

# The Psychiatric Phenotype of Anti-NMDA Receptor Encephalitis

Lucy L. Gibson, M.B.B.S., Thomas A. Pollak, M.B.B.S., M.Sc., Graham Blackman, M.B.Ch.B., Mary Thornton, M.B.Ch.B., M.Sc., Nicholas Moran, M.R.C.P., M.Sc., Anthony S. David, M.D., F.R.C.Psych.

In its early stages, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is often characterized by prominent psychiatric manifestations that can lead to delays in diagnosis and treatment. The authors aimed to address this problem by providing a detailed description of the psychiatric phenotype and demographic features that may influence presentation. Eighty-six patients with positive serum NMDAR antibodies were identified, 22 of whom met diagnostic criteria for anti-NMDAR encephalitis. Medical notes were reviewed retrospectively to rate psychiatric symptoms using standardized scales. Clinical and demographic characteristics were compared for patients with and without psychosis. Patients with psychosis exhibited severe psychopathology with a characteristic phenotype: severe and

disproportionate cognitive disturbance ( $p < 0.005$ ) with high negative symptom scores and excitability. Those presenting with psychotic symptoms were significantly younger than those without ( $p < 0.005$ ). Patients with anti-NMDAR encephalitis present with a somewhat distinct cluster of psychiatric symptoms not commonly seen in functional psychoses. When encountered, this atypical pattern should warrant further investigation and a high index of suspicion for anti-NMDAR encephalitis. The more prominent psychotic features in younger adults may reflect greater susceptibility of the young brain to exogenous psychosis.

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Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, the most common of the autoimmune encephalitis conditions, is a progressive and potentially fatal condition.<sup>1</sup> Initial cognitive deficits, psychiatric symptoms, and speech disintegration are often followed by depression of consciousness and dystonic movements. However, the condition is heterogeneous and can occur across the life span, with young women, often with ovarian teratomas, most commonly affected.<sup>2</sup> The existence of isolated psychiatric presentations that respond to immunotherapy raises concerns of missed diagnoses.<sup>3</sup> Indeed, prominent psychiatric symptoms in anti-NMDAR encephalitis result in up to 60% of patients being initially admitted to psychiatric units.<sup>4</sup> This can delay diagnosis and appropriate treatment significantly. While there is hope that with increasing recognition of the disease this number is decreasing, it remains an important differential for patients under psychiatric care.<sup>5</sup> Autonomic instability and neurological symptoms, such as seizures, have been highlighted as important signs to aid clinicians in identifying such patients; however, no defining psychiatric features have so far been found.<sup>5,6</sup>

Anti-NMDAR encephalitis can affect men and women of any age, but demographic differences may influence the clinical phenotype. Both children and men present more commonly with seizures and less prominent psychiatric and

behavioral abnormalities.<sup>7,8</sup> Age-related differences are also seen in functional psychoses, where psychosis occurs without a clearly defined organic cause; onset is rare in childhood, with the median age of first-episode psychosis in the early 20s, often slightly later in women.<sup>9</sup> Where schizophrenia-like psychosis does present in later life, there are marked differences in presentation with paranoia prominent, whereas negative symptoms and thought disorder are infrequent.<sup>10</sup> No study to date has explored how the described demographic differences in functional psychoses might be reflected in the psychiatric presentation of anti-NMDAR encephalitis.<sup>8</sup>

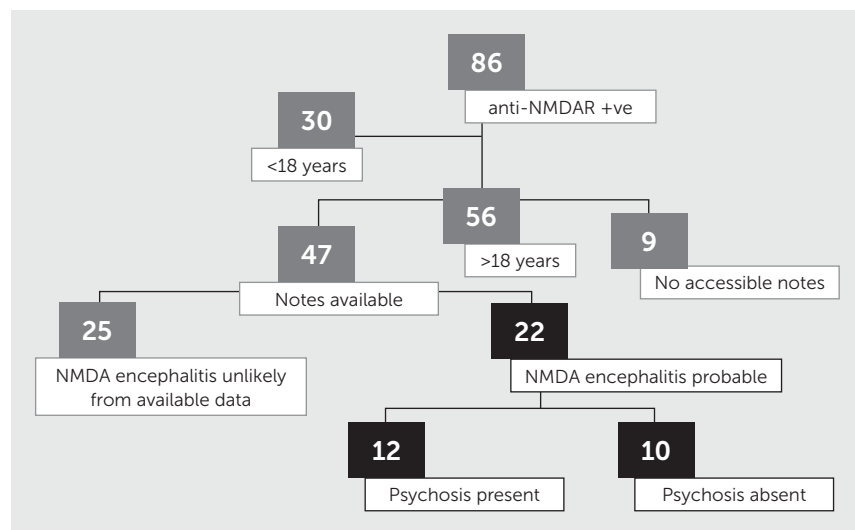
The present study was designed to address these questions by examining whether the phenomenology and pattern of psychotic symptoms might allow the identification of distinct encephalitic subgroups and also discrimination from functional or idiopathic psychosis.

