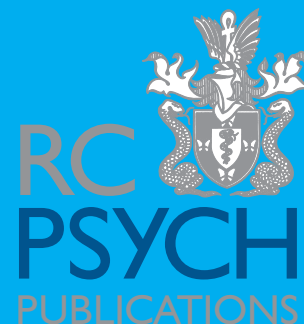


Neuropsychiatry News

Newsletter of the Section of Neuropsychiatry
Royal College of Psychiatrists



Issue 4, Spring 2011

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From the Chair

Since the last *Neuropsychiatry News*, the Section of Neuropsychiatry has continued to promote our specialism in many areas within the Royal College of Psychiatrists as well as elsewhere. We have contributed to the many initiatives undertaken by the College such as the Fair Deal campaign and the Joint Commissioning Panel. This is very important as many new psychiatric services, along with other services, are under threat at present and it is vital that the new commissioners, whom ever they might be, understand the role and usefulness of the neuropsychiatric approach. The Fair Deal campaign has, as one of its main areas of challenge, the difficulty of linking mental and physical health. Clearly, the Section of Neuropsychiatry is essential to this aspect of health promotion and has had important things to say about these links. After all, the link between mental and physical health is the central concept of neuropsychiatry.

In the new era of National Health Service (NHS) funding and 'cost efficiencies', neuropsychiatry is going to have to fight its corner. It is unfortunate that neuropsychiatry sometimes is seen, wrongly, as a very specialised and perhaps often a poorly relevant area of medicine, whereas, in reality, neuropsychiatry is essential to the whole of medical practice. Simply in financial terms, the management of complex conversion and somatoform disorders costs the NHS many millions if not billions every year. Involvement of neuropsychiatry in these conditions is vital and often it is only the trained neuropsychiatrist who can manage these clinically very

difficult situations confidently with knowledge both of psychiatric and physical medicine.

The current issue of *Neuropsychiatry News* is an excellent example of the breadth of neuropsychiatric understanding and, indeed, of the difficulties which neurologists may well have when dealing with 'functional' neurological symptoms. Neuropsychiatry is also able to take on challenging areas of practice elsewhere in the world, as the report from South Africa shows. This issue also contains an important set of screening tools for use in one of the core areas of neuropsychiatry: neuropsychiatric aspects of epilepsy. Sleep-related medicine, another core area of neuropsychiatry, is also represented in a paper which demonstrates the necessity of understanding the neuropsychiatric perspective of what, with little depth of thinking, could be seen as a purely 'neurological condition'. Basic brain sciences are also well represented, demonstrating again, the breadth and innate interest of brain-behaviour relationships.

Finally, once you have feasted on the depth and range of papers in this newsletter, you will see that the Section of Neuropsychiatry is meeting on the 8th and 9th September 2011 for a residential conference in Cambridge. And so, fired up with neuropsychiatric interest you will, no doubt, not only want to come but also want to present your own research and, if a trainee, put in an application for the Neuropsychiatry Training Award – see you there.

Dr Jonathan Bird
Chair, Section of Neuropsychiatry
Royal College of Psychiatrists



Psychiatry lessons for neurologists?

Andrew Wilner, MD

Neurohospitalist, USA

As a neurologist working for a busy in-patient consultation service, most of my patients suffer from stroke, transient ischemic attacks, seizures, confusion or episodes of loss of consciousness. They present challenges in diagnosis and management that compel me to call upon all I've learned in two residencies (neurology and internal medicine) as well as during an epilepsy fellowship.

But there is one group of patients that has me stumped. What do I do with patients who think they suffer from a neurological disease, but I can't find it?

A few case studies^a

Case study A

A seemingly well-adjusted woman, twice divorced, with a history of two strokes was admitted from the emergency room with a sudden onset of ataxia. Initially, there was nothing to suggest that this was anything but a routine neurological consultation. The emergency room physician suspected a new cerebellar stroke, as she was literally holding onto the walls to keep from falling. Yet her magnetic resonance imaging (MRI) results were normal, with no evidence of a new or old stroke. She had no nausea, vomiting, vertigo or nystagmus to suggest vestibular dysfunction. Her symptoms waxed and waned in an unusual fashion, reinforcing the possibility of a non-neurological disease. When I asked the patient about the possibility of depression, she became tearful and reluctantly admitted to years of sexual abuse from her uncle, who had just moved back to town. It became evident that the current ataxia, as well as her previous 'strokes', were psychiatric in nature, precipitated by some combination of stressors. Apparently, her 'ataxia' afforded her a reliable entry into the relative safety of the hospital. A psychiatric diagnosis had never been suspected in any prior hospital admission.

Case study B

A male patient presented with acute sensory loss on the left hemibody, and he was admitted as having recurrent stroke from the emergency room. He had a documented right basal ganglia infarct several years before, which had left him with minimal left-sided weakness. Examination revealed a dense left-sided hemisensory loss, including loss of hearing, loss of all vision and loss of all sensation, which split the body down the midline (according to the patient). His MRI did show an old right basal ganglia infarct, but the lesion was too limited to account for his current neurological deficits. His symptoms appeared to

be an elaboration of the mild weakness he had sustained from the stroke several years before. When I told the patient that he had not had an acute stroke, he became angry and left the hospital against medical advice. Several weeks later he was readmitted for yet more sensory symptoms (his third 'stroke'). Diagnosed as an 'acute stroke' in the emergency room, he was considered for tissue plasminogen activator (tPA). An MRI failed to reveal any diffusion abnormalities suggestive of acute ischaemia. His symptoms persisted, and he was eventually transferred to the rehabilitation unit. A week later, the patient developed a bizarre gait, and I was called to see him by the rehabilitation physician. He would walk and swing his left leg forwards and backwards three or four times before taking a step. He somehow managed to keep his balance during these wild gyrations. My detailed examination failed to produce a neurological explanation for these movements. I gently suggested that stress might be playing a role in these symptoms, which the patient, an unemployed father of seven children, vehemently denied. He continued his rehabilitation, ultimately improving enough to be discharged home.

Case study C

A homosexual male with 20 years of relapsing–remitting multiple sclerosis had a sudden increase in symptoms and was unable to walk. Up until then, he had managed at home with a cane and sometimes used a walker. His neurological examination was abnormal, with limb weakness, increased tone, hyperreflexia and many other signs of multiple sclerosis. Yet his MRI failed to show any acute lesions in either his brain or spinal cord. HIV was negative. It seemed that his 'multiple sclerosis exacerbation' coincided with the abrupt departure of his live-in partner of 15 years. Four days of intravenous steroids did not improve his symptoms. He was admitted to rehabilitation for 2 weeks, with eventual symptom improvement.

Diagnosis and treatment

I could give many more examples from my hospital practice, including patients with pseudoseizures, pseudomyasthenia gravis and pseudodystonia.

In each of the cases above, the initial presumption of a neurological disease led to excessive testing (MRI scans, carotid ultrasounds, cardiac echo, etc.), and prolonged hospital stays. One patient almost received tPA! My suggestion that the problem might be psychiatric instead of neurological was generally greeted with hostility by the

a. These cases are drawn from clinical practice, but have been anonymised to protect the patients' privacy.

patients and skepticism by other caregivers. Psychiatric consultation was obtained, but in my hospital, psychiatric consultations are performed by mid-level providers, whose depth of knowledge regarding conversion disorder seemed limited.

In all of these cases, I eventually chose to treat the patients as if they actually had the neurological disorder in question (i.e. stroke or multiple sclerosis exacerbation), while trying to avoid potentially toxic or dangerous interventions. This approach allowed the patients to save face and continue working with physical, occupational and rehabilitation specialists in the hope that continued medical attention (and the gift of time) might lead to recuperation. In the case of the patient with multiple sclerosis, I prescribed steroids because he expected it, and because I initially harbored some doubt whether his symptoms were neurological or psychiatric. The patient with ataxia was prescribed an antidepressant. In all cases, I offered comfort by suggesting that the current symptoms were not due to a brain abnormality, but rather precipitated by stress, a vague but nonetheless readily grasped concept, if not always accepted.

Conclusions

Despite the fact that I have a framed certificate from the American Board of Psychiatry and Neurology attesting to my diagnostic and therapeutic skills, I feel woefully ill-prepared to treat patients with psychiatric diseases

masquerading as neurological illnesses. When I was a resident, I remember performing neurology consultations in the psychiatry unit, but I don't remember doing any psychiatry consultations on the neurology floor, which would have proven helpful. As an epileptologist, I feel comfortable with the concept of pseudoseizures (non-epileptic seizures), but now it appears I must learn about pseudostroke, pseudomultiple sclerosis, pseudomyasthenia, pseudodystonia and other pseudodiseases.

According to a recent review, there is a lack of a uniformly accepted nosology and treatment plan for patients with conversion disorder.¹ How should a neurohospitalist approach these patients? What is the best treatment for those with conversion disorder? What should I expect from my psychiatry colleagues? Guidance from the psychiatry community would be welcome!

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HIV and neuropsychiatric disorders in Cape Town, South Africa

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Training in neuropsychiatry in South Africa

Neuropsychiatry is in the process of being established as a subspecialty in South Africa, as the impact of neuropsychiatric disorders in Africa is undeniable. In particular, HIV-associated neuropsychiatric disorders contribute significantly to the burden of disease. People living with HIV frequently develop neuropsychological impairment through brain involvement, despite the use of antiretroviral treatment. These neurocognitive disorders, together with other neuropsychiatric disorders associated with HIV, exert many deleterious effects on care in terms of antiretroviral treatment adherence, the impact on work performance and care-giving, as well as the comorbidity with severe mental illness. The need for a dedicated service in the context of a general division of neuropsychiatry has become essential.

The Colleges of Medicine of South Africa recognised the discipline in 2008 and now offer a certificate in neuropsychiatry for subspecialists. The Health Professions Council of South Africa has approved the registration of neuropsychiatry as a subspecialty pending approval from the Department of Health. The University of Cape Town has offered training in neuropsychiatry since 2008, with one senior registrar in the programme at any one time. At other tertiary centres, there are psychiatrists who specialise in this area, but overall the numbers of such subspecialists is extremely low.

Indeed, in low- and middle-income countries there is ongoing debate about the extent to which psychiatric subspecialties are necessary and affordable.¹ Certainly, many aspects of neuropsychiatry need to be managed by general psychiatrists, or even by primary care clinicians under supervision. However, there is a strong argument

that the primary care model can benefit from having at least some clinician-teachers with subspecialist skills.¹

Neuropsychiatric disorders in HIV

This is partly because of the particular pattern of burden of disease in low- and middle-income countries. In South Africa for example, HIV-associated neurocognitive disorders exert significant effects on many aspects of functioning, including adherence to medication, employment and risk behaviours.²⁻⁴ In addition to the high prevalence of HIV infection in South Africa, high rates of alcohol and substance misuse have been reported in HIV clinic attendees.⁵ In a study conducted by our group, the prevalence of HIV-associated dementia was 25.4%.⁶ The implications of this high frequency of HIV-associated dementia are substantial. These include the importance of identifying individuals with HIV-associated dementia or other milder forms of HIV-associated neurocognitive disorders, who are likely to require more treatment support.

