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Psychosurgery Reduces Uncertainty and Increases Free Will? A Review

Dirk De Ridder, MD, PhD*; Sven Vanneste, MSc, PhD†; Grant Gillett, MD, PhD‡; Patrick Manning, MD, PhD§; Paul Glue, MD, PhD¶; Berthold Langguth, MD, PhD**

Objective: A definition of free will is the ability to select for or against a course of action to fulfill a desire, without extrinsic or intrinsic constraints that compel the choice. Free will has been linked to the evolutionary development of flexible decision making. In order to develop flexibility in thoughts and behavioral responses, learning mechanisms have evolved as a modification of reflexive behavioral strategies. The ultimate goal of the brain is to reduce uncertainty inherently present in a changing environment. A way to reduce the uncertainty, which is encoded by the rostral anterior cingulate, is to make multiple predictions about the environment which are updated in parallel by sensory inputs. The prediction/behavioral strategy that fits the sensory input best is then selected, becomes the next percept/behavioral strategy, and is stored as a basis for future predictions. Acceptance of predictions (positive feedback) is mediated via the accumbens, and switching to other predictions by the dorsal anterior cingulate cortex (ACC) (negative feedback). Maintenance of a prediction is encoded by the pregenual ACC. Different cingulate territories are involved in rejection, acceptance and maintenance of predictions. Free will is known to be decreased in multiple psychopathologies, including obsessive compulsive disorder and addictions.

Methodology: In modern psychosurgery three target structures exist for obsessive compulsive disorder and addiction: the dorsal ACC, the nucleus accumbens, and/or the anterior limb of the internal capsula. Research in all three areas reports favorable results with acceptable side effects. Psychosurgical interventions seem to exert their effect by a common final common pathway mediated via the pregenual ACC.

Conclusion: Successful neuromodulation increases the capacity to choose from different options for the affected individual, as well as inhibiting unwanted options, therefore increasing free will and free won't.

Keywords: Accumbens, anterior cingulate, anterior limb of internal capsule, cingulotomy, free will, pregenual, psychosurgery, rostral, dorsal, tractotomy

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INTRODUCTION

Free will has been defined as the capacity to choose from different options with some degree of anticipation of consequences of each choice (1). Free will is the ability to select for or against a course of action in order to fulfill a desire, without extrinsic or intrinsic constraints that compel the choice. The ability to select against an action has both phylogenetically and ontogenetically old roots and has led to the concept of the "free won't" (2).

A link between mental disorder and freedom is clearly present in the introduction of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). It mentions "an important loss of freedom" as one of the possible defining features of mental disorders (3), with obsessive compulsive disorder (OCD) being the most clear cut mental disorder associated with a loss of freedom (3–6). In general, however, the elusive link between freedom, autonomy, and mental disorder is of major concern in forensic psychiatry, philosophical analysis of mental disorders, and analysis of recovery (7).

The unprecedented wealth of new functional and structural neuroimaging data with regards to physiological and pathophysiological brain mechanisms in mental disorders pave the way for a renaissance of psychosurgery, which can be defined as neuromodulation for mental disorders. The resurgence is based on the concept that novel functional and structural brain imaging data can pinpoint where and how in the brain dysfunctions arise that can be remediated by very specific neuromodulation interventions. This coincides

Address correspondence to: Dirk De Ridder, MD, PhD, Section of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand. Email: dirk.deridder@otago.ac.nz

* Department of Surgical Sciences, Section of Neurosurgery, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand;
† Laboratory for Clinical and Integrative Neuroscience, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX, USA;
‡ Department of Philosophy, Section of Medical Ethics, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand;
§ Department of Internal Medicine, Section of Endocrinology, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand;
¶ Department of Psychological Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; and
** Department of Psychiatry and Psychotherapy, Interdisciplinary Tinnitus Clinic, University of Regensburg, Regensburg, Germany

