‘Stimulating’ and ‘Imaging’ insights into the aetiology of visual hallucinations in Dementia with Lewy bodies

John-Paul Taylor & Daniel Collerton / Page 4
Contents

Editorial

03 Neuropsychiatry in the United Kingdom: New Opportunities and Old Challenges
Niruj Agrawal & Rafey Faruqui

Articles

04 ‘Stimulating’ and ‘Imaging’ insights into the aetiology of visual hallucinations in Dementia with Lewy bodies
John-Paul Taylor & Daniel Collerton

13 Clinical Practice Statements for the Management of Neuropsychiatric Comorbidities in Epilepsy
Seth A. Mensah & Mike P. Kerr

18 CPAP for treatment of cognitive dysfunction in Obstructive Sleep Apnoea
Mary J. Morrell, Martin Glasser, Alison McMillan, & Rosenzweig

24 Understanding the endogenous clock, sleep and the circadian rhythm.
Anne-Mary O. Abe

Meeting Report

27 Report on the Section of Neuropsychiatry Autumn Meeting 2012

29 Abstracts from Section of Neuropsychiatry Meeting September 2012

30 Reduced fractional anisotropy in the uncinate fasciculus in patients with Major Depression carrying the Met–allele of the Val66Met Brain-Derived Neurotrophic Factor Genotype
Carballedo A., Amico F., Ugwu I. et al.

31 Conversion disorder clinic – a 12 month evaluation
Rory Conn, Gary Price, Eileen Joyce

32 The use of Aripiprazole in the management of complex Gilles la Tourette syndrome (GTS): a case study.
Christopher Symeon, Kate Humphreys, Michael Kopelman, & Mervi Pitkanen

Training

33 London higher psychiatric training and Masters degree in Neurology, my experience
Yousaf Iqbal

Case Report

35 Case study: sub–clinical epilepsy presenting as cognitive impairment and depressive symptoms
K D Jethwa & V Joseph

Interview

38 An interview with Alwyn Lishman
Norman Poole

Notices

Neuropsychiatry News is produced twice a year. Articles, case-reports and service descriptions should be submitted in a MS Word format by email and should not exceed 2000 words unless agreed with the Editor. Letters should not exceed 200 words. The Editor reserves the right to edit contributions as deemed necessary. Opinions expressed in the newsletter are of the authors and not of the College. Copyright of submissions are retained by its author, but the College reserves the right to reproduce the article on the Faculty website pages.

Graphic Design Jamie Paton – jamie@twhe.co.uk
Neuropsychiatry in the United Kingdom: New Opportunities and Old Challenges

Rafey Faruqui

Chair, Section of the Neuropsychiatry, Royal College of Psychiatrists

This is an exciting time for the sub-specialty of neuropsychiatry. We are attracting an increasing number of communications from medical students, trainee doctors, and new consultants, expressing clinical and research interest in neuropsychiatry. We are developing new national networks and our professional influence is expanding in new areas of service developments.

Our new National Network of Childhood Onset Neuropsychiatric Conditions and Early Life Brain Injury was formally launched on 6th September. This initiative has proved to be an excellent success. I hope that this network will grow into a national lifespan dialogue on these early onset, and often poor prognosis disorders. We are now in process of planning a National Service Structure Audit of Young Onset Dementia Services in collaboration with our Old Age Faculty.

We are keen to develop our Interfaculty and Inter Medical Royal Colleges networking further. Our Interfaculty Working party on Alcohol and Brain Damage has been meeting regularly. The guideline development work is progressing further. We do hope that this work will lead to new service developments in different parts of the UK.

We have organized and participated in a number of conferences nationally. These conferences have proved helpful in developing new national dialogues on service need areas such as Brain injury in Intellectual disability, Epilepsy in Complex Neurodisability, and Neuropsychiatric co-morbidities. I am keen to develop new work agendas such as focusing on neuropsychiatry of serious medical illnesses, and neuropsychiatry of blast related brain injuries. You’ll be pleased to learn that the Section of Neuropsychiatry has already agreed to explore work group formation in relation to movement disorders and forensic aspects of neuropsychiatric practice.

We aim to influence neuropsychiatry training agenda further. We are actively engaged in conference planning with Academic and General & Community Faculties of the Royal College on, “Psychiatric Workforce Development: Role of Clinical Neuropsychiatry and Neurosciences Research Training”. The conference will aim at raising training awareness in relation to advances in understanding of mental illness, and training needs of a future workforce. We are continuing to work on higher specialist neuropsychiatry curriculum approval process. We plan to be in a position to influence core training through effective use of neuropsychiatry teaching at MRCPsych courses nationally.

We want to raise service delivery standards through development of a National Service Quality Assurance Network. This is a much needed area of work that we’ll be developing in the near future. We also want to actively engage in public education work and service user engagement. In this context we are exploring a proposal to launch a Head Injury Awareness campaign nationally.

I have talked about new developments and the exciting areas of neuropsychiatry influence development. However, this discussion is not complete without full recognition of the challenges ahead of us that we do need to tackle with your help and input. The biggest challenge is a our rather limited neuropsychiatry service delivery base that impacts on opportunities in relation to training organization and training delivery nationally. I am keen to start a dialogue within the Royal College and outside to help promote a wider service delivery and training resource base for neuropsychiatry.

I’ll end my brief message by talking about our efforts to develop new international networking. We were honoured by a number of senior colleagues from USA, Australia, and Malta who visited us and attended our annual residential conference at Cambridge this year. We aim to develop this exchange and dialogue further especially in order to promote our training and service quality assurance agenda further.
‘Stimulating’ and ‘Imaging’ insights into the aetiology of visual hallucinations in Dementia with Lewy bodies


Visual hallucinations (VH) have a rich variety of phenomenological manifestations, for example, ranging from the simple to the complex, from the discreet to the panoramic or the occasional to the chronic – recurrent. They also occur across a wide variety of differing pathological states, for example, Charles Bonnet syndrome, peduncular hallucinosis, functional mental illnesses, and of course, in the Lewy body diseases such as dementia with Lewy bodies (DLB).

In the present article we focus on just one aspect of understanding VH aetiology in the VH-prone patient population of DLB and describe a series of functional neuroimaging and neurophysiology experiments carried out in our group which have recently been reported in the British Journal of Psychiatry (1,2). Thus we do not presume to elaborate on all studies which have investigated VH across various disease states nor do we try to encapsulate, in full, the lively intellectual dialogues on aetiological models of VH; for these we would refer the reader to comprehensive VH reviews and discussions on this topic (for example, 3–9).

Visual hallucinations in Dementia with Lewy bodies Complex, recurrent, VHs are often refractory and serious symptoms in patients with DLB and their occurrence is often concomitant with marked visuo-perceptual deficits. Untreated, they can markedly impair patient quality of life (10) and significantly increase caregiver distress (11). Up to 60–80% of patients with DLB report VH and these rates contrast with the low rates of VH reported in Alzheimer’s disease (AD; less than 10%). Indeed, this differential prevalence highlights the importance which is attached to the presence of VH in the diagnostic criteria separating DLB from diseases such as AD (12).

In terms of phenomenology, it is notable that more simplistic VH such as tassellopies, dendropsies and fortification spectra are not reported in DLB. Instead VH in DLB tend to be complex and formed and typically are of people, animals, body parts that are either animate or static. Often these images represent recurrent stereotyped superimpositions onto the pre-existing real-world visual milieu rather than as de novo panoramic visual scenes which more commonly occur in eye disease patients. In addition, these complex VH tend to be silent with no concurrent involvement of other sensory modalities, though it should be noted that hallucinations in other modalities are often present at other times:
with the phenomenology as dream events include multiple sensory modalities and have a fluidity of content in comparison to, respectively, the unimodal nature and stereotypy of VH seen in DLB. Empirically, differences in neurotransmitter functions in sleep and VH in DLB, different time scales of the occurrence of REM sleep behaviour disorder (often antedating dementia by decades) compared to VH onset (14) as well the lack of REM sleep intrusion in PD hallucinators on polysomnography backs the conclusion that there is a lack of involvement of REM intrusion in VH manifestation in Lewy body diseases (4, 15, 16).

Rather, the superimposition of the VH on the real world visual scene is consistent with the Perceptual-Attention Deficit (PAD) model of VH (5). This model suggests that a combination of impairment in visual attention and poor visuo-perception and the unprompted or excess activity in the visual perceptual system which arises as a result could lead to the intrusion of context-specific hallucinations. A similar interactive model (6) makes predictions that poor visual input and processing in combination with defective central visual monitoring produces partial visual deprivation. As a consequence this model predicts that visual input cannot be interpreted leading to "deblocking" of visual memory contents (release phenomena) as VH.

In the context of these data and the PAD/interactive models of VH we wondered whether such activity changes in the visual system were also a factor in DLB leading to the manifestation of VH. Certainly across the Lewy disease spectrum, there is neuropathologic evidence for alterations in retinal dopaminergic function, altered inter-retinal electrophysiology and neuropathologic changes within the photoreceptors and outer plexiform layers (17). Thus the fidelity of bottom up visual input could be compromised although it should be noted that a more recent study found in Parkinson’s disease (PD) patients that despite the occurrence of visual abnormalities in PD, ocular pathology did not delineate PD hallucinators from non–hallucinators (18). Thus it may be that ocular pathology is a necessary but not a sufficient factor in the genesis of VH.

There is also evidence to suggest that some visual areas are perhaps less “active” in DLB patients. For example, hypoperfusion and hypometabolism of the occipital cortex is a feature of DLB and has been linked by some (19,20) to the presence of VH. Therefore it may be that reduced activity in these areas with concomitant failures in early visual processing i.e. poor

"He just appears in the corner of the room – a shadow man with the outline of bowler hat. It’s quite frightening." Patient quote (Fig. 1)
fidelity of bottom up transmission, is what pre-disposes individuals with DLB to VH. An underactive lower or early visual cortex may lead to an under-constraint of activity in the downstream ventral visual stream or in terms of generative models of perception, a failure to match internally generated perceptions against actual visual input arriving from the visual pathways. Thus a lack of occipital activity might indicate a failure in that matching process within occipital cortex allowing incorrect internal perceptions to persist and this might account for why VH so often occur in combination with other failures of perception.

Therefore our questions were:

- Is visual cortical activity increased or decreased in DLB patients?
- If so, are there alterations in activity in higher visual and associative areas?
- And finally, are any observed perturbations associated with the occurrence of VH?

TMS as a probe of visual cortical function

One way to address this question was the application of occipital transcranial magnetic stimulation (TMS); TMS has been widely applied tool to non-invasively probe cortical excitability and it has been highly successful in elucidating the neurobiology of motor control (through stimulation of motor cortical areas) and it has been applied in the psychiatric setting as a potential therapeutic for a wide range of symptoms (albeit with variable efficacy). However, TMS can also be used to investigate the visual system; when applied to the occiput, TMS produces transient visual percepts called phosphenes with the origin of these phenomena likely to be arising within the superficial dorsal occipital lobe. Indeed an intact striate visual cortex is required for the perception of phosphenes and phosphene threshold (PT), the stimulation intensity level at which phosphenes are just perceived, is a reliable marker of the excitability of the visual cortex.

Use of TMS to assess visual excitability in VH prone individuals is not without precedent; migraine suffers with visual aura tend to have lower phosphene thresholds (21) as do heavy users of ecstasy (3,4-Methylenedioxymethamphetamine) who have experienced VH (22). However occipital TMS had never been applied in a DLB cohort to examine VH aetiology. Therefore, using TMS in a cohort of 21 DLB and 19 age matched controls, we sought to ask whether visual cortical excitability is either increased (in line with deafferentation models of VH) or decreased (in keeping with neuroimaging data showing hypoperfusion/hypometabolism). Detailed methodology of the TMS techniques we used are described in (1) but, in brief, we applied TMS to the occiput of blind-folded subjects and sought to determine two measures of visual cortical excitability including: 1) the phosphene threshold (PT) – the level of TMS intensity at which subjects just experienced (we defined this as approximately 25% of the time) phosphenes at an optimal scalp site for eliciting phosphenes and 2) the number of scalp sites where we could elicit phosphenes from – which we defined as the phosphene response rate (PRR); a marker of the extent of the spatial distribution of excitability.

