THE ROLE OF VOLITION IN OCD THERAPY: NEUROCOGNITIVE, NEUROIMAGING, AND NEUROPLASTIC ASPECTS

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Summary

Recent arguments and evidence implicating free will (volition) in the phenomenology and treatment of Obsessive-Compulsive Disorder (OCD) are reviewed, in particular with respect to Cognitive-Behavioral Therapy (CBT). After comparisons of CBT to neuropharmacological and neurosurgical treatments and of Mindfulness-Based Cognitive-Behavioral Therapy (MBCBT) to Exposure and Response Prevention (ERP), the discussion divides into neurocognitive, neuroimaging, and neuroplastic sections. The neurocognitive section describes how volition is integral to the symptomatic manifestations of OCD and to OCD remediation with CBT. The neuroimaging section reviews findings in OCD, with special attention to Magnetic Resonance Spectroscopy (MRS). A linkage between MRS and Positron Emission Tomography (PET) results in OCD is hypothesized. Selected PET and functional MRI (fMRI) studies in OCD patients and normals are reviewed that indicate that brain blood flow and metabolism can be altered acutely by willful shifts in subject attitude, as well as chronically by CBT. These observations support the contention that human subjects, including OCD patients, are capable of "self-induced neurophysiology" and "self-directed neuroplasticity", i.e., that the willful "mind affects the brain". Cognitive evoked potential investigations that characterize the timescale of human free will are cited. The neuroplasticity section reviews evidence for plasticity in the adult brain in laboratory monkeys and human patients, in particular for plasticity putatively induced by subjective willful effort. The fronto-basal gangliar circuits of the brain, sites of pathology in OCD and likely sites of neuroplastic change in OCD recovery, are reviewed. Tonically Active Neurons (TANS) positioned at striosomal-matrisomal junctions in the caudate are discussed as possible mediators of volitional influences on behavior. It is concluded that more formal trials of MBCBT for OCD and more neuroimaging studies of volition in normals and patients should be conducted.

Key Words: Volition – Obsessive-Compulsive Disorder Treatment – Cognitive-Behavioral Therapy – Seld-induced Neurophysiology – Self-Directed Neuroplasticity

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Introduction

This review concerns the role of volition, the patient's subjective free will or willpower, in the treatment of Obsessive-Compulsive Disorder (OCD). Emphasis will be on Cognitive-Behavioral Therapy (CBT) for OCD, especially Mindfulness-Based Cognitive-Behavioral Therapy (MBCBT), where patient cooperation is central. Following this Introduction, the review is divided into four major sections.

The first major section briefly deals with skepticism towards the free will concept, reviews the status of CBT as a treatment for OCD, and compares the two major varieties of CBT for OCD: MBCBT and Exposure and Response Prevention (ERP).

The second major section (consisting of three subsections) is drawn mainly from subjective introspective experiences of OCD patients and concerns neurocognitive aspects of OCD. The first subsection argues that the mental phenomenology of OCD is highly consistent with this disorder being a disturbance that involves willpower as a key element. The second subsection attempts to illustrate how the volition of the OCD patient is a powerful tool that can be used in rehabilitation through CBT. The third subsection outlines the Four Steps method of MBCBT (Schwartz 1996), which explicitly relies upon and seeks to build-up patient willpower.

The third major section concerns neuroimaging aspects of volition and OCD. It summarizes neuro-

imaging findings in OCD pathology and treatment, with special emphasis on Magnetic Resonance Spectroscopy (MRS) results. Certain neuroimaging measures may reflect brain energy metabolism and, thus subjective energy level, a critical cofactor with willpower in generating subject behavior. An hypothesis is advanced linking MRS and Positron Emission Tomography (PET) findings in OCD. Later subsections present neuroimaging findings in normals and patients that speak directly to the power of volition to alter brain physiology. Studies mentioned include the brain motor potential experiments of Libet et al. (1983ab) concerning the restricted timescale and inhibitory character of willpower.

The fourth and final major section concerns neuroplasticity and volition. This section briefly reviews neurophysiological evidence in favor of the existence of plasticity in the adult primate brain. The notion is invoked that CBT works by inducing neuroplastic changes in the brain. The anatomy of the fronto-striato-pallido-thalamo-frontal circuits of the brain ("fronto-basal gangliar circuits" for short), sites of pathology in OCD and likely sites of neuroplastic change in OCD recovery, is reviewed. This includes a discussion of the microanatomy of the caudate nucleus, where emotional and volitional factors may interact to initiate and maintain behavior. The critical role of voluntary effort in rehabilitation is underlined and the mental force concept is discussed.

Volition and cognitive-behavioral therapy (CBT) for OCD

This major section deals with the free will concept, the status of CBT as a treatment for OCD, and the two main varieties of CBT for OCD: ERP and MBCBT.

Attitudes Towards Free Will, or Volition, in Neuroscience

Despite the ubiquity of the will in everyday life, some clinicians and researchers are reluctant to embrace it as an explanatory concept and therapeutic instrument. Perhaps this is because the will seems unscientific. There are several reasons for this. Philosophers have long debated whether human beings possess free will (Fonsegrive 1896, Alexander 1898) without any widely-accepted resolution. Therefore, many pragmatic people reflexively regard contemplation of free will (and philosophical matters in general) as an idle waste of time. Even those who are philosophically inclined may side with leading thinkers of today (e.g., Double 1991, Honderich 2000, Wegner 2002) who believe that free will is an illusion. Finally, free will is naturally and traditionally intertwined with ethical ideas of sin, guilt, and responsibility and with supernatural notions of the soul, the Afterlife, and Divine Judgment, which many consider outside the realm of proper scientific investigation. A purpose of this review is to make the free will concept more palatable to readers who entertain such qualms. To this end, we note that it is completely feasible to accept even an immaterial free will with or without adopting any of the above moral or supernatural concepts.

