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Neuropsychiatric thalamocortical dysrhythmia: surgical implications

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Neuropsychiatric surgery has had a long and complex history with examples of less than optimal surgical procedures implemented in wrong settings. Such past errors have raised important philosophic and ethical issues that remain with us for good reasons. Nevertheless, the existence of enormous suffering as a result of chronic therapy-resistant disabling neuropsychiatric disorders compels a search for alternative surgical approaches based on a sound understanding of the underlying physiopathologic mechanisms. We bring evidence from single cell physiology and magnetoencephalography for the existence of a set of neuropsychiatric disorders characterized by localized and protracted low-frequency spontaneous recurrent activation of the thalamocortical system. This condition, labeled thalamocortical dysrhythmia (TCD), underlies certain chronic psychotic, affective, and anxiety disorders as well as obsessive-compulsive disorder (OCD) and impulse control disorder (ICD). Considering the central role of recurrent oscillatory thalamocortical properties in the generation of normal hemispheric functions, we propose a surgical approach that provides re-establishment of normal thalamocortical oscillations without reduction of cortical tissue and its specific thalamic connectivity. It consists of small, strategically placed, pallidal and medial thalamic lesions that serve to make subcritical the increased low-frequency thalamocortical recurrent network activity. This result is attained via reduction of both thalamic overinhibition and low-frequency oversynchronization. Thalamic disinhibition is obtained by a lesion in the anterior medial paralimbic pallidum. The medial thalamic lesion is localized in the posterior part of the central lateral nucleus (CLN), where most cells have been shown to be locked in low-frequency production and to have lost their normal activation patterns. We present here our experience with 11 patients, including clinical follow-ups and pre- and post-surgical magnetoencephalographic (MEG) studies. The evidence speaks for a benign and efficient surgical approach and for the relevance of the patient's presurgical cognitive and social settings, making them more or less prone to postoperative psychoreactive manifestations on rekindling of personal goals and social re-entry.

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After the questionable and inordinately wide application of the prefrontal lobotomy [1,2] in the first half of the twentieth century, many groups realized the necessity of confining surgical interventions to the paralimbic (or mesocortical) domain [3]. This gave rise to the three main stereotactic operations still in use today in view of their efficiency and limited side effects: (1) the anterior cingulotomy [4], (2) the subcaudate tractotomy [5], and (3) the anterior capsulotomy [6]. These three procedures entail an interruption of the thalamocortical paralimbic frontal network. Such surgical approaches have been efficient against major depression and OCD but not against psychosis. Early on, however, Spiegel and Wycis [7] explored the possibilities of stereotactic interventions in the mediodorsal nucleus of the thalamus and described positive results in psychotic patients.

There are both older and more recent data demonstrating the physiopathologic and histologic involvement of paralimbic cortical areas and their corresponding specific thalamic partner, the mediodorsal nucleus, in the generation of the neuropsychiatric disorders. Indeed, electroencephalographic (EEG) [8–12], positron emission tomographic (PET) [13,14], histologic [15,16], and radiologic [16] studies indicate spiking activities, increased low frequencies, and hypometabolism as well as histopathologic and MRI changes in these domains.

Our surgical approach is based on two premises: the central role of the oscillatory thalamocortical properties in the generation of normal hemispheric functions [17] and the existence as a physiopathologic basis to neuropsychiatric disorders of a TCD as evidenced by thalamic single cell recordings [18,19] and magnetoencephalography [20–23] and characterized by increased low-frequency generation. In this context, we elected to normalize low-frequency production without affecting the anatomic integrity of the functional cognitive thalamocortical network.

The goal of this article is to describe this approach at the surgical, clinical, and MEG levels.

Methods

Patient group

All patients (n = 11) suffered from chronic therapy-resistant neuropsychiatric disorders, including at least one, and often several, of the following clinical manifestations: (1) psychotic hallucinatory/delusional disorder (4 patients), (2) OCD (8 patients), (3) major (or endogenous) depression (7 patients) or bipolar mood disorder (2 patients), (4) anxiety disorder (7 patients), and (5) ICD (4 patients). We believe that the presence of a high percentage of complex atypical neuropsychiatric syndromes is a result of the fact that these patients exhibited particularly resistant disease forms related to widespread and strong TCD mechanisms and were thus at the forefront in terms of surgical indication. Available drug treatments were used without success in all of them, and electroconvulsive therapy (ECT) was applied in four patients before they were referred to us. In addition, three patients came to us after prior unsuccessful interventions. One of them had a gamma knife capsulotomy, the second had a gamma knife thalamotomy, and the third had a vagal nerve stimulator. The patients, seven men and four women, ranged in age between 21 and 59 years (with a mean age of 35 years) at the time of the first surgery. The duration of the disease before the first surgery ranged between 6 and 21 years, with a mean of 15 years. Postoperative relief percentages were given by the patients themselves.

Surgical strategy

We have applied the following criteria for surgical indication: (1) a protracted evolution of the disease (many years), (2) resistance to pharmacologic and other conservative therapies, and (3) a major impact of the symptoms on the patient's quality of life.

Two surgical targets have been developed, the central lateral thalamotomy (CLT) and the anterior medial pallidotomy (AMP). The CLT targets the posterior part of the CLN, and its stereotactic coordinates are located anteroposteriorly 2 mm posterior to the posterior commissure, mediolaterally 6 mm lateral to the border of the third ventricle, and dorsoventrally at the level of the intercommissural plane. The target is reached using an anteroposterior angle of 60° and a mediolateral angle of 5° to 10°. The CLT lesion measures 4 mm in diameter over 12 to 14 mm in length.

The AMP, as its name implies, targets the paralimbic anterior and medial pallidum, and its stereotactic coordinates are located anteroposteriorly 4 mm posterior to the anterior commissure, mediolaterally 12 mm lateral to the ventricular border, and dorsoventrally 2 mm ventral to the intercommissural plane. It is reached using an anteroposterior angle of 55° and a mediolateral

angle of 20°. The AMP lesion measures 4 mm in diameter over 6 mm in length.

Physiologic confirmation of target localizations within given geometric confines is provided by microelectrode recording (Fig. 1) as well as by macrostimulation. Figure 2 displays the CLT and AMP lesions as seen on our stereotactic atlas [24] and MRI.

