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Depression after epilepsy surgery

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Abstract

Depression has become one of the most commonly reported and studied psychiatric co-morbidities of epilepsy. While different forms of depression have been specifically related to epilepsy, this paper focuses on neurobiological and psychosocial factors that predict major depression in patients with intractable focal epilepsy. It then examines how these factors may affect patient trajectories and outcome following epilepsy surgery. This provides a model of relevant clinical markers for epilepsy clinicians to identify patients at risk of depression so that preventative treatment strategies can be implemented.

INTRODUCTION

A bidirectional relationship between depression and epilepsy has been proposed to account for their heightened comorbidity in terms of a shared pathogenic mechanism.[1] Prevalence rates as high as 50% have been reported for depression in epilepsy, although this varies according to the community or hospital-based sample studied, and the focal or generalised nature of the syndrome. Nevertheless, up to one in two people with epilepsy may have a lifetime history of depression, while the risk of suicide is up to 10 times that of the normal population.[2] This impact is considered more influential than all other co-morbid conditions, with health care costs estimated at 80% higher for depressed compared with non-depressed epilepsy patients.[3]

The prevalence of depression after epilepsy surgery is particularly high, and poses a challenge for clinicians to predict as it can arise *de novo* in patients who appear euthymic before surgery.[4] Moreover post-operative suicide attempts highlight the paradoxical nature of outcome in 'successful' seizure free patients who no longer wish to live. Thus, a key goal of our Surgical Follow-up and Rehabilitation Program has been to identify those patients at risk of depression after surgery so that preventative strategies can be implemented to proactively manage this risk. The current paper focuses on the research our group has undertaken centering around two questions: (i) What are the factors that predict depression in intractable focal epilepsy? and (ii) How might these factors affect patient trajectories and outcome following epilepsy surgery? In particular, we performed a series of prospective longitudinal studies of patients undergoing mesial temporal resections (MTR) or nonmesial temporal resections (NMTR) for treatment of intractable focal epilepsy[4-10], and assessed their mood at regular intervals before and after surgery (1, 3, 6, and 12 months).

MARKERS OF DEPRESSION PRE-SURGERY

Medically intractable seizures are well known to cause a range of psychosocial sequelae, some of which have also been linked to pre-operative depression. As shown by our research and that of others (Figure 1), these include a lack of employment and financial dependence[11,12], as well as a family history of psychiatric illness, consistent with factors associated with depression in the general population.[9] A family psychiatric history is thought to confer a genetic or "innate" risk, as may certain personality traits such as high neuroticism and low extraversion, with high neuroticism also associated with poor family adjustment.[5] Thus, these findings point to important interactions between innate risk and psychosocial factors in the presentation of depression before epilepsy surgery, rather than simply attributing depression to the psychosocial effects of having a chronic illness.[10]

Neurobiological markers of depression in epilepsy have also been identified (Figure 1). In keeping with the general depression literature, our work has targeted limbic system structures and their connections known to play a role in mood disturbance. In particular, using voxel-based

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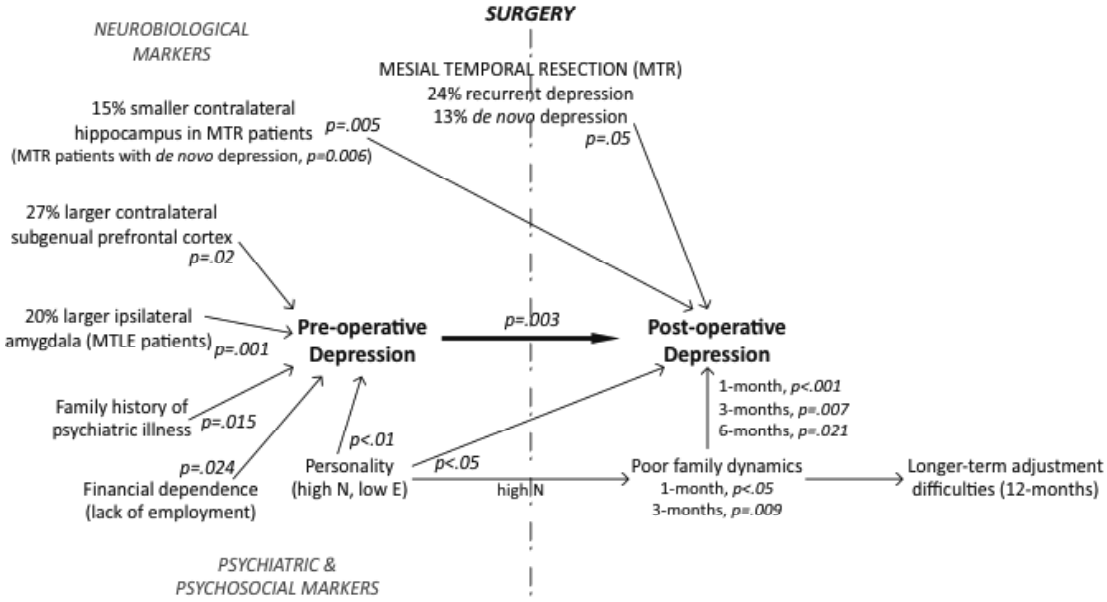

