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## Creativity and mental disorder

George Kirov and Geoffrey Miller

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## Correspondence

Edited by Kiriakos Xenitidis and  
Colin Campbell

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## Antibody-mediated encephalitis and psychosis

The four cases of *N*-methyl-D-aspartate (NMDA) receptor antibody encephalitis with associated psychosis reported in December<sup>1</sup> raise an important and emerging issue and highlight that psychiatrists should include the condition in the differential diagnosis for patients presenting with acute psychosis. But there are some aspects that need clarification. The authors state that ‘this case series demonstrates a new and treatable cause of psychosis’, inferring that the association of psychosis with these antibodies was previously unknown. However, since the first 100 patients with NMDA receptor antibody encephalitis were reported in 2008,<sup>2</sup> this association has been well documented; psychosis is typically the first presentation and many cases were seen by psychiatrists before neurologists become involved.<sup>2,3</sup>

The association of these antibodies with psychosis is highly relevant because they bind to key neuronal surface proteins and are therefore likely to be pathogenic. Indeed, NMDA receptor antibody encephalitis is a condition that responds to immunotherapy and, importantly, there is thought to be an initial ‘treatment window’ for optimal immunomodulation.<sup>4,5</sup> The authors<sup>1</sup> speculate that ‘there may be a pure psychiatric presentation associated with lower antibody titres’. Indeed, a recent study found that 3 out of 46 patients with first-episode psychosis (with no neurological or other clinically distinguishing features) had NMDA receptor antibodies.<sup>6</sup> One patient made a significant clinical improvement with plasmapheresis and steroid treatment. An additional patient had voltage-gated potassium channel antibodies, which can also be found in patients with other psychiatric presentations.<sup>5,7</sup> It now appears increasingly likely that other neuropsychiatric (e.g. catatonia) and psychiatric (e.g. obsessive-compulsive) symptoms may be associated with cell-surface neuronal antibodies.<sup>8</sup>

As Barry *et al*<sup>1</sup> point out, the condition does indeed provide some support for the NMDA receptor hypofunction hypothesis for psychosis. Some proponents of this theory have linked NMDA receptor hypofunction to first-rank psychotic symptoms in particular.<sup>9</sup> It is important that future studies of auto-antibody-associated psychosis characterise symptomatology in full, as this could allow for a level of clinical-pathological correlation rarely attained in psychiatry.

## Declaration of interest

T.R.N. is supported by the Medical Research Council. T.A.P. and B.R.L. receive support from the National Institute for Health Research. A.V. receives royalties from Athena Diagnostics. A.V. and the Nuffield Department of Clinical Neurosciences in Oxford receive royalties and payments for antibody assays. B.R.L. and A.V.

have written an editorial on this topic published in the February issue of the *Journal*.

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**Authors' reply:** We thank Pollak *et al* for reiterating that anti-NMDA receptor encephalitis should be included as a differential diagnosis for patients presenting with acute psychosis. The association of anti-NMDA receptor encephalitis with psychosis is new, having been identified only as recently as 2008,<sup>1</sup> although the disorder has likely gone unrecognised and indeed untreated previously. Although to date there are no estimates regarding population prevalence rates of anti-NMDA receptor encephalitis, the California Encephalitis Project retrospectively screened 3000 patients with idiopathic encephalitis (with dyskinesia or movement disorders) and identified 10 (0.3%) anti-NMDA receptor-positive cases.<sup>2</sup> Examining the incidence of catatonia in psychosis, Fink & Taylor estimate a prevalence of between 9 and 17% of patients in academic psychiatry in-patient units,<sup>3</sup> while Peralta *et al* found that 31% of drug-naïve patients with first-onset psychosis demonstrated at least one catatonic symptom, and found an interesting subgroup that showed a clear association with disorganisation and dyskinesia.<sup>4</sup>

The neuropsychiatric presentation underlying NMDA receptor encephalitis has only recently been published in the psychiatric literature.<sup>5</sup> Consequently, this clinical presentation involving psychiatric symptoms in approximately 77% of affected individuals has not been widely disseminated among psychiatrists. This was the driving force behind the publication of our case series.