The general surgical goal was a bilateral coupling of CLT and AMP. We report on five patients with such full surgical treatment, two patients operated on only on one side on the basis of the discovery of a unilateral thalamic causal lesion (and, in the absence of evidence to the contrary, considered fully treated), two patients partly operated on (the first with a left CLT/AMP and the other with a bilateral CLT), and two parkinsonian patients displaying endogenous neuropsychiatric manifestations (anxiodepressive episodes and ICD plus depression) and treated by a unilateral AMP.

Magnetoencephalography

Pre- and postoperative MEG recordings were performed in three patients. Analyses included power spectra and coherence studies [20,21] as well as magnetic source imaging.

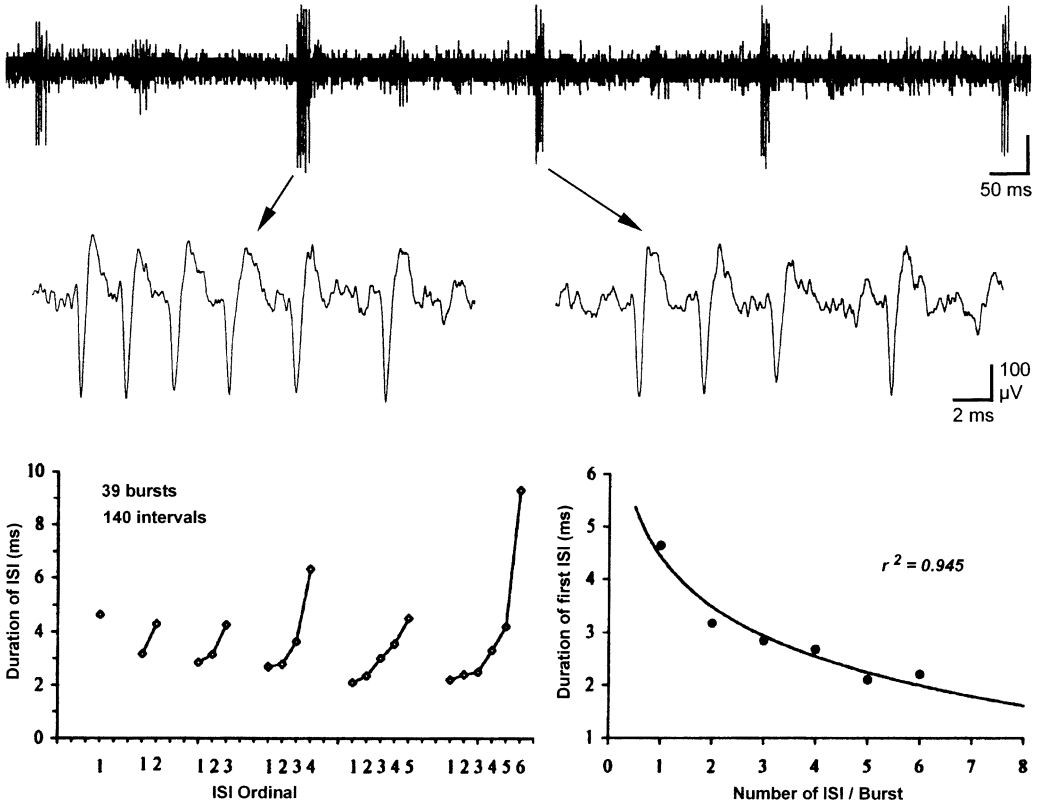


Fig. 1. Example of a unit activity recorded in the posterior part of the central lateral nucleus of the thalamus. Upper row: the discharge is composed of a series of recurring bursts of action potentials at a frequency of 3.3 Hz. Two of these bursts are shown using a faster time scale, revealing their intrinsic characteristics. Note that (1) the interspike interval (ISI) within a burst increases with each successive interval and that (2) the shorter the first ISI is in a burst, the larger is the number of spikes within this burst. These features are quantified in the two lower histograms. On the left, plotting of the duration of ISIs as a function of their position within the burst illustrates the progressive lengthening of successive intervals within bursts composed of an increasing number of action potentials. On the right, the duration of the first ISI in a burst shows a tight inverse relation to the number of following spikes within this burst (fitting with a logarithmic function). All these properties indicate that these bursts are the consequence of the deinactivation of calcium T-channels as a result of cell membrane hyperpolarization, the so-called low-threshold calcium spike bursts.