More recently, in a subsample (n=17) of the DLB patients who underwent TMS we also assessed visual cortical activity by using a neuroimaging protocol which included functional MR BOLD imaging (fMRI) of passively presented visual stimuli (simple checkerboard to activate striate visual areas, a motion stimulus activate occipito-parietal areas or the dorsal stream and a faces stimulus to elicit activity in the occipito-temporal ventral stream) as well as arterial spin labelling (ASL, a technique to indirectly assess cerebral perfusion) thus providing a complementary perspective on the visual cortical function and the relationship of this to VH in DLB (2). In the present article, we also present for the first time, preliminary data on visual cortical activity in a non-hallucinating dementia comparator group (Alzheimer's disease, AD, n=19; MMSE 19.1 +/- 5.2; mean +/- SD).

Summary of main findings

In the TMS study we were able to elicit phosphenes from the majority of subjects (>80%) regardless of group and the phenomenology of phosphenes experienced ranged from simple flashes of light, through to polychromatic blobs and, very intermittently, in six of the DLB patients with a higher tendency to hallucinate and who had worse visuo-perceptual function, the occurrence of complex VH-like phosphenes of figures and objects (see Appendix in Taylor et al.(1)).

Interestingly, both the PT and PRR parameters were comparable between DLB, AD and control groups (Fig 2) but in DLB patients there was a strong association between the severity and frequency of VH experienced and a lower PT and higher PRR (Fig 3).
In our MR study, we found comparable levels of BOLD activity in response to checkerboard and faces stimuli across the groups but reduced activity to the motion stimulus in V5 between DLB and controls (Fig. 4). Cerebral perfusion was similar between groups in lower or early visual areas (V1–V3) but was reduced in higher visual areas in DLB patients compared to the other groups.

Overall in the neuroimaging study we found no evidence of any association between the severity and frequency of VH and BOLD activations to any of our visual task probes although on ASL imaging there was a tentative relationship in DLB patients between hypoperfusion in V4 visual areas and the severity and frequency of VH as well as hypoperfusion in V1–V4 visual areas and visuo-perceptual dysfunction.

**Discussion**

From the TMS study we showed that the process of phosphene induction and levels of excitability were not widely dissimilar between DLB, AD and similarly aged controls, suggesting that, in DLB, the lower or early visual areas are reasonably intact. This observation is supported by our complementary MR data and also by a significant body of evidence suggesting limited macro and micro–structural pathology in these areas in DLB (see Taylor et al.(2) for elaboration) and might imply that the pathological processes which give rise to VH either arise up–stream (e.g. visual association areas) or down–stream (e.g. eye) to the occipital visual cortex. In addition, the lack of difference between similarly impaired DLB and AD patients may also indicate that general neurodegenerative and atrophic processes are not specifically contributory to the occurrence of VH. We did not find any group differences between our TMS measures of visual cortical excitability but yet there was a strong association in DLB patients between the severity and frequency of VH and greater phosphene excitability. Superficially, these observations appear counter–intuitive and we thought that perhaps a driving mechanism might be that there was a bimodal heterogeneity in the DLB population i.e. some patients might be much less excitable to TMS as a result of specific hypoaactivity in the visual system (consistent with the evidence suggesting occipital hypoperfusion/ hypometabolism) and in others the visual system might be much more excitable than normal as a consequence of, for example, deafferentation processes or functional receptor modification. However, no specific subgroup bimodality was evidenced in the DLB group either in the TMS parameters (see Fig. 4 in Taylor et al.(1)) or indeed in the MR imaging data. However, PTs varied considerably even in healthy controls and AD patients and thus an alternative explanation that we proffered was that VH expression in a DLB patient is dependent upon that individual’s inherent premorbid visual cortical excitability as well as the concurrent presence of Lewy body related neuropathology. This is an intriguing conjecture which unfortunately cannot be answered by our present studies but needs further support in the form of longitudinal studies of early stage DLB patients or other VH prone patient groups who subsequently develop VH to establish cause and effect.

It is likely that the origin of phosphene induction and their subsequent conscious perception while interrelated are unlikely to be co–localised. Combined TMS with electroencephalography (EEG) has suggested that the conscious perception of phosphenes is dependent upon the integrity of higher–order networks and extensive recurrent processing (23). Our TMS data showed across all subjects groups (DLB, AD and controls) that the more rich and complex the diversity of phosphene phenomenology an individual experienced, the more scalp sites from where we could elicit phosphenes and the lower the PT thus suggesting that localised occipital TMS leads to activation of higher visual areas. Therefore our phosphene parameters may be metrics of the visual cortical excitability across widespread visual cortical areas and not just lower or early visual areas. From this, one could argue that individuals with inherently increased excitability to occipital TMS have either a progressive increase in the propagation of TMS–evoked activity from early visual areas to higher areas or enhanced phosphene perception within higher visual areas themselves. This was supported by our observation that in those DLB patients with an inherently more active/excitable visual cortex, TMS occasionally elicited VH–like phosphenes and may predispose them overall to VH. The phenomenology of the VH–like phosphenes (people and objects) experienced could indicate abnormal ventral stream/temporal lobe activation and our concurrent observation of the association of hypoperfusion of V4, which is one of the first visual cortical modules of the ventral stream, in the DLB patients who hallucinate more severely would also support this. An outstanding question, however, is whether the elicitation of these VH–like phosphenes represents the de novo manifestation of pre–activated stereotypical images arising from the ventral stream (we did see some overlap in phenomenology between these phosphenes and prior spontaneous VH experienced by that...
In the context of generative models of VH, people who are prone to mismatching between internally generated perceptions (ventral stream) and the visual cortex (hence are more likely to have misperceptions and VH) may have this mismatching induced more easily by TMS. The fact that those DLB patients who experienced VH–like phosphenes were also the ones who had a tendency to have worse visuo-perceptual function might support this line of argument. Of course, our data may also suggest that the matching process of internally generated perceptions and external visual input is intact given the lack of abnormalities detected in the lower or early visual cortex on TMS and also in our MR studies. Preliminary studies (Straughan and Collerton, unpublished findings) have shown identical visual priming in PD hallucinators and non-hallucinators supporting the argument that interactions between top down and bottom up processes are normal and that perhaps areas outside of the lower or early visual cortex are perhaps more active/excitable.

Intriguing, we also seen deficits in occipito–parietal function during our BOLD fMRI motion task in DLB patients compared to controls yet no differences between DLB and controls for the faces task (which is perhaps, a more ventral, or occipito–temporal function) which seems somewhat counter–intuitive to the observations and arguments that we have previously presented. However these findings concur with the prior literature showing more obvious occipito–parietal deficits on neuroimaging in DLB (see (2) for discussion) yet on autopsy there is more Lewy body pathology in occipito–temporal and temporal areas (which co–associates with the occurrence of VH) than in parietal areas (18, 24). It may be that what is more important is the interaction between the occipito–temporal and occipito–parietal processing streams and/or disruption to visual white matter connectivity that contributes to the visuoperception difficulties and VH seen in DLB.

As a final point, we failed to see obvious occipital hypoperfusion in our ASL study; however hypoperfusion is not consistently observed in this region in DLB across studies (25) and of course perfusion as a measure of underlying neuronal activity can be critiqued given that it is an indirect quantification. However it may be that occipital hypoperfusion is much more variable in DLB than expected and, if it is present this might be more reflective as an effect of visual system dysfunction and VH rather than as a cause; this is partially backed up by our observation of an association between V1–V4 hypoperfusion and visuo-perceptual dysfunction in our DLB patients although we failed to see any association between V1–V3 perfusion and VH.

**Conclusions and future work**

Visual cortical excitability as measured on TMS appears to be broadly similar between controls and dementia patients including those with AD and those with DLB. However despite this, we found a strong coupling between VH severity and frequency and increased visual cortical excitability in DLB. Therefore while visual cortical excitability doesn’t explain VH, it may well be an important moderator in this condition.

So are there specific anatomical loci for VH in DLB? Our recent investigations in the visual system of DLB patients perhaps suggest that probably early visual cortex is not overtly disturbed; rather higher visual areas appear to be specifically dysfunctional. Whether, on the basis of interactive models of VH, there is a dysfunction in the “matching” of internally generated perceptions to external visual input needs to be clarified. In addition, other top–down contributions may also be relevant; our present discussion has tacitly avoided the consideration of top–down attentional processes in the manifestation of VH in DLB. However given the centrality of cognitive fluctuations, dysexecutive and attentional difficulties in DLB, the “attention” component of any PAD or interactive model of VH in DLB is likely to be highly relevant and needs to be considered.

One challenge in VH studies has been that, while we can probe trait i.e. DLBs who have a history of VH, we cannot reliably test for the “online state” i.e. investigate DLB before/during/after active VH. We did elicit very intermittent VH–like phosphenes in a minority of DLB subjects. If the occurrence of these could be optimised, this would provide a new approach to exploring the underlying neurophysiology of VH in DLB and other VH prone conditions in, for example, differing attentional states. Similarly the use of ambiguous form presentation such as pareidolias (26) or in virtual reality contexts (9) may also have potential as surrogates for VH activity.
Figure 2: Boxplots showing phosphene parameters in all participants (minimum, first quartile, median, third quartile and maximum displayed). (a) Phosphene threshold boxplot – there were no significant differences between the controls, DLB or AD patients for phosphene threshold ($p = 0.62$). (b) Phosphene response rate (PRR) boxplot – there were no significant differences between controls, DLB or AD patients for
Figure 3: Scatter plots showing phosphene threshold at the optimal scalp site (oPT) and phosphene response rate (PRR) in patients with dementia with Lewy bodies (DLB) against Neuropsychiatric Inventory (NPIhall) score. Vertical line demarcates maximum stimulation intensity; four patients had PT > 100%. Red lines show linear fits to data.

phosphene response rate ($p = 0.54$).
Region of Interest analysis values for Checkerboard, Motion and Faces Objects Task

Figure 4: Bar chart showing a region of interest (ROI) analysis contrasting control group vs. dementia with Lewy bodies (DLB) and Alzheimer’s disease (AD) group with regard to functional BOLD activations to different visual stimuli (mean +/- standard error). Check_V1 – checkerboard activation in V1 ROI; Check_V2/3, checkerboard activation in V2/3 ROI; Motion_MT, motion activation in ROI V5/MT; Faces_sFFA, face activation in fusiform face area. There were no significant differences between groups for ROI activations except for motion stimulus contrast as indicated by asterisk (P = 0.02).
References


Clinical Practice Statements for the Management of Neuropsychiatric Comorbidities in Epilepsy

Seth A. Mensah & Mike P. Kerr*

Welsh Neuropsychiatry Service, Whitchurch Hospital, Cardiff, United Kingdom; *Welsh Centre for Learning Disabilities, Cardiff University, Cardiff, United Kingdom

Introduction
As those of us in the section are well aware, people with epilepsy have a high prevalence of psychiatric comorbidity compared to the general population and those with other chronic medical conditions. The early identification and appropriate management of these disorders will translate into better seizure control, less adverse effects, improved quality of life, benefits for the costs of healthcare delivery and better outcomes for society at large.

At the ILAE commission on the neuropsychiatric aspects of epilepsy meeting at Chennai, India in July 2007, the production of internationally consensus-based clinical practice statements on the management of neuropsychiatric disorders associated with epilepsy was identified as an essential step towards improving the management of this important aspect of epilepsy care. Three exemplars are reported below and the reader is referred to the original article published in Epilepsia (Kerr et al; 2011) for a detailed account of the process, methodology, expert summary and clinical practice statements on all the top 10 rated clinical areas identified for clinical practice statement development. In this report we will just report 5 clinical statements for each condition. Members of the section were prominent in the production of these clinical statements and we believe they offer an important step in developing the importance of neuropsychiatric input into epilepsy care.

Depression
Assessment and Management of depressive disorders in epilepsy
Depressive disorders are the most frequent psychiatric condition in people with epilepsy. Several primary, secondary and tertiary care studies have consistently demonstrated the higher prevalence of depression in people with epilepsy over the general population and in people with chronic or paroxysmal medical conditions. Prevalence rates for depressive disorders in people with epilepsy have ranged from 11% – 75%, and even up to 80% in some studies. This relatively high prevalence, increased suicide risk, subsequent increased disability and mortality make the identification and treatment of major depression important for the optimum management of people with epilepsy especially with the increasing primary–care based management of diseases across the world.