Pollak *et al* restate our view that ‘there may be a pure psychiatric presentation associated with lower antibody titres’, and point to their own recent work showing that 3 out of 46 patients with first-episode psychosis had NMDA receptor antibodies.<sup>6</sup> This extremely important finding has profound

implications for future differential diagnoses of first-onset psychosis, potentially involving relevant auto-antibody and, specifically, anti-NMDA receptor screening. Further, plasmapheresis may be required and in some cases may even be clinically indicated before a diagnosis of NMDA receptor encephalitis is confirmed. This will have implications for hospital resources and will require close liaison between psychiatry and neurology services.

N-methyl-D-aspartate receptor hypofunction, whether due to exposure to phencyclidine ingestion, NMDA receptor auto-antibody or altered NMDA receptor trafficking,<sup>7,8</sup> is now implicated even more strongly in schizophrenia. Future studies focusing on this area may provide clues not only to the screening and management of NMDA receptor encephalitis among first-episode psychosis populations, but may also lead to a broader understanding of schizophrenia pathophysiology, with the potential for development of novel treatment strategies.

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## Occipital transcranial magnetic stimulation in dementia with Lewy bodies

The results of Taylor *et al*'s study<sup>1</sup> are intriguing, shedding light on the pathogenesis of visual hallucinations in dementia with Lewy bodies.

However, I have some concerns about its methodology. The authors did not adopt the rather restrictive (and currently used) definition of phosphene threshold (i.e. the lowest stimulus intensity required to elicit phosphenes in 50% of trials), but used a much lower value (25%) to minimise the number of participants who might not respond. Moreover, to ensure inclusion of all individuals in analyses, participants who did not report phosphenes up to 100% stimulator output were arbitrated a phosphene threshold of 101%. The authors therefore assumed that not reporting phosphenes meant having a threshold above 100%

because of an insufficient magnetic field strength from the stimulator to induce phosphenes in these individuals. However, as far as I know, to date there is no evidence definitely demonstrating such an assumption.

As a matter of fact, in most published studies of phosphene thresholds a certain number of participants do not experience phosphenes even with a maximum stimulator output. There are some reasons which may (partially) explain such a phenomenon.

First, it is possible that owing to methodological difficulties in mapping phosphene thresholds over each square millimetre of the occipital skull, the correct point for stimulation may not be identified in each participant.

Second, unlike primary motor cortex, primary visual cortex (calcarine fissure) is deeply located, lying in the mid-sagittal plane, so that the magnetic field strength applied over the entire skull may be insufficient to reach and stimulate the visual cortex. Regarding this aspect, it is noteworthy to consider that Taylor *et al* used a figure-of-eight coil (and not a circular one), which, although it is much more selective and has a higher spatial accuracy, stimulates a smaller cortical area,<sup>2,3</sup> and may generate, at least theoretically, a weaker electric current, resulting in a lower probability of evoking phosphenes.

Finally, as the authors stated, every millimetre the surface cortex is away from the stimulating coil, approximately an additional 3% of the maximum power output is required to induce an equivalent level of brain stimulation at the motor cortex (although no similar data on visual cortex stimulation are available in the literature). Such an aspect needs to be taken into account not only with regard to occipital cortical atrophy in affected patients compared with healthy controls, but also with regard to the fact that, because the lower portion of the visual cortex representing the upper visual field is farther from the scalp (as observed in magnetic resonance imaging), it is more difficult to elicit phosphenes with transcranial magnetic stimulation in the upper than in the lower visual field.<sup>4</sup> Although in the study an adjusted phosphene threshold ratio was performed to account for possible group differences in atrophy, it is not clear whether other aspects (anatomical differences in skull thickness and portion of visual cortex stimulated) were considered.

In the light of the above, I think that the authors should have performed a statistical analysis of phosphene threshold including only those participants in whom phosphenes were actually induced.

