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ARTICLE

A narrative review of ablative neurosurgery in refractory mental disorders

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SUMMARY

Neurosurgery for mental disorder (NMD) is currently performed in the UK for cases of severe depressive disorder and obsessive–compulsive disorder refractory to treatment, under stringent regulations as set out under the Mental Health Act 1983. These surgical procedures appear to be effective for a proportion of individuals in this particularly treatment-resistant cohort. The two ablative procedures currently in use in the UK are anterior cingulotomy (ACING) and anterior capsulotomy (ACAPS). After briefly outlining these procedures, their evidence base and how they compare with other neurosurgical procedures, we suggest two ways in which they could be enhanced in terms of precision, namely the use of stereotactic (Gamma Knife®) radiosurgery guided by magnetic resonance imaging as well as a detailed and expanded standardised psychopathological and neuropsychological assessment both before and after surgery. The latter should involve extended long-term follow-up. We then reflect on how such psychopathological and neuropsychological assessments could help to understand why and how these procedures relieve patients' suffering and distress.

LEARNING OBJECTIVES

After reading this article you will be able to:

- delineate the indications for NMD as well as its legal framework in the UK
- outline the two surgical procedures in use in the UK (ACING and ACAPS)
- outline the potential adverse effects of NMD and how they could be better studied.

KEYWORDS

Neurosurgery for mental disorders; refractory depressive disorder; refractory obsessive–compulsive disorder; anterior cingulate; ablative NMD.

Neurosurgery for mental disorder (NMD), a rarely discussed subject, is highly invasive – some procedures changing the brain irreversibly as well as potentially altering the individual's personality and affecting cognition. The Clinical Resource and Audit Group (CRAG) for Mental Illness launched the largest enquiry into the use of NMD in the UK, concluding that 'subject to existing and recommended additional safeguards and procedures, neurosurgery for mental disorder should continue to be available in Scotland, but only as a treatment for intractable obsessive–compulsive disorder and affective disorders (e.g., major depressive illness)' (CRAG Working Group on Mental Illness 1996). The Mental Health Act 1983 mandates that for neurosurgery patients must have capacity to provide sustained informed consent and also that a statutory second opinion must be provided by a three-person team, two of whom are not medical and whose role is to confirm that the patient is capacitous and consenting, as well as a second opinion appointed doctor (SOAD) (Zigmond 2016).

The neurosurgical procedures

ACING

Anterior cingulotomy (ACING) involves the placement of bilateral lesions in the anterior cingulate cortex (ACC) under stereotactic guidance (Fig. 1). Steele et al studied eight patients who underwent ACING (six for severe depression without psychotic symptoms, one for severe depression with psychotic symptoms and one for recurrent depressive disorder) and found that at 12 months two patients met criteria for response and three met criteria for remission based on improvement in Hamilton Rating Scale for Depression (HRSD) scores (Steele 2008). This scale considers activities of daily living ('work and activities') as well as mood, suicidality and other symptoms, such as insomnia. Of the remaining three patients, two had a clinically insignificant decrease in HRSD score and one had an increased HRSD score.

The study also found that a superior clinical response at 1 year was associated with lesions that were more anteriorly placed and, unexpectedly, of smaller volume. Importantly, there were no significant differences found between scores at baseline and 12-month follow-up for cognitive functioning (IQ) and verbal fluency (Steele 2008).

Regarding refractory obsessive–compulsive disorder (OCD), Sheth et al studied 64 patients who had undergone cingulotomy between 1989 and 2009 (Sheth 2013). Of these 64 individuals, 34 had had cingulotomy with no other subsequent procedure, and of these, 15 had achieved a full response and a further 3 showed a partial response at the first follow-up. On average there was a 36% reduction on the Yale–Brown Obsessive Compulsive Scale in the ACING-only group.

Importantly, of the 24/64 patients with either a full or partial response at initial follow-up, 83% (20) retained at least a partial response by their most recent follow-up (at a mean of 63.8 months) (Sheth 2013), arguing against any benefit being attributable to the placebo effect (known to be large with surgery (Wartolowska 2014)) and showcasing the durability of this treatment method.

The Dundee Advanced Interventions Service is currently the only centre in the UK that regularly provides NMD using ACING.