The diagnosis of depression in epilepsy requires a high degree of suspicion but a carefully obtained clinical history remains the best diagnostic tool. Recently developed rating scales, in particular the Neurological Disorders Depression Inventory for Epilepsy (NDDI–E) have been shown to be helpful in detection of depression in PWE. Current evidence suggests some improvement in recognition of depression in epilepsy but this has not translated into improved treatment.

It is now widely accepted that depression in epilepsy represents at least four aetiological processes;
1. Epilepsy factors e.g. age of onset and duration of epilepsy, laterality, aetiology and frequency of seizures,
2. Psychosocial factors e.g. perceived stigma and discrimination, adjustment to epilepsy, stressful life events,
3. Medication and individual health factors e.g. side effects of AED, mono- or polytherapy of AED, use of barbiturates, blood levels of AED
4. Sociodemographic factors e.g. age, gender, marital status, education, employment.
Depressive disorders in people with epilepsy are classified according to the temporal relationship between the onset of depressive symptomatology and seizure occurrence.

The classification is thus:
1. Peri-ictal (including pre-ictal) depression which typically presents as a dysphoric mood before or soon after seizure occurrence.
2. Ictal depression, a rare condition, which is the clinical expression of a simple partial seizure.
3. Post-ictal depression which often is prolonged, outlasting the seizure by days and at times have led patients to suicide.
4. Inter-ictal depression is the most common presentation of depressive disorders in people with epilepsy and can present as major depressive disorder with or without psychotic symptoms, and a significant proportion can present with atypical depression or Inter-ictal Dysphoric Disorder which require a high index of suspicion to detect, diagnose correctly and treat appropriately.

The management of depressive disorders in epilepsy is empirical. Approximately 60–70% of acute major depressive episodes will respond to antidepressant treatment, and early treatment intervention has been shown to reduce the episode by 50%. Depression in individuals with epilepsy can be treated with antidepressants in much the same way as people without epilepsy. The choice of antidepressants depends on: its effect on seizure threshold, the most prominent depressive symptoms, its efficacy, interactions with other drugs especially AEDs, and side effect profile. Some antidepressants can induce seizures e.g. Bupropion, Amoxapine, Maprotiline and some have been associated with anticonvulsant and mood-stabilising properties. The importance of recognising depression in people with epilepsy is not only to enable appropriate treatment to be considered but also to identify patients at risk for suicide. There is now even a more pressing need to improve identification and treatment of depression in people with epilepsy especially with depression being reported by the World Health Organisation to be the condition that would cause the most global burden by 2020. Detection of depression in people with epilepsy is poor across all levels of healthcare delivery and results in poor outcomes in terms of seizure control and quality of life. Depression in epilepsy is a strong predictor of self-perceived health status independent of seizure rate and is associated with increased health costs of epilepsy. The management of depression in people with epilepsy must be eclectic, embracing rationalisation of AEDs, judicious use of appropriate antidepressants, psychotherapy and involvement of the patient’s family in the treatment process.

Clinical Practice Statements—5 examples
1. Screening for depression using the NDDI-E or PHQ-2 should be undertaken for all new patients, for all patients attending epilepsy review with their primary care and secondary (or tertiary) care physicians on an annual basis. Even though there was overall agreement in the consensus group on this statement, concerns were raised about resource challenges, availability worldwide, and the risk of increasing psychological burden in PWE by the use of these questionnaires.

2. There should be no watchful waiting even in those deemed to be having milder depressive episodes because of 1. increased risk of suicide, 2. adverse impact of depression on quality of life and seizure control and 3. a significant overall increase in healthcare costs irrespective of seizure severity or duration. In such cases, refer to or seek advice from Mental Health Specialist Service. If episode is severe, or if suicidal ideation or risk present, refer to psychiatrist.

3. Neurologists/ Epileptologists/ Clinicians/ Internists with training/ skills in treating depression can, after diagnosing episode of depression, start an Selective Serotonin Reuptake Inhibitor (SSRI) if inter-ictal depression is identified.

4. SSRIs, where available, should be considered as first-line treatment as they have a low seizure propensity and favourable side effect profile.

5. It is necessary to ascertain whether symptoms of depression have a temporal relationship with the occurrence of seizures.
   a. Inter-ictal and peri-ictal depressive episodes may respond differently to pharmacotherapy
   b. Post-ictal depressive episodes which are important in people with partial drug resistant epilepsy respond poorly to antidepressant drugs

Non epileptic seizures
Assessment and Management of non-epileptic seizures and imitators of epilepsy
As demonstrated in the extensive literature on non epileptic seizures (NES), much is known about the
Identifying the underlying stressors and providing supportive psychotherapy can help some patients but is often insufficient or ineffective. Studies consistently identify three main comorbid diagnoses in patients with NES: Major Depressive Disorder, Post Traumatic Stress Disorder, and Cluster B personality traits characterised by impulsivity/hostility. Three additional critical areas of dysfunction in the NES population are: emotion regulation, family dynamics, and unemployment/disability. Poorer outcomes to treatment may be associated with the high number of comorbid psychiatric disorders and psychosocial stressors. Therefore, following accurate diagnosis, therapy for patients with NES may require a clear presentation of the diagnosis by the neurologist, followed by combined psychological education, psychotherapy, and pharmacotherapy, while simultaneously eliminating ineffective AEDs. Many patients with NES have already received supportive psychotherapy, which can help some patients but is often insufficient or ineffective in addressing the seizures and underlying stressors. These comorbidities may be targets for adjunctive interventions. Preliminary evidence exists that specific psychotherapies for the NES population may improve seizures and outcomes. Therefore, after establishing accurate diagnosis, treatment for patients with NES may require a clear presentation of the diagnosis, followed by combined psychological education, psychotherapy, and pharmacotherapy, while simultaneously eliminating ineffective AEDs in lone NES.

Clinical Practice Statements – examples

1. Proper diagnosis – vEEG (video telemetry) for each patient with suspected NES, refractory or pharmacoresistant seizures.

2. Presentation of the diagnosis — explain the NES diagnosis in a clear, positive, non-pejorative manner. The patient may make the diagnosis presentation to the family members if cognitively and emotionally capable. This process helps reveal the level of understanding and initial acceptance of the diagnosis by the patient. Clarifications can be made by the physician who is present. Communicate the diagnosis unambiguously to the referring physician and explain the need to eliminate unnecessary medications.

3. Psychiatric Treatment – conduct a thorough psychiatric assessment to identify predisposing factors (including comorbid psychiatric disorders), seizure precipitants and perpetuating factors. As diagnosis

The gold standard for diagnosis is video EEG. Certain seizure types, such as frontal lobe seizures (FLS), may mimic NES semiology, and conversely, ictal characteristics of NES may resemble epileptic seizures. Without video EEG, neurologists’ ability to differentiate ES from NES by history alone has a specificity of 50%. Bedside observations may also be of benefit in augmenting the video EEG interpretation to establish the NES diagnosis. Other techniques are used as adjuncts to informing the diagnosis of NES, but admission to an epilepsy monitoring unit (EMU) results in not only providing a definitive diagnosis in almost 90% of patients, but also rectifies an incorrect diagnosis of epilepsy. Good inter–rater reliability (IRR) exists for ES and moderate IRR exists for NES on video EEG.

NES is likely the result of a complex interaction between psychiatric disorders, psychosocial stressors, dysfunctional coping styles, and CNS vulnerability. Pharmacologic treatment of the commonly occurring comorbid psychiatric disorders, along with diagnosis-directed psychotherapy, may be the key to improving outcomes in these patients. Therapy will probably need to be individualised based on aetiology, level of intelligence, family dynamics, comorbid psychiatric illness, and other factors.

phenomenology of NES, including an understanding of risk factors and prognostic features. A number of studies exist on the diagnosis of NES, ictal semiology, comorbid psychiatric diagnoses, and neurological and neuropsychological characteristics of patients with NES. We, however, lack knowledge of specific treatments for NES even though treatment of NES has been reviewed many times in the literature. While the disorder is treatable, an effective treatment that yields long–term NES freedom and improved quality of life has yet to be discovered. Prior treatment reports reveal that coordination between neurologists and psychiatrists/psychologists with accurate diagnosis and prompt initiation of proper treatment with communication between care providers, patient and family yields higher treatment success. The misdiagnosis of NES is costly to patients, the healthcare system, and to society. Patients with NES are prescribed antiepileptic drugs (AEDs) that do not treat, and may exacerbate NES, have multiple lab tests performed, and may not receive the necessary mental health care that could benefit them. Differentiating NES from epilepsy (ES) is the first step in appropriate treatment.
psychosocial outcome even in patients with good seizure outcome but pre-surgical learned helplessness can have a negative impact on post-surgical psychosocial adjustment. Despite the high prevalence of psychiatric comorbidities, few epilepsy centres carry out a pre-surgical psychiatric evaluation in each patient being considered for epilepsy surgery. Epilepsy surgery has become one of the most recent revolutionary treatments of pharmaco-resistant epilepsy, with the potential to render up to 70% of patients seizure-free. Antero-temporal lobectomy is the most frequently performed procedure in most surgical centres around the world and has the best seizure outcome. While this procedure has been associated with the most frequent psychiatric complications, it has also been associated with significant improvement of pre-surgical psychiatric disorders, particularly when seizure remission is achieved.

Pre- and post-surgical psychiatric disorders have significant impact on epilepsy surgery at several levels, including:

- The potential interference of comorbid psychiatric disorders with the patient’s successful completion of pre-surgical evaluations, including the ability to make an impartial and informed decision to proceed with epilepsy surgery.
- The potential risk posed by pre-surgical psychiatric comorbidities for post-surgical psychiatric complications, presenting either as a de-novo psychiatric disorder, or an exacerbation or recurrence of a pre-surgical disorder.
- Post-surgical remission or improvement of pre-surgical psychiatric comorbidities.
- The impact of pre-surgical psychiatric pathology on post-surgical seizure outcome.
- The impact of seizure outcome on post-surgical psychiatric complications and long-term psychiatric comorbidity.
- The impact of pre- and post-surgical psychiatric disorders on the ability of the patient to adjust to a seizure-free life and obtain gainful employment after surgery. This includes the additional burden posed by psychiatric disorders on the process of undergoing surgical treatment for both the patient and the family.

**Clinical Practice Statements – 5 examples**

1. Every patient being considered for epilepsy surgery must undergo a psychiatric evaluation.

2. Neuropsychological evaluation before surgery
primarily focuses on cognitive risks and is complementary to a psychiatric evaluation but cannot replace it.

3. Psychiatric complications presenting as exacerbation or recurrence of pre-surgical psychiatric comorbidities are frequent in the first post-surgical year as are psychosocial adjustment difficulties. Patients at risk of developing such difficulties should be counselled accordingly with preventive treatments implemented where possible.

4. Unlike de-novo depression, de-novo post-surgical psychotic episodes are rare after epilepsy surgery. In addition to concern over the risk of the development of de-novo post-surgical psychotic disorders, the decision to consider epilepsy surgery in patients with refractory epilepsy and comorbid psychotic disorders remains the source of much controversy. Some centres consider a psychotic disorder as a contraindication for epilepsy surgery while others do not, as long as the patient can cooperate during the pre-surgical evaluation and has a clear understanding of the therapeutic expectations and risks.

5. Pre-surgical psychotic disorders are not a contraindication for epilepsy surgery provided that the patient is undergoing treatment and understands the nature of the evaluation and the procedure as well as the risks and therapeutic limitations of the surgical procedure.

Conclusion
There is currently enough evidence to support the identified epidemiological, aetiological and diagnostic factors in neuropsychiatric disorders associated with epilepsy but the area of management is still awash with controversies and inconclusive data. There is a dearth of high-quality evidence from well-constructed studies on which to base guidance. However, we hope that the development of these internationally derived clinical practice statements may further support the management of people with epilepsy and comorbid neuropsychiatric disorders.

Key reference
CPAP for treatment of cognitive dysfunction in Obstructive Sleep Apnoea

Mary J Morrell, Martin Glasser, Alison McMillan, Ivana Rosenzweig

Past contributions to the Newsletter have highlighted a common link between sleep disorders and neuropsychiatry (1), in particular that patients with obstructive sleep apnoea (OSA) may experience neuropsychological dysfunction (2). Excessive daytime sleepiness is the cardinal symptom of OSA and has traditionally been considered the mechanism for the neuropsychological dysfunction; recent studies have however focused on the chronic intermittent hypoxia as the causal mechanism. If OSA, in the absence of sleepiness, results in neuropsychological dysfunction these data will have important clinical implications because the 2010 National Institute of Clinical Excellence (NICE) Health Technology Appraisal concluded that continuous positive airway pressure (CPAP) is an effective and cost efficient treatment for OSA in patients with moderate to severe symptoms of sleepiness (3). The unanswered question is: should OSA patients with mild symptoms of sleepiness be offered CPAP treatment to prevent (or reverse) neuropsychological dysfunction? We suggest that this question will be best answered by scientists and clinicians working together across disciplines.

