The search for an autoimmune origin of psychotic disorders: Prevalence of autoantibodies against hippocampus antigens, glutamic acid decarboxylase and nuclear antigens

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The etiology of psychotic disorders is still unknown, but in a subgroup of patients symptoms might be caused by an autoimmune reaction. In this study, we tested patterns of autoimmune reactivity against potentially novel hippocampal antigens. Serum of a cohort of 621 individuals with psychotic disorders and 257 controls were first tested for reactivity on neuropil of rat brain sections. Brain reactive sera (67 diseased, 27 healthy) were further tested for antibody binding to glutamic acid decarboxylase (GAD) isotype 65 and 67 by cell-based assay (CBA). A sub-cohort of 199 individuals with psychotic disorders and 152 controls was tested for the prevalence of anti-nuclear antibodies (ANA) on HEp-2-substrate as well as for reactivity to double-stranded DNA, ribosomal P (RPP), and cardiolipin (CL). Incubation of rat brain with serum resulted in unidentified hippocampal binding patterns in both diseased and control groups. Upon screening with GAD CBA, one of these patterns was identified as GAD65 in one individual with schizophrenia and also in one healthy individual. Two diseased and two healthy individuals had low antibody levels targeting GAD67 by CBA. Antibody reactivity on HEp-2-substrate was increased in patients with schizoaffective disorder, but only in 3 patients did antibody testing hint at a possible diagnosis of systemic lupus erythematosus. Although reactivity of serum to intracellular antigens might be increased in patients with psychotic disorder, no specific targets could be identified. GAD antibodies are very rare and do not seem increased in patients with psychotic disorders.

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1. Introduction

The etiology of psychotic disorders is still unknown, but in a subgroup of patients the symptoms might be caused by an autoimmune reaction (Hoffmann et al., 2016). Early suspicions on a link between autoimmunity and psychotic disorders were invigorated by the discovery of brain reactive immunoglobulins (Heath and Krupp, 1967). Also, the increased occurrence of psychosis in autoimmune disorders and vice versa suggests overlapping etiological factors (Benros et al., 2014a; Benros et al., 2014b). A shared risk factor for both diseases is the prior occurrence of infections (Benros et al., 2014a; Benros et al., 2014b).
2011). In addition, a common genetic predisposition was found for schizophrenia and six immune system-related diseases, including systemic lupus erythematosus (SLE) (Pouget et al., 2019). Recently, much attention has been drawn to the role of autoantibodies targeting neuronal surface antigens (NSAbs) in the brain of patients with autoimmune encephalitis who often present with psychosis. One of the proteins targeted is the N-methyl-D-aspartate receptor (NMDAR) causing patients to develop characteristic neurologic and psychiatric symptoms (Dalmau et al., 2011). It is clinically important that these diseases respond very well to immunosuppressive treatment indicating that any neuronal damage might be largely reversible (Graus et al., 2016; Varley et al., 2017; Zandi et al., 2014).

Whether NSAbs can occur in purely psychotic patients, however, is less clear; their prevalence varies between 0 and 11% (Bergink et al., 2015; Endres et al., 2015; Lennox et al., 2017), possibly due to differences in the methodology of antibody detection and patient cohorts (Jezequel et al., 2017; Leypoldt et al., 2017; Pathmanandaavel et al., 2015). In our own studies, autoantibodies against NMDAR and five other neuronal surface antigens in patients with a broad diagnostic spectrum of psychotic disorders were found to be absent after careful cross-validation to eliminate false positives (de Witte et al., 2015; Hoffmann et al., 2019).