ACAPS

Anterior capsulotomy (ACAPS) is the only ablative neurosurgical procedure performed in England and Wales for intractable psychiatric illness. Originally described by Talairach in 1949 (Harary 2019), ACAPS places lesions in the anterior limb of the internal capsule, the large white matter bundle connecting the ACC with the thalamus, hippocampus and amygdala. ACAPS lesions are generated by the thermal effects of a radiofrequency current or focal irradiation (Christmas 2010). Between 2005 and 2009, the Mental Health Commission approved seven such interventions, which were performed at the University Hospital of Wales in Cardiff (Christmas 2010). In Dundee, ACAPS was abandoned in favour of the ACING procedure because of early reports of adverse effects with ACAPS for OCD and anxiety disorders, many coming from Sweden (Christmas 2010). A historic study involved 19 patients with mental disorders treated by thermal ACAPS, 74% (14) of whom were described as showing 'permanent improvement'; however, permanent side-effects were also experienced by 79% of patients, although these were described as predominantly mild (Herner 1961). Christmas et al studied 20 patients treated with thermal ACAPS in Dundee between 1992 and 1999 for chronic treatment-refractory major depression (Christmas 2010). Patients were reassessed at a mean follow-up of 7.0 years (s.d. = 3.4), with 50% being 'responders' and 10% (i.e. 2) having 'deteriorated' in terms of their depressive disorder. This is a significant rate of improvement, considering that these individuals were at the extreme end of the treatment-resistant depression spectrum; for example, 50% of the participants had had ≥4 courses of electroconvulsive therapy (ECT) during the presenting major depressive episode. Of note, cognitive and personality tests at long-term follow-up were reported as not significantly different from preoperative levels.

Regarding refractory OCD, a meta-analysis of all published reports on ACAPS for OCD (five studies, $n = 50$ participants) found a mean full response rate of 54% at follow-up (Brown 2016); the rate of serious or permanent adverse effects was 21.4% across studies, with seven cases (all from the study by Rück et al (2008)) of clinically significant dysfunction in executive function, apathy and disinhibition.

Issues regarding effectiveness

The numbers of patients in these studies are, unsurprisingly, small, reflecting the fact that ablative NMD is utilised as a procedure of last resort. Further studies, particularly larger ones, are therefore required to confirm these findings; however, complicating this, surgical practice (e.g. ablative procedure type and ablation method/tool) varies considerably from centre to centre as well as from patient to patient. We mentioned above that changing the lesion placement and volume may be key determinants of clinical outcome (Steele 2008). Additionally, variation regarding patient inclusion and exclusion criteria (e.g. inclusion of individuals with personality disorder and other comorbidities) further confounds comparison of reports between centres. Moreover, what makes a procedure attractive is how it compares with existing alternatives, in particular, how ACING and ACAPS compare with non-ablative procedures such as vagal nerve stimulation (VNS) or deep brain stimulation (DBS). However, even in this regard, comparison is difficult, as patients with, for example, OCD or depression, may be offered ACAPS if DBS proved unsuccessful (Christmas 2010), meaning that their illness is in fact more refractory than for the cohort receiving DBS. There are no head-to-head trials comparing DBS and ablative surgeries for OCD (Arumugham 2019). Obviously, an advantage of DBS over ablative NMD is its reversibility, but DBS is much more costly and although both procedures share the common complications of surgery, there are also complications specific to DBS, for example intracerebral haemorrhage with repositioning or removal of implanted electrodes. Recent development of non-invasive stereotactic (Gamma Knife®) radiosurgery (Lopes 2014) means that the incidence of such adverse effects with NMD might diminish in the future. Furthermore, as well as safety, the success of NMD will likely improve as it becomes possible to identify targets based on a specific patient's brain connectome (van den Heuvel 2019) as