Figure 1. Key neurobiological and psychosocial markers of patients at risk of major depression before and after surgery for intractable focal epilepsy (percentages represent average values). MTLE = mesial temporal lobe epilepsy; N = neuroticism; E = extraversion.

morphometry we found a 27% increase in the volume of the subgenual prefrontal cortex in the contralateral hemisphere of patients with a history of depression. Moreover, a subset of this sample with mesial temporal lobe seizure foci also showed a 20% increase in ipsilateral amygdala volume.[10] Consistent with previous research[13], these findings indicate that epilepsy patients with depression can have structural changes in their mood network that may be identified from neuroimaging investigations before surgery, providing the opportunity to implement preventative treatment strategies.

PROFILING TRAJECTORIES AND PREDICTING OUTCOMES POST-SURGERY

Previous research has shown that patients may follow a range of trajectories after surgery that relate not only to their seizure outcome, but also their cognitive, psychological and social functioning.[14] While many patients experience an improvement in mood after surgery, others may show exacerbation of a preexisting mood disturbance or develop *de novo* depression, despite achieving seizure freedom. Our research profiling depression after surgery suggests that around a third of patients experience major depressive disorder in the year following surgery, with similar rates for MTR and NMTR patients.[9] The majority of these patients (70%) are diagnosed within the first three months and experience persistent symptoms (65%) for at least 6 months within the follow-up period.

Having a history of depression is a strong risk factor, with our data indicating that 75% of patients experiencing depression within 12 months of surgery have a lifetime history of depression, while the remaining 25% arise *de novo*. Strikingly, we found that only MTR patients developed *de novo* depression (13%) compared with no NMTR patients.[9] Given that *de novo* patients often appear resilient before surgery and thus, can be challenging to predict, we performed a case series to identify psychosocial factors that were common across patients. These included high levels of perceived stigma before surgery, and significant family conflict after surgery. Both preceded the onset of *de novo* depression following MTR, and point to two possible mechanisms for depression after surgery. First, a neurobiological mechanism associated with disruption to limbic structures targeted by the surgical procedure, and second, psychosocial factors associated with adjusting to life after surgery. The latter can arise particularly in seizure free patients, who undergo a change in self-identity to "well" and desire increased autonomy and decreased carer support after surgery, as has been described as part of the burden of normality.[14]

Of note, family conflict after surgery was the strongest predictor of post-operative depression in our multivariate study at 1, 3, and 6 months (Figure 1). In a separate study, we also found that patient personality traits influenced family dynamics early after surgery, with more than 70% of patients with high neuroticism reporting disrupted family dynamics. This, in turn, was associated with difficulties adjusting to a seizure free life over the longer term.[8] In addition, high levels of neuroticism coupled with low levels of extraversion placed patients directly at risk of depression post-surgery.[8]

Our research has also examined neurobiological markers predictive of depression after surgery, again targeting the limbic network. Before surgery we observed, on average, a 15% decrease in hippocampal volume in the contralateral hemisphere of MTR patients who subsequently developed depression after surgery compared to those with no depression.[7] This relationship held in MTR patients who developed *de novo* depression after surgery, and there was a trend for smaller volumes (40% decrease) to be most evident in patients experiencing post-operative seizure recurrence.[7] Importantly, smaller contralateral hippocampal volumes before surgery correlated with the severity of depressive symptoms after surgery, at both 1 (r=-.46) and 3 months (r=-.42). This suggests that a smaller contralateral hippocampus may provide a structural marker of dysfunction in the mood network prior to surgery, which following mesial temporal resection, elevates the risk of depression particularly early after surgery.[7]

CONCLUSIONS

Our work highlights the relevance of a stress-vulnerability (stress-diathesis) model of depression in patients with intractable focal epilepsy. In particular, it shows how innate neurobiological factors can interact with psychosocial stressors before surgery to shape a patient's post-operative trajectory and experience of outcome. Neurobiological vulnerability for post-operative depression includes genetic factors that can be captured via a family history of psychiatric illness, as well as structural brain changes in the limbic network important for regulating mood. MTR may then further disrupt the network central to normal mood functioning after surgery. In the face of neurobiological risk, psychosocial stressors may act as a catalyst and maintaining factor, particularly for *de novo* depression. This plays out most saliently in the family in terms of financial dependence before surgery and disrupted family relationships after surgery, as the patient adjusts to post-operative life.

These findings highlight the importance of comprehensive evaluation of patients before surgery to routinely canvass psychological and social issues, in addition to medical investigations. This provides the opportunity to identify patients at risk of developing mood disturbance after surgery that can be actively managed in the pre-surgical phase. Our findings also illustrate the vital role of post-operative follow-up and rehabilitation programs that routinely assess patient mood and psychosocial functioning at regular intervals after surgery. Such programs allow patients and their families to receive appropriate psychoeducation and treatment to deal with the challenges of life after surgery.

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