Chronic intermittent hypoxia, designed to mimic the hypoxia of OSA has been shown to produce cell apoptosis within the CA1 region of the hippocampus of a rodent model and reduced performance on memory tasks (4–5). If similar lesions occur in OSA patients they may contribute to neuropsychological dysfunction. Several studies, including from our group, have employed voxel based morphometry (VBM), to analyse structural Magnetic Resonance (MR) brain scans for changes in brain morphology (Table 1). Overall OSA patients have reduced grey matter in several brain regions, including the temporal gyri, the hippocampus and the cerebellum. However, the interpretation of these results is confounded by the use of different statistical thresholds and improvements in imaging hardware and software. We put forward the notion that there is a need to understand the consequences of the structural brain deficits in order to determine the functional consequences of exposure to intermittent hypoxia and if early intervention produces a reversal of symptoms.

OSA patients may experience reduced visual search and auditory alertness that could be attributed to gray matter changes in the temporal lobe (6) as well as impaired spatial memory and motor control involving the hippocampus and cerebellum (7–8) respectively. However, the complexity of neuropsychological processing means that linking specific functions into different brain areas requires careful study design, including a control for the attention deficits associated with excessive daytime sleepiness. Taking this approach we have previously shown that OSA patients have specific difficulties in assimilating and recalling information presented verbally, whereas their ability to process visual information appears to remain intact (9). Our recent study suggests that verbal memory performance of OSA patients significantly differs from the aged matched controls. Strikingly, OSA patient’s scores in this study were more closely matched to healthy individuals a decade older.
The study of Canessa and colleagues (10) is the first to make the link between impaired neuropsychological performance, disease severity and brain structure prior to treatment. They found reduced gray matter volume in the left hippocampus, left posterior parietal cortex and right superior frontal gyrus. Moreover, these changes were associated with neuropsychological dysfunction. In the left parahippocampal gyrus the reduction in gray matter volume was associated with errors on the Stroop executive function test and in the left posterior-parietal cortex deficits were correlated a reduction in the Raven abstract reasoning test. Remarkably three months of CPAP treatment increased gray matter in the hippocampus and frontal brain regions, and these changes were correlated with improvements in executive function and short term memory.

One of the earliest VBM studied by Maguire and colleagues (11) showed increased hippocampal gray matter volume in that London taxi drivers who had taken “the knowledge” test compared to drivers who had not taken the test. Juggling is also associated with increase gray matter, proportional performance (12). This latter study also showed that removal of the stimulus for three months led to a reduction in the brain gray matter. So neural plasticity can occur, and withdrawal of stimuli is associated with atrophy. Whether treatment of OSA with CPAP can also promote plasticity and reverse the atrophy documented using VBM is unclear. The data from Canessa and colleagues imply that this is indeed the case. This notion is further supported by findings from rodent models where following termination of the intermittent hypoxia an increased expression of neuronal progenitors and mature neurons in the hippocampus is reported, with associated recovery in cognitive function (13).

Based on converging evidence from animal and human studies, it would appear that intermittent hypoxia is associated with brain atrophy and neuropsychological dysfunction that can be reversed with CPAP treatment. If this is the case we would argue in favour of early treatment, even in patients who are not subjectively sleepy. Since OSA is the third most common respiratory disorder, after asthma and chronic obstructive pulmonary disease, the social and economic consequences of early treatment in non-sleepy patients are likely to be considerable.

Recent epidemiological data suggests that the neurodegenerative process and cognitive decline start much earlier than was previously thought (14). Additionally, it would appear that even small differences in cognitive function earlier in life may increase the risk of dementia later in life. The importance of this in OSA patients is further highlighted if one takes into account that prolonged exposure to hypoxia is shown to alter the excitability and functional expression of ion channels, which may also contribute to neurodegeneration. Furthermore, hypoxia can result in the formation of β-amyloid protein and disruption of calcium homeostasis in animal studies (15). Based on these data it has been hypothesised that the accrued overall changes in chronic intermittent hypoxia may in some susceptible patients lead to the development of Alzheimer’s disease (16). Of interest, the work of Bartzokis and others suggests that later life myelinating multi-modal cognitive brain networks are most susceptible to various noxis, inclusive of hypoxia and free radicals, and it is possible that these brain regions are also particularly susceptible to hypoxic episodes in OSA patients (17–19). Despite these intuitive leaps and assumptions, the current scientific evidence is far from clear on the matter of brain changes resulting from the intermittent hypoxia, with some imaging studies supporting, and some disputing the presence of associated brain lesions and neuropsychological deficits (Table 1). It is hoped that further research using more sophisticated neuroimaging modalities will enable new insights in this area (20). What is clear is that the growing obesity epidemic means that an expanding population of OSA patients could be affected.

**A stratified approach to treatment of OSA in older people**

In addition to the growing obesity, it is also recognized that the world population is ageing. In Europe it is estimated that by 2050 the ratio of older people to children will be 2:1. This situation poses major social and economic problem requiring careful planning and clear strategies to reduce age-related health care costs. With that in view, any health care treatment that would enable older people to longer maintain their independence should be welcome.

The prevalence of OSA, defined as an AHI >10 events per hour in a working population of people between 30 – 39 years, is 5% of women and 12% of men (21). In older people (>65 years) the prevalence of sleep apnoea is at least two fold greater, with estimates ranging between 13 and 32% (22–27). The wide variation is likely to reflect the different health status of the older populations studied and the definitions of the disease. Using similar study methods and disease criteria Bixler...
et al., 1998 found the prevalence of sleep apnoea to be 24% in community dwelling older men (65 – 100 years) compared to 3% in a younger population (20 – 44 years) (24). The high prevalence of sleep apnoea in older people has led to debate regarding its consequences and whether early treatment of OSA in older people is cost-effective.

Sleep becomes more fragmented with age, independent of sleep apnoea, and there is a well documented age-related reduction in sleep quality. These features of sleep in older people have led to the suggestion that older OSA patients do not suffer symptoms of daytime sleepiness because they are habituated to the sleep disruption of OSA, and therefore may not require treatment.

A decline in cognitive function is considered part of the ageing process; particularly affected is the ability to encode new memories. OSA is also associated with cognitive dysfunction; however few studies have included older OSA patients. Mathieu et al found cognitive dysfunction was independently related to both OSA severity and increasing age, but the coexistence of both factors in their study did not appear to result in increased cognitive dysfunction (28). On the other hand, Ayalon et al showed cognitive dysfunction, on performance of the Go–No–Go cognitive task, in older OSA subjects, but no significant impairment when OSA and increasing age were considered separately (29). Finally, Cohen-Zion et al have used the rather crude tool of mini–mental state examination to study the effects of OSA on cognitive function in older patients (30–31); they found a significant association between the severity of OSA and the self-reported severity of daytime somnolence. However, again once other variables (including total sleep time) were included in the model, only the relationship between cognitive impairment and excessive somnolence remained significant. Therefore further advise on the early treatment of OSA in older people who are at increased risk of cognitive decline is required.

When cognitive function is preserved in OSA patients, functional brain imaging has shown increased brain activation compared to the activation that occurs in healthy controls performing the same task (32). These data suggests that increased cerebral recruitment is required to maintain cognitive performance. Similar preservation of cognitive function, with compensatory increased cerebral activation has been found in older subjects; however older patients with coexistent OSA show decreased cerebral activation and cognitive dysfunction (29). This suggests that age and OSA could have synergistic effects on cerebral activation and consequently cognitive function. If this is the case then early treatment may be necessary.

In summary, we highlighted areas of sleep–related research where unanswered questions could be tackled by linking the expertise of neuropsychiatry and respiratory medicine to produce improvements in patient care. Working independently is to risk repeating the mistakes of the past.....

“In the mid–17th century, Spanish seafarers sailed up the west coast of the Americas to what is now known as the Baja peninsula. The cartographers of the time simply drew a straight line up from the Strait of California to the Strait of Juan de Fuca between Vancouver Island and Washington state. Consequently, the maps that were published in 1635 show very clearly that California was an island. For 50 years, then, the years of the most constant, most crucial explorations of the California coastline, those maps went unchanged because someone continued to work with partial information, assumed that data from the past had the inerrancy of tradition and then used authority to prove it...... Vision is the ability to realize that the truth is always larger than the partial present”.

From a speech by Sister Joan Chittister
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>OSA Severity AHI (events/hr) Mean (SD)</th>
<th>Statistical analysis and threshold</th>
<th>Changes in gray matter concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macey (2002)</strong></td>
<td>21 OSA*</td>
<td>34 (20)</td>
<td>SMP V99, p&lt;0.001, uncorrected for multiple comparisons</td>
<td>Diffuse changes across the entire brain: frontal &amp; parietal cortices, temporal lobe, anterior cingulate, hippocampus &amp; cerebellum</td>
</tr>
<tr>
<td></td>
<td>21 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morrell (2003)</strong></td>
<td>7 OSA</td>
<td>Median 28 (Range 25–40)</td>
<td>SMP V99, p&lt;0.01, corrected for multiple comparisons within a small volume</td>
<td>No significant reductions across the entire brain</td>
</tr>
<tr>
<td></td>
<td>7 Controls</td>
<td></td>
<td></td>
<td>Focal reduction within the left hippocampus</td>
</tr>
<tr>
<td><strong>O’Donoghue. (2005)</strong></td>
<td>27 OSA</td>
<td>71 (17)</td>
<td>SMP V2.0, p&lt;0.05, corrected for multiple comparisons using FDR</td>
<td>No significant reductions</td>
</tr>
<tr>
<td></td>
<td>24 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morrell (2010)</strong></td>
<td>16 OSA</td>
<td>55 (Range 48–61)</td>
<td>SMP V8.0, p&lt;0.05 corrected for multiple comparisons using FDR</td>
<td>Bilateral prefrontal cortex, inferior parietal gyrus, right temporal cortex, occipital cortex, right thalamus, some basal ganglia, right hippocampus, para-hippocampus &amp; cerebellum</td>
</tr>
<tr>
<td></td>
<td>14 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Joo (2010)</strong></td>
<td>36 OSA</td>
<td>53 (Range 32–106)</td>
<td>SMP V2.0, p&lt;0.05 corrected for multiple comparisons using FDR</td>
<td>Left gyrus rectus, bilateral superior frontal gyrus, left precentral gyrus, bilateral cingulated gyrus, right insular gyrus, bilateral caudate nucleus, bilateral thalamus, bilateral amygdala, bilateral hippocampus, bilateral temporal gyrus, bilateral quadrangular lobe, bilateral hiventer lobe</td>
</tr>
<tr>
<td></td>
<td>31 Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Canessa (2010)</strong></td>
<td>17 OSA</td>
<td>56 (19)</td>
<td>SMP V5.0, p&lt;0.05 corrected for multiple comparisons using FDR</td>
<td>Left posterior-parietal cortex, right superior-frontal gyrus, left hippocampus</td>
</tr>
<tr>
<td></td>
<td>15 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Torelli (2011)</strong></td>
<td>13 OSA</td>
<td>53 (26)</td>
<td>SMP V8.0, p&lt;0.05 corrected for multiple comparisons using FWE</td>
<td>Left hippocampus, bilateral temporal lobe</td>
</tr>
<tr>
<td></td>
<td>9 controls</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Summary of Voxel Based Morphometry studies in Obstructive Sleep Apnoea
Stippled columns are studies that measured both gray matter changes in brain pre and post CPAP; Filled columns and cognitive function

* 20 patients with co-morbidities. SPM: statistical parametric map, FDR: false delivery rate; FEW: family wise error
References


Understanding the endogenous clock, sleep and the circadian rhythm.

Anne-Mary O. Abe

Introduction
Many physiological functions and behaviour occur in a cyclical manner. Sleep, many cellular, endocrine, autonomic and metabolic functions and behaviour such as feeding undergo circadian cyclical rhythm regulated by a central endogenous clock. (1) I will be describing this clock, its role and some scientific advances in this field.