Here we take the common-sense position that volition does exist. To defend this position adequately is beyond the scope of the present review. To provide, however, some passing explanation and motivation we indicate that this position stems from a *radical empiricist* perspective on what constitutes *primary data* in science (James 1912). A radical empiricist regards both subjective (e.g., sensations of willful exertion) and objective (e.g., readings on measuring instruments) mental experiences as primary data, as legitimate observations of reality. Both subjective and objective mental experiences are noted to manifest initially in the consciousness of some individual human being (a psychiatric patient, a therapist, an engineer, a laboratory technician…). Both acquire a revised status (consensus, validation, dismissal, etc.) when compared with kindred sensations of other humans (e.g., Lab Tech A agrees with Lab Tech B that a manometer reads 180 Torr, Depressive Patients C and D concur that seeing a stack of unpaid bills makes it difficult for them to focus on calculating their bank balances, but their two spouses find it difficult to empathize …). Whether one is comfortable with radical empiricism or not, we argue below that there is empirical evidence that such an entity as the will does exist and that, in any case, the free will construct is highly instrumental for understanding and treating OCD.

Cognitive-Behavioral, Neuropharmacologic, and Neurosurgical Treatment For OCD

Obsessive-Compulsive Disorder (OCD) is a prevalent and debilitating neuropsychiatric condition (Rasmussen and Eisen 1994,1998) with three major treatments: CBT (van Oppen and Arntz 1994, Greist 1996, Marks 1997, Kozak 1999, Neziroglu et al. 2000, March et al. 2001), neuropharmacology (Leonard 1997, Greist and Jefferson 1998, Goodman 1999, Pigott and Seay 1999, Albert et al. 2002, McDonough and Kennedy 2002, Vaswani et al. 2003), and neurosurgery (Mindus and Jenike 1992, Jenike 1998, Greenberg and Rezai 2003, Greenberg et al. 2003). Patient volition is an important element of all three modalities. For example, except for isolated and well-defined exceptions (e.g., unconscious patient in an emergency scenario, legal finding of lack of competency…), patient *consent* is an ethical prerequisite for all medical treatment. Whether consent has been obtained or not, patient *compliance* is a major, and often neglected, factor in success once treatment has commenced. Every psychiatrist, for example, knows that it is common for patients not to "take their meds" as prescribed and even to lie about whether they take them or not. Neurosurgical interventions typically also require patient compliance in the pre- and post-operative stages and even during procedures not involving sedation. Nonetheless, drugs and surgery do have the advantage of being able to induce therapeutic effects even when the patient is unable or unwilling to cooperate. CBT, too, can induce certain benefits "under the radar screen" as it were, for example, when a patient is put at ease by a therapist's affable tone and manner without even realizing it. But, on the whole, of the therapeutic modalities for OCD, CBT most consistently requires the willful and repeated participation of the patient in gathering the resolve to speak about

embarassing issues, in articulating his complaints, in listening attentively to the therapist, in methodically analyzing his situation, in complying with exercises in the therapist's presence and as homework, and in reporting back results. The more the patient "does work" in CBT, i.e., effortfully applies the principles prescribed by the therapist, the better the results are likely to be. Thus, the capacity of CBT to remediate OCD to some degree reflects the ability of the patient to cure him- or herself with applied volition.

What is the efficacy of CBT for OCD and how does it compare to drugs and surgery? CBT has a response rate of 50-60% among those seeking treatment, a rate considered at least as high as that of Selective Serotonin Reuptake Inhibitors (SSRIs), the most popular form of pharmacotherapy for OCD (Franklin and Foa 1998; Greist 1996, 1998; Kozak et al. 2000). For those completing treatment, CBT response rates up to 75% have been reported (Franklin and Foa 1998, Stanley and Turner 1995). Response rates of 30-80% are reported for neurosurgery, depending on procedure and outcome criteria (Rosenfeld and Lloyd 1999, Greenberg et al. 2003). No therapy is universally effective against OCD and responders to any therapy tend to retain residual symptoms (Greist et al. 1995, Abramowitz 1997, Kozak 1999, Greenberg et al. 2003). CBT and pharmacology are effective for patients of all levels of severity, while surgery, ideally, is reserved for highly disabled, otherwise intractable chronic patients (Yap 1995, Rosenfeld and Lloyd 1999, Cosgrove and Rauch 2003). Understandably, many eligible patients decline surgery or even medication due to risks and side effects. With medication, initial consent and subsequent failure to comply is common (Eisen et al. 1999), in the case of SSRIs typically due to side effects of sexual dysfunction, weight gain, and sedation. Dangers and side effects of CBT (e.g., heightened anxiety during treatment) are comparatively small making it a prime choice for many patients. Still, some patients are unsuited for CBT (e.g., those with cognitive difficulties and/or low motivation, as can be the case with comorbid depression), some do not consent (e.g., are intolerant of behavioral interventions), and some do not comply (e.g., those with low insight; Abramowitz et al. 2002). An initial course of CBT, perhaps reinforced by relapse prevention and occasional refreshers, can positively impact a patient's life for years (Marks 1997, Hand 1998, Hembree et al. 2003). Similarly, a single neurosurgical procedure usually imparts long-term recovery, but, some patients are recalled for subsequent operations (Spangler et al. 1996, Rosenfeld and Lloyd 1999). Drug regimens typically must be maintained long-term or indefinitely to uphold therapeutic response (Rasmussen and Eisen 1997, Greist et al. 2003, Hembree et al. 2003). For all three modalities, there is often a characteristic delay of weeks to months before appreciable symptom relief sets in (Ballantine et al. 1987, Schwartz 1996, Cosgrove and Ballantine 1998, Cosgrove and Rauch 2003). All three treatment modalities are frequently used in combination (Greist 1992, O'Connor et al. 1999, Foster and Eisler 2001, Foa et al. 2002, Hollander et al. 2002, Kampman et al. 2002). Thus, documented clinical experience to date strongly supports CBT as a powerful, low-risk option for primary and adjunctive treatment of many OCD patients. The success and practicality of CBT indirectly attest to the power and wisdom of exploiting patient volition in treatment.

