephalitis demonstrated that anti-NMDAR IgG antibodies resulted in internalisation of NMDAR (Masdeu et al., 2016). It is thus conceivable that increased levels of circulating IgG directed against Cav3.3 protein may replicate the disruption to R1346H-containing protein function through a reduction in the surface availability of the channel. The present study examined plasma IgG levels for two peptides derived from CACNA1I and CACNA1C proteins, respectively, in patients with schizophrenia and non-psychiatric controls. Anti-CACNA1I IgG levels were significantly increased in the patient group when compared to the control group (Table 1), suggesting that anti-CACNA1I IgG is likely involved in schizophrenia. Literature has indicated a plausible mechanism by which such IgG antibodies may potentially contribute to the development of schizophrenia, even though a direct examination of the anti-CACNA1Ia IgG effects would be required before a causative role can be established.

Despite a strong association between schizophrenia and the CACNA1C locus (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), the levels of plasma IgG against CACNA1C-derived peptide were not significantly altered in patients with schizophrenia when compared to non-psychiatric controls (Table 1). While functional genetic variants could be indicative of the presence of an autoantibody, the statistical strength of the genetic association may not be fully

Table 2
Alteration of plasma IgG levels for target peptide antigens in patients with positive symptoms (p-value*).

Antigen	Bizarre Behaviour	Persecutory Deulsions	Organised Delusions	Grandiose Delusions	Delusions of Influence	Bizarre Delusions	Widespread Delusions	Delusions of Passivity	Primary Delusional Perception
CACNA1I	0.824	0.337	0.608	0.553	0.062	0.100	0.746	0.115	0.297
CACNA1C	0.540	0.196	0.657	0.952	0.506	0.420	0.554	0.955	0.079

* The p-values of individual comparisons were combined using Fisher's Combined Probability in order to examine the association between IgG levels for the peptide antigens of interest and positive symptoms. Plasma IgG levels for the target peptides were not significantly associated with positive symptoms. The cut-off for statistical significance was $p < 0.0025$.

predictive of the likelihood of an autoantibody association. The ability of a genetic variant to predict the presence of an autoantibody likely depends upon a number of factors, including the ability of a genetic variant to result in an alteration of protein function.

A reduction in sleep spindle formation has been observed in both medicated and medication-naïve patients with schizophrenia, contributing to a well-established literature on sleep disturbances in schizophrenia (Manoach et al., 2014; Wamsley et al., 2012; Waite et al., 2020). Furthermore, sleep spindle disruption was found to correlate with positive symptoms and measures of cognitive deficits in patients with schizophrenia (Manoach et al., 2014). The present study has failed to identify an association between anti-CACNA1I IgG levels and positive symptoms, although plasma anti-CACNA1I IgG levels were significantly higher in patients who experienced the positive symptom of thought insertion than those patients who did not experience such a symptom (Supplementary Table 7). This finding is supportive of the hypothesis that anti-CACNA1I IgG could replicate the role of R1346H mutation, but further studies are required to replicate previously observed data from rats carrying the R1346H mutation and to examine this hypothesis directly.

This study did not show an association between plasma levels of IgG against the two target peptides and sleep disturbances in patients with schizophrenia (Table 3). However, the relationship between sleep spindle reduction and sleep quality is unclear as sleep spindle reduction does not appear to be altered in individuals who experienced insomnia when compared to individuals characterised as good sleepers (Bastien et al., 2009; Normand et al., 2016). Even if anti-CACNA1I IgG can duplicate the effects of R1346H mutation, the reduction in sleep spindles may not result in a measurable sleep phenotype.

There was no observed association between plasma IgG levels against the two target peptides and cognitive symptoms (Table 4). The International Classification of Diseases 11th Edition (ICD 11) has recommended that the assessment of the cognitive symptom domain in schizophrenia be based upon standardised and validated tests, whereas the OPCRIT system contains only a few categories that may act as correlates of cognitive symptoms (Keeley and Gaebel, 2017; McGuffin, 1991). Therefore, the OPCRIT system may be unable to effectively capture cognitive symptoms occurring in schizophrenia, and the association between an increase in anti-CACNA1I IgG levels and cognitive symptoms should be analysed using a tailored cognitive battery of neuropsychological assessments that consider the special cognitive impairments of this group.

Previous studies suggest that immunological alterations in schizophrenia may be associated with the presence of negative, particularly depressive symptoms (Fernandez-Egea et al., 2016; Goldsmith et al., 2019). This reflects a link between activation of proinflammatory responses and the induction of sickness behaviour that, as discussed by Maes et al. (2012), may represent related, albeit distinct, phenomena sharing common inflammatory pathways. In this study, circulating levels of IgG against the peptide antigens derived from CACNA1I and CACNA1C proteins were not significantly altered in schizophrenia patients with depressive symptoms, either in aggregate or when specific symptoms were examined (Table 5 and Supplementary Table 10). These findings tentatively suggest that increased IgG autoantibody levels observed in schizophrenia function independently of a pro-inflammatory phenotype and are consistent with the results from a recent study suggesting that pro-inflammatory markers are not elevated in the brain of individuals with anti-NMDAR encephalitis (Nóbrega et al., 2019).