Cyclical rhythmicity is thought to be the body’s mechanism via its endogenous circadian clock to allow coordination and synchronicity of various physiologic functions making it adaptable to environment and its light–day cycle, allowing the body to preserve itself when it is least needed and anticipate function and day break. (2,3) In humans the clock is found in the suprachiasmatic nucleus (SCN) of the hypothalamus. (4) The SCN runs a circadian 24 hour clock acts as a pacemaker for several central and peripheral cellular mechanisms and has a coupling role for various metabolic and homeostatic pathways.(1)

Scientific Advances
One of the early advances in this field was by Constatin Von economo during the Encephalitis Lethargica (Von economo disease) epidemic in the early 20th century. He noted that this disorder was associated with marked disruption in the sleep wake cycle and hypothalamic lesions on histopathology. He then postulated that there was a central area and pathway with a regulatory role in sleep and described areas that comprise the SCN and its efferent pathways as being the area involved in this role.(5)

Konopka et al did Drosophila fly studies that helped in further understanding the mechanisms underlying the circadian cycle. (2) genes PER (Period) and TIM (Timeless) were identified in Drosophila as affecting the timing of eclosion and locomotor activity. Using normal flies and flies with gene mutations in these domains, they exposed them to equal length of day and night and activity was monitored under infra red light, the flies with mutations in these genes had deranged rhythmicity. The long day mutant flies had 28 hour cycles and short day mutants had cycles as short as 16 hours instead of 24 hours by normal flies. (6)

Molecular pathways
In drosophila flies, Per and TIM genes are transcribed producing Per and Tim protein in the cytoplasm. PER and TIM proteins then form a complex which enters the nucleus to regulate expression of genes involved in their production through a negative feedback mechanism. In the cytoplasm the TIM protein level is low during the day as it is degraded by light, hence cytoplasmic levels are too low to activate PER and form the TIM–PER complex in the day. At dusk the Tim protein starts accumulating, Per–Tim complex levels increase, these complexes enter the nucleus and negatively inhibit its own transcription leading to reduced production and levels of Per and Tim, levels drop steadily through the night so by morning PER and TIM levels are reduced to a level at which the negative feedback mechanism is lost and its transcription starts again.(6,7)
A Similar intracellular cycle occurs in mammals with various genetic mammalian homologues of PER and TIM such as CLOCK genes (circadian locomotor output cycles kapu) discovered. Rat studies proved useful because of the cyclical nature of their behaviour, non-mutagenic mice normally sleep in light and are nocturnal in activity while the mutagenic rats for CLOCK genes had a reversal in this pattern, though overall the quantity of sleep remains the same showing that endogenous clock’s role is in sleep timing and rhythmicity not quantity.

BMal(1) (brain and muscle ARNT-like-1) and CLOCK act as transcription factors and have a central role in circadian clock function in humans. BMal1and CLOCK dimerize and couple to become transcription factors in the production of the Period (1,2,3) (Per) and Cryptochrome (1,2)(Cry) proteins (Per and Cry regulate SCN clock function mainly through its negative feedback regulation of CLOCK and Bmal(1). Per and Cry levels accumulate and form complexes which enter the nucleus to inhibit Bmal1 and CLOCK leading to degradation of Per and Cry and reducing levels of Per and Cry in the cytoplasm and an eventual loss of the negative feedback with subsequent activation of Bmal1 and CLOCK.(8,9) These are other molecular pathways and regulatory loops in which these genes and proteins are involved as well as others such as REV-ERB, ROR, and NPAS2 which are not described in this article.(10,11)

Function and Clinical Relevance:

There are clocks in all peripheral tissue that regulate the timing of important cellular activities like gene expression.(11) These peripheral clocks seem to be regulated centrally by the SCN clock. Clock genes found in peripheral tissues have oscillations that are comparable to that of SCN with a phase delay of about 4–8 hours. The precise process by which this happens is not well understood. One of the regulatory pathways postulated is via glucocorticoid pathway, as adrenalectomy brings about an altering of the light induced phase resetting that will normally occur. The SCN is not the only source of regulation in peripheral tissues as they also respond to other exogenous cues such as REV-ERB, ROR, and NPAS2 which are not described in this article.(10,11)

Sleep is regulated by the SCN clock and phased in 24–hour cycles, the advent of EEG in 1929 helped in differentiating cycles of awakening and sleep.(13) Hormones like growth hormone, prolactin, cortisol and melatonin showing circadian timing; Growth hormone secretion is maximal during sleep, Cortisol is secreted alongside the sleep cycle with lowest levels at night and rising levels in the early morning hours to peak at about 8 am. The paraventricular nucleus of the hypothalamus that regulates Adrenocorticotropin secretion is a downstream target of the suprachiasmatic nucleus.(14) Temperature regulation is also coupled to this circadian cycle as temperature falls in the evenings and rises in early hours as morning awakening occurs. This is the normal coupling system in entrained healthy individuals to the light–dark cycle. Uncoupling of this system can occur if sleep cycle is disrupted, though there is a time lag before this uncoupling happens.(15)

Studies are emerging showing that the metabolic system including, feeding behaviour and aspects of glucose metabolism may be aligned to the circadian clock with circadian disruptions leading to an increased risk of adverse metabolic outcomes.(16)

The SCN clock is described as an endogenous clock as it functions even without external cues, with the clock developed and set prenatally in foetal brains in utero. (17 18) Though it is intrinsically an endogenous system, it responds to exogenous cues known as “zeitgebers”. The most important zeitgeber is Photic stimulation with Light passing though the retina to the hypothalamus via the Retino-hypothalamic tracts. (19) Exogenous factors can affect the setting or reset the clock and this process is known as entrainment.(20) Exogenous cues have stimulated interest because of their role in travel; particularly travel across various time zones and jet lag and in the work place amongst shift workers, other exogenous cues such as physical activity, metabolic behaviour such as night time feeding, social interaction may affect the clock. Ageing causes a reduced function of the clock and an advancement of the sleep phase.(11) Sleep cycle studies have been of interest in the work place especially in industries reliant on shift workers such as the aviation industry and emergency services. Often these workers have frequent shift changes over a short period of time resulting in changes in the sleep pattern before full entrainment in the SCN can take place. It is suggested that it takes at least one week for entrainment to occur fully in the human body, hence this adjustment may not occur if shift changes occur every few days with disruption in sleep cycle and sleep deprivation. This may have a role in work related errors and incidents and in some instances, bright light has been used to artificially entrain shift workers. (20) Various disorders are associated with abnormalities of sleep timing and entrainment such as Advanced or
Delayed sleep phase timings disorders which have been linked to various PER polymorphisms. (21) Sleeping sickness is characterised by a reversal in sleep cycle thought to be contributed to by the infestation of the trypanosome parasite in the SCN. (22) Affective disorders like bipolar affective disorder and depression are associated with sleep cycle disruption. (3) It is suggested that mood stabilisers used in treatment of affective disorders may have a modulatory effect on some of the genes involved in the endogenous clock described earlier. (23) Neurodegenerative disorders like Parkinson disease and Alzheimer’s are associated with sleep cycle abnormalities like sundowning, which is thought to be mediated through SCN neurodegeneration and alterations in the CLOCK genes. (24)

**Conclusion**

There is a complex adaptable central system of circadian control regulating timing of various physiologic functions; though endogenous in nature is sensitive to external cues, which allow entrainment of the clock. Desynchrony can occur within these systems leading to disruptions in sleep timing and other functions aligned to this cycle.

**References**


4. **Snell Richard S** Clinical neuroanatomy, 6th edition chapter 13 page 378; Lippincott Williams and Wilkins.


Meeting Report

Report on the Section of Neuropsychiatry Autumn Meeting 2012

Matt Swaroop

Dr Swaroop Sangnal Matt, ST-5 in Forensic Psychiatry, North East London Training Scheme, Camlet Lodge, Enfield / National Brain Injury service, St Andrews, Northampton.

This year, The Annual Conference of The Royal College of Psychiatrists section of Neuropsychiatry was held at the beautiful and historic city of Cambridge with inspiring Robinson College as the venue. Blessed with a glorious sunny day in Cambridge’s never-ending green shades and historic architecture, we were all excited about a fabulous conference programme.

This year’s conference received a lot of attention. Over one hundred delegates attended from all over the United Kingdom as well as from USA, Canada, Australia, Netherlands and Malta. This reflects the ever-increasing popularity of Neuropsychiatry in UK, particularly amongst the trainees. I think this conference was hugely successful in attracting trainee doctors and medical students with opportunities provided to participate and present their work. As many as 20 high quality posters, mainly from trainee doctors were accepted for display and presentation.

The conference began with an interesting session on antibody-mediated encephalopathies. Alasdair Cole took us through the subtleties of antibody-mediated encephalopathy and highlighted the importance of clinical judgment in raising suspicion and requesting specific investigations that could be easily missed. In suspected cases, tests for anti-NMDAR, anti-VGKC, antinuclear antibody as well as screening for paraneoplastic syndromes could be life saving. He illustrated this with a fine example of a young girl who was in ITU for two months with history of seizures, hallucinations and abnormal thoughts. Clinicians were baffled by her presentation, as standard investigations were normal including MRI and PET-CT. She was then specifically screened for antibody-mediated encephalopathies that turned out to be positive (anti NMDAR) and responded to immunotherapy. She has made a successful recovery and even pursuing a university course.

Julia Deakin presented her research into the use of screening for anti-NMDAR antibodies in first episode psychosis and successful treatment with immunotherapy. I was jumping up in excitement when we found that nearly 6.2% of first episode psychosis patients were positive for anti NMDAR. Prospects for our patients looked bright, immunotherapy for psychosis… unbelievable. Many of us asked whether this could be applied to our chronic psychotic patients but the evidence is in early stages of development and clinical experience is not much in favour of use of immunotherapy for our chronic psychotic patient group. Delegates were interested in the costs and availability of these tests. This presentation had got us excited and informal discussion amongst delegates followed, during the tea break and throughout the rest of the conference.

Before lunch, Rafey Faruqui gave a wonderful talk on Offenders with Neuropsychiatric Conditions, which extended from a literature review into the service model descriptions and their critique. He talked about models based on social inclusion, operant learning theory, social
After the tea break, we gathered for the final session of the day for the business meeting. Rafey Faruqui chaired the meeting. He thanked the outgoing Chair Jonathan Bird for his boundless contributions to the field of Neuropsychiatry. We were delighted to learn the Section's finances are in good shape and that we are hopefully close to being accepted as a subspecialty. Niruj Agrawal, Vice Chair, reported on curriculum development work. Academic Secretary Howard Ring provided an overview of Section's academic activities. The business meeting thanked him for organizing this successful conference. Options of holding next year's conference at other venues were explored. A majority of the delegates were in favour of this being held in Cambridge or Oxford. Although this ended the day one sessions of the conference, informal discussions and debate continued at the conference dinner.

The second day of the conference began with two lectures on brain injury; Michael Dilley spoke on the nosology of Mild TBI and post-concussion syndrome. His talk generated good delegate participation and discussion on validity of different diagnostic constructs. Dr. Jon Silver, our overseas guest from USA gave an excellent talk on brain injury, focusing on patients who do not improve. After tea break, Prof Michael Kopelman gave an absorbing talk on Neurological and Psychological forms of memory disorder and we were treated with interesting case examples to illustrate this. Discussion on pathology and use of sodium amytal or benzodiazepines in retrieval of memory received a lot of interest from delegates.

The final session of the day had excellent presentations, first by Niruj Agarwal who highlighted the important role of service users in health sector and prompted us to think on various ways to enhance service user involvement in Neuropsychiatry. This was followed by two informative lectures, first a wonderful talk by Prof John Hodges about his work on Frontotemporal dementias and secondly by Valerie Voon on Neuropsychiatric aspects of Parkinson's disease. After a fascinating two days of wide-ranging topics and discussions, our conference had come to an end but with a promising note that it will be back next year with further interesting and stimulating presentations. Also for sure, there will be more trainees like me who will be drawn towards neuropsychiatry.
The Neuropsychiatry Newsletter is pleased to present to its readers the top three Abstracts presented as posters at this year’s Neuropsychiatry Conference held in September at Robinson College in Cambridge. The quality of abstracts submitted was high and the decision not easy but our Academic secretary Dr Howard Ring and your editor, Dr Norman Poole agreed that Angela Carballedo, Rory Conn and Christopher Symeon each produced a fine poster for conference. Well done, and we hope you keep up the good work.
Reduced fractional anisotropy in the uncinate fasciculus in patients with Major Depression carrying the Met-allele of the Val66Met Brain-Derived Neurotrophic Factor Genotype

Objectives
Experimental studies support a neurotrophic hypothesis of major depressive disorder (MDD). The aim of this study was to determine the effect of Val66Met brain derived neurotrophic factor (BDNF) polymorphism on the white matter fibre tracts connecting hippocampus and amygdala with the prefrontal lobe in a sample of patients with MDD and healthy controls.