## METHODS

This study was approved by the institutional review board of South London and Maudsley NHS Foundation Trust.

## Patients

In this observational retrospective cohort study, 86 patients were identified with positive serum NMDAR antibodies

**FIGURE 1. Flow Chart of Patient Selection**

between July 2010 and May 1, 2017, at Kings Health Partners, London, United Kingdom. Testing was performed at Oxford Neuroimmunology Laboratory with cell-based assays for serum samples. A live cell-based assay was used for all patients except two, whose serum was tested after December 2015 when testing methodology changed to a fixed cell-based assay. Only two of the patients underwent CSF testing of NMDAR antibodies, as NMDAR antibody testing of CSF was not common practice in the United Kingdom during the period of this study.

The international consensus criteria in the position paper by Graus et al.<sup>11</sup> were used to identify those patients with probable NMDAR encephalitis with a positive serum NMDAR antibody result and clinical features of anti-NMDAR encephalitis. Briefly, the criteria include rapid onset; at least four out of six major groups of clinical symptoms (unless accompanied by a teratoma, when only three are required); an abnormal EEG and/or CSF; and reasonable exclusion of other disorders.<sup>11</sup>

These criteria were used to retrospectively identify patients with probable NMDAR encephalitis, as all but two of our patients were diagnosed and treated prior to the publication of these criteria. These diagnostic criteria for probable anti-NMDAR encephalitis are designed for use in the absence of a serum or CSF NMDAR antibody result. Our patients both had a positive serum result and met the diagnostic criteria, leading to greater certainty of their anti-NMDAR encephalitis diagnosis. The high sensitivity and specificity of these criteria in correctly identifying patients with anti-NMDAR encephalitis have since been affirmed.<sup>12,13</sup>

### Exclusion Criteria

Patients were excluded if they were under 18 years, had insufficient clinical information available to make a diagnostic assessment, or did not meet diagnostic criteria (see Figure 1 for flow chart). Nine patients were excluded due to insufficient available clinical information. Twenty-five

patients were excluded because, despite having positive NMDAR antibodies and in some cases receiving a contemporaneous diagnosis of anti-NMDAR encephalitis from their treating clinician, they did not satisfy the Graus et al. criteria. Children were excluded due to the anticipated difficulty in making meaningful comparisons of psychiatric symptoms with adults (Figure 1).

### Inclusion Criteria

Patients over 18 years old, with a serum positive NMDAR antibody result, clinical records available at Kings College Hospital, and symptomatic features for probable anti-NMDAR encephalitis were included for analysis. Also included was a patient (#27) who had the clinical features required but did not undergo reported CSF or EEG testing, as she was admitted to a psychiatric unit. After several months, she improved spontaneously, but the treating psychiatrist acknowledged that it was likely that NMDAR encephalitis contributed to her presentation and arranged future outpatient testing, which was not available at the time of this study. Statistical analyses were performed with and without this individual without any change in significant findings.

Twenty-one other patients were identified with rapid onset of at least 4/6 groups of symptoms and abnormal CSF or EEG testing (or 3/6 symptoms alone in the presence of a teratoma) (Table 1).

### Data Collection

Data were collected by retrospectively reviewing a combination of electronic patient medical and psychiatric records. Records were used to identify demographic information, symptomatic timing onset and nadir, clinical features including psychotic symptoms, and results of investigations performed, such as other serum antibodies, EEG, CSF, and MRI.