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**Authors' reply:** We agree that phosphene thresholds are typically defined at the 50% response rate level, although it should be recognised that the setting of a threshold is an arbitrary process. A number of our participants had thresholds near and

approaching the maximum stimulator output and use of a lower level of threshold acceptance allowed for a more precise estimation of their visual cortical excitability. Importantly, given the comparability between stimulus response plots of controls and patients with dementia with Lewy bodies (Fig. 2),<sup>1</sup> it is unlikely that use of a 25% cut-off for threshold adversely affected our findings.

Dr Brigo highlights the issue of non-response to the stimulation and that this may be as a result of causes other than insufficient stimulation strength. Indeed, phosphene perception, or lack of, may not necessarily originate in the visual cortex but may depend on higher visual areas or indeed non-visual areas as well as recurrent processing.<sup>2,3</sup> However, the reasons that Dr Brigo presents to explain the non-response – including imprecision in finding the optimal position for stimulation delivery over the occiput, greater depth of the primary visual cortex leading to reduced magnetic field strength at the level of the cortex, and use of the figure-of-eight coil – are actually arguments supporting the assumption that failure to respond in some individuals is due to insufficient current stimulation to the neural locus responsible for phosphene elicitation.

In our study we sampled nine equally spaced scalp sites, giving good symmetrical cover of the occiput; this was a compromise between precision and limiting the experiment duration in a vulnerable patient group. The figure-of-eight coil has been frequently used in phosphene research (e.g. Kammer *et al*<sup>4</sup>) and was chosen because of its spatial accuracy; larger, diffuse-field coils could theoretically activate areas external to the visual areas of interest or indeed induce retinal phosphenes. In addition, we would contend that the transcranial magnetic stimulation (TMS) methodologies we employed meant that we had comparable and, in some cases, better rates of phosphene response compared with other studies in young healthy individuals.

Dr Brigo indicates potential differences in the lower and upper visual cortical activation with TMS and certainly our data of greater phosphene elicitation in the lower visual fields supports this. Our use of the adjusted phosphene threshold ratio to control for group differences in atrophy also accounted for skull thickness, although whether the positions we chose for these measurements directly related to the precise locus of stimulation on the visual cortex, we agree, is a methodological limitation. The use of magnetic resonance-guided stereotactic coil placement, for example, would help with this issue and allow for more precise threshold determination.

As suggested by Dr Brigo we performed an analysis only on those participants who responded to TMS (controls,  $n=17$ ; patients,  $n=17$ ) and the findings were in line with our main analyses: there were no significant differences between the controls and patients for phosphene threshold (controls: median 64.0% (IQR = 32.5%); patients: median 67.0% (IQR = 20.0%);  $U=139.5$ ,  $P=0.87$ ) and phosphene response rate (controls: median 6.0 (IQR = 7.0); patients: median 8 (IQR = 5);  $U=112.5$ ,  $P=0.27$ ). Correlations between the Neuropsychiatric Inventory hallucinations subscale score in patient responders and the phosphene excitability measures (phosphene threshold, Kendall's  $t = -0.28$ ,  $P=0.15$ ; phosphene response rate,  $t = 0.46$ ,  $P=0.02$ ) were in the same direction as the main analysis, although less significant owing to the smaller sample and the fact that the four patients who did not respond to TMS at the maximum stimulator output had significantly less severe and frequent visual hallucinations compared with patient responders (Mann–Whitney  $U$ -test 16.5,  $P < 0.001$ ). Clearly, the lack of phosphene response (regardless of cause) is associated with fewer visual hallucinations and thus we would argue that inclusion of non-responders in our analyses is essential in providing a more holistic understanding of

the underlying aetiology of this symptom in dementia with Lewy bodies.

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## Creativity and mental disorder

Kyaga *et al* found an intriguing association between creativity and severe mental disorder.<sup>1</sup> The study draws its strength from a large sample size. However, the retrospective data collection methodology brings with it certain inherent limitations, which the authors have acknowledged, and causal links have been hinted at in the discussion. We would like to bring to attention two issues. First, the role of potential confounders in selection of occupation has not been taken into consideration. The type of occupation one pursues is governed by multiple factors in addition to personnel interest, including educational qualification, opportunity, awareness, location of the job, financial remuneration, familial and other social commitments.<sup>2</sup> Many of these variables are likely to be affected by the psychiatric illness, although they are modifiable by many independent factors as well. Hence the occupation choices of both individuals with mental illness and their children (and other family members) are likely to be affected by many variables which need to be taken into consideration when interpreting Kyaga *et al*'s findings.