Methods
Thirty seven patients with MDD and 42 healthy volunteers were recruited. Diffusion tensor imaging (DTI) data with 61 diffusion directions were obtained with MRI 3 Tesla scanner. Deterministic tractography was applied with ExploreDTI and Val66Met BDNF SNP (rs6265) was genotyped. Fibre tracts connecting the hippocampus and amygdala with the prefrontal lobe, namely uncinate fasciculus, fornix and cingulum were analysed.

Results
A significant interaction was found in the uncinate fasciculus (UF) between BDNF alleles and diagnosis. Patients carrying the BDNF met-allele had smaller fractional anisotropy (FA) in the UF compared to those patients homozygous for val-allele and compared to healthy subjects carrying the met-allele. A significant 3-way interaction was detected between region of the cingulum (dorsal, rostral and parahippocampal regions), brain hemisphere and BDNF genotype. Larger FA was detectable in the left rostral cingulum for met-allele carriers when compared to val/val allele carriers.

Conclusions
We provide evidence for the importance of the neurotrophic involvement in limbic and prefrontal connections. The met-allele of the BDNF polymorphism seems to render subjects more vulnerable for dysfunctions associated with the UF, a tract known to be related to negative emotional–cognitive processing bias, declarative memory problems, and autonoetic self–awareness.
Conversion Disorder Clinic – A 12 Month Evaluation

Rory Conn, Gary Price, Eileen Joyce

Objectives
To evaluate 12 months data from a conversion disorder clinic, designed to establish suitability of patients for a 4 week multidisciplinary programme admission at NHNN.

Methods
All clinic attendees 1st January 2010 - 31st December 2010 were retrospectively studied, with reference to letters of referral, clinic letters and discharge summaries. Origin of referral, patient demographics, frequency of acceptance, waiting times (both referral to assessment, and acceptance to admission) are described. Frequency of ICD-10 conversion disorder subtype and chronicity of presenting symptoms are listed. Common physical precipitants and neurological co-morbid diagnoses, plus depression, are explored. HoNOS outcome data from admission is described.

Results
67 patients were evaluated during the 12 month period, 78% female, 12% male. The majority (72%) declared their ethnicity to be British. 76% were NHNN internal referrals. Mean waiting time from referral was 28 weeks (range 2–69 weeks). Mean age at assessment was 45 years (range 22–79). Mean chronicity of symptoms was 8 years (range 1–43 years). 40% of patients had a history of a physical precipitant (notably, 12% had suffered an accident, including RTAs/falls). 41% had a history of neurological co-morbidity; 66% a history of depression.

Diagnoses at assessment:
- F44.4 Dissociative Motor Disorder – 21
- F44.5 Dissociative Convulsions – 8
- F44.6 Dissociative Sensory Disorder – 1
- F44.7 Mixed Dissociative Disorder – 28
- F45.0 Somatisation Disorder – 2
- F45.2 Hyperchondriacal Disorder – 1
- F48 Neuraesthenia – 4
- F60.9 Personality Disorder, unspecified – 1
- G40 Epilepsy – 1

61% were accepted for admission. Mean wait to admission: 20.5 weeks; mean duration of admission, 3.31 weeks. Mean HoNOS score: 9.5 on admission, 6.5 on discharge.

Conclusions
Of particular interest is the proportion of patients (33%) from caring professional backgrounds eg, nursing. As in previous studies, a physical precipitant history is common. Co-morbid neurological diagnoses are often found which may represent original misdiagnosis.
The use of Aripiprazole in the management of complex Gilles de la Tourette syndrome (GTS) a case study

Christopher Symeon, Kate Humphreys, Michael Kopelman & Mervi Pitkanen

South London and Maudsley NHS Foundation Trust

Background
Mr T is a 26 year-old male who suffered a streptococcal infection aged 3 following which he developed tics, obsessions, compulsions and hyperactivity with inattention. He then had three further episodes of streptococcal infection exacerbating the underlying tics, OCD, and ADHD. He tested positive for anti-basal ganglia antibodies and was diagnosed with Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS).

Investigations
EEG, MRI and bloods confirmed no abnormalities. Echocardiography confirmed a trileaflet aortic valve with forward flow and mitral valve regurgitation. Genetic testing, including 22q11 syndrome, was negative. Addenbrooke’s Cognitive Examination–Revised (ACE–R) score was 51/100. Yale Global Tic Severity Scale score (YGTSS) was 81/100.

Treatment
A diagnosis of complex GTS was made and the treatment plan devised accordingly. Mr T had an adverse reaction to Methylphenidate with increased impulse dyscontrol and rage episodes. Clonidine caused nocturnal hypotension and was discontinued. Aripiprazole decreased his tic severity, his ADHD symptoms, and further reduced his OCD symptoms. His YGTSS score decreased to 42/100 and his ACE–R score increased to 75/100.

Discussion
Research supports the use of dopamine antagonists in the management of tics in GTS, with greatest efficacy when action is D2 selective in the prefrontal region, whereas guidelines for ADHD suggest using dopamine agonists. This complicates treatment plans in GTS patients with comorbid OCD and ADHD. Aripiprazole, with its specific partial dopamine agonist properties, addressed the co–existing hypo and hyper dopaminergic states resulting in a significant reduction in his complex GTS symptoms and improvement of function.
Higher psychiatric training offers an excellent opportunity to pursue one’s interests like studying for an academic qualification, participating in research and doing special interest clinical work. Having always been intrigued by the interface between brain and mind, I was fascinated when I heard about the opportunity of doing Masters in Neurology on the Synapse (a London Deanery communication network for post graduate trainees). I had my educational and clinical supervisors’ agreement before embarking on this programme and one year into this programme I am very pleased about making this choice.

This University College London’s Masters is a part-time flexible 2–4 years programme coordinated at the Institute of Neurology. It is designed for neurology, psychiatry or related disciplines trainees in London holding a national training number. Out of 180 credits, 45 are offered for prior learning acquired through accomplishment of Royal College membership examinations. As part of this programme you are expected to attend one day a month Neurology SpRs CALMAN teaching programme, on a range of neurology topics, which is by far the most interesting component of this programme. It carries 60 credits and learning is assessed via essays. It provided me with an opportunity to learn about core neurological conditions including head injury, CNS infections, pain management, sleep disorders, headaches, neuroradiology, neurophysiology, neurosurgical approaches, rehabilitation, dementias, neuropsychology and neuropsychiatry, to name a few. These sessions are very interactive, often audience are expected to get involved in the discussion of clinical problems and not being a neurology trainee this did raise my anxiety. However I am amazed at how useful did I find participation in the discussion and enjoyed and learned during these teaching days. Although I am learning about core neurological illnesses, my main focus remains on learning about the clinical presentations, management and recent developments in research of the conditions at the interface of neurology and psychiatry including complex neuropsychiatric problems after head injury, neurologically unexplained syndromes, epilepsies, sleep disorders, cognitive impairment and neurophysiology. Being a student at UCL also allows me easy access to its library and extensive online databases, online modules in statistics, ebrain and regular seminars and lectures.

Professor Simon Shorovon and Dr Caroline Selai are the programme directors. I get monthly tutorials/supervision which is adapted to the student’s individual needs and cover a broad range of subjects including critical appraisal of articles, essay writing, research methodology, course and project updates and discussion about current neurology and psychiatry topics. The tutorials with Dr Selai carry 15 credits. I have found programme directors incredibly supportive.

“I had come across several clinical situations where a neuropsychiatric approach helped me offer better patient care”

I am very pleased that I am able to achieve a right balance between my clinical work and this Masters as the lectures are only one day a month and it is having a minimal impact on my clinical work. I utilize my research sessions for my Masters Essays and research project. During my second year I will be focusing more on the research project which carries 60 credits. I am glad to have been able to pursue my clinical special interest sessions in parallel with the Masters programme. I must say that there are times that my evenings or weekends could get busy working on my Masters programme, but
the joy one gets when submitting the completed work is definitely worth it.

I would like to mention that the Masters programme requires a significant financial commitment as the fees are well above the study budget. I utilized substantial part of my study budget on my Masters. The London deanery or the Trust does not have any special funds to support trainees doing Masters.

Learning more about neurology, I was particularly struck by how closely this is related to psychiatry. I found that both disciplines employ multidisciplinary approach, deal with substantial enduring and chronic illnesses; neurological illnesses like movement disorders, epilepsy, multiple sclerosis, motor neuron disease carrying significant psychiatric co-morbidity, psychiatric conditions presenting in neurologically unexplained syndromes and there is substantial common semiology between these two disciplines of medicine including cognitive impairments, depression, anxiety, hallucinations, sleep disturbances, chronic fatigue, confusional states and somatization. One year into this Masters, I have already started to notice a change in my thinking, feeling better neurologically informed and skilled at systematically thinking about biopsychosocial approach in the management of patients. I had come across several clinical situations where a neuropsychiatric approach helped me offer better patient care including a recent example when a hospice team sought advice about a patient with motor neuron disease suffering symptoms of distressing emotional lability. Having learned about it during my course, I was able to do an effective literature search to advise them about the role of pharmacotherapy like selective serotonin receptor reuptake inhibitors and also direct them to an appropriate service that could further help the patient. I got a positive feedback about the improvement in his symptoms following that.

I am very glad that I chose this Masters programme as I am able to keep the right balance between clinical work and academic commitments, am better aware of the interface between neurology and psychiatry, can see it having a positive impact on my knowledge, attitude and skills about neurological and neuropsychiatric conditions enabling me to better manage patients and has increased my interest in neuropsychiatry and liaison psychiatry. I would highly recommend this programme to my colleagues.

(information about the course can be found on www.ucl.ac.uk. You can contact me at Iqbal.Yousaf@nhs.net or Mr David Blundred, the course administrator at David.blundred@ucl.ac.uk if you have specific questions about the course.)
Case study: sub-clinical epilepsy presenting as cognitive impairment and depressive symptoms

KD Jethwa, V Joseph

Senior House Officer (FY2) in Cardiology at the Glenfield Hospital in Leicester and Dr Joseph is a Consultant Psychiatrist at the Stamford Resource Centre in Lincolnshire.

Introduction
LP is a 51 year old lady, with a background of idiopathic temporal lobe epilepsy (TLE), who presented with new-onset memory impairment and word-finding difficulties. She reported being unable to recall the details of articles as she was reading the newspaper and was unable to remember previously familiar musical scores or routes around town. She was also finding it difficult to describe situations and events in conversation. These symptoms developed gradually over three years, but were becoming more problematic.

Despite adequate control of convulsive seizures with lamotrogine monotherapy temporal lobe abnormalities persisted on follow-up electro-encephalograms (EEG). Frequent, and at times prolonged, runs of low amplitude delta activity were seen over the left mid temporal lobe. Sharp and slow wave discharges were also seen affecting the right and left temporal lobes. Clinically these are experienced as transient absences or episodes of derealisation. The impact of these was material: LP would find herself getting lost in town; she could not remember short shopping lists and was finding it difficult to manage her finances. As a result of these problems LP became more withdrawn, experiencing low mood and anergia. She did not report any biological symptoms of depression. Before the onset of these difficulties LP describes herself as ‘independent, friendly and at the centre of the Morris dance group’.

LP made a partial recovery, with improved mood, following treatment with a selective serotonin re-uptake inhibitor and simple psychotherapy. Her memory problems, however, persisted. The weschler adult intelligence test demonstrated weakness in the working memory subset and reduced processing speed. In this report we attempt to delineate the relationships that exist between sub-clinical seizure activity, cognitive impairment and depressive symptoms.