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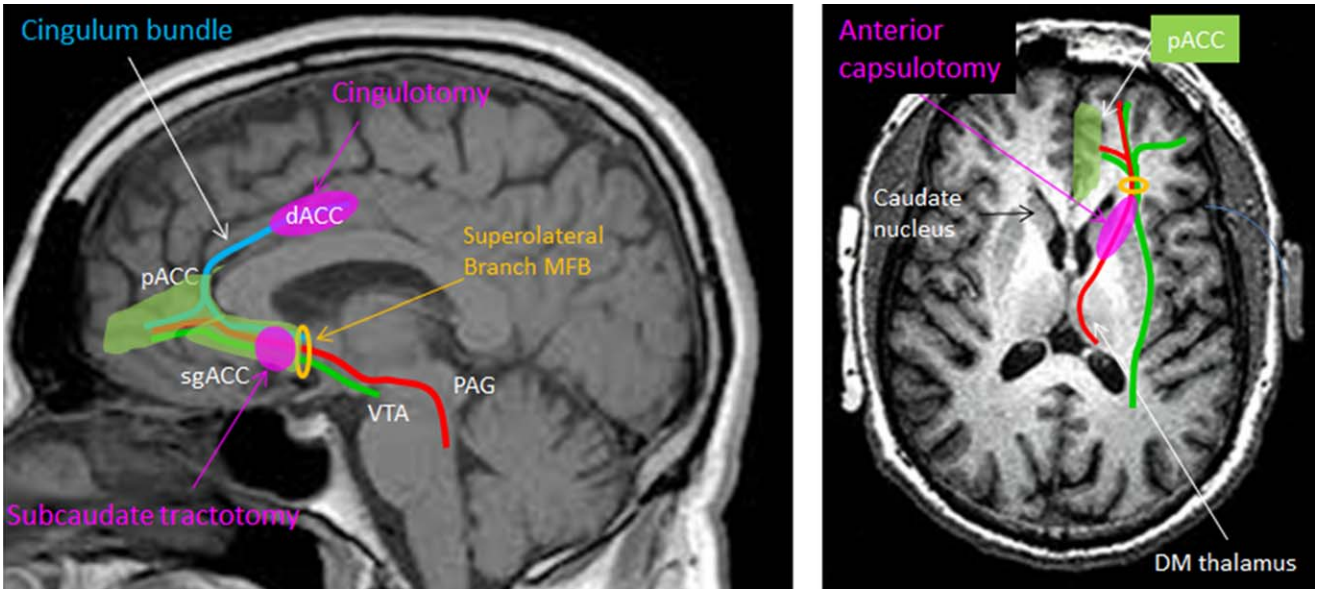

Figure 1. Psychosurgery targets (pink): (1) cingulotomy, (2) anterior capsulotomy, (3) subcaudate tractotomy, and (4) limbic leucotomy (combination of 1 + 3). The three lesions have in common that their tractographic connections (red, blue, and green lines) conjunct at the superolateral branch of the medial forebrain bundle (yellow) extending into the pregenual cingulate/ventromedial prefrontal cortex (green). The anterior capsulotomy blocks information transmission between the dorsomedial thalamus and caudate extending to the nucleus accumbens and anterior cingulate cortex (red line).

with the development of new stimulation designs (8–10), that is, new ways to electrically manipulate the brain that seem to be more powerful and more selective in modifying individual behavior (11) in comparison to classical neurostimulation designs. Some of the new stimulation designs mimic nature by copying the physiological responses of the brain, which seems to be adaptively more successful in animals (12) and humans (13).

At the same time there exist major prejudices against the continued use of neurosurgical techniques in the treatment of mental disorders, based on the unfortunate history of psycho-surgery. An essential aspect in the ethical considerations around psychosurgery is the question to which extent psychosurgery influences one of human's most valued characteristics, the choice to be oneself, to be mentally free, and to have a "free will" and/or "free won't" that can translate one's own thoughts into action or action inhibition.

Here we aim to, 1) summarize the distribution of anatomical structures involved in common psychosurgical approaches in the past and to identify a physiological basis for these targets, 2) to develop a unifying conceptual model that makes testable predictions about what psychosurgery can do and cannot do, and 3) to evaluate the relevance of psychosurgery for decision-making in mental disorders ("free will").

PSYCHOSURGERY: TARGETS

The development of stereotactic approaches in 1947 permitted smaller and better targeted lesions resulting in 4 kinds of psychosurgery: 1) cingulotomy, 2) anterior capsulotomy, 3) subcaudate tractotomy, and 4) limbic leucotomy (combination of 1 + 3) (Fig. 1).

Based on modern structural imaging with tractography it is now clear that these targets functionally converge at the pregenual anterior cingulate, extending into the orbitofrontal cortex and are connected via the forceps minor and the anterior thalamic radiations to subgenual cingulate regions (14). Anatomically, this convergence may derive from the superolateral branch of the medial forebrain bundle (MFB), a structure that connects these frontal areas to the origin of the mesolimbic dopaminergic "reward" system in the midbrain ventral tegmental area (14).

Modern psychosurgery mainly targets three structures for OCD and addiction: the dorsal part of the anterior cingulate, the nucleus accumbens, or the anterior limb of the internal capsula, and they all report favorable results with acceptable side effects. For other psychopathologies, other targets are used, (e.g., the subgenual anterior cingulate for depression, and the amygdala and posterior hypothalamus for aggression etc.). Can these three different targets (for OCD and addiction) be conceptually integrated into one anatomical and physiological model to explain the results?