Another relevant issue for consideration is the way occupation is defined in their study. The definition of occupation used in (mental) health studies has been criticised for being too restrictive.<sup>3</sup> National descriptions of occupation tend to classify only those occupations that have economic relevance.<sup>4</sup> Such an approach is likely to miss someone employed as a labourer who paints during their leisure time or to miss certain population groups. For example, in many settings the majority of women are likely to be the primary caregiver (i.e. housewife) and not formally 'employed'. Future studies could be strengthened by the use of a more comprehensive and inclusive definition of occupation.

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The article by Kyaga *et al*<sup>1</sup> is an important contribution to the understanding of the selective advantage and disadvantage of common behavioural phenotypes. The accompanying editorial by Jamison puts this work in context and points out that the overlap between creativity and mental disorder is partial.<sup>2</sup> The proportion of persons in creative professions in Sweden is about 1.1% (based on the 1990 Swedish census, ages 15–64, and excluding scientific professions). The figure for the USA is similar: 1.4%.<sup>3</sup> Our report in the neurological literature proposes that polymorphisms in the alpha-1-antitrypsin (A1AT) gene are a common genetic factor for both creativity and mental disorder.<sup>4</sup> The proportion of people in creative professions observed in 1537 consecutive patients was 3.7%. A highly significant 38% of people in creative professions carried one or more polymorphisms of the A1AT gene compared with the 13% carrier rate observed in the other participants in this study,<sup>4</sup> and similar to reported rates in European populations. When the larger proportion (20–30%) of the population that pursue creative avocations (acting, dancing, music, photography, visual arts, writing) are considered, the same relationship of A1AT carriers and creativity and ‘intense mental energy’, including clinical anxiety or bipolar disorder, is observed.<sup>4</sup> An extension of these previous clinical series now totals 3176 consecutive patients and confirms the original findings<sup>4</sup> (details available from the author on request). This means that creativity and mental disorder can overlap and one instance for many such cases may be the genetic and environmentally modulated interactions of A1AT liver protein and serum acute phase reactant. It is important to emphasise that not all artists are A1AT carriers and not all artists have intense goal-directed energy or even mood disorder, underlining the point of Jamison’s editorial. Nevertheless, it is likely that many people carrying A1AT polymorphisms trade the selective advantage of intense creative energy (blessing) for the disadvantage of susceptibility to lung and liver disease, and potentially significant recurrent mood disorder (curse). Pulmonary disease is associated with bipolar disorder (see Schmechel<sup>4</sup>), and A1AT polymorphisms would provide a genetic basis.

#### Declaration of interest

D.E.S. is principal inventor on a US patent in preliminary examination with regard to the use of A1AT as a therapeutic target in Alzheimer’s disease.

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Kyaga *et al*<sup>1</sup> have produced an excellent analysis based on the Swedish registers, which finds an increased rate of creativity in patients with schizophrenia or bipolar disorder, and their relatives. This lends support to the model for a correlation between schizophrenia, creativity and fitness that was developed jointly by one of us.<sup>2</sup> However, the authors claim that this finding supports the balancing selection hypothesis that aims to explain

why psychiatric disorders have persisted throughout evolution. The theory stipulates that if patients with such severe disorders have fewer children, then the genetic variants responsible for the illnesses should be filtered out from the general population, unless this effect is balanced by adaptive advantages harboured by these variants. Relatives of patients, who also carry such variants but are free from illness, might therefore have an increased fitness.