In many autoimmune diseases neuropsychiatric problems are common. Within the group of systemic autoimmune rheumatic diseases (SARD), especially SLE may have neurological manifestations, the so-called neuro-lupus (Damoiseaux et al., 2015; Flower et al., 2017; Pego-Reigosa and Isenberg, 2008; Unterman et al., 2011). This warrants the testing for anti-nuclear antibodies (ANA), antibodies to double-stranded (ds) DNA, anti-extractable nuclear antigens (ENA) (including Ribosomal P protein (RPP)), and cardiolipin (CL) in patients with symptoms of psychosis. For instance, the presence of anti-RPP and anti-ds DNA cross-reacting to NMDAR subunit 2 have been associated with increased risk of neuropsychiatric symptoms in SLE (Hanly et al., 2011; Ho et al., 2016). Antibodies in general have poor or no access to intracellular antigen targets and are thus unlikely to bind to them and cause a direct pathogenic effect on the function of neurons. Yet, presence of certain autoantibodies might still be indicative for other autoimmune disease mechanisms (mediated by co-existing autoantibodies or autoreactive T cells, for example) that can be targeted by immunosuppressive treatment. Autoantibodies against the intracellularly located glutamic acid decarboxylase (GAD), which is the rate-limiting enzyme in the synthesis of gamma amino-butyric acid (GABA) occur in serum and CSF of patients with several neurological and endocrine syndromes. All these syndromes are characterized by dysfunction of the GABAergic system (Alexopoulos and Dalakas, 2013; Fouka et al., 2015; Saiz et al., 2008) suggesting that in this case the autoantibodies are a relevant biomarker for an autoimmune mechanism targeting this system. GAD autoantibodies are also a biomarker for diabetes mellitus type 1, but antibodies are reported to occur in lower titers than in neurological syndromes (Nakajima et al., 2018). Notably, some GAD antibody-positive conditions are responsive to immunosuppressive treatment, e.g. autoimmune epilepsy, even though to a lesser extent than patients with NSAbs (Daif et al., 2018; Vinke et al., 2018). There is other evidence that intracellular proteins could be autoimmune targets. In an animal model for the Stiff person syndrome, intrathecal antibodies against amphiphysin, an intracellular vesicular protein, leads to symptoms of reduced GABAergic transmission (Geis et al., 2010).

Here, we further characterize the serum binding patterns on rat brain of a cohort that tested negative for antibodies against neuronal surface antigens. We extend our antigen specific search for glutamic acid decarboxylase autoantibodies and tested for the occurrence of systemic autoimmune rheumatic disease-related autoantibodies in patients with psychotic disorders and healthy individuals including anti-nuclear antibodies (ANA), and antibodies to dsDNA, RPP and CL.

2. Methods

2.1. Study population

Samples and patient data were collected with written informed consent according to national and institutional ethical guidelines and the Helsinki Declaration, with additional informed consent by legal representatives for patients under age 18. The ability to provide written informed consent was evaluated by a psychiatrist by a face-to-face interview using a series of open-ended questions evaluating comprehension, reasoning, choice making and appreciation skills of the patient. The study population represents psychotic disorders and covers potential differences in diagnosis (Table 1). This is the same population used in our earlier study on the occurrence of NSAbs (Hoffmann et al., 2019). The cohorts from Rotterdam and France are part of the European network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI, http://www.eu-gei.eu).

2.2. Psychiatric diagnosis

The diagnosis was established by the treating psychiatrists based on the DSM-IV. The group of patients with psychotic disorders included schizophrenia, schizoaffective, brief psychotic disorder, schizophréniform, and other psychotic diagnoses, i.e. psychosis not otherwise specified, delusional disorder, substance induced psychosis, paranoid, and schizoid personality disorder.