Comparison of ERP and MBCBT For OCD

What are the major varieties of CBT for OCD and how do they differ in emphasis on patient volition? ERP (Stekete et al. 1982) is the most popular form of CBT for OCD. In ERP, the patient, alone or with therapist assistance, is exposed to the very contexts and stimuli that most incite his or her OCD tensions (and which he or she may customarily avoid). During exposure the patient is prevented from carrying out his or her usual, pathological response (typically enacting an OCD ritual or compulsion) to the anxiogenic situation and, in fact, may be instructed to execute an opposite response. For example, a patient with hand-washing compulsions who specifically avoids public toilets due to contamination anxieties is prescribed precisely to touch (in the presence of a therapist and/or alone as homework) a dirty public toilet bare-handed and is forbidden to wash the hands thereafter. Over time, after repeated sessions, in many OCD patients the specific anxieties and urges begin to subside (extinction) and the patient no longer carries out the compulsions.

The less widely practiced MBCBT, exemplified by the Four Steps method (Schwartz 1996, 1998, 1999), arose in part to provide a CBT option to those OCD patients who are unwilling or unable to surmount the anxiety barriers of ERP or who are seriously averse to hygienically dubious practices (such as touching public toilets) that CBT sometimes entails. MBCBT does not systematically prescribe exposures. [Although a recent innovation within the Four Steps called "Refocus With A Star" is, in some ways, functionally equivalent to exposure therapy (Schwartz 2001)]. Instead, the patient is taught to recognize OCD obsessions and compulsions as they arise naturalistically in the mind and quietly to note them as such. As in ERP, in MBCBT, the patient is instructed never to give in to OCD compulsions, but rather than doing the opposite of what the compulsion requires, in MBCBT the patient is told to *refocus* away from the maladaptive behavior demanded by his OCD to a pleasant, adaptive substitute behavior of his or her own choosing. For example, due to checking compulsion, a patient may multiply leave the house and enter the attached garage to verify that the garage door shut behind the car after driving in the last time. Under MBCBT, that patient is prescribed, whenever the compulsion to walk to the garage rises up, to say to him- or herself, "That's not me, that's my OCD… calling me to the garage!" Then, he or she is to resist going to the garage and is instead to do another, enjoyable activity, such as shooting a game of pool or knitting a sweater for a nephew. Again, over time, and with repeated effortful practice, in many patients the specific anxieties and urges subside. Many centers, including UCLA, employ MBCBT as a valuable adjunct to drugs and ERP. (This is a radically abbreviated description. For details see Schwartz 1996, 1997; Schwartz and Begley 2002).

With respect to patient volition, for many advocates, there is a difference in doctrinal tone between ERP and MBCBT. Many practitioners of ERP see it as work-

ing because the patient *is* exposed to anxiogenic situations and *is* prevented (passive voice) from responding to them maladaptively. ERP in humans indeed is closely analogous to behavioristic paradigms in animals who are "mindlessly" spurred-on and reined-in by human or automated trainer-directed rewards and punishments. (Although one may also argue that lower animals do possess some kind and degree of mind, or even volition.) In humans and animals, extinction of physiologic and behavioral responses is ascribed to involuntary forces acting over time upon material substrata in the subject's nervous system. From an MBCBT point-of-view, however, ERP works because the patient *exposes* him- or herself to anxiogenic situations and *prevents* him- or herself (active voice) from responding to them maladaptively. The MBCBT practitioner maintains that not only confrontation of urges, but also alternative exercises of the will, such as impartial observation and refocusing of attention, lead to symptom remission. I.e., ERP emphasizes the involuntary, automatic aspects of recovery; MBCBT emphasizes the willful, mindful aspects.

Neurocognitive aspects

This major section analyses the role of volition in the symptomatology of OCD and its treatment with CBT. The Four Steps method of MBCBT is discussed from the perspective of its use of patient will.

Volition in OCD Symptomatology

For reviews of the mental phenomenology of OCD see Greist et al. (2003) and Aouizerate et al. (2004). Volition is central to the symptomatology of OCD. So much so that the existence of OCD as a well-defined clinical disorder might count as evidence that volition exists as a specific brain-associated physiologic function. The OCD patient experiences intrusive, relentlessly repetitive idiosyncratic thoughts (*obsessions*) alongside powerful urges (*compulsions*) to perform personal OCD rituals or other highly specific acts (Attiulah et al. 2000). The persistent obsessions and compulsions typically foster considerable anxiety in the patient. In particular, the patient may dread that, if he or she does not yield to a compulsion, awful consequences may result. Anxiety may also manifest somatically, as tremor of voluntary muscles, through autonomic responses, and so on. Obsessions and compulsions are addressed to the will of the patient with the apparent goal of capturing the patient's willful attention or of impelling him or her to perform the voluntary act in question. Because they are experienced as coming from outside the self and because they are unpleasant, the obsessions and compulsions of OCD are referred to as *ego-dystonic*. This terminology reflects the subjective mental experience the OCD patient has of an intrusive source of powerful anxiogenic urges, of a self or ego outfitted with a will, and of a reactive pain-and-pleasure mediating soma that these two forces vie to control.