Neuropsychiatric disorders in HIV/AIDS are common. In a study conducted in the Western Cape, patients with recently diagnosed HIV were interviewed on presentation to a hospital-based HIV clinic and then 6 months later. The overall prevalence of psychiatric disorders in the follow-up period remained high (56% of patients had at least one psychiatric disorder at baseline, and 48% of patients had at least one psychiatric disorder at 6 months). Depression and post-traumatic stress disorder were the most prevalent disorders. Depression on follow-up was significantly associated with: (a) disability in work/social/family functioning; (b) greater number of negative life events; and (c) a decline in CD4 lymphocyte count. Post-traumatic stress disorder at follow-up was significantly associated with a longer duration of infection and baseline disability in work/social/family functioning. Persistence of risky sexual behaviour was also noted. The findings emphasise the importance of regular evaluation for psychiatric disorders in patients with HIV/AIDS.⁶ At present, neither psychiatric or neurological services provide adequate care for these patients in South Africa. Health services for patients with HIV-related mental disorders are seldom integrated, are costly and frequently require multidisciplinary teams.

Recognition of the importance of HIV neuropsychiatry led to the establishment of dedicated HIV psychiatry services in the Western Cape in 2005. This is an acknowledgement of the need to address the burden of disease within this emerging field. A 1-year review of patients admitted to tertiary HIV/neuropsychiatry beds at Groote Schuur Hospital, Cape Town, was conducted in 2008. The most common reasons for admission were psychosis (39.5%) and depression (25.5%). Most patients received an antipsychotic, which was usually haloperidol. A quarter received an antidepressant. Prior to admission, 30.2% of patients were on antiretrovirals. The mean CD4 count of patients was 354 (9-1074). Almost a third required referral to another specialist medical service. Of

those with a CD4 count less than 300, the diagnosis was HIV-related in 73.7%, while in those with a higher CD4 count, HIV-related disorders were present in only 29.2%. Patients with HIV-related diagnoses stayed on average 10 days longer than those without (28.1 v. 18.9).⁶

Important aspects of neuropsychiatry in low- and middle-income countries

Other aspects of neuropsychiatry are also important in low- and middle-income countries. The overall annual incidence of traumatic brain injury in South Africa is 316 per 100 000, with over half of cases caused by interpersonal violence.⁷ In a prospective study of recovery from diffuse traumatic brain injury in Johannesburg, there was a trend for psychological problems and family relationships to worsen over time.⁷ The neuropsychiatric complications of traumatic brain injury are commonly difficult to treat. Substance misuse, particularly of methamphetamine in the Western Cape, often complicates the picture of HIV and traumatic brain injury. The rapid increase in admissions for methamphetamine misuse in Cape Town is of great concern, particularly as the drug has a number of serious, often chronic, side-effects.⁸ There is evidence to suggest that HIV infection and methamphetamine dependence are each associated with neuropsychological deficits; however, these factors in combination are associated with additive deleterious cognitive effects.⁹ Examples of other disorders which would benefit from the involvement of neuropsychiatrists include genetic conditions (e.g. Huntington's disease), infections (e.g. malaria, syphilis), neurophysiological dysfunction (e.g. epilepsy) and neurodegenerative disease (including Parkinson's disease and Alzheimer's disease).

Conclusion

Mental health services are experiencing a growing number of patients with HIV, traumatic brain injury and substance use-related disorders. Many are patients who are HIV positive in whom the CD4 count is higher than the threshold for commencement on antiretrovirals, and as such reflects the burden of mental illness in earlier stages of HIV disease. Patients commonly present with comorbid medical problems, need rapid special investigations, referral to medical specialties, and diagnostic input from neuropsychiatrists. In the era of antiretrovirals, services for this population of patient are becoming essential.

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New developments in screening for emotional complications of epilepsy

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In 2008, the Epilepsy Foundation Mood Disorders Initiative (EFMDI) published their Consensus Statement confirming a high rate of depression in people with epilepsy in North and South America.¹ Prevalence estimates range from 11% in British primary care² to 20–55% in specialist neurological centres in the UK and USA.³ These figures are beyond those expected in non-neurological chronic diseases such as asthma or diabetes,^{4,5} yet there is convincing evidence that depression is not reliably identified in these patients and therefore goes untreated, both in primary care and in specialist centres.^{6,7} One can speculate as to the reasons for this underdiagnosis; for example, depression in epilepsy is more likely to present with atypical features than in the general population, while the biological symptoms of depression can be misinterpreted as anticonvulsant side-effects. Depression is not routinely screened for in epilepsy and this would appear to be relatively simple to correct.

Untreated depression in epilepsy leads to heightened morbidity and mortality including an increased seizure frequency, reduced quality-of-life scores and dramatically increased suicide rates both compared with people with epilepsy without depression and people with depression without epilepsy.^{8–10} Given the existence of cheap and effective treatments for depression in epilepsy, the identification and application of simple, effective screening tools should provide a cost-effective means of improving quality of life and service provision to people with epilepsy worldwide. The EFMDI suggests asking all patients about anhedonia and applying a brief screening tool, with those patients screening positive being referred to a psychiatrist for confirmation and treatment.¹

There are many tools available for screening for depression but only the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and Beck Depression Inventory - II (BDI-II) have been validated.^{3,11} As mentioned above, the psychiatric profile of this population differs from other patients with depression and it would be unscientific to assume validity in this group. Our team at Atkinson Morley Neurosciences Centre in south-west London ran a 10-month trial to compare the performance of four screening tools for depression in people with epilepsy, with the aim of identifying or developing a suitable screening tool for an epilepsy out-patient clinics, which can be completed in the waiting room or online prior to the appointment.

Screening tools

In total we used four screening tools and one diagnostic tool. The Major Depression Inventory (MDI)¹² is useful for the creation of an operationalised diagnosis of depression as its questions are guided by the core and associated symptoms of ICD-10¹³/DSM-IV¹⁴ depression. The NDDI-E is, as mentioned, validated for use in epilepsy in the USA³ and was therefore recommended for use in the EFMDI statement as the screening tool of choice. In excluding questions about the biological symptoms, it is designed to reflect the cognitive profile of depression and reduce the confounding effects of anticonvulsants. The BDI-II is comparatively long and is most commonly used as a scoring tool for monitoring progress through treatment, but it has also been validated in the USA.¹¹ The Hospital Anxiety and Depression Scale (HADS)¹⁵ is divided into seven questions related to anxiety and seven related

to depression, which can be analysed separately or together. Up to now it has not been validated in epilepsy.

The final and most novel tool used was the revised emotional thermometers (ET7) (Fig. 1). This consists of seven visual analogue scales grading four domains of emotional upset (distress, anxiety, depression and anger) and three domains of emotional impact (duration, burden and the need for help). An earlier version of this tool (ET5) has been validated for use in oncology,¹⁶ but this is the first experience of its use in epilepsy. This is a visual tool using only simple language. As epilepsy is associated with intellectual disability and clinics have many patients in whom English is not a first language, this can be seen as a particular strength of the tool.

Method

Consecutive attendees at the epilepsy clinic were asked to complete the tools mentioned earlier. We excluded individuals without confirmed diagnoses of epilepsy, those with poor English skills and those with moderate to severe intellectual disability; questionnaires which were returned incomplete were also excluded from analysis. The MDI was then used to create a gold standard diagnosis of ICD-10 depressive episode and DSM-IV major depressive disorder. The four screening tools were then compared against these MDI results to plot receiver operating characteristic curves and to calculate sensitivity, specificity, positive and negative predictive values. We asked a small number of participants to time their completion of each tool and to grade the ease of completion.

Findings

A total of 266 individuals were included in the final analysis, of whom 59% were female and 66% were White

British. There was an even spread of localised, generalised and mixed seizure types across the sample. We calculated a point prevalence of 17.7% for depressive episode (ICD-10) and 18.0% for major depressive disorder (DSM-IV).

Participants scored the NDDI-E as the easiest tool to complete and, on average, it took them under 2 min. By comparison, the ET7 took under 3 min, HADS took 3–4 min and BDI-II took 4–5 min. The ET7 came off worst in ease of completion scores, suggesting that participants were unfamiliar with this new type of screening tool.

The four tools we compared had similar screening performance. All scored above 0.8 on area under the curve scores which, by convention, classifies as ‘good’ accuracy. Negative predictive values were high, ranging from 0.961 (ET7) to 0.988 (HADS). Specificity ranged from 0.744 (BDI-II) to 0.817 (NDDI-E) and positive predictive values were poor. The HADS was the most accurate, although the difference between this and the other tools was not significant. The NDDI-E performed best on efficiency analysis, taking into account speed and ease of completion.

Significance

These results suggest that any of the four tools could be accurate screening tools with high negative predictive value. In practice, this means that a subthreshold score is unlikely to come from a patient with depression. These tools perform less well on specificity and a positive score would not be diagnostic. By using screening tools which err towards sensitivity over specificity we would be likely to miss few cases of depression but we may create an untenable number of false positives; the further management of these false positives may then dictate the clinical merit of screening.

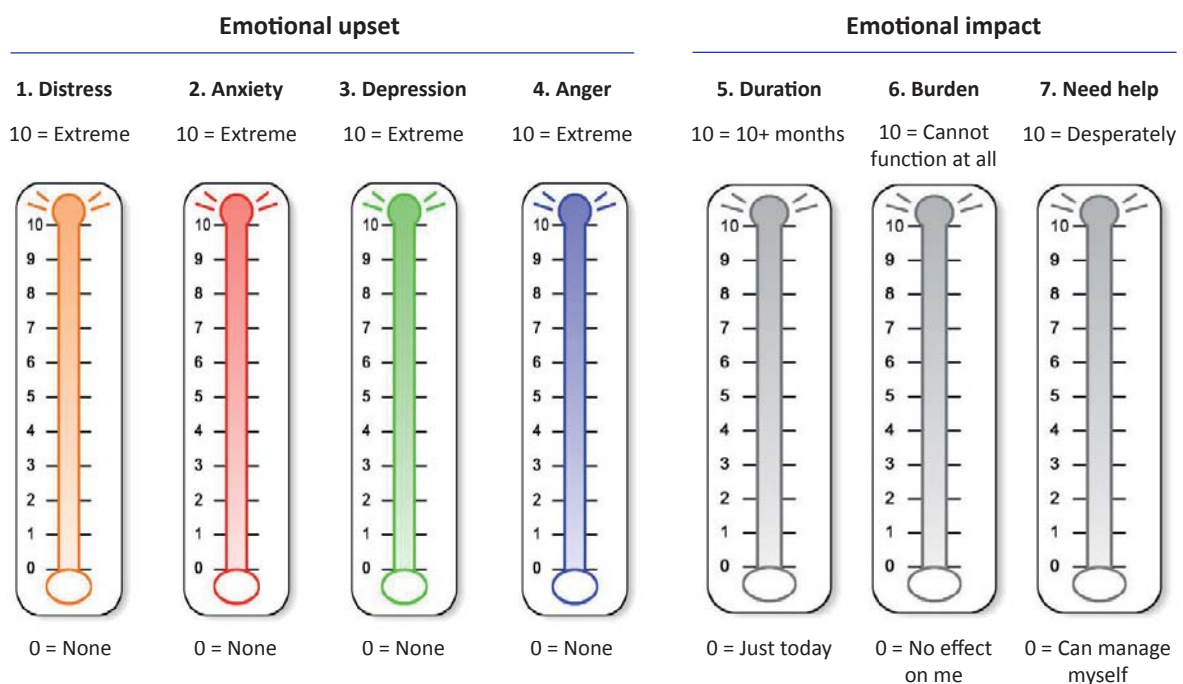


Fig. 1 The revised emotional thermometer (ET7).

Conversely, sensitivity could be argued to be the most important factor in a screening tool as the morbidity and mortality associated with missing a case of depression is sizable and initial management may be relatively simple. False positives could be identified in a short clinical interview, acknowledging that the presentation is more likely to be atypical in interictal depression.