### Measures

Psychotic symptoms were assessed using definitions from the Positive and Negative Syndrome Scale (PANSS), supplemented by the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) criteria because of their finer grained coverage of certain psychotic symptoms, such as bizarre behavior and avolition.<sup>14</sup> The quality of the patient notes varied; items were rated on the basis of the greatest intensity of symptoms documented, from initial onset to nadir. The PANSS is validated for use in first-episode psychosis and schizophrenia and has been used in anti-NMDAR encephalitis case studies.<sup>15–18</sup> Items are scored between 1 and 7 with increasing severity. Factor analyses of symptoms suggest that a five-factor model provides the best fit for PANSS

TABLE 1. Characteristics of Patients With Anti-N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis<sup>a</sup>

Patient Number, Gender, Age (years)	Psychosis	Speech Disturbance	Seizure	Move-ment Disorder	Reduced Con-sciousness	Auto-nomic Dys-function	Teratoma	EEG (Abbreviated Reports)	Tested Serum Antibody	CSF	MRI (Abbreviated Reports)
4, Female, 76	Nonpsychotic	+	-	+	+	-	-	Dominant theta background; bursts of bitemporal slow waves, left predominant	NMDAR + VGKC -	Normal	Mild cerebral small vessel disease
1, Male, 77	Nonpsychotic	+	+	+	+	+	-	Periodic temporal sharp waves and polyspikes. Diffuse low amplitude delta activity with intermixed fast activity	NMDAR + VGKC 101	Normal	Diffuse T <sub>2</sub> hyperintensity and swelling; left hippocampus, cortical/subcortical inferior frontal and temporal, insula, pulvinar; mature left middle cerebral artery territory infarct
2, Male, 40	Nonpsychotic	+	-	+	+	+	-	Slow background activity with frequent bifrontal sharp delta waves. Triphasic at times	NMDAR + VGKC - VGCaC - Ro/SSA + TPO -	WCC 25, 94% lymph	Diffuse T <sub>2</sub> hyperintensity of amygdala, hippocampus, splenium of corpus callosum and periventricular white matter bilaterally
13, Female, 27	Nonpsychotic	+	+	+	-	-	-	Runs of theta slowing and sharp waves left temporal	NMDAR + ANA -	Normal	Normal
16, Female, 71	Nonpsychotic	+	+	+	+	+	-	Nearly continuous periodic sharpened slow waves (PLEDs) left temporal, parietal and occipital	NMDAR + LGI1 - CASPR2 - TPO 61 ANA - ds DNA -	OCB matched	T <sub>2</sub> hyperintensity cortical/subcortical in posterior temporal and parietal lobes, left temporal lobe most extensive
9, Female, 54	Nonpsychotic	-	+	+	+	-	-	Mild, diffuse background slowing	NMDAR + VGKC 277 Hu - Yo -	N/A	Nonspecific scattered foci of T <sub>2</sub> high signal in cerebral white matter bilaterally

continued

TABLE 1, continued

Patient Number, Gender, Age (years)	Psychosis	Speech Disturbance	Seizure	Movement Disorder	Reduced Consciousness	Auto-nomic Dysfunction	Teratoma	EEG (Abbreviated Reports)	Tested Serum Antibody	CSF	MRI (Abbreviated Reports)
23, Male, 42	Nonpsychotic	+	+	+	–	–	–	Intermittent bitemporal slowing with spikes and sharpened slow waves	NMDAR + GAD +	OCB unmatched	Resection cavity in right temporal lobe; Known temporal lobe glioma resection ≥20years prior
24, Female, 69	Nonpsychotic	+	–	–	+	+	–	Frequent slow/sharp waves, bifronto-temporal, left emphasis	NMDAR + Hu – Yo –	N/A	Generalized volume loss.
15, Male, 72	Nonpsychotic	+	–	+	+	–	–	Diffusely slow background, left temporal focal slowing	NMDAR + VGKC –	Normal	Extensive T <sub>2</sub> hyperintensity in insula, parietal and lateral temporal lobe
49, Female, 44	Nonpsychotic	+	–	+	+	+	–	Bifrontal and left temporal sharp and slow waves	NMDAR + VGKC 101 Hu – Yo –	Normal	T <sub>2</sub> /flair hyperintensity bilaterally in caudate heads, putamina, globus pallidus, midbrain and right tail of hippocampus
6, Female, 29	Psychotic	+	+	+	+	+	+	Slowed background activity, frequent left temporal sharp waves	NMDAR + VGKC – ANA – TPO – dsDNA –	WCC 31 94% lymph	Normal
7, Female, 36	Psychotic	+	–	+	+	+	+	Normal	NMDAR + VGKC – VGCaC – ANCA – dsDNA – GAD low + Hu – Yo –	OCB unmatched	Small area of cortical T <sub>2</sub> high signal in the posterior right cerebellar hemisphere