The causal relationships
The schematic below shows the causal links that exist between LP’s symptoms. LP’s depression can be thought of as reactive to a stressor (memory impairment) and/or endogenous reflecting some underlying neuropathology. Her epilepsy can cause depression directly, by affecting neural networks and brain chemistry, or indirectly by the negative appraisal of symptoms (absences and cognitive impairment) and their real-world impact (difficulties with finances). Interestingly financial difficulties in later-life depression are more strongly associated with cognitive impairment rather than the severity of depression (1). To compound this, depression occurring de novo is associated with its own negative impact on cognitive functioning. The subjective perception of cognition is related to mood and not actual performance (2). Cognitive or attentional biases towards negative ideation and specific deficits in attention and short-term memory (3) will also have a pathoplastic effect on the natural history of LP’s problems.

- Epilepsy
- Depression
- Cognitive impairments

The impact of sub-clinical seizure activity is relatively under-researched. Anecdotally sub-clinical seizures have been associated with cognitive impairment and behavioural problems. This report will focus on these areas.
Sub-clinical epilepsy and cognitive impairment

Sub-clinical seizure activity can result in delayed reactions, inaccurate responses or complete cessation of a task (4). In this study motor responses to auditory or visual stimuli were recorded with simultaneous EEG monitoring. The effects of these transitory impairments are material and site-specific with right-sided discharges affecting verbal responses and left-sided discharges producing deficits more demonstrable during non-verbal reasoning tasks (5). The everyday impact of these events remains largely unknown however errors in reading have been reported in children (5). The deficits associated with these discharges may explain LP’s poor short-term memory and difficulties manipulating numerical data: sub-clinical EEG activity would delay her response or prevent her from connecting the different ideas involved so that her solution would be incorrect or incomplete.

Even between seizures subtle cognitive deficits may persist by virtue of the neuronal pathology associated with epilepsy. Seizure-induced neurogenesis maybe associated with lasting cognitive impairment. Patients with TLE have been found to have impaired declarative memory of past events, especially those occurring after the onset of illness (6). There appears to be impairment in both the formation and recollection of memories.

The potential impact of sub-clinical EEG discharges is wide-ranging. Therefore an important practical issue is whether anti-epileptic medication is effective. Preliminary studies have suggested that the suppression of discharges is associated with improved psychosocial function (7). In a rat model both topiramate and lamotrigine inhibited seizure-induced proliferation of neural progenitors with the latter inhibiting aberrant neuronal regeneration in the hippocampus (8), which may be associated with improved, or stable, cognitive outcomes.

Sub-clinical epilepsy and depression

Depression is common in patients with epilepsy. Left temporal lobe abnormalities in patients with epilepsy predict a higher likelihood of depressive illness (9). Psychiatric conditions, including depression, are especially prevalent in patients with TLE (10, 11). This may reflect a common underlying neuropathology (12), a reaction to the illness, the iatrogenic effects of anti-epileptic medications (13) or indeed a combination of latter. The neurobiological control of mood is complex: some anti-epileptics, e.g. lamotrigine, improve mood (9), but nearly all are sedative which may compound depressive symptoms. Anti-depressants that work on a number of different receptors, e.g. venlafaxine, are the most appropriate pharmacological treatments for depression in patients with epilepsy (13).

It has also been noted that during partial and sub-clinical seizures awareness of sensory stimuli continues, but the capacity to respond to them is lost (4). This opens up the possibility that perhaps ‘psychiatric phenomena’, including feelings of derealisation, depersonalisation and even delusional mood, may be the consequence of sub-clinical seizures directly or via psychological reactions. These ‘affectively charged’ experiences can be the only symptom of certain temporal lobe epilepsies (14). These ‘affectively charged’ ideas maybe reactionary to the experience of sub-clinical seizure activity, where the individual tries to make sense of these alien and frightening experiences contextuvalising them within their own narrative. Alternatively they may represent as experiences with a ‘built-in’ emotional element such déjà vu or jamais vu.

Concluding remarks

Helping LP regain her independence is the key role of the therapeutic relationship. This is achieved partly by maximising her medications and better understanding the neuro-chemical bases of her illness. The provision of simple psychotherapies and occupational therapy was invaluable in helping her gain a better understanding of the problems. She was empowered to formulate strategies to help herself on a day-to-day basis. Pharmacotherapy and a multi-disciplinary team approach are needed (15) if we are to help our patients holistically, in a way that really means something to them.

References


In March 2012 I had the great pleasure of talking with Professor Alwyn Lishman for the Neuropsychiatry Newsletter in the first of what I hope to become an regular series of interviews of the great and the good in neuropsychiatry. I am grateful to Professor Lishman for his indulgence and patience and also to Dr Jonathan Bird who kindly orchestrated the meeting and joined us in the discussion.
Interview with Professor William Alwyn Lishman

Norman Poole
Consultant Liaison Psychiatrist, Royal London Hospital

In March 2012 I had the great pleasure of talking with Professor Alwyn Lishman for the Neuropsychiatry Newsletter in the first of what I hope to become an regular series of interviews of the great and the good in neuropsychiatry. I am grateful to Professor Lishman for his indulgence and patience and also to Dr Jonathan Bird who kindly orchestrated the meeting and joined us in the discussion.

Q: Am I right in thinking you trained initially as a neurologist?
A: I didn’t have what you’d call a proper training. What happened was that I had to go into the army as a national serviceman. And there I got my membership (MRCP) at an early stage. At that point the army was running down tremendously and they had no neurology specialist, so I was made an army specialist neurologist. I was put in charge of the hospital, medical division and given a rank of major, having just been a captain for a few months. So I’d been a sort of consultant neurologist in the army. Then I was beckoned to go to the Radcliffe, and Charles Whitty went to Australia for two months and I was a locum consultant neurologist. So I’d had an extraordinary accelerated career to function as a neurologist.

Q: How then did you cross over to psychiatry?
A: I can remember the very day I made the decision. A very great neurologist visited the hospital and I realised with a terrible thud that there was nothing he could do for patients that I couldn’t do, that the only thing he had over me was academic knowledge of the brain. And that was not my idea of being a doctor. So I thought: I want to stick with what I’ve got but broaden it. So that’s when I went to the Maudsley and learned about all the other avenues: talking, social psychiatry, holistic psychiatry. There were so many wonderful facets to psychiatry that there weren’t in neurology. I found that tremendously liberating and that’s what I enjoy doing as a doctor. I found some of the patients a terrible bore and a bind, but you always get that. But they were so much more of a challenge than neurological patients. By the time you’ve seen your fiftieth MS patient you really were just distressed for them. It was very difficult to know what to do next for them. Even Parkinson’s disease — there was very little you could do. Drugs hadn’t come in properly. So it was a barren field for me as a clinician.

Q: Given all the treatments available today in neurology do you think you would make the same decision now?
A: No, it would be much harder for me to make that decision because not only have they got more treatment and more avenues, but being a psychiatrist is much less appealing as far as I can see. Community psychiatry would never have appealed to me, sitting around in a circle with lots of nurses. I think it’s very hard to get the right clinical atmosphere that suits your personality. I think I was always rather bossy – not obviously bossy, but secretly incredibly bossy. And that’s not good in modern psychiatry. I’d have found it hard being part of a team. Actually, I know what I’d have done: I’d have quickly become a proper neuropsychiatrist!

Q: So, how did it come about that you became a neuropsychiatrist?
A: So I was at the Maudsley resisting becoming an academic for the simple reason that I thought of the awful things that happened to academics at the Maudsley. If they fell out with the head of department they perished. Aubrey Lewis was very autocratic. Aubrey Lewis wanted me to become a physiologist. He sent for me and said: ‘You’re wasting your time in psychiatry.’ I was also a physiologist before I came into medicine. I did quite a bit of work and published quite a few papers. And he said: ‘We need a professor of physiology who is also a psychiatrist.’ And I resisted it. The first job I applied for was senior lectureship at the Royal London. And I didn’t get it. It went to Arthur Crisp. The next one I applied for was at King’s but they appointed a man who had come from Sheffield and he lasted about six months and went to America. This sort of thing happened in those days. It didn’t matter how many prizes you got. And at that point Dennis Lee sent for me. He’d been on the appointments committee and he said: ‘I’ve got to tell you Lishman, I was the one who persuaded them not to have you. You’re a backroom
Q: Where does Queen’s Square fit in?
A: That was the third one I applied for. I went to see Eliot Slater. Eliot had a terrible time there. He got the funds together for a chair and the medical committee voted not to accept them. So he said to me: ‘Go there, have a wonderful time but don’t stay more than a couple of years, because they’ll do to you what they did to me.’ In fact they were very welcoming to me and very helpful indeed. When Denis Hill beckoned me to come back [to the Maudsley] I thought: I’ll do what Eliot said, I’ve had my two years and it’s been interesting. Also, some of the neurologists were extremely hostile to a psychiatrist. I won’t mention their names even now, but the ones who were wonderful I will: Dennis Williams, Macdonald Critchley and Charles Simons were marvellous. But others were very dismissive. They would ask you to see a patient and you’d spend hours, and you’d come back tomorrow and the patient would have been sent out. They weren’t good doctors some of them. They were fascinated by patients as specimens, really. I didn’t want to live in that world forever.

Q: When were you at the Maudsley?
A: The first 12 years I was a consultant from 1967 onwards. I was a general psychiatrist there, and I took my share of all the patients with everyone else. Then, I began to specialise. There were no neurologists on the staff of the Maudsley, so if someone had a patient who was twitching or something odd was going on, they’d ask me to see them. So I became a sort of quasi-neurologist specialist. And that meant that if in fact began taking over patients on other wards into my own care and I got to be increasingly neuro-psychiatric instead of general. Then, I got a personal chair and the chair was called neuro-psychiatry and that was when I was 49 years old. And it was the first time I was ever paid as an academic. I had always had an NHS salary. So as usual I had sort of drifted. I never determined things for myself, I drifted.

Q: What qualities do you think make a good neuro-psychiatrist?
A: First of all you’ve got to be a good neurologist and a good psychiatrist. I don’t mean that you have to have a lot of experience of neurology but you have to have a passion to understand the brain. And then the rest of it is being a good psychiatrist and treating patients properly and well. And being able to teach is terribly important, being able to pass all that knowledge on. That by the way, was partly why I took on the book.

Q: How did the first edition of Organic Psychiatry come about?
A: I can tell you exactly. For about three years Blackwell’s had been getting in touch with me, saying: ‘We have been advised that there is a need for a book to get the organic slant on psychiatric illness, that puts the brain back into psychiatry. We’ve been advised that you’re the man to do it.’ I think it was Sir Charles Simons who was advising them because he and I were very friendly at that time. Either him or Norman Geschwind in America. Anyway, they kept going on at me and I kept saying no. I was getting advice from people who said don’t get tangled with that. The reason why I finally did it was quite ridiculous. I’m slightly ashamed of this, but I wanted a Bechstein grand piano and I saw one. I happened to be left a very small legacy, £200 or £300 from an uncle. The same week I got the offer of a substantial advance for the book, so I thought I’d go for it.

“You have got to have a finger in every pie in psychiatry and be ready to turn your hand to whatever is the most important avenue: an EEG one day, a bit of talking about a dream another day.”

Q: I have heard writing the first edition was very hard.
A: Oh yes, terribly hard. The month that I began we adopted a baby, so I’d got ready, with my desk and papers and all my books around me. And lo and behold the phone rang and this child arrived within three weeks. And so suddenly I was plunged into fatherhood. I still got on with it, with her in the highchair beside while I was writing for hours on end. The next thing that happened was that my mother–in–law got a brain tumour and I put the book away. I got it out again a year later and my own mother got Alzheimer’s, 300 miles away. And I had to go up and down to the north of England a great deal, so I had to the put the book away again. So it was very very traumatic, and each time I put it away it was my wife who was saying: take it out again. So it was seven years being written. And it was colossally difficult because I’d never written anything that long before. With the subsequent editions I got into a sort of writer’s frame of mind. And I was able to keep going, sometimes for 24 hours at a
stretch, which is like being an athlete in a sort of way. The first edition was training me to write, and I was very obsessional about the grammar being right. My wife was an expert in this sort of thing, so she read it all and perfected my style. It was an incredible experience to do it. I’m not sure it was wise to do it. I then had to do a second edition and a third edition. It absorbed a lot of my life.

