

A long career in epilepsy: a neuropsychologist reflects

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Epilepsy has been a constant throughout my working life, shaping my clinical, teaching and research endeavours. When I began working in epilepsy more than four decades ago neuropsychologists were a rare commodity. Nowadays we form an integral part of a good quality epilepsy service. There is no way I could have envisaged, as I saw my first patient, that as my career draws to an end I would be facing people wearing a mask, gloves, scrubs with surgical wipes at the ready. In the early months of the pandemic my contact with patients was undertaken remotely. During the Summer we began to reinstate face to face encounters, albeit tentatively. By Autumn it seemed we might be through the worst. Unfortunately this was not the case and as I write we are well into our third lockdown in the UK and the ravages of this pandemic seem relentless with overflowing hospitals, physically and emotionally drained staff and the threats, uncertainties and restrictions caused by this virus adding to the psychosocial burden of living with epilepsy.

And in the beginning

My first encounter with epilepsy was during my primary school years. I must have been about ten when it came to light that one of my classmates had seizures. She had an attack at school, not personally witnessed but for a while it became the subject of playground whispers, and what might now be deemed fake news. This was fairly short-lived as a focus of attention although upon reflection our words and perhaps actions had some lasting negative psychological effects. I remember her however as socially outgoing and I was not aware that our class teacher treated her much differently and she did seem to take an active part in school life. She went swimming and she was selected for the school choir, I did not make the grade for that. She went on school trips and on one such outing when she fell in the murky ditch around Burgh Castle, an old Roman Fort, this was due to silliness and not a seizure, as I recall. Indeed she took the lead from me in the end of term school play when I had to miss the final weeks of primary school because I had contracted mumps. Our paths never crossed again as we attended different secondary schools. Much later I did learn that she had died, seemingly out of the blue in her forties, a victim of SUDEP perhaps?

My next exposure to epilepsy came many years later, excepting woefully fleeting commentary as part of my undergraduate psychology degree. On January 6th 1978 I entered the portal of Maida Vale Hospital ,part of the National Hospitals for Nervous Diseases. That is when I began my PhD under the supervision of Professor, then Dr Michael Trimble. My quest was to investigate the cognitive side effects of anti-seizure medications something that had received scant attention and presented what was to be a considerable methodological challenge. At the time epilepsy was not a favoured field of study as encapsulated in the words of my supervisor ' *Epilepsy was considered not quite a respectable subject for neurologists to be interested in*'. A view that has definitely changed.

Anti seizure drugs

When I began my research anti-seizure drugs, were commonly known as anticonvulsant drugs. Indeed my thesis was entitled , *The effect of anticonvulsant drugs on cognitive functioning*. In the late 1970s clinicians had comparatively few drugs at their disposal. Second generation drugs had not long been introduced. Carbamazepine and sodium valproate were the new kids on the block. Investigations into their efficacy and side effects profile relative to first generation drugs however were increasing. Research into cognitive effects however was limited and interpretation of existing studies was not straightforward particularly those with cross sectional designs. Many available neuropsychological tests were not suitable tools as practice/boredom effects would confound the outcomes of longitudinal designs. My research involved novel assessment methods with tests designed to reflect cognitive complaints, primarily memory difficulties and processing slowness. To try and maximise test sensitivity we developed where possible parallel versions. We also employed tachistoscopic presentation to increase the precision of stimulus delivery. Response time was selected as a key outcome measure. The equipment felt very much state of the art but looking back it seems rather archaic particularly when viewed against currently available technologies.

To test whether our battery was fit for purpose we embarked on healthy volunteer studies. There were a few existing trials but most looked at the effects of single doses. Not for us, we had

volunteers taking drugs at a standard clinical daily dose for two weeks in a double blind cross over design with placebo. In turn we assessed phenytoin, carbamazepine, sodium valproate and clobazam. My first peer reviewed publication as lead author emerged from these studies (1). I can still recall the thrill reading my acceptance letter and the celebratory glass of Beajolais Nouveau in Covent Garden. It was around this time I gave my first international presentation at a symposium in Gothenberg, Sweden. A trip not without drama as I managed to miss the flight and arrive a day late. I was devastated by my ineptitude but this quickly dissipated following the welcome I received from the other workshop participants , mostly eminent and well established epileptologists.