These are screening tools and treatment should not be started purely on the basis of a positive result, therefore we dispute the claim that screening might promote inappropriate prescribing of antidepressants. A positive screening result should lead to questioning about the patient's mood state in the clinical interview, directing a few simple questions at the core symptoms of depression such as anhedonia. Only after this stage fails to exclude depression should a referral to a psychiatrist be considered. Neurologists may feel uncomfortable in making psychiatric diagnoses and prescribing psychiatric medicines, and should be supported by their colleagues in psychiatric and primary care.

Participants appeared to find the BDI-II hard to complete because of its duration and the intimate nature of some of its questions, this being the only tool to ask about libido or to ask directly about suicide. Some individuals needed support on the ET7, with the most common difficulties being where on the graphic to make their mark and an explanation of the concepts of 'duration' and 'emotional upset'. Further versions of the tool may need to clarify these issues as we had expected the visual analogue scale to have practical advantages making it more suitable for use in busy multicultural neurology out-patient clinics. It is easy to analyse, requiring less scoring than the other tools and being less dependent on advanced understanding of the English language. These advantages may outweigh the lower absolute accuracy in certain sub-populations. The two groups of patients in whom we feel the ET7 might be particularly useful, notably those with intellectual disabilities and those with poor English skills, were excluded from analysis amidst concerns that they would not be able to complete the more complex and wordy tools. We cannot safely extrapolate, therefore, from our results to these sub-populations.

In the process of data collection, some individuals who felt themselves to have emotional difficulties relating to the presence of chronic illness seemed eager to discuss these with the researcher. This is relevant because it implies that completion of a screening tool gives the individuals permission to talk about the emotional aspects of their illness; in this way the provision of a tool in itself promotes recognition of these important comorbidities. This phenomenon may, in practice, further improve sensitivity of tools at the expense of specificity.

A substantial number of patients declined participation for unspecified reasons which might bias these results. Previous papers have suggested generally higher point prevalence of depression in tertiary care

for epilepsy than the 18% we found, so there may be a higher proportion of those with depression declining participation.

Conclusions

All four tools are accurate, but for practical reasons, notably patient acceptability and ease of clinician scoring, we recommend the use of NDDI-E in neurology out-patient clinics. In cases where a non-verbal tool is needed, such as where English comprehension is poor, we would suggest consideration of a modified version of the ET7.

The balance of overidentification of cases is preferable to one which would favour specificity and thus lead to many cases being missed. After all, depression is relatively easy to diagnose and treat in most instances and there is strong evidence to suggest it is undertreated in this population, and that this is leading to preventable morbidity and mortality in patients with epilepsy.

Authors

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Summary of the Royal College of Psychiatrists’ WHO ICD-11 Working Group

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The ICD-11 is designated to be submitted for approval to the World Health Assembly in 2013 or 2014. It will then be printed in all the World Health Organization (WHO) working languages, some 20 years after its predecessor. This extended interval between ICD-10 and ICD-11 relates, according to Professor Norman Sartorius, to the need for there to be:

- sufficiently established scientific evidence bases
- comprehensive consultation with an ever expanding groups of stakeholders
- appropriate flexibilities due to the increasing complexity of the introduction of new valid classifications at a time of worldwide limits on financial demands.

Earlier considerations¹ outlined that individual nosological classificatory positions of syndromes and/or disorders may best not be covered through chapter structures, but by ensuring that single categories have a variety of dimensions describing the disorder without overly specified, categorical, individual disorders in ICD-11’s proposed format.

The organisation of the revision process

The process of ICD-11’s revision involves consultations with individuals, groups of experts/specialists and institutions. Thorough literature reviews, the assembly of proposals, the drafting of criteria for the use of each category and other preparation of the regime followed suite thereafter.

The organisation of the revision process included the WHO’s Topic Advisory Group (TAG/MND; convened between 2007 and 2009), which, divided into subgroups, is entrusted with specific tasks.

1. Epidemiology subgroup.
2. WHO (ICD-11) and American Psychiatric Association (APA) DSM-5 Harmonisation Group – comprising

experts from DSM-5 and WHO TAG/MND executive team members. In 2009, the WHO’s TAG/MND Group recommended the creation of five new working groups:

- Mental Disorders Seen in Primary Care
 - Health Problems Related to Substance Misuse
 - Childhood Mental Disorders
 - Mental Retardation (probably to be called Intellectual Disability in ICD-11)
 - Personality Disorder.
3. The WHO then created a Coordinating Group to establish a Global Scientific Partnership Network (GSPN), with interdisciplinary experts working on these.
 4. Professional non-governmental organisations have also been invited to participate. The subgroups’ remit included the consideration of the topics summarised in Box 1.

The key challenge, according to Professor Sartorius’ final comments, is that

Box 1 WHO ICD-11 revision: the issues involved

- Criteria for changes of the classification or its categories
- Categories or dimensions?
- One or more versions of the classification?
- Should national adaptations of the ICD be seen as the way to deal with culture or having specific issues?
- Should the next version of the classifications be directive or reflective?
- What shape should the primary care version take?
- What will happen once the classification is produced and published?

Sartorius¹

'...those charged with this task are in constant communication with scientists and the many users of the classifications so that they become aware of issues when it is still possible to consider solutions and incorporate them into the current revisions. The decision to produce living documents that can be changed when necessary is no doubt a consequence of the awareness of their creators that this communication must be maintained after publication and that it will be necessary to constantly work on the classifications to ensure that they continue to reflect the evidence and respond to the needs of their users.'

The Royal College of Psychiatrists' WHO ICD-11 Working Group

The Royal College of Psychiatrists' WHO ICD-11 Consultation Summary² emerged from the wide-ranging consultation of College members, individual faculties, divisions and interest groups as well as stakeholders.

The Working Group convened under its Chairman, Professor Terry Brugha, and comprised academic clinicians, research-based academics and practicing senior clinicians working in and across all domains and syndromes pertinent to the nosological classification issues ICD-11 is charged with addressing.

In contrast to the longer running organisation of the APA's DSM-5 consultation process, the Working Group used electronic communication, telephone, paperwork and (only) a total of four (self-funded) meetings at the Royal College of Psychiatrists. Although the presentation of individual dimensions and mental health syndromes remained succinct in nature and quality of submission, the Group was able to submit supporting précis of evidence to produce a final draft. Ongoing consultation with the President, the Registrar and key members of the Working Group led to a final, nearly 12-hour revision meeting before submission, amendments and approval from the Royal College of Psychiatrists' Executive before being sent to Geneva.

A brief outline of the Consultation Summary is quoted below.

'There was little support for wholesale change in broad categories (i.e. F0, F1, F2 etc) but widespread support for reorganisation and fewer rather than more specific categories in ICD-11 compared with its predecessor. Where ICD-10 categories are retained, there should be a branching tree structure with the highest level or entry point (i.e. any disorder, any common mental disorder, psychosis) being a legitimate classification allowing for provisional, evolving or uncertain situations. These broad categories may then have deeper level, sub-categories, probably fewer than in ICD-10, but all with access to dimensional or other 'Specifiers' for clinically relevant psychopathology beyond that which defines the main category (e.g. affective dimensions in F20, or anxiety symptoms in F30) and, where known, underlying causal process or pathology (e.g. fronto-temporal dementia).

*Depending on availability of time for observation and expertise, significance and impact, categories should preferably have robust dimensional descriptors, such as personality, course of illness, life cycle, social markers, and general intellectual ability. In the furtherance of continuity of reliable description, redefining existing retained categories should be avoided.'*²

Professor Terry Brugha and the Working Group Members subsequently submitted a rapid response to the *BMJ* to various discussions which confirmed that

*'...The Royal College of Psychiatrists has recently submitted proposals to the independent consultation for ICD11 which is being developed in harmony with DSMV.'*³

These make the case for a diagnostic system with broad categories of clinically relevant specifiers. A much improved, integrated and useful classification would result, which could embrace entry groups such as psychosis unspecified and other common mental disorders, narrowing to categories such as neuropsychiatric, affective and non-affective psychosis, and emotional, substance misuse and developmental disorders.

*'Specifiers for individual categories would be those which are clinically relevant, e.g. childbirth-related co-existing drug misuse, or personality type. Continuity between childhood disorders, such as conduct disorder and ADHD, and their adult counterparts would also be incorporated. Classification systems need to be inclusive but only to the extent that they are comprehensible and useful for clinicians, researchers, managers, service users and carers. The scientific evidence for benefit over risk must first be developed and rigorously tested before broadening the scope of classification to include less severe forms of presentation but doing so could also potentially allow for early intervention and even prevention of mental disorder.'*³

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The Newcastle Neurobehavioural Unit: description of an existing service and future developments

Janet Grace, Laura Gough & Laura Shotton

Newcastle Neurobehavioural Unit

The Newcastle Neurobehavioural In-patient Unit (NBIPU) is a 14-bedded regional in-patient only service within the Walkergate Park Hospital Centre, which also contains regional neurorehabilitation services and regional neuropsychiatry services. The NBIPU was established by Professor Stephen Tyrer in 1998 in response to an identified local and regional need.

The unit is divided along the lines of physical need, with a six-bedded unit for patients with a high degree of physical dependency, such as hoisting, and a 'walking wounded' eight-bedded unit. Additionally, there are two community homes for long-stay patients attached to the service, which provide homes for life for patients with catastrophic brain injury.

In 2007 the NBIPU moved from the grounds of the Prudhoe Hospital Northumberland to a purpose built unit on the outskirts of Newcastle. We now take patients from around the northern region (Tyne and Wear, Northumberland, Cumbria, Durham and Middlesbrough).

The NBIPU takes patients with acquired brain injury of any cause as well as occasionally providing a service for patients with pre-existing behavioural problems who require rehabilitation. The model of care on the ward bridges disciplines of neurorehabilitation, neuropsychiatry and neurobehaviour. The ward is staffed by an experienced team of behavioural nurses, mainly from an intellectual disability background. There is a full multidisciplinary team comprising neuropsychology, occupational therapy, physiotherapy, speech and language therapy, dietetics, and social and recreational therapy.

The multidisciplinary team uses a positive contingency programming approach wherever possible to tackle

unwanted behaviours. Neurobehavioural rehabilitation is based on the model of positive programming developed by the Institute of Applied Behavioural Analysis. Initially on admission, a behavioural baseline is established through direct observation, behavioural recordings, review of medical records and collateral information gathered from carers and families. Further to a thorough assessment and having established the nature, frequency, severity and duration of challenging behaviours, a behavioural management plan is developed. These plans predominantly comprise proactive strategies which can be grouped into three broad domains.

1. Ecological strategies that aim to ensure a smooth fit between the individual and the environment. This includes consideration of physical aspects of the environment, structure and routine, in addition to the interpersonal dynamics within the environment (e.g. staff interactions, service user numbers and mix).
2. Positive programming, which involves rehabilitation of or development of general skills and adaptive coping strategies. Having identified the function of the behaviour(s), one of the aims would be to teach or encourage the person to use alternative and appropriate strategies that have an equivalent or related function to the behaviour.
3. Focused support which is provided through the use of various reinforcement schedules, for example, positive reinforcement of lower rates of behaviour, periods of time in which there have been no challenging behaviours and alternative or incompatible behaviours. Positive reinforcements are identified in relation to the function of the person's behaviour and their motivational drives.

The development of behaviour management plans aim to prevent the occurrence of challenging behaviour. However, when behavioural problems do occur, reactive strategies that are specific to the individual's behavioural assessment and problems are utilised in order to resolve the situation safely and quickly.