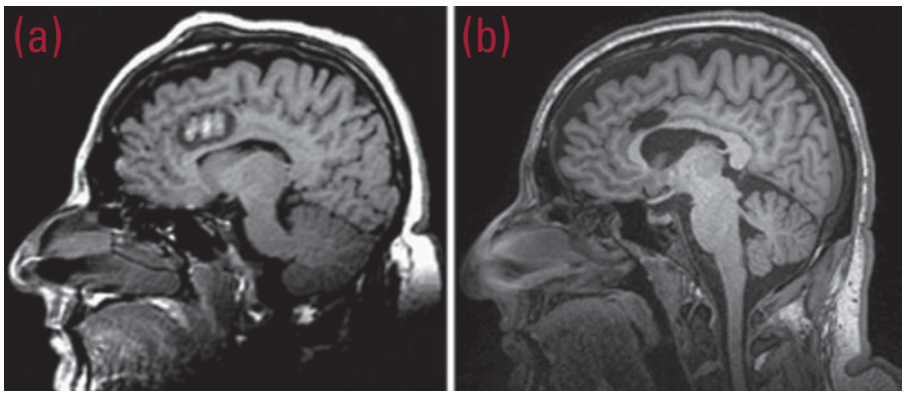

FIG 1 Para-sagittal T_1-weighted magnetic resonance imaging of the left hemisphere, showing the anterior cingulotomy (ACING) lesions on (a) post-operative day 1 and (b) 78 months later. This patient had a 'triple' dorsal anterior cingulotomy, meaning three pairs of lesions were made in a single procedure. Reproduced with permission from Sheth et al (2013); © 2013 American Association of Neurological Surgeons.

these inter-individual differences may partly account for the person-to-person variation in outcomes. Importantly, while NMD may reduce symptom severity in depression or OCD, pharmacological therapy is still needed alongside NMD.

Moreover, although we have earlier stated that ablative procedures may be a promising form of treatment, for non-ablative NMD, particularly DBS, the data on treating depression have been uncertain. A recent multicentre randomised sham-controlled trial was halted early because of the lack of statistically significant antidepressant response to active subcallosal cingulate DBS at the *a priori* 6-month time point (Cromwell 2019); it also remains unclear whether benefits are sustained after stimulation is discontinued.

We next discuss the role of the ACC in cognition and why its lesions or lesions to its connections with the hippocampus, amygdala or thalamus can have a therapeutic effect on refractory depressive disorder and OCD.

The anterior cingulate cortex

The ACC receives input from the orbitofrontal cortex (OFC), an area which processes the value of stimuli ('reward' or 'pleasure'/hedonic value), and its damage can have a variety of effects. Lesions of the ACC in rats impair their ability to take account of the costs of actions (Rushworth 2004). Functional magnetic resonance imaging (fMRI) studies in humans (Fig. 2) indicate that activity in regions of the ACC correlates with subjective pleasantness/unpleasantness of a stimulus (such as odour, labelled in Fig. 2 as 3–10) (Rolls 2019).

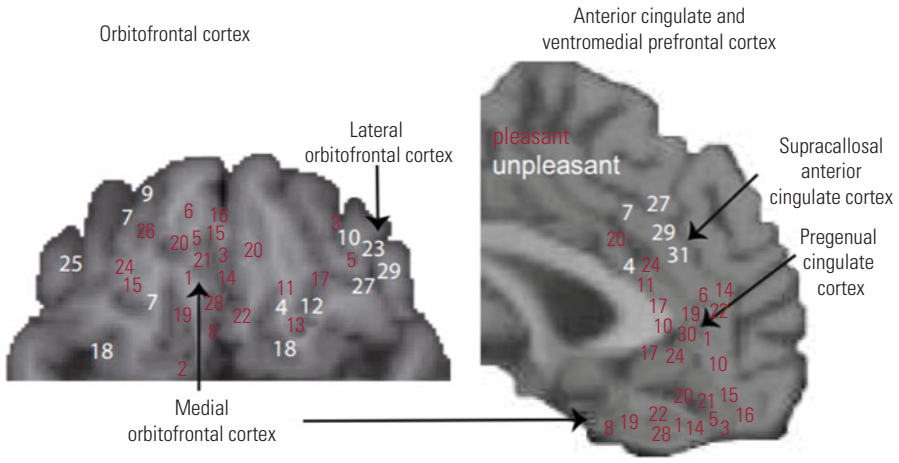

FIG 2 Functional magnetic resonance imaging maps of subjective pleasure ('hedonic tone' or 'liking') in the orbitofrontal cortex (ventral view, left) and the anterior cingulate cortex (sagittal view, right). Numbers in red indicate sites where activations correlate with subjective pleasantness and those in white indicate sites where activations correlate with subjective unpleasantness. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) from Rolls (2019).