Anatomically, the anterior limb of the interior capsula contains different fiber tracts: frontothalamic and thalamofrontal as well as frontopontine and frontostriatal and thalamostriatal and striatostriatal fibers (15–17). Thalamofrontal and frontothalamic reciprocal fibers run between the anterior thalamic nuclei and the anterior cingulate gyrus, the mediodorsal thalamic nucleus and the orbitofrontal, ventromedial as well as the frontopolar and dorsolateral prefrontal cortex. The fibers from the ventral anterior thalamic nucleus, parafascicular and centromedian nucleus run to different parts of the prefrontal cortex (15–17). In obsessive-compulsive disorder, there is a structural hyperconnectivity between the thalamus, the orbitofrontal cortex, and the anterior cingulate cortex (ACC) as confirmed by volume enlargement in the internal capsule (18). The same is noted for other disorders with obsessive symptoms such as internet obsession, (19) gambling addiction (20), and even irritable bowel syndrome (21).

THE BAYESIAN PREDICTIVE BRAIN

Physiologically the brain can be conceptualized as a Helmholtz machine (22) which contstantly makes multiple (23,24) predictions about the world and then updates them in a Bayesian way through active sensorimotor exploration of the environment (25–27). It does so to reduce the inherent uncertainty present in a changing environment full of positive and negative affordances. This minimizes

informational (= Shannonian) free energy, which has been proposed as a universal principle governing adaptive brain function and structure (28). Uncertainty is primordially encoded by activation in the rostral anterior cingulate cortex (rACC) (29–33). Uncertainty is defined as a state in which a given representation of the world cannot be adopted as a guide to subsequent behavior, cognition, or emotional processing (34), in other words Shannonian entropy or informational uncertainty (26,30). Uncertainty in any environment can be reduced by acquiring more data, by seeking out more information in the environment, (29) or by drawing on memory if it is not presently available or accessible (e.g., due to sensory deafferentation) (26).

Bayesian inference can therefore be conceptualized as the use of sensorimotor information from the environment to update memory-based prior representations or models of the world (held before acquiring new inputs) to produce posterior representations (that emerge after acquiring those inputs) and which integrate action-relevant information (35). This mechanism permits decision making based on predictions updated by actively sampling the environment for confirmation or rejection of the memory based top-down predictions (36)—a crucial mechanism in the neural basis of (perceived) human freedom of action (37) and inhibition of action. Our evolutionary-evolved brain potential to generate multiple action plans is constrained by what is stored in memory and by what is present in the environment. Thus, the feeling of an absolute free will is actually an illusion, as there is likely no unlimited (=completely free) amount of representations generated, due to the inherent constraints (23). But even though neuroscience might not be able to determine whether "free will" in itself really exists, it can help unravel the mechanisms of the illusionary "experience of free will."

The Neuroanatomy of the Predictive Brain

The neuroanatomy of this Bayesian mechanism is still being elucidated but some anatomical structures are likely to be implicated. The Bayesian cycle entails a prediction leading to an anticipation, followed by an evaluation of the prediction error, and subsequently an outcome, with either or positive or negative feedback (38), requiring an update of the prediction or further exploration of the internal or external environment. The reward feedback system involves the nucleus accumbens, medial dorsal nucleus of the thalamus, pregenual anterior cingulate cortex/ventral medial prefrontal cortex, insula, and amygdala (39).

It has been proposed that the nucleus accumbens is involved in reward prediction whereas the caudate nucleus is involved in prediction error monitoring (40) (i.e., the evaluation phase). The caudate nucleus is involved in the acceptance or rejection of propositions about the world (34), guiding subsequent behavior, emotion, and cognition, and this both for prediction error encoding in classical and instrumental learning (41), irrespective of whether these prediction errors are based on model free or model based reinforcement learning (42–45). The nucleus accumbens is involved in all stages as it has to first predict the error, subsequently hold the prediction in the evaluation phase, and then adjust it during the outcome phase for both for positive and negative rewards (38,39). However the nucleus accumbens is only involved in model free reinforcement (42), that is, in reward prediction error coding in instrumental (=operant) conditioning, but not in classical (=Pavlovian) conditioning (41). It has recently been proposed that the Dirichlet process mixtures permits multiple predictions or behavioral responses to be generated and evaluated in parallel, as a Dirichlet process is a probability distribution whose domain is itself a set of probability distributions (46). This permits to update multiple predictions/behavioral strategies (n = 3–4) in parallel and to decide whether to stay with the ongoing prediction/behavioral strategy, switch to other prediction/behavioral strategy, or form a new prediction/behavioral strategy. Reliability the current prediction/behavioral strategy is encoded by vmPFC and pgACC (i.e., the pgACC/vmPFC encodes the current prediction is good), whereas the reliability of alternative predictions/behavioral strategies is encoded by the dorsolateral prefrontal cortex (DLPFC) (24). The vmPFC seems indeed to encode the prior Bayesian belief (47), that is, as long as the current strategy is reliable the posterior belief equals the prior belief. When the reliability of the current prediction/behavioral strategy decreases, the prediction/behavioral strategy switches to an alternative, encoded by the dACC, and the confirmation of a new prediction as actor is encoded by the nucleus accumbens (ventral striatum) (24).