A higher level of creativity could indeed be advantageous and increase fitness, as outlined by the authors. However, there are many other qualities that can also increase fitness, for example being faster, stronger, having a higher cognitive ability, being more attractive or living longer. The only outcome that matters for evolution is how many children an individual will leave, because if one does not pass on his or her genetic variants, these variants will disappear from the population. However, a systematic review found that patients with schizophrenia have a fertility ratio of only 0.39 compared with the general population,<sup>3</sup> and a more recent study of the Danish population also found strongly reduced rates for both schizophrenia and bipolar disorder.<sup>4</sup> More importantly, any possible increased fertility among relatives is too small to compensate for the strongly reduced fertility of patients.<sup>3,5</sup>

In contrast, the alternative mutation selection hypothesis, which the authors also discuss, can explain this apparent paradox, provided new (*de novo*) mutations replenish those that are lost because of reduced fitness. We found that about 5% of probands with schizophrenia had a *de novo* copy number variation (CNV), a twofold higher rate than in controls.<sup>5</sup> A large proportion of these CNVs appear to be under strong selection pressure. In fact, the ten best supported CNV loci that increase risk to develop this disorder have high mutation rates (a *de novo* CNV occurring in between 1:3500 and 1:30 000 individuals), and are under strong selection pressure. This leads to the elimination from the general population of each new mutation at these loci in less than five generations on average.<sup>6</sup> We anticipate that ongoing next-generation sequencing studies will also implicate the more numerous point mutations, and could help resolve this debate.

Increased creativity among individuals with severe psychiatric disorders is an advantage to them and their relatives and could cause increased fitness in relatives, but *de novo* mutations appear to be more relevant for the persistence of these disorders in the population.

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**Authors' reply:** Patra & Balhara point to limitations of retrospective designs. However, it should be noted that our data were collected prospectively and thus not open to recall bias. They also stress that many factors are important when choosing occupation, many of which are in turn influenced by psychiatric disorders. There are indeed a plethora of determinants of occupational choices, but we addressed the bias of psychiatric disorder *per se* by also investigating the patient's healthy relatives, where we found a stronger association with creative occupations than among the patients themselves.

We agree with Patra & Balhara that using the term occupation is likely to miss creative activity unrelated to economic production, and therefore commented in the paper that schizophrenia might be associated with creative avocational rather than vocational activities. The aim of our study was, however, not to problematise the concept of occupation, but to use these validated occupations as a proxy for creativity. Thus, those with creative occupations are on average more creative than other people.

Schmechel gives an interesting reference regarding alpha-1-antitrypsin polymorphisms and both artistic avocations and occupations, adding to the list of recently found polymorphisms associated with increased creativity as well as to observations of alterations in white matter integrity in both psychopathology and creativity.<sup>1</sup> Indeed, if we believe that the association between creativity and psychopathology is contingent on genetic factors, we should give high priority to elucidate the specific genetic mechanism.

Kirov & Miller point out the paradox of high heritability and low fertility combined with a stable prevalence of schizophrenia, which was early noted by the Swedish psychiatrist Essen-Möller.<sup>2</sup> These findings have been repeatedly demonstrated in schizophrenia and to some extent, although with conflicting results, in bipolar disorder.<sup>3</sup> However, fertility rates may be biased and it has been argued that reduced fertility in patients with schizophrenia and their relatives does not constitute evidence against sexual selection on susceptibility genes for schizophrenia.<sup>4</sup>

We agree that mutation selection is one likely mechanism by which the persistence of psychiatric disorder can be explained, albeit some discrepancy between different psychiatric disorders seems warranted. This does not, however, rule out the presence of balancing selection. To cite Keller & Miller:<sup>5</sup> 'The normal range of creativity may be nearly neutral (or under balancing selection). Most of the genetic risk of mental disorders comes from harmful mutations. High creativity has negative effects on fitness when coupled with a high mutation background because it increases the risk of mental disorders, but it has positive effects when in a low mutation background.' In fact, 'creativity could be a sexually selected signal, designed to partially reveal one's mutation load: only those with a low mutation load can afford the cost of being creative.'<sup>5</sup> In this way, these authors have elegantly explained both the age-old observation of genius and madness, while preceding future results of next-generation sequencing studies.

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