In the time since using positive approaches to manage behaviour there has been much success in reducing the frequency, severity and duration of challenging behaviour from case to case. It is probable that this success is, in part, due to patient consent and involvement in developing the programme and staff consistency in implementing the programme. To ensure that these positive outcomes are maintained in the in-patient setting, staff training has been established and is ongoing to ensure consistent utilisation of this model of working.



The Newcastle Neurobehavioural Unit.

Collected data

Diagnostically, of the 36 patients admitted over the past 18 months, 16 (44%) had traumatic brain injury, 4 (11%) had a subarachnoid hemorrhage, 5 (17%) had hypoxic/hypoglycaemic brain injury and the remainder of the diagnoses included inflammatory demyelination of unknown origin, viral encephalitis, meningioma, herpes simplex encephalitis and cerebral abscess.

On admission, 20% (7/36 patients) had physical aggression, 40% (14/36) had verbal aggression and 31% (16/36) had a tendency to wander. Sixteen (31%) patients were disorientated needing redirection and two (6%) displayed sexually inappropriate behaviour. Other behaviours such as importuning, exposure and spitting accounted for 35% of unwanted behaviours. Rating of behaviour was carried out using the Neuropsychiatric Inventory¹ and the Health of the Nation Outcome Scales for Acquired Brain Injury (HoNOS-ABI; www.rcpsych.ac.uk/pdf/HoNOS_ABI.pdf). Out of 36 patients, 10 and 4 had disturbance of social interaction on admission and on discharge respectively. The rate for self-injurious behaviour reduced from 5 out of 36 to 1 out of 36 on discharge.

The range of duration of admission was 4–43 weeks with a mean of 16 weeks (s.d. = 11). Patients with hypoxic/hypoglycaemic brain injury had a significantly longer duration of stay than any other diagnostic category (28 weeks compared with 15 weeks).

The worst single prognostic indicator was heavy alcohol use or dependency which was associated with a longer duration of in-patient treatment, with a mean stay of 6.5 weeks for patients with no alcohol dependency and a mean stay of nearly 20 weeks for those with significant alcohol problems ($F = 8.260$, $P = 0.014$).

Although it is clear from the collected data that there are significant changes to the presentation and function of patients on the NBIPU, many patients have significant problems on discharge.

In addition to the data that are collected by us for reference to service development, data are collected separately by an independent rater who contacts each patient or a member of their family on discharge. These data are accessible for ward staff in an anonymised form but have also been useful in identifying the need for specialist community follow-up.

We are a regional service that covers approximately 3 million people. The region is geographically challenging and it is not practically feasible to provide a complete 'hands on' service for patients leaving the NBIPU. Additionally, services for people with behavioural, emotional and cognitive symptoms after acquired brain injury are a good example of a postcode lottery, with patchy provision of acquired brain injury teams and different referral criteria for each team.

Future developments

A successful Work Force Innovation and Development Fund bid was made to the Strategic Health Authority for funding for a community neurobehavioural team.

Our proposal is to pilot a tertiary team for patients discharged from the NBIPU. This team will be embedded in the in-patient team and only accept patients from this team. For each patient discharged from the NBIPU, an individual assessment of their needs will be made and an individual care and training package developed. There will be an emphasis on maintaining consistency of the behavioural programme established on the in-patient unit. Assessment will cover risk and need and a training programme driven by patient goals as well as professional assessment will be formulated. This training programme will cover general aspects of behavioural management and issues specific and pertinent to the patient. The training programme will be applicable to all involved in that patient's care, including family and friends as well as other agencies. After an initial period of high frequency training, a supervision model will be used, with arranged and reactive support provided. Data will be collected to test the following hypotheses.

- The ecological validity of the NBIPU can be improved by the transitional team
- The community neurobehavioural team will reduce carer distress
- The community neurobehavioural team will reduce readmissions and use of other services
- Long-term behavioural disturbance will be reduced by putting in place a behavioural framework
- Long-term function and sequelae of function such as self-esteem will be improved by long-term follow-up

Data will be used via a group analysis and by single-case methodology. A control group is intrinsic in this study as the funding covers patients in the north-east Strategic Health Authority region.

We hope to be able to complete the evaluation of this model within 2 years.

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Temporal lobe epilepsy psychopathology: snapshot from a referral centre

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People with epilepsy are at a high risk of developing mental health problems.^{1–3} Temporal lobe epilepsy is frequently associated with a poor seizure response to anti-epileptic drugs, particularly individuals with mesial temporal sclerosis.⁴ Some authors argue that patients with temporal lobe epilepsy present a high propensity to develop psychiatric disorders due to the role of the limbic system in regulating emotions, mood and behaviour.^{5–7}

Psychiatric disorders in epilepsy arise in a context of neurophysiological changes caused by seizures, anti-epileptic drug side-effects, individual vulnerability and subjective experience of psychosocial impact.⁸ Thus, professionals usually face a challenging task: to recognise and treat properly neuropsychiatric disorders in epilepsy. In this study we evaluated the frequency, intensity and clinical correlates of psychiatric disorders in a group of patients with temporal lobe epilepsy in a specialised centre in Brazil.

Method

A cross-sectional study was conducted with 73 patients with temporal lobe epilepsy. All patients were monitored by the Epilepsy Clinic of the Neurology Unit, University Hospital, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil, which is a regional referral centre for difficult-to-control epilepsy. We included patients with temporal lobe epilepsy according to the International League Against Epilepsy (ILAE) criteria,⁹ those aged >18 years and capable of providing written informed consent. Patients with severe medical or neurological disease other than epilepsy or history of previous neurosurgery were excluded.

Clinical and sociodemographic data were collected and a neuropsychiatric evaluation was performed with the following instruments: Mini-Mental State Examination (MMSE),¹⁰ structured clinical interview (MINI-Plus),¹¹ Hamilton Rating Scale for Anxiety (HRSA),¹² Hamilton Rating Scale for Depression (HRSD)¹³ and Brief Psychiatric Rating Scale (BPRS).¹⁴ Descriptive analysis of categorical variables and proportions were calculated and presented. For comparison of categorical variables between groups, Fisher's Exact test was performed and continuous variables were evaluated using the Kruskal–Wallis test.

Results

Clinical and sociodemographic aspects

The population in the study consisted of relatively young patients (mean 42.2 years), with childhood onset seizures (mean age 8.5 years) and long duration of illness (mean 33.7 years). A combination of focal seizure types was observed (95.9% complex partial, 42.5% simple partial seizures and 38.4% secondarily generalised). The majority of patients were refractory (80.8%), most of them (87.7%) were on more than one anti-epileptic drug, with a mean frequency of seizures of 4.8 per month.

Evaluation of neuropsychiatric symptoms and syndromes

Despite extensive description in literature, mental disorders in epilepsy are neglected in ICD-10 and DSM-IV, which tend to label such cases as caused by a general condition or as 'organic'. For this reason, we followed the psychiatric diagnosis from the recommendations of the ILAE Commission on Psychobiology of Epilepsy in order to conduct a more descriptive classification, correlating clinical variables (e.g. ictal and interictal symptoms, relationship with anti-epileptic drug therapy) and avoiding pre-setting all cases with an 'organic' aetiologic label.^{15,16}

Patients with temporal lobe epilepsy showed a high frequency of lifetime psychiatric disorders, mainly mood and anxiety disorders (Table 1). Paradoxically, depression had not been properly diagnosed or treated. Only one patient (6.3%) diagnosed with major depressive disorder was taking antidepressants and scored 33 on the HRSD. The results on the clinical, sociodemographic and psychopathological evaluation have been described in detail elsewhere.¹⁷

The role of mesial temporal sclerosis

Patients were divided into four groups: 25 patients with right mesial temporal sclerosis (RMTS), 30 with left mesial temporal sclerosis (LMTS), 8 with bitemporal mesial temporal sclerosis (BMTS) and 10 without mesial temporal sclerosis (WMTS). Groups were statistically different regarding gender ($P=0.043$), as there were only two (20%) women in the WMTS group. Also, groups

Table 1 Psychiatric disorders in patients with temporal lobe epilepsy according to the MINI-Plus^{11,a}

Psychiatric disorder	Patients (<i>n</i> = 73), <i>n</i> (%)
Any disorder	
Current	43 (58.9)
Lifetime	51 (69.9)
Bipolar disorder	7 (9.6)
Major depressive episode	
Current	20 (27.4)
Lifetime	27 (37.0)
Anxiety disorders	31 (42.5)
Obsessive–compulsive disorder	8 (11.0)
Psychosis	4 (5.5)
Somatoform disorders	10 (13.7)

a. Patients may have more than one diagnosis.

showed differences according to the duration of epilepsy ($P = 0.047$): the WMTS group had a shorter duration of epilepsy and a mean duration of 22 years, whereas the other groups showed mean duration of epilepsy above 30 years. There were no other significant differences on sociodemographic or clinical variables.

Patients with left mesial temporal sclerosis had a higher frequency of mood and anxiety disorders, although only anxiety disorders reach statistical significance ($P = 0.006$) when all groups were compared. Higher scores on the HRSA ($P = 0.012$) and on the HRSD ($P = 0.03$) were also linked to left mesial temporal sclerosis. The BMTS group had a somewhat higher frequency of psychosis (25%) when compared with the other groups (<5%), although this difference did not reach statistical significance ($P = 0.14$). Additionally, both BMTS and LMTS groups presented with high scores on the BPRS ($P = 0.06$).

Discussion

We described a cross-sectional neuropsychiatric evaluation of patients with temporal lobe epilepsy in a tertiary care service. Most of these patients have multiple confounding factors, such as long duration epilepsy, refractory seizures and polytherapy, which make firm conclusions difficult. Other limitations are the sample size and lack of a control group. Nevertheless, the detailed clinical assessment permits a multidimensional psychopathological overview which brings relevance to this report.

Anxiety disorders, as a group, were the most frequent diagnosis. Furthermore, our data reinforce the view that major depression, as a discrete condition, is the most common mental disorder in people with epilepsy.¹⁸ The study also highlights the underdiagnosis and undertreatment of depression in epilepsy and the need for new clinical strategies. It is therefore timely that we have recently validated a useful screening tool for depression in epilepsy, the Portuguese–Brazilian version of the Neurological Disorders Depression Inventory

for Epilepsy (NDDI-E),¹⁹ that takes only about 3 min to complete and is specifically designed for the needs of this population.^{19,20}

Depression and anxiety share common features^{21,22} that might reflect common pathogenic mechanisms involving the limbic system.^{23–27} In the present study, anxiety disorders were more likely to occur in patients with left mesial temporal sclerosis that also had higher scores on the HRSA and HRSD. These data are in line with the literature that reports that anxiety disorders are associated with functional impairment in left limbic structures.^{28–30} However, these findings must be interpreted with caution as the aetiology of mental disorders in epilepsy is multifactorial and result from a complex interaction of neurobiological and psychosocial aspects.

The relatively low frequency of psychotic disorders in our population (5.5%) compared with the literature description (around 19%)^{6,31,32} may have different explanations such as methodological differences, outpatient profiles, sample size and also the exclusion of patients with severe cognitive impairment. The involvement of bilateral cerebral dysfunction in psychosis is demonstrated by some authors suggesting a greater rate of bitemporal foci not only among patients with temporal lobe epilepsy and postictal psychosis, but also among those with chronic psychoses.^{32–36} In the present study, although not statistically significant, it is possible to discern a suggestion of increased frequency of psychotic disorders in the BMTS group, supporting a bitemporal involvement in psychosis.