Positive Feedback

In the outcome stage, positive feedback activates the nucleus accumbens and posterior cingulate cortex (38,48,49) to moderate rest and digest routines via the parasympathetic system (50) as well as the pregenual anterior cingulate cortex and medial orbitofrontal cortex (38), encoding pleasure (51–54) via a μ-opioid mechanism (55). But the pgACC is also functionally connected to the periaqueductal grey (PAG) (56), a connection that mediates pain suppression, irrespective of the mechanism by which pain suppression is obtained (peripheral nerve blocks, opioid analgesia, acupuncture, Gasserian-, thalamic- or motor cortex stimulation, placebo or cognitive distraction) (57). This operates not only for physical but also for mental pain (58) by preventing further input of pain/noxious stimuli at the periphery (55), and a similar mechanism has been proposed for sound (59–62), and aggression (63–66), suggesting that this type of suppression of further information input could be a fairly universal nonspecific mechanism. Indeed the percentage of time a person perceives a phantom sound is correlated to the activity of the pgACC (62), and electrical stimulation of the DLPFC suppresses phantom sound mediated through the pgACC (67). This has been attributed to a deficiency of a noise cancelling system (61) centered on the vmPFC/pgACC (59,60,62). A deficiency in this stimulus-inhibiting pathway can lead to spontaneous pain such as in fibromyalgia (68), troublesome tinnitus (60,61) and self-reported craving (69,70). These are all associated with of a lack of pleasantness, which is encoded by normal activation of the pregenual ACC (53). Therefore, whereas subjective unpleasantness is encoded by the rostral ACC (71), intrinsically linked to uncertainty (29,32,34,72), pleasantness is encoded by the pregenual ACC (53).

The fact that the pregenual anterior cingulate cortex has also been implicated in increased pain perception is explained by the quadratic U-response of the pregenual anterior cingulate cortex activity in pain intensity coding (73). It seems that when the brain has acquired enough information to reduce uncertainty, it will generate a feeling of pleasure to indicate it has acquired enough information via a pgACC-orbitofrontal circuit, and will therefore reduce further unnecessary input via a pgACC-PAG circuit.

Negative Feedback

In case of negative feedback, the dorsal anterior cingulate cortex plus insula (38,48,74) as well as the habenula (48,74) and lateral prefrontal cortex (38) are activated, signifying the salience (75) of the missing input, and urging action (76) to get more input, for which mobilizing energy via the sympathetic system (50) is required, or to switch to an alternative behavioral strategy (24). The connectivity between the VLPFC and the pre-supplementary motor area (pre-SMA) (77,78), as well as the dACC's direct close connection to the

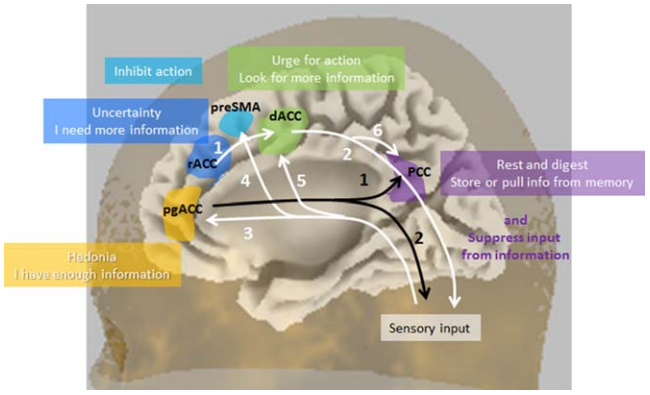

Figure 2. Heuristic universal model for information processing. Predictions are matched with sensory input. Uncertainty encoded in the rACC activates the dACC (white arrow 1) creating an urge for action as to obtain more input from the environment (white arrow 2). If by obtaining more input predictions are confirmed (white arrow 3), no further information is needed, resulting in inhibition of action (white arrow 4) and storing the current model in memory (black arrow 1) via the PCC as well as signaling to rest and digest (via parasympathetic control in PCC) (black arrow 1). The pgACC will subsequently suppress further input (black arrow 2) and the signal is translated to a feeling of pleasure. In case of continuing uncertainty the dACC will be activated (white arrow 5) continuing the urge to acquire more input, either by active exploration of the environment (white arrow 2) or from memory (white arrow 6).

pre-SMA (79) will permit to inhibit the current behavior strategy (80), essential when switching to an alternative strategy.

This explains why the glutaminergic activation in the dorsal anterior cingulate cortex (and nucleus accumbens) (81) is related to cue evoked craving ("give me more") (69,82,83) and nucleus accumbens activation can be considered as an anti-craving mechanism ("I have enough") (84), by accepting the new behavioral strategy (24).

