Dear Sirs,

Schizophrenia is a common, heterogenous and complex disorder with unknown aetiology [1]. There is established evidence for N-methyl-D-aspartate receptor (NMDAR) hypofunction [2] as a central component of the functional dysconnectivity that is the most accepted model for symptoms [3], and increasing evidence for potassium channel dysfunction [4]. Moreover, autoimmune mechanisms have been proposed, perhaps in subgroups of patients [5, 6]. In the last few years, antibodies to neuronal cell surface antigens have been identified in cases of autoimmune encephalitis that respond to immunotherapy [7, 8]. Over two-thirds of patients with NMDAR antibody encephalitis, and some with potassium channel antibody-associated limbic encephalitis, have prominent psychiatric symptoms, or may present to psychiatric services in the first instance [7, 9, 10]. The psychiatric symptoms are those seen in schizophrenia including delusions, hallucinations, and catatonic movement disorder. There is good evidence for specificity and pathogenicity of these antibodies, with absence in large numbers of healthy individuals and those with other neurological diseases [9, 11, 12]. However, there have been no cases of NMDAR or potassium channel antibodies identified in patients with purely psychiatric disorders. We hypothesized that these antibodies would be present in a proportion of patients with early schizophrenia, in the absence of overt seizures, movement disorders, or other neurological signs.

Serum was obtained prospectively from a cohort \( n = 46 \) of patients at first presentation of psychosis to an epidemiologically principled early intervention for psychosis service (http://www.cameo.nhs.uk), which provides 3 years of treatment and follow up when possible. We retrospectively measured NMDAR antibodies using a cell based assay and subjective visual scoring system [9]. We identified antibodies to components of potassium channel complexes (VGKCs) by radioimmunoassay [8]. The sera were tested blind to diagnostic status. Patients with positive results were retrospectively interviewed and extensively investigated. Full clinical details are given in the Table and supplementary information.

Patients 1 and 2 had NMDAR antibodies, [patient 1: score 2, (range 0–4, normal 0–0.5, Fig. 1); patient 2: score 1]. Patient 1 was unwell for 6 months before recovering; he was well and antibody negative at 3 years. Patient 2 has had a protracted course; antibodies remained repeatedly positive at 24–35 months follow up, but were then negative at 36 months. Patient 3 had VGKC antibodies \( (1,435 \text{ pM}; \text{normal } <100) \), was unwell for 6 months before recovering, but has subsequently relapsed after 1 year and has now associated limbic encephalitis, have prominent psychiatric symptoms, or may present to psychiatric services in the first instance [7, 9, 10]. The psychiatric symptoms are those seen in schizophrenia including delusions, hallucinations, and catatonic movement disorder. There is good evidence for specificity and pathogenicity of these antibodies, with absence in large numbers of healthy individuals and those with other neurological diseases [9, 11, 12]. However, there have been no cases of NMDAR or potassium channel antibodies identified in patients with purely psychiatric disorders. We hypothesized that these antibodies would be present in a proportion of patients with early schizophrenia, in the absence of overt seizures, movement disorders, or other neurological signs.

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been lost to follow up. There were no clinical features to
differentiate these cases from other cases of psychosis in
Cameo (Table 1), even in retrospect, and the autoantibody
positive cases fulfilled criteria for DSM-IV schizophrenia.
No patient had physical neurological symptoms or signs.

A further patient, patient 4, with first episode psychosis
identified after the prospective cohort, had NMDAR anti-
bodies (score 1.5). He was unwell for 4 months, partially
responsive and then relapsing despite treatment with anti-
psychotics. To reduce the levels of NMDAR antibodies he
received plasmapheresis and made a significant clinical
improvement 3 weeks later, improving further with pred-
nisolone. He remains clinically and functionally improved
at 7 month follow up, on no antipsychotic medication. This
is the first case description, to our knowledge, of a patient
with NMDAR antibodies and a purely psychiatric presen-
tation responding to immunotherapy.

These preliminary data show that some patients with
schizophrenia have potentially pathogenic autoantibodies
to relevant membrane proteins. Three of the patients had
NMDAR antibodies, which have been shown to reduce
NMDAR clusters in vivo [12], which mirrors that seen in
models of schizophrenia [13]. All of our antibody positive
cases (6.5% of 46) fulfilled DSMIV criteria for schizo-
phrenia and the patients were tested early in the course of
their illness. None of the chronic schizophrenia controls in
our large case series had NMDAR antibodies [9], but this
could be because NMDAR and VGKC antibodies sponta-
neously drop with time ([14]; SRI, AV unpublished data); this
suggests a critical early period of illness for detection
and treatment. We did not measure antibody in CSF, and
future prospective systematic studies of antibody in paired
serum and CSF will be informative.

The 46 patients in the Cameo cohort were given DSM-
IV diagnoses a year after intake to the service. Of these,

Table 1 Demographic and clinical data for antibody positive cases

| Patient | Antibody, | Time to recovery, Total follow up (months) | Cognitive deficits | Positive psychotic symptoms | Illness duration at intake/assay (days) |
|---------|-----------|------------------------------------------|-------------------|----------------------------|----------------------------------------|
| 1       | NMDAR     | 36                                       | Chronic           | Grandiose and paranoid delusions | 21                                     |
| 2       | NMDAR     | 12                                       | Chronic           | Auditory hallucinations.       | 28                                     |
| 3       | VGKC      | 7                                       | Chronic           | Paranoid delusions, thought disorder | 14                                     |
| 4       | NMDAR     | 7                                       | Chronic           | Paranoid delusions, thought disorder | 19                                     |
|         | NMDAR     | 7                                       | Chronic           | Paranoid delusions, thought disorder | 19                                     |

Note: Table includes demographic data and clinical features for patients with antibodies. The table compares the time to recovery, total follow up, cognitive deficits, positive psychotic symptoms, and illness duration at intake/assay for different patients.
63% had a diagnosis of schizophrenia. Other psychotic diagnoses were psychosis not otherwise specified (15%), bipolar affective disorder (13%), schizoaffective disorder (4%), major depression with psychosis (2%) and delusional disorder (2%). It is therefore possible that the proportion of cases with diagnoses of schizophrenia that have specific antibodies is higher than the proportion described here. However, there is significant diagnostic instability in patients with early psychosis, due to the threshold of chronicity required for a diagnosis of schizophrenia. There is also increasing evidence of shared heritability between the psychotic disorders and consequently a move away from the use of categorical diagnoses in those with psychotic disorders.

There is a need for a systematic screen of available neuronal surface antigens in first episode psychosis and schizophrenia to characterise the true prevalence of these antibodies among different population groups, with implications for diagnosis, prognosis and treatment.

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