Conclusions

Temporal lobe epilepsy is related to a high frequency of psychiatric disorders such as anxiety and depression which are usually underdiagnosed and undertreated. Patients with left mesial temporal lobe lesions seem to be more susceptible to psychiatric conditions such as anxiety disorders, while psychosis may show a special correlation with bilateral damage in mesial temporal lobes.

The nature of temporal lobe epilepsy psychopathology is far from being understood. Further studies should combine modern technologies such as functional neuroimaging, with traditional and detailed clinical assessment. Meanwhile, busy specialised centres around the world have an important and basic task: to practice and improve clinical skills to diagnose and treat psychiatric comorbidities in epilepsy, chiefly refractory temporal lobe epilepsy.

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Neuropsychiatric comorbidity predicts therapeutic outcome in idiopathic restless legs syndrome

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Restless legs syndrome (RLS) is one of the most common neurological disorders affecting about 10% of the German population.¹ It is characterised by an irresistible urge to move the legs and sometimes other body parts, which is usually accompanied by discomfort, occurs or worsens at rest, has a circadian rhythm with most pronounced symptoms at night and can be relieved by moving around.

Although a large number of randomised controlled trials demonstrate efficacy of dopaminergic, opioid and anti-epileptic drugs in the treatment of the typical RLS symptoms, epidemiological studies suggest that RLS is often insufficiently treated. To further examine this apparent discrepancy we investigated 100 patients with idiopathic RLS for 12 months prospectively, applying individual treatment strategies that followed the RLS treatment guidelines of the German Neurological Society.² Treatment success was measured using standardised scales for RLS symptom severity (International Restless Legs Syndrome Study Group Rating Scale, IRLS) and for RLS-related quality of life (RLS quality-of-life questionnaire, RLS-QoL). Results showed that neither RLS symptom severity nor RLS-related quality of life improved in this cohort after 12 months of guideline-based treatment. For more detailed information on the study background, methods, medication and cohorts we refer the reader to the original article.² Here, we focus on potential reasons for the poor treatment outcome in this group of patients with RLS.

Background

Comorbidity is common in RLS and other than somatic disorders such as iron deficiency, low serum ferritin and

cardiovascular disorders, it also includes a wide number of neuropsychiatric disorders such as depression, anxiety or pain disorders such as fibromyalgia and migraine.³⁻⁵ In our study cohort, neuropsychiatric comorbidity affected 64% of all patients. In addition to the above named conditions, various somatoform disorders such as irritable bowel syndrome were frequently found. An overview on the frequency of these disorders is given in Fig. 1. Interestingly, in a principal component analysis for data reduction of overall 25 variables including baseline disease severity, quality of life, demographic and disease-related factors, medication and comorbidity, the neuropsychiatric disorders all projected solely on one out of overall five independent components. This component was then referred to as 'neuropsychiatric comorbidity' and was the only factor that statistically related to treatment outcome.²

Results

Further analysis of the group with neuropsychiatric comorbidities revealed a clinically striking impact on treatment success. There was no statistical difference regarding the impact of any single neuropsychiatric comorbidity, therefore comparisons were performed between two groups: participants with (NP+) and without (NP-) neuropsychiatric comorbidity (Table 1). At baseline both groups did not differ regarding demographic factors, disease-related factors, baseline symptom severity and quality of life. During the 12-month observational interval, the NP+ group had significantly more physician contacts ($P < 0.001$) compared with the NP- group and were more often referred to specialists by the treating primary care physician ($P = 0.003$). However, after 12 months of

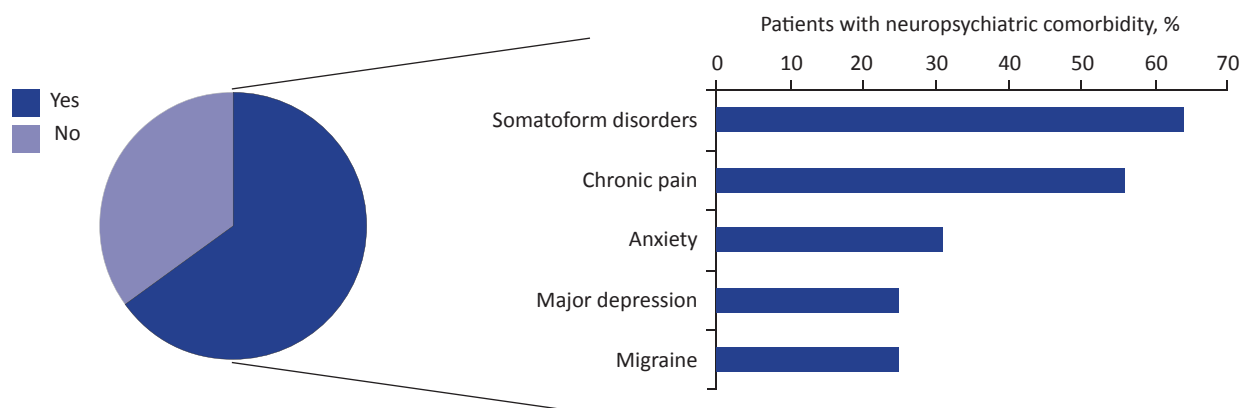


Fig.1 Neuropsychiatric comorbidity. The percentages add up to more than 100% as some patients had more than one neuropsychiatric comorbidity.

Table 1 Clinical data

	NP- group (n = 36)	NP+ group (n = 64)	P
Age, years: mean (s.d.)	63 (8)	61 (10)	n.s.
Gender, F:M	23:13	35:29	n.s.
Age at symptom onset, years: mean (s.d.)	38 (20)	36 (20)	n.s.
Disease duration, years: mean (s.d.)	25 (19)	24 (19)	n.s.
Physician contacts, n: median (range)	0 (0–4)	5 (2–16)	<0.001
Specialist contacts, n: median (range)	0 (0–2)	1 (0–10)	0.003
IRLS, mean (s.d.)			
Baseline	24 (8)	25 (5)	n.s.
12-month follow-up	19 (9)	26 (8)	<0.001
RLS-QoL, mean (s.d.)			
Baseline	38 (9)	30 (7)	n.s.
12-month follow-up	41 (8)	29 (7)	<0.001

IRLS, International Restless Legs Syndrome Study Group Rating Scale; RLS-QoL, restless legs syndrome quality-of-life questionnaire; n.s., not significant.

treatment, no significant improvement could be found in RLS symptom severity ($P = 0.35$) or RLS-related quality of life ($P = 0.43$). In contrast, the NP- group showed significant improvement in both RLS symptom severity ($P = 0.005$) and RLS-related quality of life ($P = 0.008$). Of the NP- group, 80% improved with regard to symptom severity and 78% regarding RLS-related quality of life. Overall, 92% of this group (33 of 36 patients) improved on at least one of these measures of treatment success. Of these 33 patients, 88% showed a clinically significant (>20%) improvement, which resulted in a clinically significant improvement in 81% of the patients of the whole NP- group (29 of 36 patients). In contrast, only 30% of the NP+ group showed improvement in symptom severity and 33% in quality of life. Of the whole NP+ group, only 34% improved on either measure (22 of 64 patients); a clinically significant improvement was only observed in 46% of these 22 patients. Therefore, of the whole NP+ cohort, only 16% (10 of 64 patients) improved significantly regarding either RLS symptom severity and/or RLS-related quality of life (Fig. 2).

Discussion

From these results it can be concluded that neuropsychiatric comorbidity has a major impact on treatment outcome in RLS. These data question the current concept of neuropsychiatric symptoms as a consequence of more or less severe RLS symptoms, the resulting sleep disturbance and distress.⁶ In this case, one would have expected that neuropsychiatric comorbidity is related to the severity of RLS symptoms and should have improved along with RLS symptoms. This, however, was not the case in our study. Instead, RLS symptoms could not be reduced in the NP+ group. This might indicate that (a) the frequently observed neuropsychiatric symptoms are part of the RLS pathology rather than a secondary condition or that (b) neuropsychiatric symptoms influence the perception of RLS symptoms or both.

Clinical implications

Findings of this study may have profound therapeutic implications for clinical practice. Only a minority of patients with RLS and neuropsychiatric comorbidity will truly benefit from the RLS medication, whereas patients with RLS free of these symptoms seem to have a good prognosis regarding overall treatment success. This certainly does not mean that dopaminergic treatment should be omitted in patients with neuropsychiatric comorbidity. More likely, it seems necessary to complement the RLS drug therapy by other treatment strategies such as client-centered therapy, behavioural therapy or psychotherapy and, if necessary, medication for the neuropsychiatric symptoms. One small interventional study speaks in favor of this concept.⁷

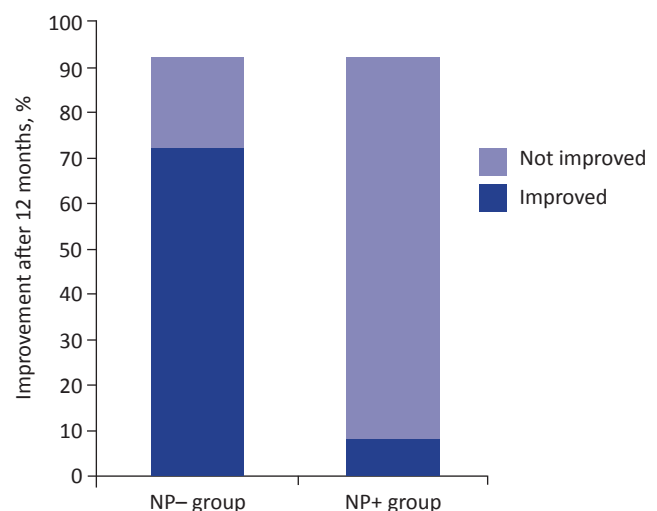


Fig. 2 Percentage of patients with restless legs syndrome (RLS) with clinically significant improvement after 12 months. Clinically significant improvement is defined as either an improvement >20% on the International Restless Legs Syndrome Study Group Rating Scale (symptom severity) and/or on the RLS quality-of-life questionnaire. NP+, patients with psychiatric comorbidity; NP-, patients without psychiatric comorbidity.

Future trials will have to show whether neuropsychiatric comorbidity will indeed be a valuable therapeutic target to improve medical care for patients with RLS.

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Use of HoNOS as an outcome measure in an in-patient treatment programme for conversion disorders

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Approximately 30% of neurology out-patient clinic attendees present with medically unexplained symptoms.¹ It has been shown that the longer a person has conversion symptoms, the more resistant to treatment they are,^{2,3} but that they are also more likely to improve if there is co-existing anxiety or depression that can be treated.³

There is no universally accepted treatment regimen for conversion disorders and limited evidence for any specific approach.⁴ Treatment of psychiatric morbidity, psychotherapy to deal with maladaptive responses and sometimes physiotherapy are the norm, although the provision for these is not necessarily widespread throughout the UK and services are rarely coordinated.

This preliminary study aims to review the outcomes for a dedicated multidisciplinary in-patient treatment programme based at the National Hospital for Neurology and Neurosurgery in London. The study focuses on

changes in the Health of the Nation Outcome Scales (HoNOS) as this has been the most robustly collected measure over the past year. Some consideration about changes in the individual subscales for HoNOS will be given to assess their contribution to the overall improvement.

The treatment programme

At the National Hospital for Neurology and Neurosurgery the 4-week multidisciplinary treatment programme for conversion disorders combines intensive cognitive-behavioural therapy, physiotherapy and occupational therapy, alongside consultant-led neuropsychiatric and neurological input. Suitability for the programme is determined by a multidisciplinary assessment.