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Damage to the ACC in humans has been noted to influence the subjective experience of emotions. For example, one study (Hornak 2003) looked at patients who had had selective surgical lesions, including lesions of the anterior ventral part of the ACC and/or medial prefrontal cortex (Brodmann area 9, BA9), for a variety of medical reasons, including tumours and epilepsy. Participants were asked on a questionnaire whether, since the surgery, they had had a change in either the intensity or the frequency of their experience of emotions that featured in two (one facial and one vocal) expression identification tests. Hypersensitivity to sad events was reported by seven out of ten patients whose lesions included the medial BA9/ACC region, and several of these individuals described themselves as having become far more 'emotional' compared with before surgery. Five individuals reported that both sadness and happiness had increased in intensity and frequency, suggesting that lesions in medial BA9/ACC regions can exaggerate both positive and negative affective responses.

ACC damage can also produce impoverished action generation in the presence of normal motor ability – individuals with such lesions can show akinetic mutism, leading to the proposal that the ACC has a primary role in motivating or 'energising' behaviour (Holroyd 2012). There are models that variously relate the ACC to several different functions, including conflict monitoring, reward processing, action selection and decision-making. However, damage to the ACC mostly spares performance on tasks that exercise these functions, but as stated above, it leads to impoverished action generation. Trying to offer a unifying model, Holroyd & McClure (Holroyd 2015) have proposed a rostral/caudal model of the ACC, the hierarchical reinforcement learning (HRL) ACC model, where mid-level modules associated with a caudal region of the ACC select tasks for execution and apply control signals that attenuate effort-related costs incurred by an action selection mechanism in the striatum. Conversely, high-level modules located in the rostral ACC select the 'meta-task' for execution and apply a control signal over the caudal ACC that attenuates effortful costs incurred in task switching, facilitating shifts between different task strategies (Holroyd 2015). According to this model, the role of the ACC in rodent model foraging relates to increased control by caudal ACC for exploiting a current patch versus increased control by rostral ACC for switching to alternative patches.

Location of the anterior cingulotomy lesion

The optimal location and volume of ACING lesions are not known. Interestingly, the rostral ACC has been identified in neuroimaging studies as the region of the ACC most affected in people with depressive illness (Ebmeier 2006) and there is evidence that rostral ACING lesions placed within this region are more therapeutically effective (Steele 2008) (Fig. 3).

Notably, Boccard et al (Boccard 2014) have described the efficacy of DBS targeting the rostral aspect of the dorsal ACC in the treatment of chronic pain refractory to medical treatment; this led them to suggest that this area is key in conferring emotional valence to pain. According to Holroyd & McClure (Holroyd 2015), lesions placed more anteriorly in rodents damage higher level modules implicated in task switching. It has previously been reported that patients treated with ACING and/or ACAPS exhibit a general impairment in accuracy of recognition of dynamic emotional displays (i.e. a changing processing task involving identifying the key emotion portrayed in each video in a set of 28 clips) compared with healthy, never-depressed controls (Ridout 2007). There were three groups in the study: neurosurgery-treated and non-depressed following treatment ($n = 4$); neurosurgery-treated and still depressed ($n = 5$); and never-depressed healthy controls ($n = 20$). Both neurosurgery-treated groups were significantly impaired in recognition of emotions compared with the healthy controls, but there was no significant difference between the treated groups (Ridout 2007). This would suggest that the surgery itself leads to this neurocognitive problem. However, it also suggests that creating this impairment in emotion recognition is not therapeutic for all patients with depression, who present with different constellations of symptoms.

It is possible that rostral lesions within the ACC can affect task switching in emotional processing as well as task switching in the motor domain. As regards subjective emotional processing, such lesions could be reversing the fixed ambivalence, loss of interest or pleasure and feelings of worthlessness characteristic of a depressive episode. The change in motor task switching could be reversing the slowing of thought and motor activity as well as the reduced ability to concentrate or the indecisiveness shown by severely depressed people.