INTERACTION BETWEEN FREE WILL, FREE WON'T AND POSITIVE AND NEGATIVE FEEDBACK

Flexible behavior is based on two functions: 1) the ability to predict future outcomes; and 2) the ability to cancel them when they are unlikely to accomplish valuable results and replace them by alternative behavioral strategies (85).

A recent study has looked at the neural circuits involved in flexible behavioral adaptations (24). In this seminal study on behavioral adaptation, it was shown that whether or not the current behavioral strategy was reliable was encoded by the pgACC/vmPFC and the reliability of alternative strategies is encoded by the DLPFC (24). If the reliability of the alternative becomes larger than the reliability of the current behavioral strategy the current one will be rejected by the VLPFC. This is followed by switching to a new behavioral strategy by the dACC and acceptance of the new behavioral strategy by the nucleus accumbens (24). If the reliability of the actor is less than the reliability of the alternatives the actor will be inhibited. Thus a medial and lateral tract exists related to behavioral flexibility. The medial tract consists of the vmPFC, pgACC, dACC, and ventral striatum (nucleus accumbens) and makes inferences about the actor (=current) strategy that, through reinforcement learning, selects and learns the actions maximizing reward (24). The lateral track consists of the FPC and mid-LPC and makes inferences about two or three alternative strategies stored in long-term memory. The FPC concurrently infers the absolute reliability of these alternative strategies from action outcomes and the mid-LPC detects when one becomes reliable for retrieving it as actor.

Thus, it appears that decision making depends on a constant comparison between multiple memory based predictions. Simplifying this model one can propose that predictions are matched with sensory input. If predictions are confirmed, no further information is needed, the current behavioral strategy is reliable as encoded by the pgACC, resulting in activation of the PCC (48) signaling to rest and digest via parasympathetic activation (50) and to store the current strategy in memory and maintain it as the current strategy to use (via nucleus accumbens) (Fig. 2). The pgACC will subsequently suppress further input, and recalculate the reliability of the current strategy (Fig. 2) and via its connectivity to the orbitofrontal cortex encode to a feeling of pleasure (Fig. 2).

In case of continuing uncertainty, the dACC will be activated mediating the urge for action (76) to acquire more input, either by active exploration of the environment or from memory (Fig. 2). When more input arrives, it may 1) or may not 2) be enough (based on the prediction error) and will either activate the PCC (enough) or the dACC (not enough) (Fig. 2). If the uncertainty remains, the dACC will switch to an alternative behavioral strategy, which fits better with sensed input. As mentioned, free will has been defined as the capacity to choose from different options with some degree of anticipation of consequences of each choice. Predictions can be right or wrong, depending on the intention or goal. Negative and positive feedback are mediated by the habenula and accumbens, respectively, (48), two central hubs of the reward system interacting with the ventral tegmental area (86,87). Thus, the reward system might influence the illusion of the free will by providing a very strong positive reward prediction linked to the substance of abuse, that is, obtaining an abnormal high reliability as current actor, thereby preventing alternative predictions, behavioral strategies or thoughts to obtain a reliability that can outdo the reliability of the current actor, limiting a free choice of the next course of thought or the next course of action.

Loss of Freedom in Mental Disorders and Psychosurgical Approaches

For OCD or addiction, two well-known pathologies associated with a decrease in free will (3–6), the dACC, the nucleus accumbens or the anterior limb of the internal capsula are targeted in current neuromodulatory approaches. Other diseases, such as kleptomania, tics in Tourette's syndrome, and so forth, also limit the freedom of an individual (3).

In addiction, the pregenual anterior cingulate is overactive (88) and the impulsivity to use the addicted substance is increased (89), in other words, alternative behavioral strategies are used less, and this has been linked to pregenual anterior cingulate activity. In a similar way, the pregenual ACC is implicated in OCD: using magnetic resonance imaging spectroscopy, it has been shown that the benefit of CBT for OCD is related to neurochemical changes in the pregenual anterior cingulate cortex further demonstrating that the pgACC is an important node in diseases that limit free will.

Even though free will might be an illusion (23), patients do perceive a mental freedom when successfully treated for their addiction (De Ridder, in press). They perceive a suppression of the hyperfocusing and motivational hypersalience attached to the substance of abuse which gives them the freedom to engage in other aspects of life, and having more thoughts, not being hijacked anymore by an all overwhelming thought and urge to obtain the substance of abuse. In other words, it liberates them to have more control over their thoughts and actions. Thus, psychosurgery increases their capacity to choose from different options with some degree of

anticipation of consequences of each choice, in contrast to previously when the addicted person only perceived one real option, which was to obtain the substance of abuse at whatever cost (see criteria in DSM IV and V). A similar experience is felt for obsessive and compulsive thoughts in OCD.