The case-load varies, but typically includes patients with dissociative convulsions, dissociative motor and sensory disorders, for example paralysis, tremors, blindness, amnesia and speech disorders. The programme is individually tailored for each patient's needs. The programme is viewed as the start of the recovery process, so referrals are made back to the relevant local teams to continue the work on discharge from the unit.

Outcome measures

The HoNOS was developed by the Royal College of Psychiatrists in 1998⁵ and is part of the National Health

Service Mental Health Minimum Dataset (www.ic.nhs.uk/services/datasets/dataset-list/mental-health). It is a 12-item clinician-administered tool for assessing a wide range of symptoms and functioning, including an 'other' scale on which conversion symptoms can specifically be measured. They have been validated to detect change in psychiatric patients, although this validity has been questioned.^{6,7} There is scarce data on the use of HoNOS in conversion disorders.

Method

Every patient has HoNOS measured on admission and discharge to the neuropsychiatric unit. Data from these measures were collected prospectively alongside the patient's age, gender, diagnosis and length of stay, and then analysed for all patients admitted to the programme during 2010.

Data were analysed using the statistical package SPSS. Paired *t*-tests were carried out, comparing the admission and discharge HoNOS scores.

Results

A total of 46 patients were admitted to the multi-disciplinary conversion disorders treatment programme during 2010. Full data were available for 37 patients, 80.4% of the total; HoNOS scores were not available for the 9 missing patients, which were excluded from further analysis.

Demographic data

Patient demographics are shown in Table 1. The gender ratio was 10 males:36 females (21.7%:78.3%), with a mean age of 41.6 years (range 18–82). Overall, 87.0% ($n = 40$) of patients had a diagnosis of F44.X ICD-10⁸ conversion (dissociative) disorders; others included F45.0 somatisation disorder ($n = 1$), F48.0 neurasthenia ($n = 3$) and R52.2 chronic pain disorder ($n = 2$). Mean length of stay was 3.39 weeks.

Table 1 Demographics showing ICD-10 diagnoses of patients admitted to in-patient treatment programme in 2010

Diagnosis	Number of patients	Male	Female
F41.1 Dissociative fugue	1	1	0
F44.4 Dissociative motor disorder	19	5	14
F44.5 Dissociative convulsions	7	0	7
F44.7 Mixed dissociative disorder	13	1	12
F45.0 Somatisation disorder	1	1	0
F48 Neurasthenia	3	1	2
R52.2 Chronic pain disorder	2	1	1

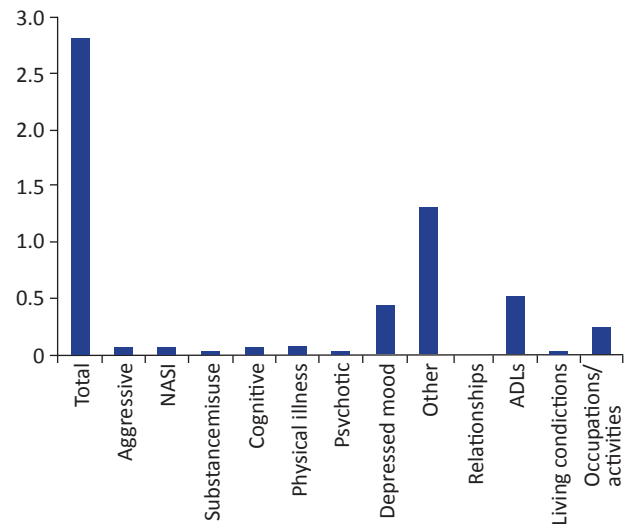


Fig. 1 Total HoNOS and subscale mean score improvements. NASI, non-accidental self-injury; Other, conversion symptoms; ADLs, activities of daily living.

Change in HoNOS results

Comparisons were made between change in total HoNOS score and change in each of the 12 subscales (Fig. 1). The mean change in total HoNOS scores from admission to discharge was 2.87 (s.d. = 2.49, 95% CI 2.04–3.69). The change was largest in the subscale for 'other' (conversion symptoms) (mean 1.35, s.d. = 1.09, 95% CI 0.99–1.71). The mean change for depressed mood was 0.43 (s.d. = 0.73, 95% CI 0.19–0.68) and 0.51 for activities of daily living (s.d. = 0.77, 95% CI 0.26–0.77).

Further analysis determined the statistical significance and effect sizes of the three scales with the largest change; depressed mood, other (conversion symptoms) and activities of daily living (Table 2).

As in Audin et al,⁹ effect sizes were calculated by dividing the mean change score by the standard deviation of the mean score on admission. Cohen¹⁰ described effect sizes as small = 0.2, medium = 0.5, and large = 0.8.

Discussion

This is the first study the authors could identify reviewing the use of HoNOS as an outcome measure for the treatment of conversion disorders. The data from this cohort of patients show that the average HoNOS total score improvement was 2.87 points during the treatment programme. It is not entirely clear from the literature what constitutes a significant change in HoNOS.

Further analysis of the data by reviewing the individual subscales reveals that the majority of the change is due to improvement in conversion symptom scores, by a mean of 1.43 points. The improvements in ability to carry out activities of daily living and in depressed mood are almost equal, with mean improvements of 0.51 and 0.43 points respectively. All of these changes show high statistical significance, but the largest effect size is seen in the change to conversion symptoms.

Table 2 Breakdown of mean admission and discharge HoNOS scores, with *P*-values and effect sizes

HoNOS score	Mean score at admission (s.d.) (range)	Mean score at discharge (s.d.) (range)	Mean change (s.d.) (95% CI)	<i>t</i>	<i>P</i>	Effect size
Total HoNOS	10.51 (4.23) 4–20)	7.65 (4.10) (1–18)	2.87 (2.49) (2.04–3.69)	7.01	3.16 x 10 ⁻⁸	0.67
Depressed mood	1.16 (1.21) (1–4)	0.73 (0.93) (0–3)	0.43 (0.73) (0.19–0.68)	3.61	9.17 x 10 ⁻⁴	0.36
Conversion symptoms	3.49 (0.77) (1–4)	2.14 (1.16) (0–4)	1.35 (1.09) (0.99–1.71)	7.57	5.93 x 10 ⁻⁹	1.75
Activities of daily living	1.97 (1.32) (0–4)	1.46 (1.17) (0–4)	0.51 (0.77) (0.26–0.77)	4.07	2.48 x 10 ⁻⁴	0.39

This preliminary study demonstrates that the treatment programme improves HoNOS results, with the biggest change being in the conversion scale. One limitation of using HoNOS in this group of patients is that it is not possible to double code for the 'other' category which is used for conversion symptoms, so, for example, anxiety or sleep problems cannot be counted alongside conversion symptoms.

A further study is under way to include a wider range of outcome measures including the Hospital Anxiety and Depression Scale, Work and Social Adjustment Scale, Fear Questionnaire, Clinical Global Improvement, Common Neurological Symptoms and Illness Perception Questionnaire (additional information about patient reported outcomes may also be added to this list). This study will include data from initial multidisciplinary team clinic assessments through to 3- and 6-month follow-ups to see whether change is maintained. It will also aim to establish which outcome measures are most valid, and which are better able to detect clinical change in this group of patients.

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The British Neuropsychiatry Association and Royal College of Psychiatrists' (Section of Neuropsychiatry) Joint Annual Conference on Sleep

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As psychiatrists, we ask about sleep in nearly every assessment we perform. It is a standard topic when screening for depression or assessing disrupted circadian cycles in psychosis or delirium, and reflects hugely on our patients' qualities of life. Yet how much do we really know about sleep? We are told that 1/10 of the adult British population suffers with clinically significant insomnia, more in a psychiatric population. Yet how many of us

would routinely stretch a sleep history beyond three or four questions? Rather, we tend to add it to our catalogue of symptoms related to a unifying diagnosis, blaming sleep disturbance on medication, substance misuse, lack of tiring activities or inaccurate reporting.

Are we doing our patients a disservice? In placing the blame on the concomitant psychiatric diagnosis,

we may be missing primary sleep disorders. In failing to take focused sleep histories, we miss fundamental detail about the contributory physiological and the psychological factors that can differentiate one tired patient from the next. By merely prescribing hypnotics or stimulants, we fail to get to the root of the problem and offer only temporary relief.

A relentless inability to gain refreshing sleep is a major hurdle to psychological health and may even be the primary aetiology in some of our clinic patients. Yet we tend to give our patients permission to talk about the distress of insomnia only to advance them to another topic without validating their upset with further questions. I sympathise, recalling slumberless travels around South African youth hostels with a friend who had apnoea, and attended this joint conference hoping to learn more about the topic for application both in my clinical and personal life. I was not alone. Coffee breaks were vibrant with heartfelt stories of snoring partners, student flats on busy roads and other tales all reflecting the same fact – when it comes to insomnia, we can all be empathic.

The nature of this conference, particularly the day shared with the Royal College of Psychiatrists, dictates collaboration between psychiatrists, neurologists and all those inbetween. This is a strength of the meeting as skills are pooled and experiences shared. Neuroscience junkies were treated to an opening talk by Professor Elemer Szabadi aimed at refreshing our knowledge on the alerting and sedating neural networks relevant to the topic, while Katharina Wulff's overview of the anatomy, physiology and functioning of circadian rhythms left us wondering about the role of the body clock and its relationship to both light and dark.

Clinically, we were encouraged to divide sleep disorders into excess need for sleep (hypersomnia), reduced sleep (insomnia) and disorders within sleep (parasomnia). Adrian Williams covered the causes of hypersomnia, from periodic limb movement disorder to sleep apnoea. Sofia Eriksson encouraged us to tease the diagnosis of the parasomnias from both clinical observation and a thorough history, while sharing some clips of narcolepsy, non-rapid eye movement sleep disorders and nocturnal frontal lobe seizures, which those of us who do not work in a sleep clinic can only otherwise read about in textbooks.

After this grounding in the neurological approach, the afternoon took a more psychiatric slant as the topic drifted towards that most common of psychiatric complaints, poor sleep. Hugh Selsick directed us in how to take a thorough sleep history, expanding on those three or four questions we know to ask and encouraging us to think as diagnosticians about sleep disturbances. The timing of this talk was delicately selected, having been lectured on problems getting to sleep, problems during sleep and excessive tiredness after sleep, we were

being given the skills to distinguish the three based on a clinical and informant history.

Colin Espie's talk on psychological management of insomnia sparked much debate, most notably around the unfamiliar topic of cognitive-behavioural therapy for insomnia (CBT-i). He argued convincingly that insomnia should be treated alongside co-existing psychiatric disorder rather than as a symptom of that disorder. We were given a brief overview of the five-session CBT-i course applied at the Glasgow Sleep Centre, directed at normalising the sleep experience. Thinking beyond sleep hygiene, the Centre focuses on relaxation and managing worrying thoughts including those related directly to sleep, before putting the day to rest and moving on to the development of a sleep pattern. We may hear more about this one as it becomes more widely available.

This linked in nicely with Sue Wilson's concluding talk as she covered the latest British Association for Psychopharmacology (BAP) guidelines for the management of sleep disorders, where the mostly inaccessible CBT-i is recommended as first line alongside hypnotic drugs. Indicative, perhaps, of the perceived lack of guidance in treatment of these disorders, discussion here was fruitful covering the selection process for the BAP consensus group, the power of the placebo effect and the practical difference between guidelines and clinical practice, particularly over the issue of melatonin and CBT.