Profiling NMD patients

Psychopathological profile

Although the data regarding outcomes of anterior cingulate NMD for refractory depressive episodes and OCD are encouraging, as discussed above, considering the extreme treatment resistance of the disorders affecting the patients receiving the surgery, questions remain from both a basic neuroscience

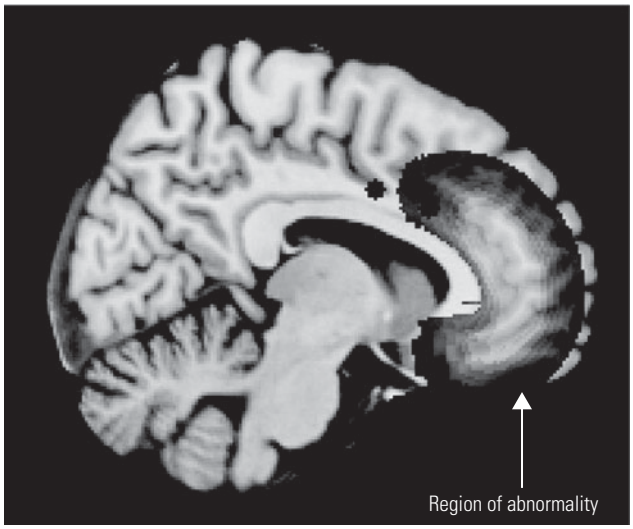

FIG 3 The location of anterior cingulotomy (ACING) lesions in a cohort of individuals with major depression. The kidney-shaped region indicates finding of abnormality on neuroimaging in the medial prefrontal region in individuals with clinical depression; the two black stars show the most anterior and posterior ACING lesion locations in the cohort. The more therapeutically effective anterior ACING lesions lie within the region reported to be abnormal; the more ineffective posterior lesions do not. Reproduced with permission from Steele et al (2008); © 2008 Society of Biological Psychiatry.

and a clinical perspective. One issue refers to the clinical heterogeneity of depressive symptoms. For example, it is unclear whether NMD is particularly effective in reducing the intensity of certain depressive symptoms (e.g. anhedonia, psychomotor retardation, hopeless or worthlessness). It is also unclear whether specific locations of the lesion could be associated with the amelioration of specific symptoms. Clearly, a granular characterisation pre-surgery and post-surgery would allow us to start answering these questions. The same issue is relevant to refractory obsessive–compulsive symptoms, also heterogeneous in nature. For example, are certain anterior cingulate lesions more effective in reducing the intensity of obsessions (a purely ideational phenomenon) or compulsions (an observable behavioural phenomenon) or both? Again, more granular descriptions of the OCD symptoms would allow us to consider answers to these questions.

Although we focus here on ablative procedures, we would recommend as further reading the work of Goodman et al (2020), who consider DBS targeting the ventral anterior limb of the internal capsule in patients with severe and intractable OCD with reference to various features, including mood, energy and anxiety.

Neuropsychological profile

Another issue is that ACING and ACAPS disturb the function of the frontal lobes, a large and heterogeneous area of the human brain, whose dysfunction or damage can have both a neuropsychological as well as a psychosocial impact. Would it be possible to establish a neuropsychological and psychosocial signature associated with damage to the rostral areas of the anterior cingulate? Would it be possible to distinguish an effective neurosurgical intervention from one that risks inducing features of a frontal lobe/dysexecutive syndrome? For example, Brown et al's meta-analysis described seven cases with a clinically significant dysfunction in executive function as well as apathy and disinhibition (Brown 2016). In contrast, Steele et al found that in patients who had received ACING, 'there were no significant differences between scores at baseline and at 12-month follow-up for intelligence quotient (IQ) and verbal fluency' (Steele 2008). Similarly, Christmas et al reported that the neurocognitive and personality outcomes at long-term follow-up were not significantly different from pre-operative baseline, even with a suggestion of a trend towards improved executive functioning (Christmas 2010). When frontal lobe lesions are discussed, there is often reference to historical cases such as Phineas Gage (Damasio 1994), characterised by disorganisation, aggression and irritability. However, this is not always the outcome; notably, patients who historically had 'lobotomies' (interventions aimed at damaging connections within the frontal lobe) were often described as 'quiet, placid' (Nijensohn 2015). Some case reports have noted that acquired brain injury can ameliorate symptoms of mental illness while grossly preserving cognition. Take for example the case of a patient with OCD who experienced a left frontal lobe injury due to a self-inflicted gunshot wound (Solyom 1987). This individual showed a significant improvement in OCD