The same dACC and insular hyperactivity is involved in tics, and can be seen as an urge for action (76). All of the diseases characterized by an increased urge for a specific action have been labeled under the overlapping term of reward deficiency syndromes (90,91). The reward deficiency syndrome has been linked to dopamine gene polymorphisms (DRD2, DRD1, DAT1) (92). The key polymorphism (DRD2) is known to limit learning from negative feedback (i.e., learning from errors (93)), thereby limiting the capacity for flexible decision making. It has also been shown that symptomatic treatment of these syndromes, for example, food addiction by bariatric surgery in these genetically prone patients, often results in an "addiction transfer" [i.e., another addiction arises (92)], potentially continuing the decrease in mental freedom.

In obsessive-compulsive disorders there is an abnormal functional connectivity between the nucleus accumbens and the pregenual anterior cingulate cortex correlating with symptom severity (94). Nucleus accumbens stimulation for obsessive-compulsive disorders has a beneficial effect in 60% of patients (95–97) by normalizing functional connectivity between the nucleus accumbens and the pregenual anterior cingulate cortex (98) thereby normalizing dopamine release (99) (Table 1). Cingulotomy for obsessive-compulsive disorders has a long term beneficial effect in 30–69% of patients (100,101) (Table 1) inducing atrophy in the caudate nucleus (102) and therefore interfering with prediction error monitoring. The major output of the caudate nucleus is to the pregenual cingulate cortex, which is under the influence of dopamine as is the output from the nucleus accumbens to the pregenual anterior cingulate cortex (103) either via the sgACC (104) or via the PCC (48). It is of interest that in a recent comparison of successful vs. unsuccessful cingulotomies for obsessive-compulsive disorders, the critical area seems to be located rostrally rather than dorsally in the anterior cingulate cortex (105). This suggests that removing uncertainty is more efficient for symptom reduction than suppressing the urge for action.

The anterior limb of the internal capsula is targeted both with lesioning as with stimulation for obsessive-compulsive disorders (106) (Table 1). Lesioning has a successful outcome in 50–70% of patients (101,107–109). Chronic anterior capsular stimulation for obsessive-compulsive disorders has a beneficial effect in 50% of patients (110–112). It decreases metabolic activity in subgenual anterior cingulate cortex and preoperative resting metabolic activity in the subgenual anterior cingulate cortex may predict therapeutic response. Therapeutic response correlates with changes in the metabolism of the nucleus accumbens (113). Therefore, it might essentially exert its clinical effect by similar mechanisms as nucleus accumbens stimulation. It is of interest that combining cingulotomy with accumbens stimulation does not yield better results than cingulotomy alone (114), which could be explained by the fact that they influence the same final common pathway probably involving the pregenual anterior cingulate cortex—the area where all four psychosurgical approaches converge in their effects.

In addition, cingulotomies have been performed with some success (115,116) (Table 1) even though for Walter Freeman this was a contraindication for frontal lobotomies (117). Cingulotomies in addiction aim to stop the obsessive-compulsive desire for drugs (115). Different success rates for different drugs of addiction have been reported: 80% for morphine, 90% for meperidine, 68% for alcohol (118), and 62% for heroine (115,118). In a large study with opiate addicts in Russia, 62% were improved (119), at the moment of discharge, all patients were craving-free for opiates. After two years, 45% of the 187 patients interviewed were drug-free and 17% were in remission for more than two years, and in 13% there was a partial improvement. In 12%, there was no change (115,119). Also nucleus accumbens lesioning (120) and stimulation has been performed with success (121,122) (Table 1). The therapeutic effect for lesioning was considered excellent in 26.9% of patients and good in 38.5%, but 57% relapsed within a year (120). This could possibly be explained by what is known from animal studies: four weeks after a lesion of the nucleus accumbens a spontaneous recovery of the induced behavioral deficit (hypomobility) was observed, associated with reinnervation of the nucleus accumbens and normalization of dopamine levels and dopamine metabolism within 24 weeks (123). This suggests that stimulation might be a better mode of neuromodulation. Of the 18 published cases of nucleus accumbens stimulation, 50% were cured, 10% improved, and 40% unchanged (95). However, this data probably overstates results as many were case reports. In a retrospective analysis of 10 patients with nicotine addiction who received n. accumbens stimulation for other indications, 3 (30%) stopped smoking, whereas the other 7 (70%) continued (124). Anterior capsulotomies have to our knowledge not been performed for such addiction. Even though psychosurgical interventions have their merit, a lack of clear understanding of the intricate psychopathological mechanisms involved clearly limit their overall success rate. Based on the above-mentioned discussion it would be interesting to investigate whether to select the accumbens or the dACC as a target might depend on whether the addiction is a habit or the consequence of goal-directed behavior, as the neural correlates differ. For maladaptive habits the nucleus accumbens seems the best target by interfering with model free reinforcement learning (42), whereas for model-based goal directed behavior the dACC might be a better target (42).