In looking for a specific take-home message that might best benefit our patients, we return to the psychological. Insomnia is a complex phenomenon that is poorly served in current psychiatric history taking. Many of its maintaining features relate to the anxieties of not being able to sleep. The more an individual makes effort to sleep by paying selective attention to sleeping and the consequences of insomnia, the harder it becomes. Sleep can only happen involuntarily and bedtime anxieties will compound its emergence. Hypnotics are generally effective if prescribed properly, but we serve our patients better by providing accurate diagnosis and identification of the psychological components maintaining the disorder.

For more information on sleep disorders, go to the British Sleep Society's website at www.sleeping.org.uk or visit www.sleepio.com to take the Great British Sleep Survey. The BAP Consensus Statement is available at www.bap.org.uk/pdfs/BAP_Sleep_Guidelines.pdf

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Disordered emotional processes in thalamic lesions: experimental and clinical studies

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The role of the thalamus in processing the emotional information has not received as much attention as other brain regions.

Interestingly, Li et al¹ stressed the role of the paraventricular nucleus of the thalamus (PVT) in view of its unique and very dense projection to the shell of the nucleus accumbens, the bed nucleus of the stria terminalis and the central nucleus of the amygdala,² which collectively form an anatomical macrostructure called the extended amygdalae.³

Furthermore, the authors added that the potential contribution of other thalamic nuclei (Table 1) such as midline and intralaminar nuclei, which project to functionally distinct regions of the cortex and subcortical regions to emotional arousal, still remains as a source of controversy and requires further elucidation.¹

Anatomical pathways for emotional processes

Thalamocortical loops, connecting functionally segregated, higher order cortical regions and basal ganglia, have been proposed for limbic and prefrontal areas relevant for both affective and cognitive processes (Fig. 1).⁴ The role of the thalamus, however, was defined as mediating emotional intensity, mainly via activations in its mediodorsal compartment. In humans, recent investigations confirmed functional and structural specificity of thalamocortical connectivities.^{5,6} Previous studies indicate that layer V corticothalamic neurons innervate through some large terminals thalamic neurons that project widely to superficial cortical layers. Thus, the large population of prefrontal projection neurons in layer V may drive thalamic neuron. It does trigger synchronisation via involvement of several cortical areas through widespread thalamocortical projections to layer I. According to Xiao et al,⁷ those pathways may underlie the synthesis of cognition and emotion.

Studies in monkeys show clear anatomical and functional distinctions among networks connecting with subregions within the prefrontal cortex. Three such networks are centred on lateral orbitofrontal cortex, medial frontal and cingulate cortex, and lateral prefrontal cortex and all have been identified with distinct cognitive roles. Klein et al⁸ showed similar topography of mediodorsal thalamus prefrontal connections, using non-invasive imaging and diffusion tractography in humans and macaques. Non-invasive imaging and diffusion tractography suggested that there was a high probability of interconnection between medial MD and lateral orbitofrontal cortex, between caudodorsal MD and medial frontal/cingulate cortex, and between lateral mediodorsal and lateral prefrontal cortex, in both species.⁸

The thalamus is part of the limbic system, the region of the brain largely associated with the emotions and is well recognised as the final relay station for perceptual data before it is passed on to the cerebral cortex. It receives input from diverse brain areas, primarily including all the senses except olfaction.

Lesion or stimulation of the medial dorsal and anterior nuclei of the thalamus is associated with changes in emotional reactivity. For example, Li and colleagues¹ described changes in emotional behaviour in rats produced by orexin microinjections in the PVT, which innervates areas of amygdala zone. In this study, microinjections of orexins (hypocretins), which have excitatory actions on neurons in the PVT in the midline thalamus were used to examine whether the PVT modulates the expression of emotional behaviour. Both orexin-A and orexin-B microinjections in the PVT increased the expression of freezing and grooming behaviours, which are indicative of a negative emotional state. The results indicate that microinjections of orexins in the PVT made the test situation more aversive and produced avoidance behaviours. This suggests that orexins may

Table 1 Six major functional classes of thalamic nuclei with particular emphasis on emotional processing

Reticular nuclei	Intralaminar nuclei	Sensory nuclei	Effector nuclei	Associate nuclei (medial magnocellular)	Limbic nuclei
Arousal Rhythmicity	Arousal Motivation Affective components of pain	N/A	N/A	Drive Motivation Inhibition Emotion	Emotional experience and expression Drive Motivation

N/A, insufficient evidence base supporting the nucleus involvement in emotional processing.

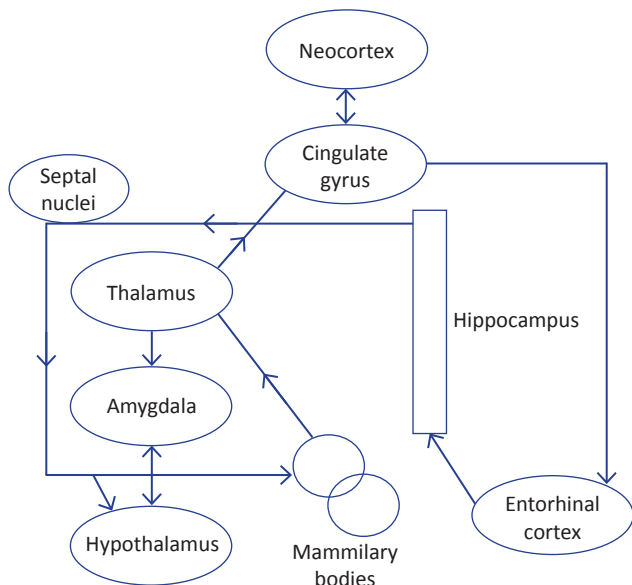


Fig. 1 Various tracts involving the thalamus in processing of emotions. Adapted from Oliveria et al.⁹

act at the PVT to modulate behaviours associated with a negative emotional state.¹

However, the importance of these nuclei on the regulation of emotional behaviour is not due to the thalamus itself, but to the connections of these nuclei with other limbic system structures. The medial dorsal nucleus makes connections with cortical zones of the prefrontal area and with the hypothalamus. The anterior nuclei connect with the mammillary bodies, and through them, via fornix, with the hippocampus and the cingulate gyrus, thus taking part in the Papez's circuit.⁹

Theories of emotions

The James–Lange Theory of Emotion was one of the earliest theories to describe the process of emotional reactions. The theory states that, following a stimulus, physiological arousal occurs first, then psychological emotion is experienced. This theory was challenged by the Cannon–Bard theory suggesting that we feel emotions and experience physiological reactions simultaneously.¹⁰

These were physiological theories and they did not have access to neuroimaging techniques to which we have access to today.

The rationale for the review of this paper is:

1. to integrate and consolidate knowledge about the involvement of the thalamus in key emotional processing;
2. to examine how the emotional reorganisation post-stroke would affect emotion recognition.

Disordered emotional processes in thalamic lesions

Intact processing of emotional stimuli is critical in communication, in view of the enormous amount of information contained.

Although a number of studies have examined emotion recognition¹¹ in damage of subcortical structures, mostly amygdala^{12,13} and basal ganglia,^{14–16} few have considered the role of the thalamus in emotional processing. In thalamic lesion literature, relatively little is known about the global aspects of emotional processing and association between emotional deficits (in emotional decoding, emotional empathy, etc.) and treatment provided.

Cheung et al¹⁷ described the differential effects of the thalamus on facial emotion recognition as well as lateralisation effect. The authors compared the task performance of 38 patients with subcortical strokes including 6 patients with thalamic lesions with 19 matched healthy controls. The participants were presented with morphed photographs of facial emotion expressions over multiple trials. They were requested to classify each of these morphed photographs according to Ekman's six basic emotion categories. Faces are diverse in appearance and play an important social role, not only revealing our emotions and intentions (through muscle configurations and direction of gaze), but also providing detailed information about identity, gender, age and ethnicity.¹⁸ The findings indicated that the clinical participants had impaired facial emotion recognition, although no clear lateralisation pattern of impairment was observed. The patients with localised thalamic damage performed significantly worse in recognising sadness than the controls.

Persistent disturbance in affective component manifested by hypomania and prosopoaffective agnosia was described by Vuilleumier et al,¹⁹ in a 63-year-old patient with right thalamic infarct. Detailed behavioural and neuropsychological assessment were performed 18 months after the stroke and revealed a prosopoaffective agnosia. Prosopoaffective agnosia is defined as impairment in the identification of emotional facial expressions with preserved discrimination of facial identity. Difficulties in reasoning on humour and other signs of mild right hemisphere dysfunction were present, but other perceptual, frontal and abstract-reasoning cognitive functions were unimpaired. Prosopoaffective agnosia has not been reported previously in thalamic lesions or in mania. The authors discussed the hypothetical relationships between a right hemisphere deficit in processing emotions and relapsing of the patient's hypomanic behaviour.

Heldt & Falls found that bilateral lesions of the auditory thalamus in rats disrupts the circuit of fear production although does not impair the inhibition of fear conditioned to an auditory stimulus.²⁰ Rats with bilateral thalamic lesions were provided with Pavlovian conditioned inhibition training in which a light was paired with shock and a noise and a light compound was presented in the absence of shock. Both fear and the inhibition of fear were measured with the fear-potentiated startle effect. Lesions of the auditory thalamus did not have an impact on the ability of the

noise to inhibit the fear expression, whereas the ability of the noise was affected to produce fear-potentiated startle after it had been subsequently paired with shock. The authors concluded that the auditory thalamus is not an essential part of the circuit that mediates the inhibition of fear to auditory stimuli.²⁰

In their case report, Clarke and colleagues²¹ described cognitive and emotional functioning of a 54-year-old patient who had an isolated left polar thalamic infarct and acute global amnesia with slight frontal type dysfunction. The authors have not measured emotional deficits as such, although described significant changes in the patient's mood, motivational level and also in her personality. The patient presented with marked mood fluctuations, varying between an exaggerated sadness and tearfulness and emotional indifference. Interestingly, the patient showed her inability to understand the emotional content of her interactions with others. The authors suggested that the anterior thalamic nuclei play a role in emotional involvement linked to ipsilateral hemispheric functions.²¹

Conclusions

This article has tried to highlight animal studies, various tracts involving the thalamus and has also considered studies involving patients with thalamic lesions in an attempt to link emotional processing with the thalamus.

The studies included in this review do indicate a relationship between the thalamus and deficits in processing of emotions. Further longitudinal studies of patients with thalamic lesions may reveal better understanding of the theory of neuroplasticity thus helping rehabilitation programmes in patients who have suffered brain injury.

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Progress with the NMDA receptor in schizophrenia: an update

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Schizophrenia and psychosis are increasingly considered the products of diverse, interconnected genetic, environmental, biological and psychological processes. The exact combination of aetiological factors likely varies from patient to patient, even if the diagnosis of schizophrenia per ICD and DSM criteria relies on a standard, shared clinical syndrome.