The structure of mental phenomena in OCD also bespeaks a (dysfunctional) working relationship between emotions and the will. In OCD, the connection between compulsive act and consequences putatively averted may be realistic (e.g., a compulsion to return repeatedly to check if a car door is locked for fear that the car might be stolen), tenuous (e.g., a compulsion to wash the hands after shaking even the clean hand of another for fear of contamination), or fantastic, so-called "magical thinking" (e.g., a compulsion to knock on wood three times whenever an airplane flies overhead in order to prevent a crash). The pathological thought processes in OCD are generally logical in structure (they follow "if… then… else" syntax; they classify objects systematically into categories, such as "clean" and "contaminated"; they respect associative links between concepts) but seldom *reasonable*. Instead powerful emotions in OCD drive an overestimation of risk and an undue respect for the trivial, so-called "overvalued ideas" (e.g., a patient checks the closet repeatedly before retiring at night based on the vanishingly small risk that a burglar may be hiding in there; a patient spends 20 min adjusting a crookedly hanging picture frame because the last vestige of asymmetry in its position is disturbing; Kozak and Foa 1994). It is also common in OCD for symptoms to generalize (e.g., a patient initially regards the toilet bowl as contaminated, then the whole toilet, then the rest of the bathroom, then the entire house,…) and for novel variations on symptoms to emerge (e.g., a patient initially fears that others are contaminating him or her, then additionally begins to fear that he or she is contaminating others). Thus, the logical cognitive and creative machinery of the brain can be recruited in response to OCD provocations. The will likewise is in intimate contact with the rational and creative faculties in its role as their persistent prodder and director; the will likewise avails itself of the (sparse or bountiful) possibilities generated by these faculties. Like the ego-centered, diversely independent, and myriad actions that can be pursued by the will, the specific symptomatic expressions of OCD are idiosyncratic, arbitrary, and essentially infinite in number. This high degree of similarity of character suggests that volition is centrally intertwined with the psychopathology of OCD.

Mental suffering in OCD is intimately tied-in to its relationship to the will. The content of OCD obsessions and compulsions can be hyper-conscientious (urges to check with multiple redundancy if appliances have been turned off, if doors have been locked, etc.), neutral (repeating banal words and phrases, recounting numbers of mundane objects, etc.), or negative (blasphemous, obscene, embarrassing, anti-social, self-destructive, etc.). Hyper-conscientious and neutral obsessions and compulsions are upsetting because they are useless and time-wasting, i.e., they offend the ostensive teleological functions of the will. Negative obsessions and compulsions additionally inflame the patient's anxieties due to their horrific character. Obsessions are distressing to the patient because they cannot be suppressed with the will. If the patient believes or suspects that they arise from past or present vices and misdeeds (failures of will), i.e., because he or she is a morally weak or inferior human being, the patient may suffer additional distress due to guilt and shame. Compulsions are distressing because they insist upon a response from the patient's will. However strong a compulsion, the patient must ultimately consent to it of his or her own free will if it is to be performed. Thus, yielding to compulsions can also induce guilt feelings in the patient. Inter-

estingly, although OCD patients *habitually* yield to hyper-conscientious and to neutral compulsions, they *never*–despite mental torment–submit to acting on negative (blasphemous, violent, etc.) obsessions (Schwartz 1996). This is an important further indication that a final veto power of the will is intact in OCD and it is tremendously relieving and therapeutic to explain to patients that they *never* actually will commit the taboo acts of their fancy. The prominence and pervasiveness of guilt and conscience in OCD again suggest involvement of volition in this condition since the experience of guilt and conscience depends upon an at least implicit belief in free will on the part of the patient. As the foregoing implies, remnants of willpower that are intact in the OCD patient form a foundation upon which CBT can build.

OCD also often entails misapplication and distortion of the will. "Magical thinking" is a common feature in OCD presentations (Einstein and Menzies 2004). It represents a pathologically exaggerated and distorted operational concept of the power and burden of the will. For example, catastrophic events can magically be "forestalled" by the willful performance of certain nominally empty rituals. This represents perhaps an expression of the *hyper-responsibility* (Salkovskis 1985, Rachman 1993) prevalent in OCD patients. Symptoms of the hoarding subtype of OCD, in contrast, may be interpreted as an alternative strategy for dealing with willful responsibility. When faced with the decision to read or to discard a magazine, for example, a hoarder may put off the decision by pigeon-holing it into a pile. Similarly, OCD patients habitually spend enormous amounts of time wrapped up in burning, but, in practical terms, trivial obsessions and compulsions instead of confronting critical issues in their lives. Conscious, bull-by-the-horns self-direction is replaced with ritual. Thus, the mental symptoms of OCD reflect disturbances of the volitional function. There is an exaggerated sense of the power and burden of the will; the will is called upon to pay attention to trivial matters and to carry out useless, even counter-productive deeds; guilt is felt for things that the will is not really responsible for; and, because a high priority is assigned to everything, there is a certain weakness of the will in making decisions (Frost and Shows 1993, Ferrari and McCrown 1994).