continued

TABLE 1, continued

Patient Number, Gender, Age (years)	Psychosis	Speech Disturbance	Seizure	Movement Disorder	Reduced Consciousness	Autonomic Dysfunction	Teratoma	EEG (Abbreviated Reports)	Tested Serum Antibody	CSF	MRI (Abbreviated Reports)
12, Female, 22	Psychotic	+	+	+	+	+	+	Diffuse bilateral left predominant fronto-temporal slow wave with sharpened theta activity	NMDAR + ANCA – dsDNA – GAD –	WCC 30	Diffuse cerebral edema and mild bilateral uncus herniation; diffuse leptomeningeal enhancement
14, Female, 45	Psychotic	+	+	+	+	–	–	Theta and delta transients mainly left temporal	NMDAR +	IgG 37	Normal
17, Female, 22	Psychotic	+	+	+	+	+	+	Right fronto-temporal sharp and slow waves and independent left sharp transients	NMDAR + VGKC – ANCA – dsDNA – GAD –	Protein 0.47g/dL	Normal
18, Female, 23	Psychotic	+	–	+	+	+	–	Diffusely slow background with frontal bilateral high amplitude delta slow waves	ganglioside – NMDAR + (CSF and serum) VGKC –	Normal (no OCB, WCC<5) NMDA +	Normal
19, Female, 32	Psychotic	+	+	+	–	–	–	Abnormal (report unavailable)	NMDAR + (CSF and serum) VGKC –	OCB unmatched NMDA+	Left mesial temporal sclerosis
5, Female, 52	Psychotic	+	–	+	–	+	–	Sharp spikes in temporal area	VGKC – NMDAR + VGKC – Hu – Yo –	Normal	Mild small vessel disease cerebral hemispheres
11, Female, 19	Psychotic	+	–	+	–	+	+	Normal	NMDAR + VGKC – Hu – Yo –	Normal	Normal
20, Male, 56	Psychotic	+	+	–	–	+	–	Focal slowing over left temporal with sharp waves seen intermixed and independently	NMDAR + VGKC 193 Hu – Yo –	Normal	Normal
27, Female, 33	Psychotic	+	–	+	–	+	–	Not available	NMDAR + VGKC – TPO –	N/A	N/A

continued

TABLE 1, continued

Patient Number, Gender, Age (years)	Psychosis	Speech Disturbance	Seizure	Movement Disorder	Reduced Consciousness	Automatic Dysfunctions	Teratoma	EEG (Abbreviated Reports)	Tested Serum Antibody	CSF	MRI (Abbreviated Reports)
48, Male, 37	Psychotic	+	+	+	-	-	-	Frequent right temporal delta brush activity	NMDAR +	OCB unmatched	T <sub>2</sub> hyperintensity and volume loss, right temporal pole and hippocampus; recent HSV encephalitis

<sup>a</sup> The + symbol denotes the presence of the symptom or the antibody indicated; the - symbol denotes the absence of the symptom or the antibody indicated. ANCA=antineutrophil cytoplasmic antibodies; anti-GAD=glutamic acid decarboxylase antibody; anti-NMDAR=N-methyl-D-aspartate receptor antibody; ANA=anti-nuclear antibody; anti-TPO=thyroid peroxidase antibody; anti-VGCaC=voltage gated calcium channel antibodies; anti-VGKC=voltage gated potassium channel antibodies; CASPR2=contactin-associated protein 2; ds DNA=double stranded DNA; LGI1=leucine-rich glioma inactivated 1; HSV=herpes simplex virus; OCB=oligoclonal bands; WCC=white cell count.