2.3. Rat brain immunohistochemistry

Procedures were approved by the animal experiment committee at Maastricht University as well as the central committee of animal experiment (CCD) (WP 2016-005-001). Neuronal autoantibodies were identified by IHC on rat brain tissue following standard methods (Gresa-Arribas et al., 2014; Hoffmann et al., 2019; Titulaer et al., 2014). In brief, Lewis rat brains were fixed for 1 h in 4% paraformaldehyde and cryoprotected in 30% sucrose solution. After blocking with 0.3% H2O2 and 5% goat serum, sections were incubated with human serum diluted 1:200 in 5% goat serum overnight at 4 °C. After incubating with biotinylated goat anti-human IgG (Fc γ: 1:3200, 109–066–008, Jackson ImmunoResearch) for 2 h at 20 °C, tissue was incubated with VECTASTAIN Elite ABC kit (Vector lab., # PK 6100) for 1 h at 20 °C and the reactivity developed using diaminobenzidine. Staining included serum samples from healthy individuals as negative controls, and from autoimmune encephalitis patients (against various autoantigens) as positive controls. Images were taken by the VENTANA iScan HT slide scanner (20× objective) and observed on the screen (Ventana Image Viewer). A grade between 0 and 3 was given based on the intensity and contrast of reactivity of sera against the hippocampal neuropil. All stainings that were scored 1–3 and inconclusive cases were repeated and validated by two independent observers of whom at least one was blinded. Those with inconsistent results were repeated at least once more and a final score (1 = borderline, 2 = weak positive, 3 = strong positive) was given according to all images of one sample.

2.4. Screening anti-GAD autoantibodies with CBA

Specific antibody screening detection was performed using an in-house CBA for glutamic acid decarboxylase isotypes 65 kDa and 67 kDa (GAD65, GAD67). The GAD plasmids expressed human GAD65 and GAD67 with the pcMV6-XL5 plasmid which was a kind gift from Dr. Francesc Graus (IDIBAPS, Barcelona) (Arino et al., 2014). HEK293 cells were plated on coverslips and transfected with 4 μg expression vectors of the respective human antigens and expression allowed for 22–26 h. Cells were fixed in 3.6% formaldehyde (#F006, TAAB) for 10 min and permeabilized with 0.3% Triton-X-100 for 10 min. After blocking with 1% bovine serum albumin (BSA) for 1 h, cells were incubated with...
human sera diluted 1:40 in 1% BSA together with an antibody targeting the respective antigen (rabbit-anti-GAD65 (clone 7309LB, gift from Christina Hampe, 1:1000); or rabbit-anti-GAD67 (clone 10266/20B, gift from Christina Hampe, 1:1000)) for 1 h at 20 °C. Reactivity was visualized after incubation with secondary antibodies goat-anti-human-IgG Fc antibodies. Enzyme substrate (TMB) was then added to the wells and the presence of antibodies was detected by a color change produced by the conversion of TMB substrate to a colored reaction product. The reaction was stopped with H2SO4 and the intensity of the color change read by a spectrophotometer at 450 nm. Results are expressed in ELISA Units per milliliter (EU/ml) and reported as positive or negative. Threshold for positivity was >50 for dsDNA and >20 EU/ml for all other antigens.

2.6. Statistics

To test for the difference of rat brain IHC and ANA indirect immunofluorescence scores between the groups, we performed a non-parametric Kruskal-Wallis test. All tests were done in IBM SPSS Statistics version 23.0 for Windows.

3. Results

3.1. Novel hippocampal patterns of rat brain IHC are not specific for mental disorder

In a first step, we screened 621 patients with psychotic disorders and 257 healthy individuals for the presence of NSAbs. As reported in our previous publication, we did not identify any sera with antibodies against NMDAR (Glul1 alone and Glun1/GluN2B), leucine-rich glioma-inactivated 1 (LG11), α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptor (AMPA), or γ-aminobutyric acid receptor subunit A and B (GABAαR, GABAβR). One serum sample (from a control participant) had autoantibodies targeting contactin-associated protein-like 2 (Caspr2) at a dilution 1:100 in the live version of the CBA. Further, only 2 sera contained antibodies binding to neurons at a dilution of 1:50; one was from a patient with schizophrenia and one was from a control participant. (Hoffmann et al., 2019)

Yet, the rat brain IHC revealed some distinct hippocampal patterns, that we present here. Several sera gave unknown patterns on the hippocampal neuropil, suggesting that they target novel cell surface or synaptic antigens. Hippocampal stainings with strong binding (grading 3) could be grouped according to similarity into eight patterns (see Fig. 1, Pattern A-H). Two of these samples (indicated with * in Fig. 1) were the sera previously reported to be reactive on live neurons (Hoffmann et al., 2019). Pattern A was prominent and seen with the rat brain IHC and ANA indirect immunofluorescence scores between the groups, we performed a non-parametric Kruskal-Wallis test. All tests were done in IBM SPSS Statistics version 23.0 for Windows.