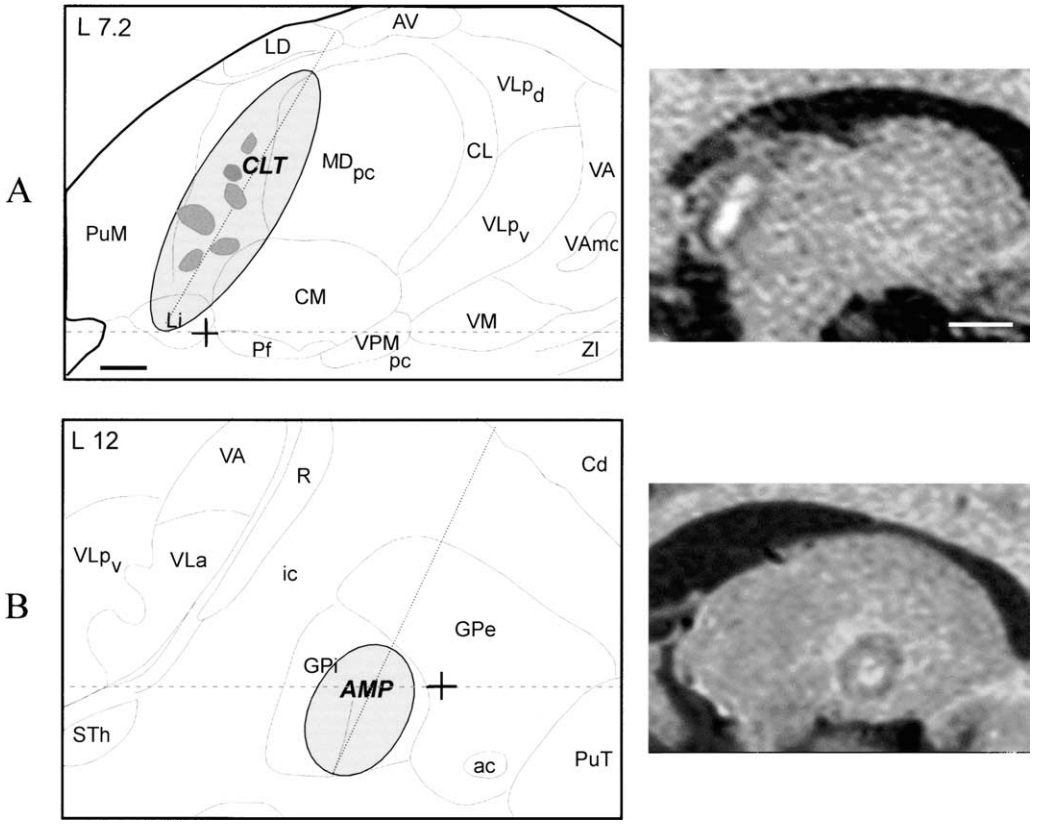


Fig. 2. Sagittal atlas projections (left column) and 2-day postoperative T1-weighted MRI images (right column) of central lateral thalamotomy (A) and anterior medial pallidotomy (B) lesions. The coordinates of atlas sections are 7.2 mm (A) and 12 mm (B) lateral to the ventricular border, and the crosses indicate the position of the posterior (A) and anterior (B) commissures. In both series, sections are oriented with posterior to the left and the intercommissural plane (represented by an interrupted line in the left panels) horizontal. The lesions represented in atlas sections do not include the edematous area seen on MRI. Stippled areas in the central lateral nucleus represent densocellular clusters. ac = anterior commissure; AV = anteroventral nucleus; Cd = caudate nucleus; CL = central lateral nucleus; CM = centre médian nucleus; LD = lateral dorsal nucleus; Li = limitans nucleus; GPi,e = internal and external pallidum; MDpc = mediodorsal nucleus, parvocellular division; Pf = parafascicular nucleus; PuM = medial pulvinar; PuT = putamen; R = reticular nucleus; STh = subthalamic nucleus; VA = ventral anterior nucleus; Vamc = magnocellular division of VA; VLp(d,v) = ventral lateral posterior nucleus, dorsal and ventral divisions; Vla = ventral lateral anterior nucleus; VM = ventral medial nucleus; VPMpc = ventral posterior medial nucleus, parvocellular division; ZI = zona incerta. Scale bars: 2 mm in atlas and 10 mm in MRI.

A whole-head, 148-channel, MEG system (4D Neuroimaging, San Diego, CA) was used for all patients. Spontaneous brain activity was continuously recorded for 5 minutes while the patient reclined and was asked to stay alert with eyes closed or eyes open. The bandpass was 0.1 to 100 Hz, and the sample rate was 508 Hz. The electrocardiogram was simultaneously recorded digitally for off-line heartbeat artifact rejection. Spectral analysis of 5-second windows using the multitaper technique and cross-correlation between spectral amplitudes at different frequencies was performed with in-house software and commercial Matlab 6 (Mathworks, Natick, MA) on a Linux (Red Hat, Raleigh, NC) cluster computer system. Artifacts emanating from cardiac and other distant sources were removed by the software in a channel-specific manner.

As for magnetic source imaging, the Fourier-transformed signals obtained with the multitaper method were expanded with the singular value decomposition for frequencies of interest. A complex space mode for each frequency was composed using the first five singular vectors. A

volumetric source space was constructed using the averaged MRI MNI-152 [25] provided in SPM99. Voxels with a gray matter probability higher than 0.4 were selected. This probabilistic source space was transformed onto a head-centered coordinate system and scaled. The lead field operator was computed using a spherically symmetric volume conductor model. Inverse source imaging of the space modes at frequencies of interest were computed using a recursively weighted minimum-norm algorithm [26]. Noise reduction was performed with Tikhonov regularization using the generalized cross-validation criterion. The current density solutions were smoothed with a three-dimensional gaussian kernel. For visualization, smoothed solutions were linearly interpolated onto the tessellated cortical surfaces of a sealed MRI previously segmented using Free Surfer [27].

Results

Patient descriptions

Patient 1, born in 1970, experienced a 10-year history of a complex neuropsychiatric syndrome, including schizoaffective (delusions and bipolar disorder) and anxiety disorders as well as ICD and OCD. He underwent surgery on the left side only on the basis of the discovery of a small, vascular, probably developmental, inactive abnormality in his left mediodorsal thalamic nucleus. At a follow-up of 1 year after the left-sided CLT/AMP, he presents with 100% relief of the schizoaffective, OCD, and ICD symptomatology but with only 50% relief of his anxiety and hyperactivity. His global improvement estimation is 60%. His drug intake could be markedly reduced. He experienced only one reactive depressive episode in the postoperative phase, caused by the concurrence of multiple acute mental stressors, from which he fully recovered over a few weeks. Independence level and daily activities have increased significantly. His clinical improvements correlate with the MEG recordings shown in Figure 3 before and 1 year after surgery.

Patient 2, born in 1957, had a 20-year history of a schizoaffective disorder characterized by delusional, hallucinatory, and affective bipolar manifestations with a few ICD elements. Over a few weeks after the second CLT/AMP, he experienced progressive and then complete symptom relief, which is still present 2 years after surgery. In the interim period, he presented with two episodes of agitation, anxiety, confusion, and depression resulting from personal and social stressors, with activation of powerful guilt and feelings of self-insufficiency. Medication is being tapered slowly in view of its 20-year use. Figures 3 and 4 display the patient's MEG findings before and 3 months after surgery.

Patient 3, born in 1956, suffered from a 14-year syndrome characterized by the coupling of an OCD with major depression in addition to anxiety and psychotic elements. Six years after the bilateral CLT/AMP, the patient presents with complete relief of the OCD, anxiety, major depressive, and psychotic manifestations and has redeveloped a social and professional life to a degree inconceivable before surgery. She still experiences moderate to strong episodes of reactive depression based on marked insufficiency feelings, frustrating/disappointing confrontations, and unfulfilled personal wishes.

Patient 4, born in 1980, was affected for 14 years by a complex syndrome with OCD and ICD as well as anxiety and psychotic disorders. At the follow-up 6 months after the bilateral CLT/AMP and with a significant drug reduction, there is relief of the psychotic elements, at least a 50% reduction of the OCD, and only moderate improvement of the anxiety and ICD. Although the patient could never conduct social interaction for more than a few minutes before surgery, after surgery, he can have hour-long discussions with members of the team. Anxiety and impulse control problems are centered on year-long difficulties in social and familial interactions.