TABLE 2. Demographic and Clinical Characteristics of Patients With and Without Psychosis <sup>a</sup>					
Characteristic	With Psychosis (N=12)		Without Psychosis (N=10)		p
	N	%	N	%	
Female	10/12	83	6/10	60	0.348
Psychiatric admission	7/12	58	0/10	0	<b>0.005</b>
Psychiatric review	12/12	100	4/10	40	<b>0.003</b>
Presence of teratoma	5/12	42	0/10	0	<b>0.040</b>
Seizures present	7/12	58.3	5/10	50	1.00
Movement disorder	11/12	91.7	9/10	90	1.00
Autonomic instability	9/12	75	5/10	50	0.378
Reduced consciousness	6/12	50	8/10	80	0.204
Abnormal EEG	9/11	82	10/10	100	0.476
CSF: pleocytosis or oligoclonal bands	5/11	45	3/8	38	1.00
MRI suggestive of encephalitis	3/11	27	4/10	40	0.659
	Mean	SD	Mean	SD	
Age (years)	33.8	12.0	57.2	18.0	<b>0.003</b>
MRS at nadir	4.0	0.95	3.9	1.4	0.842

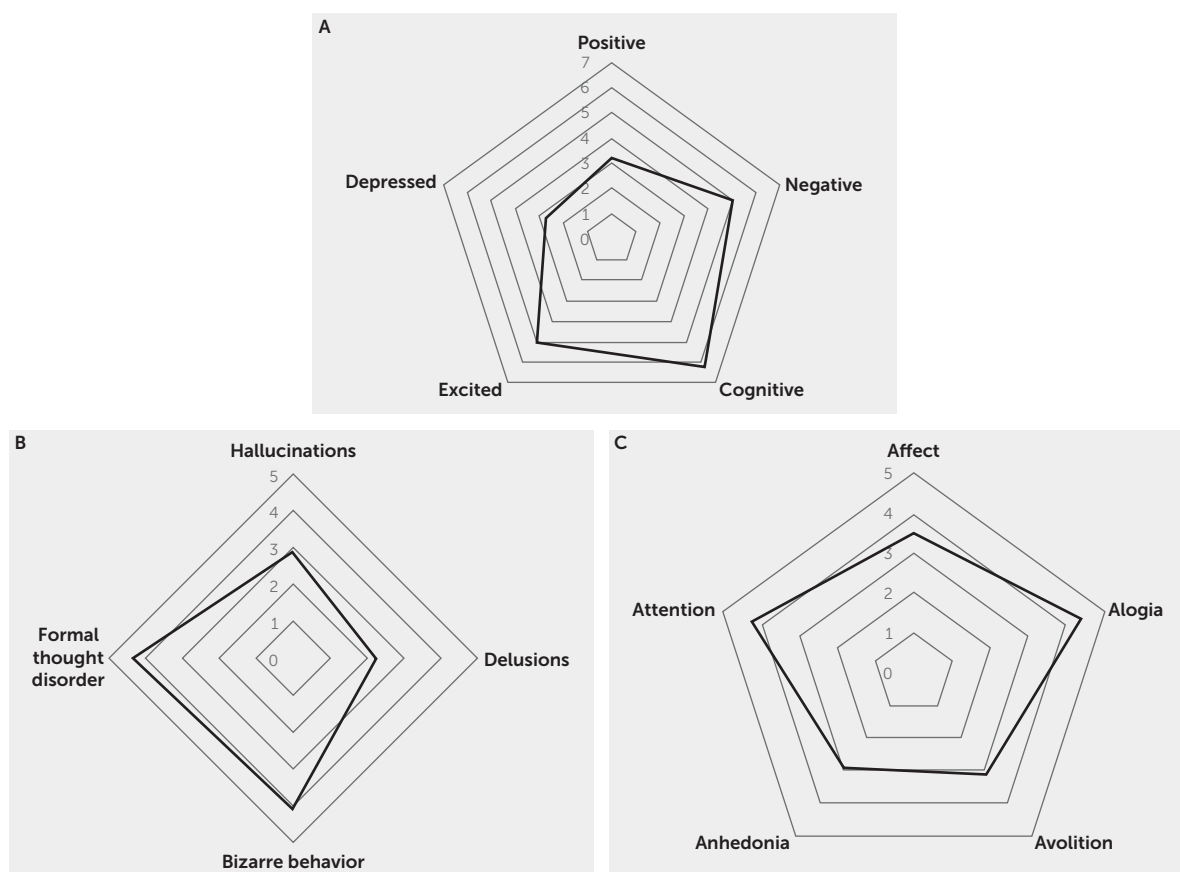
<sup>a</sup> Statistically significant data are indicated in bold. MRS=Modified Rankin Scale.