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| Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 | Cohort 5 | Cohort 6 |
|----------|----------|----------|----------|----------|----------|
| Healthy, n | Py psychotic disorders, n | Source | Criteria | Time-span | Reference |
| 13 | 203 | University Psychiatric Center Catholic University Leuven in Kortenberg | Patients: DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder | November 2003 to July 2007 | (De Hert et al., 2006) |
| – | 23 | – | DSM-IV diagnosis of psychotic disorder or mood disorders with psychotic features; substance-induced psychosis were excluded | June 2010 to May 2014 | (Szoke et al., 2014) |
| – | – | Istanbul University, Aziz Sancar Institute of Experimental Medicine | DSM-IV diagnosis of schizophrenia | – | – |
| 44 | – | Erasmus Medical Center (EMC) Rotterdam. | Consecutively admitted patients which initially presented with psychosis, and were finally diagnosed with schizophrenia, as well with a range of other mental disorders | – | – |
| 200 | – | Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) | Absence of any psychiatric diagnosis according to DSM-IV criteria | – | – |
| Blood donors, confirmed to be healthy by general indicators, tested by interviews, hemoglobin and other blood parameters, blood pressure, pulse, and body temperature as well as the absence of infectious diseases | March 2014 | Sanquin Maastricht | Blood donors, confirmed to be healthy by general indicators, tested by interviews, hemoglobin and other blood parameters, blood pressure, pulse, and body temperature as well as the absence of infectious diseases | – | – |

**Table 1**

Demographic description of cohorts.

**Source:** University Psychiatric Center Catholic University Leuven in Kortenberg

**Criteria:** Patients: DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder

**Healthy:** No psychiatric antecedents or medication

**Time-span:** November 2003 to July 2007

**Reference:** (De Hert et al., 2006)
patients with depression and/or anxiety we also found some novel staining patterns on the hippocampus (Zong et al., 2020). Some of these were overlapping with the here reported reactivity, e.g. the here reported pattern A has similarity with the pattern C reported for 4 patients in the study by Zong et al. Interestingly, two samples resulting in this pattern that had higher antibody titers in that study also tested positive on live neurons. Further the here reported pattern C (2 schizophrenia patients, 1 healthy individual) was also reported for 2 healthy controls labeled as pattern K by Zong et al.. Pattern D (1 schizophrenia patient, 1 control individual) was similar to that in a previously published staining by Bergink et al. (2015) with serum from a patient with post-partum psychosis, which was also reactive to live neurons.

3.2. Autoantibodies against GAD65 and GAD67 are rare and do not differ between healthy controls and disease groups

Some of the IHC positive sera might also have autoantibodies targeting intracellular neuronal antigens. As GAD is an antigen that is related to neurological syndromes with GABA disturbances, we extended our antigen-specific screening of all sera that were graded 1–3a with CBA testing for GAD65 and GAD67 reactivity. An overview of all the autoantibody screening results is shown in Table 2. Two sera were found to be reactive to GAD65 and GAD67; one of a schizophrenia patient (Fig. 1, Pattern F) and one of a healthy participant. We further identified 4 sera reactive to GAD67 alone (at a max. dilution 1:100 or 1:200). Most GAD67 antibodies cross-react to GAD65 as they bind to a common epitope. This has been observed for antibodies occurring in patients with diabetes as well as in neurological conditions (Gresa-Arribas et al., 2015; Jayakrishnan et al., 2011). However, a case of cerebellar ataxia presented with antibodies restricted to the GAD67 isotype, indicating the possibility that there is another type of GAD67 antibodies (Guasp et al., 2016). As there is not enough research on GAD65/67 antibody reactivity in psychiatric disorders, we prefer not to make the assumption of cross-reactivity.