Of course there are problems extrapolating findings from healthy volunteers to clinical settings, where the adverse cognitive effects of seizures, mood and other factors kick in. Longitudinal studies with patients posed much more of a challenge. I settled for following people undergoing planned drug changes with reassessments scheduled three months and for some cohorts six months later. I explored the impact of changing from poly-therapy to monotherapy, switching to carbamazepine and I also looked at performance at high versus low drug load with drug levels available at the time of testing. Patients on stable therapy constituted my control group although several frustratingly changed status due to unforeseen drug changes. I vividly remember one of the first people I enrolled. I was going to see him before he started treatment, such drug naïve patients were rare in our clinical setting. I remember the satisfaction of collecting and collating his data. I was on my way - what could go wrong – well he was ‘lost to follow up’ as he moved to Canada a month after I saw him and a trip out there apparently was not in the budget.

Notwithstanding the weaker designs of these clinical studies the findings provided evidence that drugs can have adverse cognitive side effects. Research into the cognitive effects of epilepsy drugs has continued apace and publications run into several thousands. Over the years research findings have been conflicting and there have been some bitter debates fuelled in part by most research being funded by pharmaceutical companies. There are now more drugs available, upwards of

fifteen when I last counted. Conflicting findings should not be surprising, as studies vary with regard to many pertinent variables including the study design, the cohort studied, the statistical analysis and changes in seizure control and mood. My clinical experience has reinforced my opinion that any drug can exert adverse effects although some are more culpable than others. Group findings will mask negative and indeed positive effects at an individual level. I have known patients cognitively unscathed on drugs with a bad press and rendered seizure free. Drugs are commonly blamed by patients and their families and in some cases the drug may be the culprit but cognitive side effects may be the cost of good seizure control. Cognitive difficulties however are often driven by the underlying pathology and unstable neuronal networks that cause the seizures. It is integral to our role as clinical neuropsychologists to assess whether medication is likely a dominant cause. While consideration of adverse drug effects has remained a concern, a major focus of my subsequent clinical and research work has been epilepsy surgery.

Surgery

Epilepsy surgery had a chequered history during the last century with some noteworthy disastrous cognitive outcomes in the 1960s. HM at the Montreal Neurological Institute was rendered amnesic following a bilateral temporal lobe resection that necessitated staff supported living for the rest of his long life. NT a patient at the National Hospitals in London also became amnesic but this was following a unilateral temporal lobe resection. EEGs had recorded right temporal lobe epileptic abnormalities while her neuropsychological profile supported a verbal memory deficit. This discordant data was written up and published as a case study demonstrating atypical cerebral organisation. NT's resected right temporal lobe tissue was found to be normal but following her death many decades later left hippocampal sclerosis was identified. The wrong temporal lobe had been removed.

It was the advent of MRI scanning that was the catalyst for the subsequent burgeoning of surgical treatment for epilepsy from the 1990s. The early temporal lobe surgeries, although devastating with

regard to the cognitive outcomes, did result in extensive neuropsychological research. Indeed HM alone has been the subject of hundreds of scientific publications. From a personal perspective, these dreadful surgical sequelae served to highlight the crucial and unique role of the neuropsychologist within surgical programmes and also contributed to the evolution of clinical neuropsychology as a profession.

I have been fortunate to have been part of the epilepsy surgery treatment programme at the National Hospital for Neurology and Neurosurgery since its renaissance. I saw my first pre surgical patient on November 20th 1986. He had left temporal lobe epilepsy and he underwent resective surgery in December that year . He had remained seizure free when last followed up, was working full-time and driving. In 1992 a research grant enabled us to study the cognitive impact of surgery more systematically. Dr Sallie Baxendale came on board, initially as a research psychologist and subsequently as a clinician. She was, and continues to be a driving force behind our neuropsychological clinical and research work. Since its inception we have undertaken approaching 3000 pre-surgical evaluations and monitored the outcome of the many hundreds who proceeded to surgery. Alongside the clinical work we have maintained a productive research programme together with other members of our epilepsy research group. Through our neuropsychological research we strive to improve our assessment methods and to utilise clinical data to inform the surgical decision making process. Epilepsy surgery is elective and patients and families need accurate information not only on the likelihood of attaining seizure freedom but on the possible cognitive and psychological outcomes.