LIMITATIONS OF THE FRAMEWORK

As with all conceptual or heuristic frameworks, the model provided has to be verified and adjusted, based on the outcome of clinical studies performed using the model. Furthermore it is unlikely that one model will explain the pathophysiology in all patients, even from a theoretical basis. For example, if the Bayesian model is correct, it can be assumed there might actually be 3 different subgroups of addictions and OCD. Bayes' theorem states that $P(A/B) = P(A) \times P(B/A)/P(B)$, with P being the probability, A = prediction or hypothesis and B the evidence (obtained from the environment). Thus, the posterior belief $P(A/B)$, which drives the current behavioral strategy (addicted or OCD) is dependent on the probability of the prediction the brain makes $P(A)$, but also on the evidence the brain obtains via the senses $P(B)$ to update the model the brain has of the world, which determines the likelihood that the evidence is correct given the prediction $P(B/A)$. Thus, in addiction and OCD there may be a dysfunctional prediction, a dysfunctional evidence gathering or a dysfunctional updating, theoretically each with a different underlying pathophysiology, and potentially with a different target. This could hypothetically also explain why psychosurgery on average only has a 30–40% success rate, if the current neuromodulation strategies only treat one of the three theoretical causes.

Another hypothetical explanation why only 30–40% of patients respond to neurostimulation could be related to the genotype of the patient. It has been shown that the genetic polymorphisms of the dopamine (DRD2, ANKK1, DAT1, DBH, and DRD4) (125) and opioidergic genes (OPRM1, OPRD1, and OPRK1) (126) moderate the

Table 1. Overview of Studies on Cingulotomies or Brain Stimulation for OCD or Addiction.

	Manuscript	Target	*n*	Lesion/Stimulation	Outcome
OCD	98	Accumbens	31 (review)	Stimulation	42% responders
	99	Accumbens	5	Stimulation	50% responders
	100	Accumbens	16	Stimulation	
	110	ALIC	35	Lesion	22 recovered, 10 significantly improved, 10 improved, 3 not improved. YBOCS average from 21.2 to 4.4
	112	ALIC	19	Lesion	YBOCS from 33.5 to 16.3, response in 12 patients >35%, 9 in remission (YBOCS < 16)
	114	ALIC	4	Stimulation	1 in 4 29.3 to 26.5 for group
	115	ALIC	6	Stimulation	YBOCS from 32.3 to 19.8, response in 4 patients, CGS from 5 to 3.3
Addiction	121	ACC	73	Lesion	improvement 80% of morphine, 90% of meperidine, and in 68% of alcohol addicts
	122	ACC	348	Lesion	62% improve, 45% drug-free and 17% in remission (>two years), in 13% partial improvement, 12% unchanged
	123	Accumbens	28	Lesion	outcome excellent in 26.9%, good in 38.5%, but 57% relapsed within a year
	98	Accumbens	18	Stimulation	50% cured, 10% improved, and 40% unchanged
	127	Accumbens	10	Stimulation	30 stopped smoking, 70% continued

Example studies with five or less patients were not included for cingulotomies for OCD.

effects of pharmacotherapy of alcohol, opioid, and cocaine addiction. The question arises whether the same holds for DBS. In Parkinson's disease, there is a suggestion that patients with Parkinson's disease related genes (parkin mutation) could be better candidates for DBS (127). However, these data were not replicated in another study where patients without specific mutations (LRRK2, PRKN, and PINK1) responded equally good to DBS as the patients with mutations (128). For noninvasive stimulation (TMS, tDCS) patients with a BDNF polymorphism also seem to have a different response rate to the noninvasive neuromodulation (129). Whether or not there may be a genetic predisposition for responders to electrical stimulation in addiction or OCD is currently unknown.

Furthermore, as mentioned, lesioning of the accumbens has a high rate of relapse, possibly due to inherent repair mechanisms of lesioning. This might result in a similar effect with high frequency stimulation (130 Hz) of the nucleus accumbens, which can be regarded as a virtual lesion, due to the induction of electrophysiological silence (130). Thus, some new approach should be developed to obtain longer lasting results.