Those sera reactive to GAD65 and GAD67 showed hippocampal reactivity pattern specific to GAD65, which is the same pattern in e.g. GAD antibody-positive epilepsy (Niehusmann et al., 2009). Those sera reactive to GAD67 alone had each a different hippocampal binding pattern and therefore were considered to contain neuronal autoantibodies or autoantibodies against unknown antigens (Fig. 2). In conclusion, we identified 2 sera reactive to GAD65 and GAD67 (Table 3).

3.3. Serum reactivity to HEp-2 substrate is increased in individuals with schizoaffective disorder, but specific autoantibodies against dsDNA, RPP, and CL are not

We investigated the prevalence of SARD-related autoantibodies in sera of a sub-cohort consisting of 199 patients with psychotic disorders, and 152 healthy individuals (Table 2). The reactivity of sera to ANAs on HEp-2 cells was increased in individuals with schizoaffective disorder compared to healthy individuals (Kruskal Wallis, p = 0.011). However, the number of sera testing positive for specific antigens (dsDNA, RPP, and CL) here was too low for relevant statistical analysis. We found that 3 sera (2 schizophrenia, 1 schizoaffective disorder) were consistently positive in different diagnostic assays (Table A.1), so it might be relevant to examine for clinical signs of SLE in these patients.
4. Discussion

In our cohort of patients with psychotic disorders only two samples were considered positive for GAD autoantibodies; one schizophrenia patient and one control. This suggests that serum GAD autoantibodies at high titers are very rare (2 out of 621) in schizophrenia-spectrum disorders. A previous meta-analysis on the prevalence of GAD autoantibodies in patients with psychosis reported that patients were more likely to have GAD65 antibodies than controls (odds ratio [OR], 2.24; 95%CI: 1.28–3.92%; P = 0.005; eight studies; I² = 0%) with a pooled prevalence of 5.8% (Grain et al., 2017). However, previous studies were using the more sensitive radio immuno assay (RIA), radio immunoprecipitation

Table 2
Autoantibody screening results.

| Methods: IHC rat brainb | Tested, no. | Controlsa | Psychotic disorders | Schizophrenia | Schizoaffective | Brief psychotic disorder | Schizophreniform | Other psychotic diagnoses |
|------------------------|------------|------------|---------------------|---------------|----------------|-------------------------|----------------|-------------------------|
| Grade = 1, no. (%)     | 257        | 621        | 476                 | 44            | 38             | 47                      | 16             |                         |
| Grade = 2, no. (%)     |             |            |                     |               |                |                         |                 |                         |
| Grade = 3, no. (%)     |             |            |                     |               |                |                         |                 |                         |
| CBA (IHC - cohort)     | 27         | 67         | 49                  | 7             | 5              | 3                       |                 |                         |
| Identified antigen     | 1× GAD65; 2× GAD67 | 1× GAD65; 2× GAD67 | 1× GAD65; 1× GAD67 |                 |                 |                         |                 |                         |
| SARD-related antibodies | Tested, no. | 152        | 199                 | 114           | 40             | 43                      | 2              |                         |
| Positive, no. (%)      |             |            |                     |               |                |                         |                 |                         |
| ENA ELISA Positive, no. (%) | 2 (1.3) | 4 (2) | 2 (1.8) | 2 (5.1) | 0 (0) |                         |                 |                         |
| dsDNA ELISA Positive, no. (%) | 1 (0.7) | 7 (3.5) | 4 (3.5) | 3 (7.7) | 0 (0) |                         |                 |                         |
| RPP ELISA/LIA Positive, no. (%) | 9 (5.9) | 7 (3.5) | 5 (4.5) | 2 (5.1) | 0 (0) |                         |                 |                         |
| CL ELISA Positive, no. (%) | 12 (7.9) | 9 (4.5) | 6 (5.5) | 2 (5.1) | 1 (2.3) |                         |                 |                         |
| No. (IgA/IgG/IgM)      | (1/5/0)    | (3/1/1)    | (1/1/1)             | (1/0/0)       | (1/0/0)        |                         |                 |                         |

a Controls consist of 200 blood donors and 57 individuals without psychiatric diagnosis.

b Data taken from Hoffmann et al. (2019).