Patient 5, born in 1971, suffered from an OCD associated with outspoken vegetative manifestations (ie, sweating, daily vomiting) and anxiety for 6 years before surgery. At a follow-up 2 years after the bilateral CLT/AMP, he enjoys complete relief of his OCD symptoms. In the context of a preexistent substance use disorder, the patient is currently in a withdrawal process from benzodiazepine dependence marked by anxiety.

Patient 6, born in 1973, suffered from a 21-year OCD coupled with major depression. Immediately after the second CLT/AMP, she described complete relief of her obsessive manifestations and was shaken by the emptiness left by their disappearance. One and a half year later, she complains about obsessive ideas that she has great difficulty in describing. She shows signs of an anxiodepressive state and, only recently, motivation for psychotherapeutic treatment. The facts

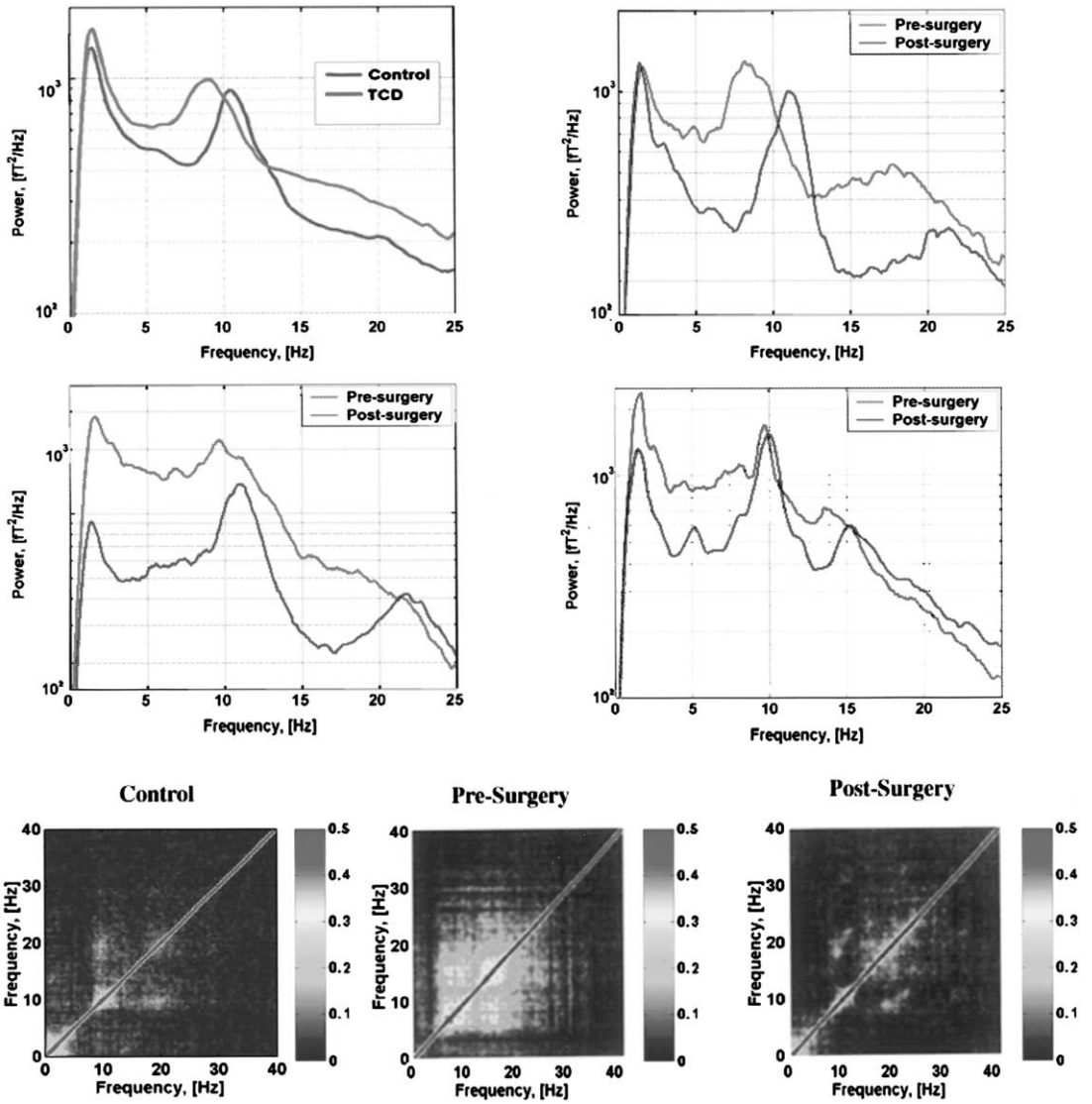


Fig. 3. Magnetoencephalographic data from three patients in this series. Power spectra (four top panels) and coherence plots (three bottom panels) are displayed. The top left panel shows the power spectra from controls (blue) and thalamocortical dysrhythmia (TCD) patients, including neuropsychiatric as well as parkinsonian, neurogenic pain, and tinnitus patients. A peak shift into the theta domain and power increase in the theta and beta bands are demonstrated for TCD patients in comparison to controls. The top right panel presents the power spectrum of Patient 2, with a postoperative (blue) curve demonstrating the reappearance of the alpha peak and the power decrease in the theta and beta bands. The postoperative power spectra of Patient 7 (middle left) and Patient 1 (middle right) are mainly characterized by a reduction in theta and beta power, allowing reappearance (Patient 7) or better visualization (Patient 1) of the alpha peak. Coherence was analyzed applying a cross-correlation analysis of the variation along time of the spectral power for frequencies between 0 and 40 Hz. The bottom left panel shows such coherence for controls, the middle panel shows coherence for Patient 2 before surgery, and the right panel shows coherence for the same patient after surgery. (See also Color Plate 1.)

that she has no memories, even as a child, of obsession-free moments and that several first-degree relatives also suffer from neuropsychiatric disorders provide a formidable barrier to adjustment of her perspective toward a disease-free existence. Given this context, a drug reduction has not yet been possible.