data.<sup>15</sup> Items were pooled using the Wallwork five-factor model using positive symptoms (delusions, grandiosity, suspiciousness, unusual thought content); negative symptoms (blunted affect, emotional withdrawal, poor rapport, lack of spontaneity, passive social withdrawal, motor retardation); cognitive disorganization (conceptual disorganization, difficulty in abstraction, poor attention); excited (excitement, hostility, uncooperativeness, poor impulse control); and depressed (anxiety, guilt feelings, depression).<sup>16</sup> The SAPS and SANS items are scored from 0 (absent) to 5 (greatest severity). For all patients, symptoms were rated retrospectively by two independent clinicians from the available medical and psychiatric notes. Interrater reliability was assessed with a weighted kappa, which showed acceptable agreement between the two clinicians; Kw=0.62 for PANSS, Kw=0.60 for SAPS/SANS.<sup>19</sup>

Statistical Analyses

Outcomes were compared with respect to symptom pattern using descriptive statistics. Where hallucinations or delusions were reported, the patient was defined as psychotic. On this basis two patient groups were created: psychotic and nonpsychotic. Memory disturbance, speech impairments (aphasia, subjective word finding difficulty, expressive and receptive dysphasia), confusion, and disorientation were not considered to be psychotic phenomena. The two groups were compared on mean age and Modified Rankin Scale (MRS) at nadir with a two-tailed Student's t test.<sup>20</sup> All other comparisons were performed using Fisher's exact test. For the psychotic patient group, within-subject symptom profiles for the PANSS, SAPS and SANS were compared with within-subjects analysis of variance (ANOVA). These

**FIGURE 2. Mean Scores for the Positive and Negative Symptom Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS)<sup>a</sup>**



<sup>a</sup> Panel A shows the mean scores on the Wallwork domains of PANSS. Panel B shows the mean global symptom scores on the Scale for the Assessment of Positive Symptoms. Panel C shows the mean global symptom scores for SANS.

analyses are based on the mean aggregate score of the two independent rating clinicians.

## RESULTS

### Descriptive Data

Just under half of the adults (47%, N=22) with serum NMDAR antibodies satisfied the clinical criteria for probable NMDAR antibody encephalitis and were included in the subsequent analyses. Seventy-three percent (N=16) were female; the mean age was 44 (range, 19–77 years); and 55% (N=12) were acutely psychotic based on the presence of hallucinations or delusions. Thirty-two percent (N=7) had an admission to a psychiatric unit prior to a diagnosis of anti-NMDAR encephalitis.

**Clinical symptoms.** Fifty-five percent (N=12) presented with seizures: two patients with generalized seizures, seven with partial seizures (most commonly complex partial), and three with both generalized and partial seizures. Ninety-one percent (N=20) presented with movement disorder; these were classified into dyskinesia, rigidity/abnormal posture, or movement disorder as per Graus et al.<sup>11</sup> Six patients

presented with dyskinesia alone (67% of which were oro-facial in nature), one with hypertonicity, four with another movement disorder such as dystonia, and nine with more than one of these three symptom groups.

**Investigations.** Ninety percent (N=19) had an abnormal EEG; 42% (N=8) had CSF showing oligoclonal bands or pleocytosis; 33% (N=7) had MRI brain changes suggestive of encephalitis; 23% (N=5) had an ovarian teratoma. Details of these clinical symptoms and investigations are shown in Table 1.

### Psychosis

Patients presenting with psychotic symptoms were significantly younger than those without (33.8 years versus 57.2 years,  $t=3.50$ ,  $df=15.2$ ,  $p<0.005$ ). There was no significant gender difference in patients with or without psychosis ( $p=0.4$ ); however, patients with psychosis were significantly more likely to have an ovarian teratoma ( $p=0.040$ ). Patients with psychosis were more likely to have a psychiatric inpatient admission ( $p=0.005$ ) and psychiatric review while on a medical ward ( $p<0.005$ ). There was no difference in overall clinical severity at nadir between patients with



psychosis and patients without psychosis (based on MRS,  $t(20) = -0.201$ ,  $p = 0.8$ ). See Table 2 for figures.