Fig. 2. Rat brain immunohistochemistry (IHC) for GAD+ cases. Case 1 shows a typical GAD65+/67+ antibody binding pattern similar to serum from a patient with GAD+ epilepsy. Case 6 shows unknown binding pattern of serum with GAD67 autoantibodies. More details of cases can be found in Table 3.
Table 3

| Case 1 | GAD65/67 | 1:6400 | Schizophrenia | 43 | f | 3/pos. | Yes | GAD65/67 |
| Case 2 | GAD65/67 | 1:3200 | Control\(^a\) | 59 | m | 2/NA | Yes | GAD65/67 |
| Case 3 | GAD67 | 1:100 | Schizophrenia | 31 | f | 1/pos. | No | ND |
| Case 4 | GAD67 | 1:100 | Control\(^a\) | 55 | f | 1/pos. | No | ND |
| Case 5 | GAD67 | 1:200 | Psychosis NOS | 32 | m | 1/pos. | No | ND |
| Case 6 | GAD67 | 1:100 | Control\(^a\) | 68 | m | 2/pos. | No | ND |

Conc. = highest still positive serum concentration, UM = Maastricht University, IDIBAPS = Institut d’investigacions Biomèdiques August Pi i Sunyer, ND = not determined.
\(^a\) CBA for GAD was performed on fixed cells.
\(^b\) IHC at UM was graded 0–3 and at IDIBAPS positive/negative.
\(^c\) Indicates whether the IHC hippocampal pattern resembled the typical pattern of the antigen identified by CBA.
\(^d\) A conclusion was drawn based on the combination of different methods. Only, if a sera was tested positive by CBA and the IHC pattern correlated with the CBA results, it was considered positive.
\(^e\) Controls consisted of blood donors and individuals without psychiatric diagnosis.

assay (RIPA), or enzyme-linked immunosorbent assay (ELISA). Therefore, reported results likely included also the lower antibody titers. From our unpublished studies, we know that the CBA and IHC detect GAD antibodies of higher titer and we expected higher titers to be more relevant for autoimmune-related neurological diseases while low titers are usually a diagnostic marker for diabetes mellitus type 1. A diagnosis of diabetes, however, was not excluded, which is a confounding factor, especially because patients with schizophrenia have a higher risk for comorbid diabetes mellitus type 1 (Benros et al., 2014b).

None of the patients in our study had a registered diagnosis of SLE, though we detected autoantibodies to specific SLE related antigens in 3 patients. Further clinical assessment of these patients would be necessary to determine a possible diagnosis of SLE. SARD-related autoantibodies, particularly those in SLE, have been associated with the occurrence of neuropsychiatric symptoms, also referred to as neuropsychiatric lupus (NPSLE) (Tay and Mak, 2017) whereby the most common symptoms are depression, cognitive dysfunction and anxiety. The reported prevalence of psychosis in SLE varies greatly depending on the population with 2.3% in an English population (Pego-Reigosa and Isenberg, 2008), and up to 11% in a black Caribbean study population (Flower et al., 2017).

Little has been reported on the prevalence of SLE in patients with schizophrenia spectrum disorders. In the overall population of Europe the prevalence is estimated to be 35/100000 and 110/100000 in Afro-Caribbean people (Rees et al., 2017). In a large Danish National Register study of 7704 schizophrenia patients, none was reported with a diagnosis of SLE (Eaton et al., 2006). Yet, cases of patients presenting with a psychotic disorder or atypical SLE with predominant psychiatric manifestations have been described before (Lungen et al., 2019; Mack et al., 2017) and raise the question whether atypical presentation of SLE might hamper the diagnosis in patients presenting with psychotic disorders. In these cases, psychiatric symptoms might represent a prodromal stage of the disease or a subtype of SLE with isolated CNS involvement.

Marrie et al. found that the incidence of psychiatric comorbidity is elevated in the immune-mediated inflammatory diseases (IMID) population (such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis) as compared with a matched population as early as 5 years before diagnosis (Marrie et al., 2019). Whether this reflects shared risk factors for psychiatric disorders and IMID, a shared etiology or other etiology is still matter of debate.