One important benefit of our research has been the phasing out of the sodium amytal test. When we began this invasive procedure was undertaken in every candidate to establish language dominance and to ascertain the amnesic risk of surgery. Through research our understanding of pre-surgical neuropsychological findings has increased and this together with more reliance on other electrophysiological and neuroimaging findings has allowed us to reduce, albeit initially gradually,

the number of procedures undertaken. The ultimate removal of this invasive, risky and costly (psychological and financial) test has made a major contribution to patient care and, under normal circumstances, avoids a delay along the often long surgical pathway (2). Working on the surgical programme has been immensely fulfilling. It has been gratifying to meet individuals who no longer have seizures and are beginning to reap the psychosocial benefits. Not all outcomes are positive and for some surgical cases adverse cognitive and psychiatric outcomes can be devastating and ongoing research must continue to try and minimise such eventualities.

Seizures

More difficult to explore than treatment effects has been the cognitive impact of seizures. Do seizures cause brain damage? Frequently patients and families voice this concern and worry that with every seizure brain cells die. Over the years I have been amazed by the robustness of the brain and how some people continue to function at a high level after years of poorly controlled seizures. Clearly seizures are not blameless but methodologically it has been difficult to study. We did however demonstrate that a high frequency of tonic-clonic seizures over ten years was associated with generalised cognitive decline and frequent focal events with more circumscribed declines, with memory and executive functions most susceptible. An important finding from this study was that pharmacologically treated patients who experienced significant periods of remission after years of poorly controlled had much better cognitive outcomes (3).

Memory

Memory difficulties and decline are a common complaint of people with epilepsy and one of the most frequent reasons for a referral to our service. Living with a memory problem is stressful and with advancing age fears of dementia come to the fore. Memory is not just about the past, it influences our present and guides our future. It defines our sense of self and our relationship with others. Research studies over many decades have confirmed an increased risk of memory problems

in epilepsy and many disease and treatment factors have been implicated and investigated. Research into memory functions has provided a rich vein of neuropsychological data that has contributed to our understanding of the biological basis of memory and underpinned theoretical models of memory function. Scant attention however has been devoted to interventions that might ameliorate memory problems or at least reduce their far reaching impact.

I have long been aware of this gap in our evidence base. Indeed the first research grant I was awarded included a study to explore the effectiveness of memory rehabilitation strategies. This highlighted the difficulties in carry out such research. In a recent study we explored the efficacy of strategies to optimise memory functions including the benefit of an on line mental training programme, promoted as having cognitive enhancing properties. We observed improvements in between one in three and one in two of the study participants following our outpatient based intervention, compared with one in five in the control group. Improvements were most evident in association with conventional memory rehabilitation and there was no evidence that the internet brain training programme employed had added value although it was preferred by younger participants (4). Our research findings have helped guide our subsequent clinical work and our current emphasis is often on helping people and their families to develop techniques to enable them to live with memory problems. Mobile phone advances have been a considerable asset in this regard and can provide individuals with an external well-functioning temporal lobe.

Going forward

It is with considerable trepidation we enter 2021. We are endeavouring to keep our neuropsychological service going and the vaccine programme in the UK brings promise but everything remains so fragile. A Covid case in the staff team would seriously disrupt our currently limited outpatient and inpatient work. Covid collateral damage already is considerable and it will continue to rise. Our epilepsy surgery programme has been on hold for a year with only emergency neurosurgeries taking place. Epilepsy is life threatening and deaths may ensue in the inevitable long

delays before surgery can resume. Psychological distress has been high for those who were only weeks away from their operation before the service was suspended. Several patients who had surgery early last year have not been able to access the full range of post-operative follow up support particularly those who have developed mood disorders. Many patients with epilepsy have been classified as vulnerable and have been shielding. Some individuals have been confined to home for almost a year and this has been extremely debilitating for those living in cramped accommodation without any outdoor space, those who live alone and those with learning disabilities who lack the capacity to understand why they cannot go out. Undoubtedly Covid will become a future cause of epilepsy. It is increasingly recognised that this virus can cause brain infections, haemorrhages and strokes which in turn may trigger seizures and leave individuals with residual cognitive problems. I fear we will be living in the aftermath of the Covid pandemic for a long time.

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