Q: Who inspired your career in neuropsychiatry?
A: I’m very inspired by the people who have done doctorates with me or worked closely with me: Michael Kopelman, Tony David, Robin Jacobson, Maria Ron, Simon Fleminger and Eileen Joyce. They, I think, are the leaders at the moment. But in terms of the great neuropsychiatrists of the past, before my time? I didn’t know them. They were just names to me. Plus Denis Hill of course. He was the prime example of all. He was known as the epilepsy psychiatrist but he was a much more broadly based man than that. He was incredibly broad because he was a proponent of psychoanalysis. His wife was a psychotherapist. So he would be my big hero. And who else would there be? Willy Mayer-Gross, who I got to know a little when he came to England. Before that neuropsychiatry got a bad reputation. That was Wilhelm Griesinger at the Charité Hospital. He said mental disorders are brain disorders. Full stop. And he tried to make the whole of psychiatry nothing but brain science. Of course that made it very unpopular in the world in general because people were saying: this is a ridiculously narrow view. What he did was, he managed to produce lots of people, like Alzheimer and Wernicke, whose names have lived on. But it was a very narrow approach and I doubt if you talked to your patients very much. I suppose he would have given them pills if pills had been around, but he was a very narrow-minded man. And that was another reason I didn’t like to call my book Neuropsychiatry. I was frightened it would be made unpopular by its title.

Q: Why did you call the book Organic Psychiatry rather than a neuropsychiatry text?
A: The reason I called it Organic Psychiatry is very simple. As I wrote the book I did the head injury, I did the epilepsy and I did the strokes, and then I decided I had to do the metabolic disorders and go into diabetes and all the parathyroid disorders and so on. And I realised that this would not be neuropsychiatry — it’s general medicine in relation to psychiatry. So the book should have been called ‘Neuropsychiatry / Organic Psychiatry / Liaison Psychiatry’. I thought I’d found the best compromise with organic. But then people started talking about organic milk and organic meat and people made a lot of fun of it. I like the term less every time I go into a supermarket. It’s been taken over, you see.

Q: Although Lishman’s is a text on biological psychiatry it does not ignore the psychological and social aspects of illness.
A: You have got to have a finger in every pie in psychiatry and be ready to turn your hand to whatever is the most important avenue: an EEG one day, a bit of talking about a dream another day. You just follow your nose. All psychiatrists should be all types of psychiatrist. You shouldn’t turn your back on talking therapies as many patients need this. I’ve always said the fundamental skill of a psychiatrist is being able to talk meaningfully and helpfully with patients. Just as the fundamental skill of the physician might be using the stethoscope we use talking, so I made a bit of a fuss about that over the years. I get less and less patient with psycho-analysis as I get older. It wasn’t a bad first go but is full of desperately silly fallacies and the other awful thing is you need to be a millionaire to have a proper analysis. Briefer forms are so important because life is just too short and people don’t have enough money for that sort of indulgence, certainly not in England. The sort of psychotherapy that I believed in was distributive I suppose you would call it. Just going through people’s problems with life and trying to help them with it in a straightforward, commonsensical way.

Q: Why did you call the book Organic Psychiatry rather than a neuropsychiatry text?
A: The reason I called it Organic Psychiatry is very simple. As I wrote the book I did the head injury, I did the epilepsy and I did the strokes, and then I decided I had to do the metabolic disorders and go into diabetes and all the parathyroid disorders and so on. And I realised that this would not be neuropsychiatry — it’s general medicine in relation to psychiatry. So the book should have been called ‘Neuropsychiatry / Organic Psychiatry / Liaison Psychiatry’. I thought I’d found the best compromise with organic. But then people started talking about organic milk and organic meat and people made a lot of fun of it. I like the term less every time I go into a supermarket. It’s been taken over, you see.

Q: Although Lishman’s is a text on biological psychiatry it does not ignore the psychological and social aspects of illness.
A: You have got to have a finger in every pie in psychiatry and be ready to turn your hand to whatever is the most important avenue: an EEG one day, a bit of talking about a dream another day. You just follow your nose. All psychiatrists should be all types of psychiatrist. You shouldn’t turn your back on talking therapies as many patients need this. I’ve always said the fundamental skill of a psychiatrist is being able to talk meaningfully and helpfully with patients. Just as the fundamental skill of the physician might be using the stethoscope we use talking, so I made a bit of a fuss about that over the years. I get less and less patient with psycho-analysis as I get older. It wasn’t a bad first go but is full of desperately silly fallacies and the other awful thing is you need to be a millionaire to have a proper analysis. Briefer forms are so important because life is just too short and people don’t have enough money for that sort of indulgence, certainly not in England. The sort of psychotherapy that I believed in was distributive I suppose you would call it. Just going through people’s problems with life and trying to help them with it in a straightforward, commonsensical way.

Q: But you never planned a career in medicine or psychiatry?
A: My father had started medicine but then went to the First World War and had been a prisoner of war. He went back to medical school but could never pass his exams because he’d been so ill. So my parents were saying ‘Alwyn’s going to be a doctor’ ever since I was three years old. I never knew why until after my father died. I don’t blame them. He would have been a wonderful doctor, far cleverer than me but he worked in a very humble capacity all his life.

Music was my passion as a child. I demanded a piano from the age of five and they couldn’t prise me away from it. I took music lessons until the month before my finals. I was equally in the music department and the medical department. I have always split myself like that, doing two things at once, neurology and psychiatry, physiology and neurology. It’s extraordinary how I’ve never been content to do just one thing.
**Support when facing threats to your job**
The College is very aware that the NHS changes and current financial climate are leading to many and varied changes in services, and that there are many of you facing difficult and uncertain times. Service changes, tendering processes and drive for efficiencies are leading to threats of redundancies, actual redundancies, loss of posts and decrease in paid Programme Activities. There are also Psychiatrists facing a potential loss of earnings as a result of changes in the legal system. As a result many feel under considerable stress due to the uncertainty and possible changes in lifestyle. It can be difficult to know where to turn at such times.

**There are no clear answers, but here are some thoughts on what might help:**

1. The British Medical Association provides assistance with employment and contractual issues. This is an important avenue of support when faced with service or contractual changes or the possibility of redundancy. To contact the BMA for employment and general information queries, telephone 0300 123 12333. Lines are open Monday–Friday, 8.30–6.00pm. Alternatively, visit their website at: http://www.bma.org.uk/_top/contact_us/index.isp and use the feedback form to contact an adviser.

2. Consider what procedures are available to you within your organisation to review your position or offer advice. This could include discussion at a Medical Staff Committee meeting, Local Negotiating Committee meeting or discussion with Human Resources.

3. The Psychiatrists Support Service is a confidential telephone advice service providing support and signposting for members of the Royal College of Psychiatrists. Contact can be made on telephone 0207 2450 412. The Support Service Manager will listen to the details of your situation and review them with the Specialist Adviser who leads the service. You will then be directed to an appropriate organisation to provide the necessary support or referred to a College member for focused advice.

4. Informal discussion with your colleagues. You may be surprised to learn that others may be experiencing similar anxieties. Your colleagues may have helpful ideas about what you could consider doing and help you to explore your options.

5. The British Medical Association Counselling Service and Doctors for Doctor's service provide a confidential service where doctors can discuss problems and get support. You can either speak to a counsellor or a doctor–advisor. To make contact telephone 08459 200 169.

6. Support for Doctors is a website developed by the Royal Medical Benevolent Fund and provides a lot of useful information (www.support4doctors.org). The Royal Medical Benevolent Fund can also provide support for doctors and their families facing financial problems.

7. The BMA can direct you towards financial advisors, or you may wish to make contact with an advisor independently.

8. You may want to consider avenues of alternative income or a portfolio career. Information and contacts for the College ‘Private and Independent Practice Special Interest Group’ is available on the College website, Members Section, and an information guide ‘On planning a portfolio career’ is on the Psychiatrists Support Service website (available at: [www.rcpsych.ac.uk/pss](http://www.rcpsych.ac.uk/pss)). The British Medical Association also provides information and seminars on setting up a private practice. 9. You may want to consider an alternative career or specialty. Talking to colleagues may generate ideas. The Medical Forum offers career planning support (see [http://medicalforum.com](http://medicalforum.com) The British Medical Association also provides careers counselling, and your local Deanery may have a careers advisory service.

Above all it is important to look after yourself. Talk to your family, friends and colleagues. Maintain a healthy lifestyle and work life balance. You might find the information guides available on the Psychiatrists Support Service website helpful, in particular advice on dealing with stress (available at: [www.rcpsych.ac.uk/pss](http://www.rcpsych.ac.uk/pss))

The College is keen to hear from you and to understand what is happening to jobs and services. Please do contact Charlotte Collins, Workforce Manager, on ccollins@rcpsyh.ac.uk with any news or updates.
24th Annual Meeting
American Neuropsychiatric Association
April 3 - 6, 2013

The Boston Park Plaza Hotel & Towers
50 Park Plaza at Arlington Street
Boston, MA 02116 – 3912

Up to date information is available at: www.anpaonline.org

KEYNOTE ADDRESS
Social Cognition and the Frontal Lobes: A 35 Year Odyssey
Donald T. Stuss, Ph.D.
The Ontario Brain Institute

The theme of the 2013 Annual Meeting will be: DISORDERS OF NEURODEVELOPMENT: A LIFESPAN PERSPECTIVE
The sessions will focus on Autism, Attention Deficit Hyperactivity Disorder and Gilles de la Tourette Syndrome

Each of these three symposia will include three one-hour component lectures on:
1 Epidemiology, phenomenology, and neuropathophysiology;
2 Presentation, evaluation, and treatment in children and adolescents;
3 Presentation, evaluation, and treatment in adults, including issues related to aging with these disorders

AUTISM
Chair: Donald C. Rojas, Ph.D.

ATTENTION DEFICIT HYPERACTIVITY DISORDER
Chair: Martha Denckla, M.D.

GILLES DE LA TOURETTE SYNDROME
Chair: Michael Trimble, FRCP, FRCPsych

THE NEUROPSYCHIATRY OF REWARD SYSTEMS
Chair: Daniel R. Wilson, M.D., Ph.D.
Eric J. Nestler, M.D., Ph.D.
David A. Silbersweig, M.D.
Morten L. Kringelbach, D.Phil.

RESEARCH COMMITTEE REPORT ON SOMATOFORM DISORDERS
Valerie Voon, M.D.

PRE-MEETING SYMPOSIA
NEUROBEHAVIORAL ISSUES IN SLEEP: MOOD, MEMORY, AND OTHER MISCHIEF
Chair: Daniel I Kaufer, M.D.
What goes to sleep at night? A functional neuroimaging approach to a good night’s rest Eric A. Nofzinger, M.D.

WHY GO TO SLEEP AT NIGHT? THE NEUROPSYCHIATRIC FUNCTIONS OF SLEEP
Robert Strickgold, M.D., Ph.D.

FRONTAL-SUBCORTICAL CIRCUITS
Chair: Jeremy D. Schmahmann, M.D.

CLINICAL PLATFORM PRESENTATIONS
Chair: Sheldon Benjamin, M.D.

RESEARCH PLATFORM PRESENTATIONS
Chair: Jeremy D. Schmahmann, M.D.
Members of the Section of Neuropsychiatry of the Royal College of Psychiatrists are invited to register as members of ANPA. Website: www.anpaonline.org (Please click RCP on registration form)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2013 Meeting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Member</td>
<td>435</td>
<td>485</td>
<td>535</td>
</tr>
<tr>
<td>Non Member</td>
<td>575</td>
<td>625</td>
<td>675</td>
</tr>
<tr>
<td>Trainee</td>
<td>215</td>
<td>235</td>
<td>235</td>
</tr>
<tr>
<td>Trainee Non Member</td>
<td>290</td>
<td>310</td>
<td>330</td>
</tr>
<tr>
<td><strong>2013 Pre–Meeting Sessions Frontal–Subcortical Circuits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>100</td>
<td>125</td>
<td>150</td>
</tr>
<tr>
<td>Non Member</td>
<td>150</td>
<td>175</td>
<td>200</td>
</tr>
<tr>
<td>Trainee</td>
<td>50</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Trainee Non Member</td>
<td>70</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td><strong>Neurobehavioral Issues in Sleep</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>100</td>
<td>125</td>
<td>150</td>
</tr>
<tr>
<td>Non Member</td>
<td>150</td>
<td>175</td>
<td>200</td>
</tr>
<tr>
<td>Trainee</td>
<td>50</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Trainee Non Member</td>
<td>70</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>