As a limitation of this study, the results from the use of OPCRIT data to analyse associations between circulating IgG against voltage gated calcium channels and schizophrenic symptoms should be interpreted cautiously. Although the OPCRIT system is a useful and reliable tool for the diagnosis of schizophrenia, the data presented are primarily expressed in terms of the presence and persistence of a particular symptom, rather than a scoring system for severity, distinguishing it from rating scales such as the Positive and Negative Syndrome Scale (PANSS) (McGuffin, 1991; Kay et al., 1987). Additionally, while the symptom categories of OPCRIT data correspond to modern symptom domains in schizophrenia, they are not expressed in these terms, especially in the cataloguing of cognitive symptoms. Therefore, associations between increased anti-CACNA1I IgG levels and any behavioural or symptomatic outcome will require further examination, and the associations presented here should be interpreted cautiously. Furthermore, circulating IgG against Voltage-Gated Calcium channels (VGCCs) have been found to be associated with Lambert-Eaton Myasthenic Syndrome (LEMS), a neuromuscular disorder characterised by muscle weakness and is characterised as a paraneoplastic syndrome (Mareska and Gutmann, 2004). Autoantibodies against VGCCs in LEMS are typically directed against the Cav 2.1 subunit and may also play a role in the development cerebellar degeneration (Winklehner et al., 2022), however, this study did not examine plasma IgG against the Cav 2.1 subunit;

Table 3
Alteration of plasma IgG levels for target peptide antigens in patients with sleep disturbances (p-value).

Antigen	Initial Insomnia	Early Morning Waking	Excessive Sleep	Broken Sleep	Reduced Need for Sleep	combined p-value*
CACNA1I	0.498	0.396	0.288	0.384	0.427	0.839
CACNA1C	0.909	0.955	0.355	0.33	0.271	0.478

* The p-values of individual comparisons were combined using Fisher's Combined Probability in order to examine the association between IgG levels for the peptide antigens of interest and sleep disturbances. Plasma IgG levels for the target peptides were not significantly associated with sleep disturbances. The cut-off for statistical significance was $p < 0.05$.

Other Primary Delusions	Thought Insertion	Thought Withdrawl	Thought Broadcast	Delusions of Guilt	Nihilistic Delusions	Thought Echo	Third Person Auditory Hallucinations	Running Commentary	Abusive Voices	Other Hallucinations	combined p-value*
0.666	0.002	0.601	0.228	0.965	0.339	0.086	0.540	0.330	0.603	0.650	0.997
0.437	0.074	0.983	0.151	0.958	0.637	0.129	0.010	0.380	0.155	0.697	0.999

Table 4
Alteration of plasma IgG levels for target peptide antigens in patients with cognitive symptoms (p-value).

Antigen				combined p-value*
	Distractable	Poor Concentration	Insight	
CACNA1I	0.427	0.988	0.415	0.607
CACNA1C	0.271	0.841	0.762	0.514

* The p-values of individual comparisons were combined using Fisher's Combined Probability in order to examine the association between plasma IgG levels for the peptide antigens of interest and sleep disturbances. Plasma IgG levels for the target peptides were not significantly associated with cognitive symptoms. The cut-off for statistical significance was $p < 0.05$.

Table 5
Alteration of plasma IgG levels for target peptide antigens in patients with depressive symptoms (p-value).

Antigen								combined p-value*
	Slowed Activity	Low Energy	Negative Thought Disorder	Dysphoria	Anhedonia	Self-Reproach	Suicidal Ideation	
CACNA1I	0.458	0.484	0.405	0.922	0.895	0.83	0.5	0.971
CACNA1C	0.291	0.104	0.532	0.059	0.33	0.356	0.938	0.363

* The p-values of individual comparisons were combined using Fisher's Combined Probability in order to examine the association between plasma IgG levels for the peptide antigens of interest and sleep disturbances. Plasma IgG levels for the target peptides were not significantly associated with depressive symptoms. The cut-off for statistical significance was $p < 0.05$.

because of the targeted approach towards antigen identification, it may be possible that IgG against other VGCC subunits and other epitopes on Cav subunits 3.3 and 2.1 may nonetheless be present in patients with schizophrenia. Finally, due to the lack of known positive and negative samples, it was impossible to validate cut-off values in order to determine positive and negative thresholds in this assay, and therefore differences in the median of the specific binding index were examined in this study.

In conclusion, this study is the first to document increased levels of circulating IgG directed against the Cav3.3 protein in patients with schizophrenia. Plasma anti-CACNA1I IgG levels were elevated in individuals with schizophrenia who experienced the positive symptom of thought insertion, but not other positive symptoms examined. Further studies are required to examine the hypothesis that circulating IgG directed against this peptide may duplicate the phenotype that was previously characterised from the CACNA1I mutation R1346H specifically and to examine the impact of anti- CACNA1I autoantibodies more generally. Functional studies examining the effects of anti-CACNA1I IgG may help validate the associations observed in the present study.

Declaration of competing interest

The above authors declare that they have no conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100603.

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