**Psychosis subgroup: PANSS symptom profile.** For the 12 patients with psychosis according to our definition, PANSS scores indicated a severe degree of psychopathology; mean score 135.2 (range, 86–169).<sup>21</sup> The highest mean scores were on items of conceptual disorganization (6.4), poor abstract thinking (6.1), attention (6.1), and poor rapport (6.2). Low scores were seen on items measuring guilt (1.5) and somatic concern (1.8).

PANSS five-factor analysis showed some symptomatic domains to be disproportionately affected (Figure 2A). Within-subjects ANOVA showed a significant difference between the means of the five domains ( $F = 19.3$ ,  $df = 4, 44$ ,  $p < 0.005$ ), with post hoc tests indicating that patients had more significant cognitive symptoms than depressive ( $p < 0.005$ ) or positive features ( $p = 0.003$ ). Patients exhibited high negative symptom scores (Figure 2A).

**Psychosis subgroup: SAPS and SANS profile.** A significant effect for SAPS subscale on ANOVA ( $F = 20.469$ ,  $df = 3, 33$ ,  $p < 0.005$ ) indicated a higher degree of thought disorder and bizarre behavior than other SAPS factors (Figure 2B). Post hoc analyses on the SAPS showed that formal thought disorder was significantly more severe than delusional ( $p = 0.002$ ) or hallucinatory behavior ( $p < 0.005$ ). Similarly, patients were more affected by bizarre behavior than hallucinations ( $p < 0.005$ ) or delusions ( $p = 0.002$ ). A qualitative review of the notes revealed that delusions were often poorly formed and unstable.

On the SANS, the observed differences between the means were also significant ( $F = 9.07$ ,  $df = 1.81, 20.0$ ,  $p = 0.002$ ), with speech production and attention most profoundly impaired (Figure 2C).

**Nonpsychosis subgroup: symptom profile.** Ten patients did not have psychotic symptoms, 80% ( $N = 8$ ) presented with confusion and disorientation, 60% ( $N = 6$ ) had memory deficits, 30% ( $N = 3$ ) were aphasic, and a further 40% ( $N = 4$ ) presented with partial language disturbance: one predominantly expressive, one receptive, and two with receptive and expressive components. These distinctions were documented by the treating clinician. Four were unable to reliably follow commands, and three had symptoms of low mood. In one patient, this was particularly severe, with quiet speech and psychomotor retardation.

Finally, a contrast between older and younger patients based on a cut-off of 40 years revealed no significant differences in gender, symptom groups other than psychosis, or abnormalities on clinical investigations.

## DISCUSSION

Much of the literature to date on the psychiatric features of anti-NMDAR encephalitis has highlighted prominent

positive symptoms such as bizarre behavior, hallucinations, and delusions. However, the detailed description of psychopathology in our patient group has revealed for the first time, in addition to positive and classic encephalitic symptoms marked negative symptoms as commonly described in functional psychoses such as schizophrenia. This is congruent with an animal model of anti-NMDAR encephalitis that showed profound memory deficits and anhedonia.<sup>22</sup> However, this does little to distinguish the psychiatric features of anti-NMDAR encephalitis from other psychiatric populations.

Apparent differences did emerge when considering the phenomenology of the psychosis seen in anti-NMDAR encephalitis. In particular, patients had severe cognitive disturbance relative to other domains; marked cognitive impairment is a clear phenotypic red flag for anti-NMDA encephalitis. There was a tendency for patients to be more disturbed by thought disorder and bizarre behavior as opposed to delusions and hallucinations, in contrast with the typical presentation in first-episode psychosis and schizophrenia populations.<sup>23</sup> Furthermore, clinicians should not let the presence of negative symptoms distract from the possibility of anti-NMDAR encephalitis; indeed, particular suspicion should be aroused in cases of prominent alolia and distractibility, less common in functional psychoses.<sup>23</sup> Given the difficulty in diagnosing anti-NMDAR encephalitis, such unusual presentations within psychiatric inpatients should warrant further investigation and antibody testing.