Volition in CBT For OCD

Volition is likewise a key factor in CBT for OCD. Just as OCD symptomatology represents a disturbance of the will, CBT for OCD consists in relearning proper mastery of the will. It has already been mentioned that ERP, the most widely used form of CBT for OCD, although usually thought of as an involuntary, behavioristic technique, may alternatively be seen as an exercise of the OCD patient's will to expose him- or herself voluntarily to anxiogenic situations whilst voluntarily refraining from the compulsions associated therewith.

Emotions, in particular negative affect, clearly aggravate the relentless, repetitive character of OCD thoughts. Two factors allay exaggerated or persistent and ruminative responses to emotional impulses in normals and in OCD patients. The first is the tendency for OCD thoughts to dissipate, as they either transition from short- to long-term memory or are forgotten. The second is willpower. Willpower feeds a compulsion if it gives in to it. Willpower unsuccessfully delays an obsession if it tries to suppress it. But if willpower does the opposite of what a compulsion requires, observes a compulsion without yielding to it, or redirects attention to an alternative, adaptive action, these therapeutic responses ultimately lead the obsession to decay.

In cognitive therapy it is therefore important to instruct the patient to recognize OCD patterns whenever they crop up in thought. This is so that the patient will know which (healthy) thoughts it is okay to comply with and which (unhealthy OCD) thoughts the patient should do the opposite of, quietly observe without yielding to, or redirect attention away from. It is also important to cultivate wisdom or reason, rather than superficial, ineffectual rationalization, in the patient; to teach benign neglect, to ignore things that are not genuinely high priority. The patient can also be taught to recognize hyperrationality–considering even remote possibilities, giving weight to even trivial factors– as a typical OCD thought pattern.

The Four Steps Method of CBT For OCD

The Four Steps method of MBCBT for OCD (Schwartz 1996) explicitly incorporates willful action as a key element of therapy. The Four Steps of OCD therapy are: Relabel, Reattribute, Refocus, and Revalue. In Relabel, the patient learns to recognize OCD obsessions or compulsions whenever they arise in the mind and to relabel them as such. The key rule here is: "If it feels like OCD– it is!" I.e., because obsessive thoughts are so prevalent in the typical OCD patient's mind, when wondering whether or not a particular thought stems from OCD the default option is: Yes, it is OCD. The patient grows in mindful awareness that the intrusive thoughts are not normal, but rather are symptoms of a brain disorder. Rather than try to force the thoughts away, the patient is instructed simply to observe them with the perspective of an Impartial Spectator (an arbiter of common sense, of reason rather than mere rationalization). Thus, the patient learns to use the will properly, by not exercising it against things (the urges) over which the will has no control, but rather by reserving the will for what it does have control over– the patient's responses to the urges. In Reattribute, the patient instructs himself that the obsessions and compulsions he or she experiences do not arise because he or she is a bad person; rather they are a product of a brain-based medical condition (OCD). Thus, the OCD thoughts are not meaningful, not to be taken at face value, but rather are false messages from the brain. The Reattribute step is especially useful for treating symmetry compulsions if the patient can realize that the need to "get the right feeling", for "evenness" or a sense of completion is actually a product of OCD. Whenever he or she encounters an OCD thought, the patient tells him- or herself, "It's not me, it's the OCD!" The patient willfully adopts the perspective of an Impartial Spectator using "effort of attention" (James 1892/1992) to observe OCD symptoms dispassionately rather than identifying with them. In Refocus, with considerable effort of free will (or "free won't"; Schwartz and Begley 2002, Chapter 9), the pa-

tient resists OCD compulsions and redirects attention towards alternative, adaptive ego-syntonic behaviors. Finally, in Revalue, effortfully maintaining the perspective of the Impartial Spectator, the patient realizes that the OCD feeling is not worth listening to, is not to be taken at face value. Repeated adoption of the Impartial Spectator frame-of-mind eventually leads to a sense of freedom and an enhancement of the ability to make self-directed choices. Thus, the therapy establishes a proper delineation of the domains of the willful and the involuntary.

Thus, the overall strategy of MBCBT is a healthy restructuring of the perceived and practiced role of the will in the management of everyday thoughts and emotions. The patient is assured that he or she is not responsible for the (often shameful and horrific) contents of his or her OCD thoughts. Nor is he or she to atone for all that OCD has done up to the present, the years of life wasted in meaningless rituals and so on. *But*, now that the patient does understand the true state-of-affairs, he or she *is* responsible for doing something about it, for taking charge of his or her life. In particular, the patient is responsible for recognizing OCD obsessions for what they are, for *not* giving in to the frequent and myriad compulsions, for actively refocusing on alternative, ego-syntonic activities, etc.

The efficacy of the Four Steps method in treating OCD has been proved on hundreds of patients at UCLA, but little tested in formal trials. Important exceptions include the work of Schwartz et al. (1996) and of Benazon et al. (2002). In the context of depression, Teasdale and co-workers (Segal et al. 2002, Teasdale et al. 2002) have demonstrated remarkable treatment power of the closely related Mindfulness-Based Cognitive Therapy (MBCT), especially in preventing relapse. Larger trials of MBCBT at additional centers represent an important unmet need in OCD research.