Patient 7, born in 1970, suffered from a 20-year neuropsychiatric syndrome characterized by obsessive, anxiety, and depressive disorders associated with anger, pain, tinnitus, and dyskinetic elements. MRI examinations showed the presence of an inactive, probably old, vascular anomaly in the left mediodorsal nucleus, which was submitted to gamma knife surgery with no change in symptomatology. Multiple ECT sessions were applied without results, and a vagal nerve stimulator brought no relief but only an increase in anxiety. A unilateral left-sided CLT/AMP (considered in principle to be sufficient, as for Patient 1) was performed. One year and a half later, the patient describes an at least 50% improvement of his OCD, 90% relief of anxiety, 70% relief of depression and pain, 20% relief of tinnitus, 80% relief of dyskinesias, but only a slight (30%) improvement of anger. The global improvement rate is 70%. The patient's evolution is colored by (1) the fear that something still may progress in his brain and jeopardize his improvements and future, and (2) the mismatch between what is/has been and what should be, associated with marked feelings of self-insufficiency. There is a clear-cut increase of independence and 60% improvement of daily activities (the patient traveled two times on his own from the Midwest to New York City and found the office of one of the authors, an activity that would have been impossible before surgery without his parents). He is presently on one antidepressant drug at a low dose only and is undergoing psychotherapy. His MEG recordings before and a year and a half after surgery correlate well with these clinical results and are shown in Figure 3.

Patient 8, born in 1970, suffered from an 18-year OCD associated with an anxiety disorder and depression. Repeated ECT and a gamma knife bilateral capsulotomy did not improve the symptomatology and may have triggered anxiodepressive manifestations. At a follow-up of 9 months after the first left-sided CLT/AMP, a differentiated result is observed, with strong improvement of one OCD element (obsessive social component) but lack of improvement of another (obsessive cleanliness). There have been variable but overall significant improvements in daily activities and independence. A second CLT/AMP is being considered.

Patient 9, born in 1971, suffered from a 13-year OCD associated with major depressive episodes. During the 2 years after the bilateral CLT, there have been fluctuating degrees of response of the OCD symptoms, ranging between 50% and 100% improvement. There were no postoperative major depressive episodes. The acute postoperative evolution was characterized by total control of the OCD symptomatology, resulting in a state of massive anxiety as a result of the emptiness after suppression of the constant obsessive ideas. The patient's spontaneous interpretation concerning the fluctuating reappearance of obsessions was that her anxiety was so severe that she herself reactivated some of them to relieve her inner tension. This psychodynamic context was complicated by the presence of an excess in self-demands so as to comply with a strict and perfectionist picture of herself. At the moment, we await complementary evidence to ascertain better the necessity of a bilateral AMP.

Patient 10, born in 1937, suffered in the context of a parkinsonian disease from a 16-year neuropsychiatric depressive disorder and ICD. For 5 years after a right-sided AMP coupled to a subthalamotomy to alleviate his motor syndrome, the patient presented with complete relief of both motor and neuropsychiatric symptoms. Recently, disease progression at both motor and neuropsychiatric levels poses the question of surgical restabilization of the other hemisphere.

Patient 11, born in 1944, suffered in the context of a parkinsonian disease from a 13-year major depressive disorder characterized by unmotivated abrupt anxiodepressive episodes. He presented 80% to100% relief of this disorder during a year and a half after a left-sided CLT/AMP coupled to a pallidothalamic tractotomy [19]. As for the previous patient, disease progression at both motor and neuropsychiatric levels raises the possibility of a right-sided intervention.

Summarizing (Table 1), all patients demonstrated significant to complete relief from their neuropsychiatric ailments. We observed the following postoperative reactive manifestations: (1) anxiety (1 patient), (2) anxiodepressive state (3 patients), (3) anxiety and nonacceptance/frustration (3 patients), and (4) frustration and depression (1 patient). A conceptual rigidity with lack of adaptation to the new situation was seen in two patients.

Table 1
Overview of patient data

Patient	Age (years)	Disease duration (years)	ECT	GK	VNS	Causal lesion	Symptoms	Operation	Relief (%)				
									PSY	DEP/BIP	OCD	ICD	ANX
1	31	10				L Thal/MD	PSY/BIP/ANX/OCD/ICD	L CLT/AMP	100	100	100	100	50
2	43	20	+				PSY/BIP/ICD	Bilateral CLT/AMP	100	100		100	
3	36	14	+				OCD/DEP/ANX/PSY	Bilateral CLT/AMP	100	100	100		100
4	21	14					OCD/ICD/ANX/PSY	Bilateral CLT/AMP	100		50	<50	<50
5	28	6					OCD/ANX	Bilateral CLT/AMP			100		0
6	27	21					OCD/DEP	Bilateral CLT/AMP		100	0		
7	30	20	+	+	+	L Thal/MD	OCD/ANX/DEP	L CLT/AMP		70	>50		90
8	31	18	+	+			OCD/ANX/DEP	L CLT/AMP			<50		
9	29	13					OCD/DEP	Bilateral CLT		100	75		
10	59	16					DEP/ICD	R AMP		100		100	
11	50	13					ANX/DEP	L CLT/AMP		90			90

Abbreviations: ECT, electroconvulsive theraphy; GK, gamma knife; VNS, vagal nerve stimulator; L, left; Thal, thalamus; MD, mediodorsal nucleus of the thalamus; R, right; CLT/AMP, central lateral thalamotomy and anterior medial pallidotomy; PSY, psychotic disorder; BIP, bipolar affective disorder; ANX, anxiety disorder; OCD, obsessive-compulsive disorder; ICD, impulse control disorder; DEP, major depression; F, frustration.

Percentages correspond to relief estimation by the patients.

Magnetoencephalographic data

Preoperative MEG recordings demonstrated a marked increase of power in the theta domain (4–8 Hz), with the presence of a variable number of identifiable peaks (see Fig. 3). In addition, there was an increase of beta power and of the coherence between the theta domain and the alpha and beta (9–13 Hz and 13–30 Hz) ranges. After surgery, we observed a clear-cut decrease in theta power down to values comparable with those of controls and the reappearance of a normal alpha peak at or above 10 Hz. There was also a reduction of beta power. Interfrequency coherence came down close to that of controls. In terms of source localization, Fig. 4 displays in Patient 2 the presence of a domain of increased theta activity (selected according to his power spectrum between 4 and 10 Hz) in the right-sided medial and lateral temporopolar, anterior parahippocampal, orbitofrontal, and basal medial prefrontal cortices. After surgery, this paralimbic theta focus disappeared. There was maintenance of well-defined bilateral mu Rolandic activity as well as discrete temporal and occipital, probably normal, slow rhythmicity. The Rolandic mu rhythm, which is considered a normal EEG component, was also described in individuals with mild to moderate anxiety, irritability, and emotional instability [28].