This pattern of symptoms mirrors those seen in pharmacological models of NMDAR hypofunction. Prominent negative symptoms, cognitive impairment, and thought disorder with relatively less severe hallucinations and delusions are characteristic in ketamine-induced models of psychosis.<sup>24,25</sup> While in anti-NMDAR encephalitis the down-regulation of receptors is antibody mediated, ketamine non-competitively antagonizes NMDAR.<sup>25,26</sup> Given that NMDAR hypofunction is common to both, the degree of similarity in symptom profile is perhaps unsurprising. This lends support to suggestions of a unique psychopathological profile arising from glutamatergic psychosis, as well as a potential mechanism underpinning the dimensions of psychosis seen in anti-NMDAR encephalitis.

Those encephalitis patients with prominent psychotic features were significantly younger than those without. This, without any other differences seen in symptoms or investigations, is consistent with greater susceptibility of the young brain to psychosis. Indeed, in general psychiatry, the higher incidence and greater severity of psychosis in younger (versus older) adults is well recognized.<sup>27</sup>

## Limitations

Few of our patients underwent CSF antibody testing and no confirmatory immunoassays were included, as these had not been commonly used in U.K. clinical practice at the time of the study. For a diagnosis of definite anti-NMDAR encephalitis, Graus et al. require either positive CSF NMDAR



antibody or confirmatory immunoassays in addition to cell-based assay.<sup>11</sup> Consequently, only two of our patient sample can be said to have definite anti-NMDAR encephalitis.

In order to mitigate diagnostic concerns and avoid including patients with potentially false positive serum antibodies, we selected patients who were both seropositive and who also met the more clinically stringent criteria for probable anti-NMDAR encephalitis. These criteria are designed to identify patients with probable anti-NMDAR encephalitis in the absence of antibody results. By selecting only patients who met these criteria and also had serum antibodies, we enriched their pretest probability. Indeed, two recent validation studies in adult and pediatric populations demonstrate a high specificity for anti-NMDAR encephalitis using these criteria alone, with a false positive rate of under 4%.<sup>12,13</sup> There is also a suggestion that in older adults the criteria may not recognize the clinical diversity seen.<sup>13</sup> Given that our patients did not meet the definite criteria on immunoassay grounds and yet were all seropositive for NMDAR antibodies and met criteria for probable anti-NMDAR encephalitis, these patients occupy a diagnostic terrain somewhere between probable and definite anti-NMDAR encephalitis. We can also be reassured by the low false positive rates seen in validation studies. Nonetheless, replication in a patient group with CSF-confirmed anti-NMDAR encephalitis is desirable.

The small sample and retrospective review of case notes were limitations of this study; older patients appeared to be overrepresented relative to previous studies. The described differences are qualitative: direct comparisons of features between idiopathic and secondary psychosis are difficult without matched controls. A future case-control study to compare psychotic features of patients with anti-NMDAR encephalitis and first-episode idiopathic psychosis would be a valuable next step.

The PANSS is typically conducted as a clinical interview, but the retrospective nature of this study only allowed for review of the clinical notes. However, the dual rating by independent clinicians achieving agreement of  $K_W=0.62$  indicates that despite this limitation, clinicians were able to reliably assess psychiatric symptoms from the recorded notes.

## CONCLUSIONS

We have characterized in detail the nature and range of psychopathology present in a sample of adults presenting with probable anti-NMDAR encephalitis, outlining a psychiatric phenotype with a distinctive constellation of psychotic and cognitive features. While replication in a larger prospective study using CSF to confirm the diagnosis is clearly desirable, further work might also be directed at uncovering mechanisms whereby NMDAR antibodies lead to this particular pattern of symptoms, which would have implications across neuropsychiatric disorders.

## AUTHOR AND ARTICLE INFORMATION

From the Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, London (LLG, TAP, GB, ASD); South London and Maudsley NHS Foundation Trust, London (LLG, GB, MT); and the Department of Neuroscience, Kent and Canterbury Hospital, East Kent Hospitals University Foundation Trust, Kent, United Kingdom (NM).

Send correspondence to Dr. Gibson; e-mail: Lucy.Gibson@slam.nhs.uk

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