Excessive dopaminergic activity is one factor classically associated with psychosis, and antipsychotic-mediated dopamine blockade is effective in ameliorating symptoms (primarily positive symptoms) of schizophrenia.¹ The excitatory neurotransmitter, glutamate, has also been implicated in many neurological and psychiatric disorders. Its 'excitotoxic' effect, mediated following receptor binding by excess calcium influx and subsequent neuronal cell death, has been linked to epilepsy, the evolution of cerebral ischaemia, neuropathic pain and neurodegenerative disorders such as Huntington's, Parkinson's and Alzheimer's diseases.²

In contrast, reductions in glutamate neurotransmission by *N*-methyl-*D*-aspartate receptor (NMDAR) antagonists such as ketamine or phencyclidine mimic the clinical picture in schizophrenia.³ Glutamate, and particularly NMDAR, hypofunction has therefore been posited as a causative mechanism in models of psychosis. Glutamate antagonism can result in the negative and cognitive symptoms seen in schizophrenia, and potentially perpetuate (positive) symptoms by upregulating downstream dopamine transmission and by inhibiting gamma-aminobutyric acid (GABA) interneurons. The importance of the glutamate NMDAR is further supported by brain imaging studies demonstrating its reduced function in schizophrenia (e.g. single-photon emission tomography [¹²³I] radiotracer CNS-1261 binding in the left hippocampus), and by the discovery that genes regulating the NMDAR are associated with schizophrenia.^{3,4}

So, a 'balance' in glutamate neurotransmission is seen to be desirable in reducing the risk of a number of neurological and psychiatric disorders, and the NMDAR is a credible and exciting therapeutic target. In schizophrenia, attempts to upregulate glutamate transmission via the NMDAR are underway.

The receptor

N-methyl-*D*-aspartate receptors are most densely distributed in the forebrain (cortex, hippocampus, thalamus), with lower levels found in the basal ganglia, cerebellum and spinal cord.² Activation results in neuronal calcium influx, particularly important for

synaptic plasticity and long-term potentiation, and therefore optimal learning and memory.⁵ Each NMDAR is an ionotropic doubly-gated cation (calcium) channel composed of isoforms of NR1 (binds glycine/*D*-serine), NR2 (binds glutamate) and/or NR3 subunits (also binds glycine). The channel is regulated by voltage-dependent magnesium blockade, and only operates efficiently in the presence of membrane current and co-transmitter ligand binding (i.e. glutamate and glycine/*D*-serine).^{2,6}

Causes of NMDAR hypofunction and potential therapeutic targets

Genetics and signalling pathways

A number of genes implicated in the development of schizophrenia influence NMDAR function.⁷⁻¹⁰ *DISC-1* encodes a protein which influences NMDAR-dependent signalling via Rac1, a G-protein involved in dendritic morphology and plasticity.⁷ The neuroregulin 1 gene (*NRG1*) is implicated in enhancing Erb4 signalling, thereby suppressing NMDAR signalling in the prefrontal cortex.⁸ The dysbindin gene, *DTNBP1*, is associated with NR1/2A expression and NMDAR-mediated current in prefrontal and hippocampal neurons, while the gene brain-derived neurotrophic factor (*BDNF*) is thought to modulate NMDAR channel opening.^{9,10} The pathways incorporating these (and other) gene products represent potential therapeutic targets in the treatment of schizophrenia.

NMDAR co-agonists and antagonists

D-serine and/or glycine are essential for efficient NMDAR channel opening. A Cochrane review published in 2006 reported that the administration of these obligatory co-agonists with antipsychotic drugs was somewhat effective in reducing negative symptoms in schizophrenia, but there was no statistically significant effect on positive symptoms.¹¹ However, participants in many included studies were treatment-resistant cases, and data were considered by the authors to be too few and inconsistent.

Availability of *D*-serine is regulated by the enzymes serine racemase and *D*-amino acid oxidase. Drugs regulating these enzymes represent further potential therapeutic strategies, as do drugs regulating GlyT1, a glycine transporter found in glial cells and neurons that modulates glycine availability. Sarcosine, a GlyT1 inhibitor, has been found in early studies to be of benefit in reducing symptoms of schizophrenia when given alone or in combination with risperidone, but not in combination with clozapine.¹²⁻¹⁴

Kynurenate and *N*-acetyl aspartyl glutamate (NAAG) are endogenous antagonists at NMDAR glycine sites. Kynurenate has been found to be raised in the premotor cortex of patients with schizophrenia, potentially causing NMDAR hypofunction, while glutamate carboxypeptidase II (GCPII), the enzyme that degrades NAAG, has been found to be decreased in this same area, again potentially causing NMDAR hypofunction.^{15,16} D-amino acid oxidase inhibitors and drugs modulating GCPII represent further potential therapeutic strategies.¹⁷ It is too early to say whether these drugs, alone or in combination with D-serine or existing antipsychotics, will turn out to be credible pharmacotherapeutic agents in schizophrenia.

NMDAR antibodies

In 2005, Vitaliani et al reported a syndrome of memory decline, psychopathology, seizures and autonomic instability.¹⁸ This syndrome was subsequently attributed to an encephalitis caused by anti-NMDAR antibodies, often but not always in the context of systemic malignancy (mostly ovarian teratomas and testicular germ cell tumours).^{18,19} In October 2010, Zandi et al reported in their prospective study that 6.52% ($n = 3/46$) of patients with first presentation psychosis were NMDAR antibody positive.²⁰ One further patient was voltage-gated potassium channel antibody positive, classically associated with paraneoplastic limbic encephalitis. *N*-methyl-*D*-aspartate receptor antibodies were not found in chronic schizophrenia controls. *N*-methyl-*D*-aspartate receptor antibodies have been shown to cause a titre dependent, selective and reversible decrease in NMDAR surface density and synaptic localisation without influencing AMPA or GABA receptors, number of synapses, dendritic spines/complexity, or cell survival.²¹ Patients with NMDAR encephalitis have responded well to immunotherapy and this could be studied as a potential treatment in NMDAR antibody positive psychosis.^{19,20} Paired serum/cerebral spinal fluid studies have yet to take place in patients with schizophrenia.

Post-translational phosphorylation

Post-translational modification (phosphorylation, ubiquitination, glycosylation) influences receptor function, and can similarly influence NMDAR function and receptor localisation. In the frontal cortex and hippocampus of patients with schizophrenia, reduced phosphorylation by protein kinase A (PKA) at serine 897 of the NR1 subunit has been reported.²² Knock-in mice with an alanine in place of this phosphate have impaired function of NMDA and AMPA glutamate receptors, impaired synaptic plasticity, and abnormal sensorimotor gating and social behaviour.²³ It is unclear whether reduced phosphorylation is a cause or a compensatory response in chronic schizophrenia. One potential effect of this abnormal phosphorylation is to impair retention and extrusion of NR subunits from the endoplasmic reticulum of neurons, conceivably controlling the number

of NMDARs. The activated metabotropic glutamate receptor, mGluR5, also phosphorylates the NR1 subunit (at a different site) and enhances ion flux through the NMDAR channel. Positive allosteric modulators of mGluR5 and mGluR2 are being investigated as treatments for schizophrenia.^{24–27}

Conclusions

Although NMDAR hypofunction is accepted as having an important role in schizophrenia, finding an effective approach in upregulating NMDA receptors without the negative effects of glutamatergic hyperactivity and excitotoxicity remains an ongoing challenge. The complexity of modulatory and signalling pathways associated with the NMDA receptor, and the multiple potential mechanisms of NMDAR hypofunction, means that any number of approaches can be taken in the search for a therapeutic agent.

Although this is an exciting area of research, no agent has yet been demonstrated to sufficiently ameliorate symptoms (especially the negative and cognitive symptoms typically more resistant to existing antipsychotics) as to be recommended in day-to-day clinical practice. A new-generation antipsychotic that targets both dopamine and glutamatergic pathways could, however, be a conceivable development, either as a treatment for established psychosis or perhaps even as a prophylactic agent in the prevention of psychosis in high-risk individuals.

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Notices

Section of Neuropsychiatry Annual Residential Conference

8–9 September 2011, Robinson College, Cambridge

CALL FOR POSTERS

Instructions on the preparation of abstracts

1. Abstracts should be typed single spaced, font size 10, in Verdana, in Word format using standard text, or text-only format. Apple Mac documents cannot be accepted.
2. The title should be in bold, followed by the full name(s) of the author and all co-authors, including titles (e.g. Dr) and their affiliations.
3. Hand-written abstracts will not be accepted.
4. The title must contain no abbreviations.
5. The abstract must be no longer than 300 words.
6. The abstract should present in order: the aims, methods, results and comments or conclusions. If no information is given in the abstract about the results of the study, the authors must include a covering letter of explanation with their submission.
7. Bibliographic references, tables and appendices must not be included in the abstract.
8. Please make sure you check all spelling carefully.

Clinical cases, and posters within the themes of psychopharmacology and neuropsychiatry, and alcohol and neuropsychiatry will be welcome.

How to send abstracts

Abstracts should be emailed to dgoka@rcpsych.ac.uk with a subject reference of 'Your Surname – NEU 2011'. The following information should be included in the covering message.

- Name of main presenting author
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Contact: Conference Office, Royal College of Psychiatrists. Email: dgoka@rcpsych.ac.uk, tel: +44 (0)20 7235 2351 ext. 6145.

Instructions for poster presentations

- If your abstract is accepted for poster presentation at the meeting, the size of the poster board that you will be allocated is 2 m high x 1 m wide.
- The top line(s) should give the title of your abstract with lettering not less than 2.5 cm high.
- The next line(s) should indicate the author(s) and their affiliations.
- Continue with the introduction, methods, results and discussion as appropriate. The poster should end with the conclusions.
- You are advised to bring your own adhesive Velcro or pins for mounting the presentation on the board.
- Hand-outs, citations and contact details for distribution to interested delegates are always appreciated.

Please note that we are unable to return posters to presenters if they are left behind at the end of the meeting.

The conference fee will apply to submitted poster presenters.

Section of Neuropsychiatry Trainee Award

The Section of Neuropsychiatry has established an annual award for trainees. This award is given for the best original research, audit, literature review or clinically focused essay in the field of neuropsychiatry.

Aim: To promote the highest standards of critical thinking and communication by psychiatry trainees in the field of neuropsychiatry.

Prize: £500 and a certificate.

Frequency: Annually.

Eligibility: The award is open to all psychiatry trainees (CT1–3 and ST4–6) working in the UK. Trainees can win this prize only once during their career.

Where presented: Section of Neuropsychiatry Annual Meeting in September (each year) and the winner is announced during the Annual Meeting as well. Prize and certificate will be posted after the conference.

Regulations

Applications for the award will be invited at least 4 months before the Annual Meeting.

- I. The spirit of the award is to recognise the excellence of the trainee's work. The award is intended for those who have taken the lead in the work that has resulted in the submission, as well as for the submission itself.
- II. In the first stage, the judges will independently rate all submissions and shortlist a maximum of three potential candidates for the award by weighing the merits of each submission.
- III. Shortlisted applicants will be invited to present their work during the Annual Meeting.
- IV. The judging panel will individually mark the candidates' presentations and will subsequently meet to decide the winner.

- V. The award-winner will be announced during the annual conference.
- VI. The award-winner will be expected to provide a summary article for the Section of Neuropsychiatry newsletter. Work may later on be submitted for publication to a journal.
- VII. In the absence of a suitable application, the Section of Neuropsychiatry may decide not to give the award at all for that year.
- VIII. The decision of the judges will be final and binding on all concerned. No appeals will be allowed.

Application procedure

1. Candidates are asked to submit a covering letter application by email explaining clearly in a maximum of 300 words the reason for their application and its suitability for this award. They should clearly specify their role in any collaborative projects.
2. In addition, they should submit a description of a research or audit project, a review article or an essay. The total length excluding references should not exceed 5000 words.
3. The application should be accompanied by a letter from their educational/research supervisor supporting their application and highlighting the trainee's contribution to the project.
4. Failure to follow the procedure will automatically disqualify the candidate and no resubmissions will be allowed for that year.

Closing date: End of June each year.

Submissions to: Vice-Chair, Section of Neuropsychiatry, The Royal College of Psychiatrists, c/o Kitti Kottasz, Committee Manager, tel: 0207 235 2351 ext. 6299, email: kkottasz@rcpsych.ac.uk

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