Neuroimaging aspects

This major section concerns neuroimaging aspects of volition and OCD. It summarizes neuroimaging findings in OCD pathology and treatment, with special emphasis on MRS. Connections between [18F]fluorodeoxyglucose PET (^{18}FDG-PET) and proton MRS (^{1}H MRS) observations in OCD and other conditions are hypothesized. We also discuss cognitive neuroimaging findings in OCD patients and normals that are germane to issues of free will and the brain, including studies of electric motor potentials. The latter suggest that free will has an inhibitory character and acts over a timescale ≥ 100 ms. We apologize in advance for loose usage of the term "neuroimaging" to include single-voxel MR spectra and single-channel EEG traces.

Summary of Pathological Neuroimaging Findings in OCD

Several high-quality reviews of the neuroimaging literature in OCD have appeared over the years (e.g., Baxter 1992, Baxter et al. 2000, Rauch and Savage 2000, Rauch 2003). Neuroimaging findings in OCD mainly concern node structures of the fronto-striato-pallido-thalamo-frontal circuits of the brain ("fronto-basal gangliar circuits" for short) and their interconnecting white matter. These circuit loops are central to the pathophysiology of OCD and related disorders, such as Tourette's syndrome and trichotillomania (Rapoport and Wise 1988; Modell et al. 1989; Baxter et al. 1990, 1992; Insel 1992; Rauch and Jenike 1993, 1997; reviewed by Rauch at al. 1998, Saxena et al. 1998, Rauch and Savage 2000). The specific syndrome manifested by a patient depends on which part of the striatum and associated loops are impacted ("striatal topography hypothesis"). The lateral orbitofrontal (orbitofrontal cortex, caudate head, globus pallidus, dorsomedial thalamus, and other structures) and limbic (anterior cingulate, nucleus accumbens, ventral pallidum, ventral anterior thalamus, and other structures) loops are central to OCD pathophysiology.

Briefly, the key pathological neuroimaging findings in these structures in OCD are as follows (Rauch 2003): 1) Volumetric MRI and ^{1}H MRS suggest white-matter irregularities and striatal pathology; 2) In the rest state, patients exhibit above-normal glucose metabolic rate (GMR; as evidenced by ^{18}FDG-PET) and/or regional cerebral blood flow (rCBF; as evidenced by $H_2{}^{15}O$-PET) in one or more node structures; and 3) rCBF and/or neuronal activity (as evidenced by BOLD-Effect fMRI) are further elevated beyond rest levels during OCD symptom provocation (a near immediate effect). Overall, there is clear and long-standing neuroimaging evidence of structural, metabolic, and functional abnormalities in fronto-basal gangliar loop structures linked to the presence and symptomatic expression of OCD.

Pathological ^{1}H MRS Findings in OCD

Relative to PET and fMRI, MRS results in OCD have received limited attention (Rauch 2003). Therefore, in the following we comment on some aspects of ^{1}H MRS results. First, for those unfamiliar with the methodology, we review the chief metabolite endpoints of ^{1}H MRS and their interpretations. At standard clinical magnetic field strength (1.5 T) and short echo-time (≤30 ms), the water-suppressed proton MR spectrum of the human brain presents the following series of principal resonances of physiologically significant neurometabolites (Frahm et al. 1989). Centered at 2.02 ppm is the "NAA" peak. (In this review, abbreviations for MRS resonances appear in quotes while abbreviations for the chemical metabolite compounds generating these resonances appear without quotation marks). The area of the "NAA" peak is proportional to the concentration of *N*-acetyl compounds, chiefly *N*-acetyl-aspartate (NAA) and *N*-acetyl-aspartyl-glutamate (NAAG), in the tissue scanned. Neighboring "NAA" at 2.1-2.5 ppm is the "Glx" peak. Its area is proportional to the summed concentrations of glutamate (Glu) + glutamine (Gln) + GABA. Next, the "Cr" peak (3.02 ppm) represents the sum of creatine (Cr) + phosphocreatine (PCr). Then the "Cho" peak (3.24 ppm) represents the sum of multiple choline-containing compounds, including phosphocholine (PC), glycerophosphocholine (GPC), choline proper (Cho), and

others (Barker et al. 1994). Finally, closest to water at 3.56 ppm, the "mI" peak mainly represents the sugar *myo*-inositol (mI).

The structural and physiologic correlates of these ^{1}H MRS metabolites are not all certain. There exist, however, the following rough interpretive frameworks. Because *N*-acetyl compounds are abundant in neurons and scarce in mature glial cells, "NAA" area is widely taken as an indirect metric of tissue neuron density (Birken and Oldendorf 1989, Urenjak et al. 1992, Michaelis et al. 1993). Because Cr and PCr, choline compounds, and mI are present at substantially higher concentrations in glia than in neurons (Urenjak et al. 1992, Brand et al. 1993) the "Cr", "Cho", and "mI" peaks can be taken as even more indirect markers of tissue glial density, or as markers of "total cell" (neurons + glia) density. The physiologic function(s) of NAA are unknown, but the case is getting stronger that it is an important neuronal osmolyte that transports water generated by energetic metabolism out of the cell (Baslow 2002). Glu, Gln, and GABA, apart from being important neurotransmitters, are involved in energetic metabolism *via* the Krebs Cycle (Petroff et al. 2000). Cr and PCr famously interreact in ATP-transduction in brain and muscle (Siesjö 1978; see below). Thus, "Cr" area might in some indirect manner reflect the state of cell-energy metabolism. Choline compounds (Aiken and Gillies 1996) and mI (Manji et al. 1996) participate in phospholipid metabolism. Therefore, abnormal "Cho" and/or "mI" peaks might signal cell-membrane disorder. In particular, high "Cho" areas might signal enhanced membrane turnover (synthesis and/or degradation) because cytosolic choline compounds generally contribute to "Cho" area, whilst membrane-integral choline compounds are typically MRS invisible. Thus, ^{1}H MRS provides clues to the cellular composition and energetic and membrane status of brain tissues. The putative relationship of certain MRS endpoints to brain energy metabolism is relevant to the present review in so far as brain energetic state profoundly influences passive aspects of subjective experience, which interact with active willpower in initiating and maintaining behavior.