Discussion

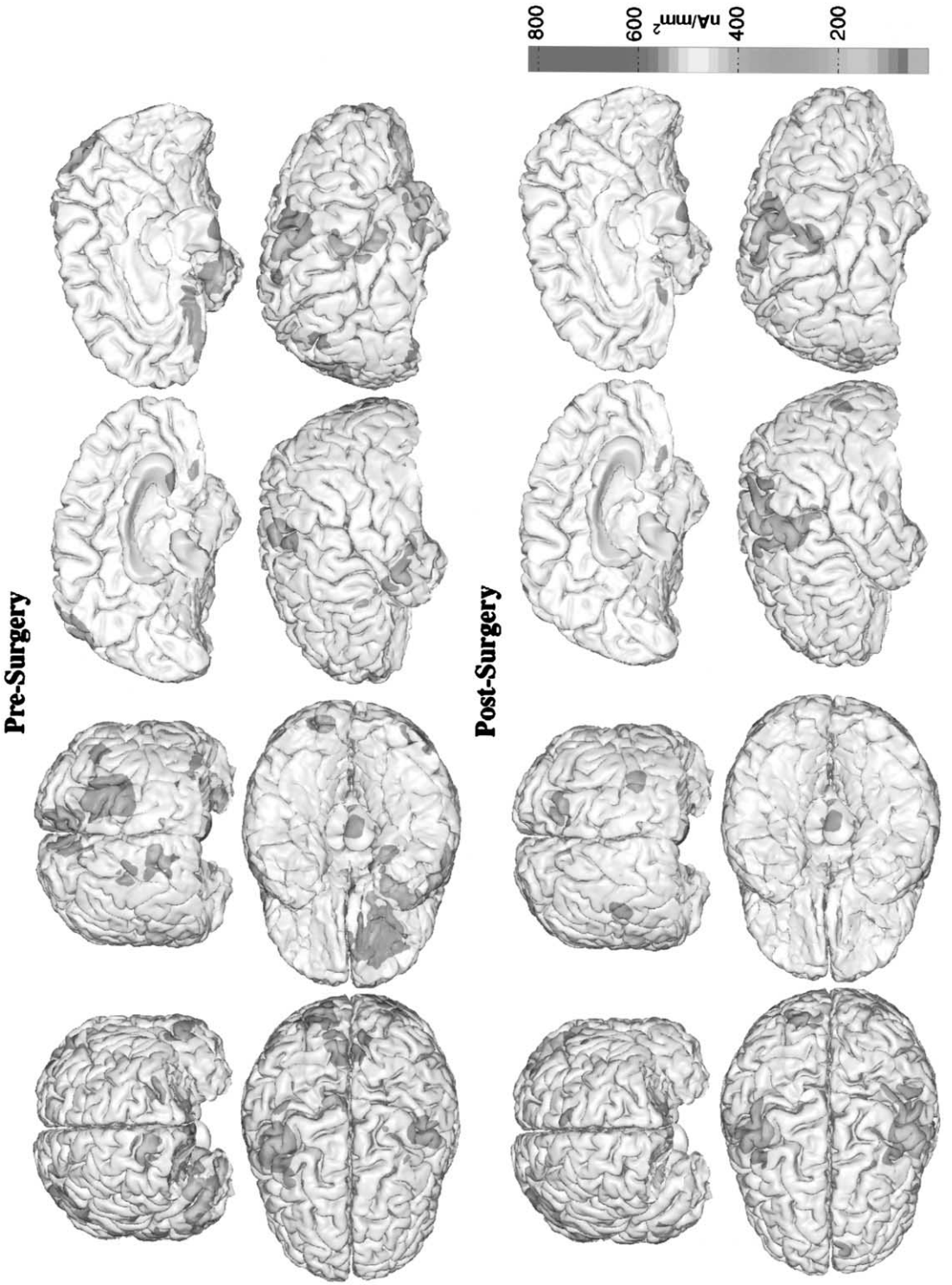
The neuropsychiatric thalamocortical dysrhythmia

Evidence is presented both at the single cell and MEG levels that a TCD, as previously defined [18–23], underlies certain of the main neuropsychiatric disorders, namely, psychotic and affective disorders as well as ICD and ICD. This TCD is characterized by the following sequential set of events (Fig. 5):

1. Hyperpolarization through disfacilitation and/or overinhibition of thalamic relay and/or reticular cells by the disease source. In psychotic disorders, such a source anomaly may be found in the paralimbic cortical domain or in the paralimbic striatum [16,29,30], with the cortical anomaly providing corticothalamic disfacilitation and the striatal anomaly providing pallidothalamic overinhibition. The possibility of the alternative triggering of a neuropsychiatric disorder by a chronic dysfunction of the cognitive network (comprising conceptual, emotional, mnestic, and attentional functions) is discussed later in this article.
2. This hyperpolarized state is the source of calcium T-channel deinactivation [31], causing the production of low-threshold calcium spike (LTS) bursts by thalamic (see Fig. 1) and/or reticular neurones.
3. Neurones in such a state impose a slow rhythmicity to the thalamocortical loops they are part of, being locked in the theta low-frequency domain by their ionic properties. Recurrent divergent corticothalamic and reticulothalamic projections back to the thalamus provide the necessary coherent diffusion of these frequencies to various related cortical areas. Our MEG recordings (see Fig. 3) indeed demonstrate increased theta power. Its existence has also been revealed by EEG studies [9,12] and may be directly correlated with cortical [14] and thalamic [13] hypometabolism in PET studies.
4. The final step in the description of this syndrome is the proposed existence of activation of high-frequency (beta and gamma) cortical domains as the result of an asymmetric corticocortical GABA-ergic collateral inhibition [20,21]. The proposed mechanism, an "edge effect" as observed in the retina as a result of lateral inhibition, would result from the asymmetric inhibition between a low-frequency cortical area and neighboring high-frequency domains, providing a ring of reduced inhibition onto, and thus activation of, the cortex surrounding this low-frequency area. Our coherence studies [20,21] support the proposition of such an edge effect, as evidenced by an increased multifrequency coherence between theta and beta domains, which is an event seen with much less prominence in the normal brain. This activation of high-frequency areas might express itself through abnormal EEG spiking activity, as demonstrated in psychotic patients [8,11].