In the last 10 years, 16 novel autoimmune diseases of the CNS have been identified, leading to new treatment strategies for neurological and psychiatric syndromes (Dalmau et al., 2017). However, our previous studies (de Witte et al., 2015; Hoffmann et al., 2019) indicate that the prevalence of NSAbs is very low in patients with psychotic disorders and not different from the prevalence in control populations. It should be mentioned however, that the percentage of patients with an autoimmune origin of the disease might still be larger, but the tested autoimmune antibodies are signs of specific disorders that only affect a small number of individuals. It was our strategy to select a very heterogeneous population to represent a wide spectrum of patients. Treatment-resistant and acute/recent onset patients have been reported to have a higher prevalence of known autoimmune encephalitis-related autoantibodies (Pollak et al., 2019). Whether this is also the case for potentially novel antigens or SARD-related autoimmunity remains to be shown.

Our finding of reactive autoantibodies to rat brain warrants further research for the identification of the antigen as their target. As most of the sera were not reactive to live neurons, they potentially target intracellular or glial antigens. Neuronal surface receptors and channels have a high homology between rat and human so rat tissue can be used for detection of most human antibodies against these antigens. Some antigens however, e.g. dopamine receptor 2 are not detected by rat brain IHC. Especially considering that novel antigens might be targeted in psychotic patients, one has to be aware that these might be missed when using the rat brain IHC. Also, we confirmed neuronal specificity on primary cultured life neurons, but we cannot exclude that (i) some neuronal antigens are expressed at a very low level in the cultured environment, or (ii) some antibodies target other cell types, e.g. microglia or astrocytes. Finally, a combination of serum analysis with cerebrospinal fluid (CSF) is always desirable as the presence of intrathecal antibodies increases the likelihood for disease relevance. Some antibodies, such as anti-NMDAR are better detectable in CSF, whereas others, such as those targeting LGI-1 and AQ4 might only be detectable in serum (Graus et al., 2016). General CSF analysis including white blood cell count, oligoclonal bands, and protein concentration can give further indications of increased intrathecal inflammation. CSF and serum analysis in 456 patients with schizoprogeniform syndromes also found that established anti-neuronal IgG antibodies are rare in serum (Endres et al., 2020). The study further reports, that antibodies are even rarer in the CSF but CSF alterations revealed a substantial subgroup with neuroinflammatory signs.

5. Conclusion

Autoantibodies against nuclear antigens, cardiopin and GAD are rare in psychotic disorders. Serum reactivity on brain tissue indicates antibodies binding to unidentified antigens and future studies should thus focus on the identification of potentially novel antigens, including those targeting microglia and astrocytes as well as their disease relevance. The occurrence of SLE-related autoantibodies in 3 patients with schizophrenia-spectrum disorders warrants further research into the prevalence of atypical (undiagnosed) SLE in psychiatric disorders as well as whether psychotic symptoms are increased in the years preceding a diagnosis of SLE. The role of T-cell autoimmunity has not been addressed in our study but might represent an important pathogenic mechanism. Additionally, a better characterization of the patient cohort including neurological and general CSF examination is desirable to increase the chance of identifying individuals with an autoimmune origin of the disease.
Appendix A

Table A1

| Diagnose                                      | Age | Sex | Illness duration (yrs.) |
|-----------------------------------------------|-----|-----|------------------------|
| Schizophrenia (paranoid type)                 | 39  | Male| 0.5                    |
| Schizofrontal disorder                        | 23  | Female| 8                      |
| Schizophrenia (paranoid type)                 | 21  | Female| 4.9                    |

ELISA = enzyme-linked immunosorbent assay, RPP = ribosomal protein P, dsDNA = double-stranded deoxyribonucleic acid, ANA = anti-nuclear antibodies, CL = cardiolipin, ANA IFA = immunofluorescence on Hep-2 substrate for detection of antinuclear antibodies.

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