There are relatively few published MRS studies of OCD. Ohara et al. (1999) acquired ^{1}H MRS from the right lenticular nucleus and found no differences between OCD patients and controls. This may have been because metabolite levels sampled from the lenticular nucleus represent an average of the putamen and the globus pallidus, two heterogeneous nuclei. Such "partial voluming effects" plague MRS studies, especially those using large acquisition volume ("voxel") sizes. Bartha et al. (1998) found below-normal "NAA" in left striatum of OCD patients. As volumes of left and right caudate were normal in OCD in this study, this suggests that MRS can detect neuronal pathology in OCD not visible even to quantitative structural MRI. Ebert et al. (1997) measured levels of *N*-acetyl compounds relative to those of creatine + phosphocreatine ("NAA/Cr"). It is a common practice in MRS to express metabolite levels as ratios to "Cr"; a practice that unfortunately renders results ambiguous to interpret. In right striatum and midline anterior cingulate, "NAA/Cr" was lower in OCD patients than in healthy controls. These findings could be due either to lower "NAA" or to higher "Cr" in patients. "NAA/Cr" was especially low in male patients. In the cingulate, "NAA/Cr" correlated negatively with Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al. 1989) score. In a study that took an interestingly unconventional approach to MRS, Grachev and Apkarian (2000) acquired ^{1}H MRS in thalamus and in dorsolateral prefrontal, orbitofrontal, cingulate, insular, and sensorimotor cortices of normals who were evaluated with the State-Trait Anxiety Inventory. In orbitofrontal cortex only, "NAA/Cr", "GABA/Cr", "(GABA+Glu)/Cr", "Gln/Cr", "Glc/Cr", and "mI/Cr" were all higher for high-anxiety than for low-anxiety normals (Glc = glucose). "NAA/Cr" and "Gln/Cr" in orbitofrontal cortex both correlated positively with total anxiety score. Note that these results could bespeak an elevation of all resonances other than "Cr" and/or a decrease in "Cr" itself in orbitofrontal cortex of more anxious subjects. These findings suggest a sensitivity of orbitofrontal cortex metabolism to normal anxiety or *vice-versa*. Taken together, the above studies hint at shifts in neuronal integrity and/or in energetic metabolism in fronto-basal gangliar loop structures in OCD patients and anxious normals.

Summary of Neuroimaging Findings in OCD Treatment

The above-cited reviews also discuss neuroimaging studies of OCD treatment. The principal findings are (Rauch 2003): 1) Elevated GMR, rCBF, and/or BOLD Effect in fronto-basal gangliar loop node structures in OCD are attenuated after successful treatment with SSRIs and/or CBT and 2) Pre-treatment activity within the orbitofrontal cortex predicts subsequent response to drugs or CBT. Thus, certain neuroimaging abnormalities discovered in OCD are reversible with treatment and some have prognostic value.

Alongside the above-discussed lateral orbitofrontal and limbic "worry circuits" thought to promote OCD symptoms, the dorsolateral prefrontal loop (dorsolateral prefrontal cortex, caudate head, globus pallidus, dorsomedial thalamus, and other structures) is hypothesized to constitute a "therapy circuit" for OCD (Schwartz 1999, Schwartz and Begley 2002). Willful intervention on the part of the OCD patient practicing MBCBT may be mediated by this circuit. Repeated refusal to submit to compulsions and active substitution of alternative, ego-syntonic activities on the part of the patient is thought to strengthen the therapy circuit whilst allowing the worry circuits to weaken. To date, direct neuroimaging investigation of the dorsolateral prefrontal circuit in OCD has been limited. Studies are underway at UCLA. Studies by Beauregard et al. (2001) and Ochsner et al. (2002) in normals strongly suggest this role for prefrontal cortex will be seen in OCD and other conditions.

Symptom Provocation Reversal: An Experimental Paradigm For OCD Treatment

PET and fMRI findings mentioned above suggest an important experimental paradigm that remains to be tested in OCD: *symptom provocation reversal*. In this

paradigm, a treatment-naïve OCD patient undergoes fMRI and/or $H_2{}^{15}O$-PET to test for elevated BOLD and/or rCBF response during OCD symptom provocation. Then, following successful treatment, the patient is again exposed to symptom provocation in the scanner and the neuroimaging responses noted. An hypothetical result is failure to observe the pathological pre-treatment exaggerated response to provocation. In its place, one might expect a normalized or an overly attenuated response, or a change in the brain topographic distribution of the response. Acute conscious control over the brain response can also be tested by instructing the patient while in the scanner, e.g., "Now just let your OCD loose!", "Now just quietly observe your urge without giving in to it!", … If symptom provocation reversal is present chronically and not under the patient's conscious control, this might suggest that therapy was effective mainly through avolitional mechanisms (e.g., extinction following ERP or suppression of urges following SSRI treatment). If, however, symptom provocation reversal is present acutely and under the patient's conscious control, that would suggest that the patient's conscious will has been (and perhaps even remains) instrumental in recovery (e.g., following MBCBT). A symptom provocation reversal paradigm might thus contribute to understanding the relative roles of volitional and automated processes in patient reaction to OCD treatment. Using a similar such paradigm, Paquette et al. (2003) showed that effective CBT changed the BOLD fMRI response to symptom provocation in the dorsolateral prefrontal cortex of patients with spider phobia. Beauregard et al. (2001) and Ochsner et al. (2002) have applied analogous provocation reversal paradigms with normals subjected to erotic or stressful stimuli.