Surgical control of the thalamocortical dysrhythmia

Considering the central role of resonant oscillatory thalamocortical properties in the generation of normal hemispheric functions, we propose a surgical approach that does not imply a reduction of functional thalamocortical loops and is based on regulation toward normality of


Pre-Surgery
Post-Surgery
800
600
400
200
nA/mm²

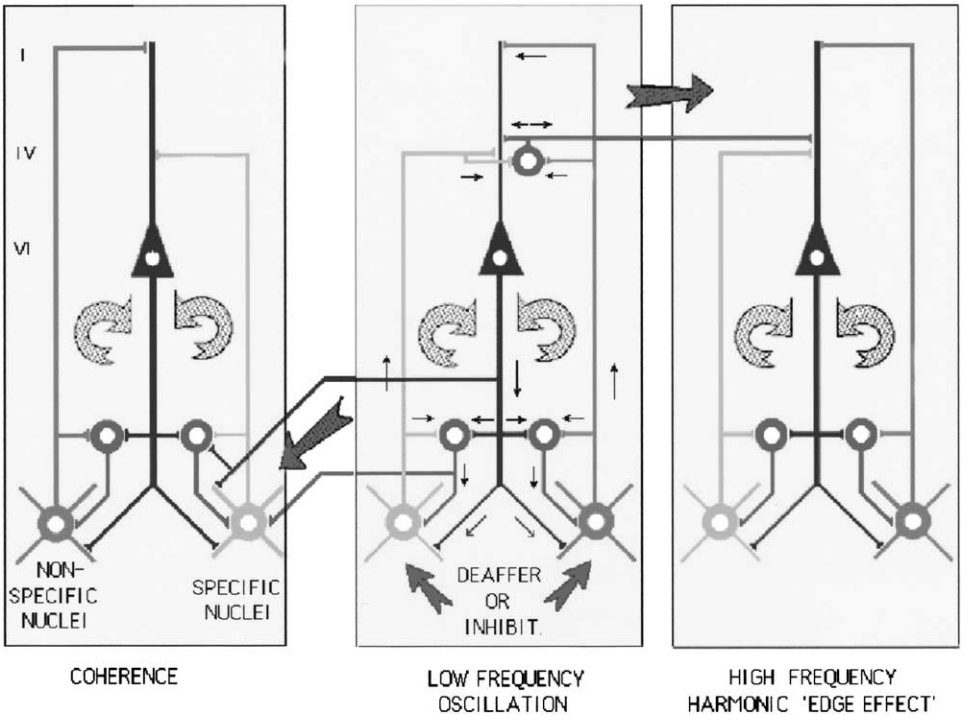


Fig. 5. Schematic diagram of the thalamocortical circuits that support the thalamocortical dysrhythmia mechanisms. Three thalamocortical modules are shown, each with its specific (yellow) and nonspecific (green) thalamic relay cell projecting to the cortex and reticular nucleus, one (blue) pyramidal cell with its corticothalamic and corticoreticular output, and two reticular cells (red) with their projections back to thalamic relay cells. Three thalamocorticothalamic loops are thus displayed, with their feed-forward thalamocortical activation and their respective recurrent feedback corticothalamic and corticoreticulothalamic activation inhibition. The conjunction of the specific and nonspecific loops is proposed to generate increased cortical activation through temporal coincidence. Either thalamic cell disfacilitation or overinhibition (central module) hyperpolarizes thalamic cell membranes. This allows the deinactivation of calcium T-channels and the generation of low-threshold calcium spike bursts, thus resulting in low-frequency thalamocortical oscillation. Divergent corticothalamic and reticulothalamic projections (from central module to left module) provide the substrate for low-frequency coherent discharge of an increasing number of thalamocortical modules. At the cortical level, low-frequency activation of corticocortical inhibitory interneurones (red), by reducing lateral inhibitory drive, results in high-frequency coherent activation of the neighboring (right) cortical module (edge effect). (See also Color Plate 3.)

dysrhythmic thalamocortical oscillations as documented by our MEG data. For this purpose, we use small pallidal and medial thalamic lesions, the goal of which is to make subcritical the increased low-frequency thalamocortical generation, in other words, to move the dynamic properties of the system away from the increased low-frequency coherent activity. The CLT has as a goal a reduction of low-frequency overamplification and oversynchronization, which can be accomplished by a carefully placed and restricted lesion in the medial thalamus. A similar if less well-defined procedure has been known as medial thalamotomy since the dawn of stereotactic neurosurgery [32]. The rationale and general results of this operation are in full accordance with long-standing electrophysiologic studies [33] demonstrating the progressive spread of the

Fig. 4. Magnetoencephalographic source localization for Patient 2. Projection of 4- to 10-Hz activity onto the patient's MRI examination before (eight top images) and after (eight bottom images) surgery. The thalamocortical dysrhythmia of this patient is localized in the right-sided paralimbic domain comprising the temporopolar, anterior parahippocampal, orbitofrontal, and basal medial prefrontal areas. This low-frequency focus disappears after surgery. (See also Color Plate 2.)

cortical recruiting response during low-frequency stimulation of the medial thalamus. In addition, the thalamic nonspecific system has been shown to serve as a temporal coincidence activator when summed with the thalamic specific input to the same cortical site [34]. We have taken advantage of physiopathologic data to focus our medial thalamotomy target on the posterior part of the CLN, where more than 95% of the cells produced spontaneous LTS bursts (see Fig. 1) and/or were unresponsive to stimuli [18]. By doing so, we restrict the lesion to the affected site and spare the other medial thalamic subnuclei, which, over time, seem to have taken over the function originally fulfilled by the CLT. This is a reasonable conjecture given the fact that patients experience no obvious reduction in sensory, motor, or cognitive abilities after CLT. The second target, the AMP, addresses the issue of reducing thalamic excess inhibition. In the case of neuropsychiatric disorders, this reduction in inhibition (or disinhibition) is attained by targeting the paralimbic anterior internal pallidum [30].