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symptoms (based on Leyton Obsessive Inventory scores) which was maintained at 2-year follow-up and preservation of IQ when comparing pre- and post-lesion Weschler Adult Intelligence Scale scores. Although admittedly he had a marked impairment in performance on the Controlled Oral Word Association Test (sensitive to left frontal lobe lesion), as regards personality, there was no new disinhibition or amotivation. As to the exact region affected, a computed tomography head scan showed bullet fragmentation along a path through the splenium of the corpus callosum.

We would suggest that the questions posed in the previous paragraph can only be answered with a more comprehensive and sensitive neuropsychological characterisation of patients before and after the neurosurgical procedure. Standardised test batteries such as the Behavioural Assessment of the Dysexecutive Syndrome (BADS) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) have been utilised only occasionally. For example, Christmas et al found significant differences in the Intra-Extra Dimensional Set Shift (IED) task (Christmas 2010), a computerised analogue of the Wisconsin Card Sorting test and part of the CANTAB battery, suggesting that patients who had undergone ACAPS had sustained actual damage to the frontostriatal areas. The BADS or the CANTAB, along with other neuropsychological tests, would provide a detailed profile of the effect of NMD on patients' heterogeneous frontal lobe/executive functions, with the BADS having ecological validity.

Conclusions

There is evidence that supports the use of ablative NMD, both ACING and ACAPS, for the treatment of capacitous individuals who can consent to the intervention and who suffer from an extremely treatment-resistant depressive or obsessive–compulsive disorder. A comprehensive and detailed assessment and characterisation of patients undergoing NMD is required to understand its mechanism of action, to minimise irreversible side-effects and to contribute to a better understanding of the role of the ACC in human cognition. A better evidence base will require the use of standardised psychopathological instruments to characterise mental symptoms as well as standardised cognitive tests and psychosocial assessment of social, familial and occupational performance (including third-party information), both before and after the neurosurgical procedures. Once this information is obtained, correlations between neurobiological and psychosocial variables will be possible, using cluster analysis, multidimensional scaling or factor analysis, correlating the location of the lesion, the clinical response and the neuropsychological effects of neurosurgery for refractory mental disorders.

MCQ answers
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Author contributions

Both authors contributed to the conception of the work, the analysis and interpretation of data, drafting and revising the manuscript and approving the final version; and both are accountable for the accuracy and integrity of the manuscript.

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Declaration of interest

None.

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MCQs

1 Indications for neurosurgery include:

a severe substance use disorder
b refractory depressive disorder
c treatment-resistant schizophrenia
d borderline personality disorder
e none of the above.

2 The Mental Health Act mandates that for neurosurgery, patients must have:

a capacity to provide sustained informed consent
b a statutory opinion provided by two persons who are not medical and whose role is to confirm that the patient is capacitous and consenting
c a statutory second opinion provided by a second opinion appointed doctor (SOAD)
d b and c
e a and b and c.

3 The neurosurgical procedures currently used for refractory depressive episodes are:

a posterior cingulotomy
b posterior capsulotomy
c anterior cingulotomy
d right pallidotomy
e left thalamotomy.

4 Regarding the location of the anterior cingulotomy lesion:

a neuroimaging studies have shown that the rostral anterior cingulate cortex (ACC) is the region of the ACC most affected in depressive illness
b lesions in the posterior ACC are more therapeutically effective
c neuroimaging studies have shown that the rostral ACC is the region of the ACC most affected in OCD
d all of the above are true
e none of the above is true.

5 Regarding the assessment of people who have neurosurgery for mental disorders:

a follow-up of a year post-surgery is adequate
b a brief cognitive assessment before and after surgery is enough
c a detailed and comprehensive psychopathological and functional assessment is unnecessary
d a standardised psychiatric, neuropsychological and social assessment should be administered before and after the surgical procedure, with very long-term regular follow-up
e none of the above is true.