FUTURE OF PSYCHOSURGERY

The results of psychosurgery can be improved in at least 3 ways: 1) Better targeting, 2) Better stimulation designs, and 3) More physiological stimulation. A first improvement can be based on finding better targets, depending on the assumed different subtypes of addiction and OCD as described above. But apart from better targeting, also the development of new stimulation designs might help improve results. Indeed, for example burst stimulation seems to yield better results in cortex stimulation, both somatosensory cortex (131), auditory cortex (9), cingulate cortex (132) as well as in spinal cord stimulation (133–137) and peripheral nerve stimulation (138,139), and there is no reason to a priori believe the same rationale will not be applicable for deep brain stimulation. A third approach to developing better treatments could be based on a seminal study in tinnitus in rats, in which neurostimulation was paired with external stimuli (140). In this approach, electrical stimuli are not given constantly, as is routinely being done in traditional neurostimulation, but only on the moment an external stimulus is provided, as to recondition the brain. The feasibility of this approach has been translated to humans (141,142), albeit with less success than in animals, but the principle can be adapted to stimulating the reward and disreward or antireward system (143). It is theoretically conceivable that by pairing the presentation of a substance of abuse, for example alcohol, to a disrewarding stimulation in the habenula (48,74) could remove the salience of the alcohol, and simultaneous pairing of nonalcoholic drinks to a rewarding stimulation in the nucleus accumbens could increase the salience of nonalcoholic drinks. However, to develop reconditioning stimulation, very specific waveforms need to be developed that give maximal reward by stimulating the nucleus accumbens or give maximal disreward by stimulating the habenula. A technique has been developed in animals based on self-stimulation that can discriminate which waveform or stimulation

design rats prefer over others, thereby optimizing the waveform to the target (144). As the nucleus accumbens and anterior cingulate cortex in rats and humans seems to respond in similar ways (in studies analyzing the reward system in pain) (145), it can be assumed that translating animal data to humans is worthwhile.

CONCLUSION

Thus, in conclusion, a simplified physiological explanation of psychosurgical results demonstrates that all psychosurgical interventions seem to exert their effect by a common final pathway mediated via the pregenual anterior cingulate cortex. The pregenual anterior cingulate cortex encodes pleasure and suppresses further input of the same stimulus, thereby decreasing OCD-like and addictive behavior. Psychosurgery most likely modulates the reliability calculation of the currently employed behavioral strategy by modulating vmPFC/pgACC activity (24). In other words, from a Bayesian point of view psychosurgery modulates the abnormal "prior" belief, encoded in the vmPFC (47), which is too rigid in addiction and OCD, and thereby permits alternative behavioral strategies to become used instead of the addictive or OCD strategy. This, by definition, will increase the behavioral options, thereby increasing flexible decision making and free will. The pregenual anterior cingulate cortex is modulated by the dorsal ACC (via the caudate nucleus) and nucleus accumbens (via the sgACC and the PCC) (i.e., by positive and negative feedback related to predictions). In successful neuromodulation, either suppressing negative feedback via cingulotomy or activating positive feedback via nucleus accumbens stimulation, the capacity to choose from different options for the affected individual is increased. In this overall model, freeing up of possible life choices allows more scope for the exercise of life skills—adaptive responses—and therefore of the ability to exert one's will or power in a situation. An intriguing hypothesis resulting from this conceptual model is that predominantly "free won't" might be modulated by psychosurgical approaches, as intentional inhibition is influenced by context-dependent neural activation in mPFC/pgACC (80), which is indeed a universal, nonspecific inhibitory structure, as it suppresses pain (55,146), sound (60–62), aggression (63–66), and balance (Alsalman, submitted) input. In other words our capacity to freely cancel those actions we do not wish to perform, such as compulsive actions or persistence intake of substances of abuse.

Now the following questions arise: what do patients have to sacrifice for this beneficial effect? What are the side-effects of psychosurgical interventions? Cingulotomies seem to have few side-effects with the exception of surgical risk; language, memory, motor, visual-constructional, and intellectual functions remain unaffected (147), but focused attention (147,148) and behavioral spontaneity (149) are reduced as might be expected from down-tuning task specific drivers. On the other hand an increase in emotional well-being is reported with improvements in tension, anger, and psychasthenia (150).

However, many psychosurgical interventions in the past have not been successful. Alcoholism for example, is a negative predictor for the outcome of lobotomies in schizophrenic patients having been linked to "complete irresponsibility" postoperatively (117) (p 518). Also the development of addictions after lobotomies has been reported in rare instances (117) (pp. 194–195). Thus, the use of reversible psychosurgery approaches such as electrical stimulation, which also can be fine-tuned to the needs of the patient by reprogramming the stimulation design, seems clinically preferable to lesioning in most patients.

With the resurgence of pathophysiology-based psychological neuromodulation it is important that theoretical models are developed that can help us understand the function of possible neuromodulation targets and make predictions about possible neuromodulation targets. The present conceptual model offers a clear foundation on the basis of which further modelling can incorporate data from functional neuroimaging, as well as from trials of surgical and nonsurgical neuromodulation, in an attempt to improve psychosurgical treatments by more pathophysiological based approaches.

Authorship Statements

Drs. De Ridder and Vanneste wrote the manuscript. Dr. Gillet provided important intellectual input with regards to the ethics of the study. Dr. Manning assisted with the concept of feedback mechanisms. Drs. Glue and Langguth were responsible for the psychosurgery aspects. All authors read and approved the final version of the manuscript

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