The results presented here for 11 patients unequivocally demonstrate that this surgical approach has significant therapeutic value against symptoms pertaining to psychotic, major depressive, and bipolar disorders as well as OCD and ICD. There is, however, a clear-cut limit concerning reactive, as opposed to endogenous, symptoms in the domains of anxiety, depression, and frustration. Postoperative reactive decompensations are understandable by the fact that the disinhibitory approach presented here may result in a momentary hyperactive phase during the acute postoperative period. This condition serves to emphasize the fundamental difference between the procedure described here and the other available surgical approaches, such as capsulotomies, cingulotomies, and subcaudate tractotomies, in which the goal is a reduction of cortical activity through thalamocortical disconnection.

As expected given the nature of the lesions, we did not observe permanent classical postoperative prefrontal deficits. Patient 6 presented with neuropsychologic impairments in the executive and memory domains, which were fully compatible with her anxiodepressive postoperative reactive profile [35] and happened in the context of a maintained general cognitive performance and improved general IQ. Patient 3 presented with clear-cut neuropsychologic improvements in a large number of domains, including prefrontal and perceptual functions. The neuropsychologic-sparing quality of CLT has been documented in a large group of patients suffering from other TCDs (manuscript in preparation). A future systematic study will address this issue concerning the coupling of CLT and AMP lesions. The observed patient histories already dispel the possibility of adverse postoperative prefrontal abulic manifestations or personality changes, however, and neither patients nor families complained about a personality reduction or alteration.

Thalamocortical slow burn

Evidence of progressive cortical [36] and thalamic [16] atrophy has been documented in patients suffering from neuropsychiatric disorders. This phenomenon leads to thalamocortical self-destruction. One likely mechanism for such morbidity is a persistent increase in calcium entry into the thalamic cells generating LTS bursts, which may cause long-term deleterious effects (eg, via calcium-triggered apoptosis). Furthermore, the continuous high-frequency cortical activation caused by the edge effect provides a framework for the development of excitotoxicity of cortical cells. Under these conditions, the system may fall into a self-reduction mode, a sort of "slow burn" with loss of neuronal substrate. This process serves to reinforce the TCD, however, as the level of thalamocortical and corticothalamic activation decreases and exposes thalamic cells to more disfacilitation and, consequently, to more LTS burst generation and more low-frequency production. If this is confirmed, the surgical treatment of a TCD would not only provide symptom relief and disease control but would additionally acquire a protective role.

The cognitive factor

By cognitive, we mean conceptual, emotional, mnestic, and attentional functions, which are supported by the activation of the widespread paralimbic (or mesocortical) and association networks [3] located in dorsolateral and medial prefrontal, orbitofrontal, cingulate, posterior parietal, insular, and medial temporal areas. Accumulating evidence from EEG and MEG studies underscores the fact that conceptual and mnestic [10,37–39] as well as emotional [40] activation in human beings increases low-frequency theta activity. A low-frequency increase may thus arise either on the basis of a disease-related or endogenous abnormal input to the thalamus (as the result of a micro- or macroscopic brain anomaly) or via

a "top-down" mechanism driven by mental activity and generating low frequencies on a reactive basis. This finding provides a substratum for (1) the appearance of reactive phenomena in the postoperative period, (2) the genesis of chronic reactive psychiatric disorders with a long-term unsolved mental conflict at their source, and (3) the grouping of many if not all neuropsychiatric disorders into a dynamic realm of thalamocortical dysfunction. Indeed, whether their triggering mechanism is endogenous or reactive, they may be regarded as mirroring an uninterrupted continuum of uncontrollable and thus disturbing low-frequency distortions of the cognitive network. In this sense, the loss of control that may occur in any healthy human brain during strong stimulus-bound transitory emotional reactions may be viewed as a short-lived and in this sense not unhealthy (although sometimes quite undesirable) TCD phenomenon.

Our clinical observations show that surgery can provide marked reduction or even suppression of the disease-related TCD but does not address the cognitive reactive manifestations of the patient to her/his new postoperative situation. Fear, expectations, despair, and frustration may even increase for a time after surgery, representing a powerful cognitive source for increased low-frequency activity necessitating intensive psychotherapeutic support. Our experience has shown that this situation provides a new chance to approach and solve long-standing resistant emotional conflicts by psychotherapy, however.

Such postoperative reactive manifestations are represented by anxious or anxiodepressive states and are also characterized by nonacceptance/frustration postures possibly leading to depression or by lack of adaptation to the new situation. Distinctive characteristics indicating a reactive basis to these observations are (1) symptomatology not present before surgery in relation to the new postoperative situation (eg, Patient 9), (2) large variations across time and according to situations (eg, Patients 4, 6, and 7), (3) difficulties in describing the symptoms (eg, Patient 6), and (4) symptoms fitting well with the personal internal and situational profile (eg, Patients 1, 2, 3, 4, 6, and 7).

Psychotic and affective (bipolar and major depressive) disorders described are viewed here as having an endogenous origin and are well controlled by the CLT/AMP. OCD and ICD manifestations also receded after surgery, but the issue of the endogenous or reactive origin of these disease entities remains as yet unresolved. As for the postoperative anxiodepressive and frustration-related manifestations, the question may be raised as to their origin and their resistance to surgery in view of the fact that anxious and depressive symptoms on the other side may respond to surgery. One possibility is that these manifestations may be responsive to surgery in the measure in which they are endogenous. Another way of viewing this is that whereas all anxiodepressive and frustration-related disorders are of reactive origin, some of them may be self-entertained, thus presenting the observed resistance to surgery. Along this line, postoperative anxiety reactions may be initially strong but amenable to external and internal relieving factors and may thus subside relatively quickly and easily (Patients 1 and 2). To the contrary, frustration/anger and conceptual rigidity do not cause direct suffering, and frustration is even self-entertained. Nonacceptance of a given situation recedes only when the person has decided that it should indeed recede. This mental profile may thus represent a stronger challenge for the relevant network and correlate with more difficult and protracted postoperative evolutions (Patients 3, 4, 6, and 7).

Summary

Clearly, more clinical experience must be amassed to define in detail the possibilities of this surgical approach in disabling neuropsychiatric disorders. We propose, however, that the evidence for benign and efficient surgical intervention against the neuropsychiatric TCD syndrome is already compelling. The potential appearance of strong postoperative reactive manifestations requires a close association between surgery and psychotherapy, with the latter providing support for the integration of the new situation as well as the resolution of old unresolved issues.

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