Neuroimages as Didactic Aides in OCD Treatment

An important aspect of neuroimaging in OCD that has been little discussed in the literature to date is the integration of neuroimages themselves directly into CBT, a routine practice at UCLA. An OCD patient is shown, for example, axial ^{18}FDG-PET sections of the brain. The brains are of normals and of representative OCD patients (perhaps even him- or herself). Other such sections depict regional GMR of patients in fronto-basal gangliar loop structures before and after treatment. Such images have been incorporated into a popular manual for self-help and therapist-assisted treatment (Schwartz 1996). They serve multiple educational and motivational functions. First, comparison of normal and OCD scans helps convince the patient that he or she is indeed suffering from a medical condition and not, say, from a moral defect. Second, the therapist employs the images to explain the roles of orbitofrontal cortex, basal ganglia, and other brain structures in OCD. Third, the after images of OCD, illustrating post-treatment reductions in GMR, instill tremendous hope in many patients. Hope that therapy can induce physiologic changes in the brain and hope that the patient will get better, if he or she stays the course. This is especially important for CBT. The images show patients that psychological therapy has real physical effects just as drug treatment does, and that the mind *can* change the brain. This point should be emphasized. Because OCD is "la maladie de la doute" ("the disease of doubt"), patients will seize immediately upon any proposition with the slightest tinge of verisimilitude– if it means bad news. If the proposition means good news, patients must be confronted– repeatedly –with the most concrete evidence at hand, before they will slowly come to accept it. The objectivity of the neuroimages and their association with technological and medical authority are significant assets in this regard.

^{1}H MRS Findings in OCD Treatment

Two MRS papers have special relevance to OCD treatment. Strauss et al. (1997) used ^{19}F MRS to monitor brain levels of fluvoxamine in adult responders with OCD. Steady-state brain levels were reached after 30 days of dosing. Mean steady-state levels were 24 times higher in brain than in plasma. Steady-state brain levels did not correlate with dose. This suggests that active levels of SSRIs may be much higher than suggested by blood draws and underscores the importance of titrating SSRI dose to individual patient therapeutic and side effect response. Using ^{1}H MRS, Benazon et al. (2003) found no changes in metabolites in pediatric OCD patients following successful CBT. Lest one conclude, however, that CBT does not alter brain function in OCD, it should be noted that this study acquired ^{1}H MRS exclusively from the *left* caudate head. Since prior studies (Baxter et al. 1992, Schwartz et al. 1996) found greater response to CBT in *right* caudate head, Benazon et al. (2003) may have missed potential metabolite responses due to unilateral acquisition. Studies in child and adult OCD are underway at UCLA acquiring ^{1}H MRSI before and after CBT bilaterally from caudate head (and from anterior cingulate, frontal white matter, and other brain regions) to test this possibility.

In addition to Benazon et al. (2003), the Wayne State group has made several other significant contributions to MRS of pediatric OCD. In left caudate of patients, they demonstrated elevated "Glx" levels that declined in response to paroxetine treatment and in correlation with declining symptom severity (Rosenberg et al. 2000). Apart from showing the sensitivity of ^{1}H MRS measures to the presence and severity of OCD, this study provides evidence of neurotransmitter or cell-energetic disturbances even in left caudate in this condition. In a case study, the "Glx" decrease persisted after discontinuation of medication (Bolton et al. 2001). This suggests that long-term therapeutic and/or untoward effects may be induced by pharmacologic treatment in the patient brain. If the identically acquired data of Rosenberg et al. (2000) and of Benazon et al. (2003) are pooled and reanalyzed, pre-treatment pediatric OCD patients had, in addition to significantly higher "Glx", significantly higher "Cr" and "Cho" and a trend to higher "mI" than healthy controls in left caudate head. In addition to providing further evidence of cell-energetic and/or cell-membrane abnormalities in the caudate in OCD, these results may stem from excess glial numbers and/or metabolism in this nucleus. Note that high levels of "Glx" may be driven by elevated brain Gln, which is synthesized only in glial cells (Martinez-Hernandez et al. 1977) and broken down only in neurons (Kvamme et al. 1985). Fitzgerald et al. (2000) measured below-

normal "NAA/Cho" and "NAA/(Cho+Cr)" bilaterally in medial but not lateral thalamus in pediatric OCD. Note that the medial thalamus participates in the dorsolateral prefrontal, lateral orbitofrontal, and limbic loops implicated in OCD; the lateral thalamus participates in the motor and oculomotor fronto-basal gangliar loops (Alexander et al. 1986,1990; Alexander 1994). Subsequent measurements of Smith et al. (2003) suggest that high "Cho" contributes to the low values of "NAA/Cho" and "NAA/(Cho+Cr)" in the medial thalamus of pediatric OCD patients. Above-normal gray-matter volume of the thalamus was also determined by volumetric MRI in medication-free adult (Kim et al. 2001) and pediatric (Gilbert et al. 2000) OCD patients. Paroxetine treatment led to subsequent thalamic volume reduction (Gilbert et al. 2000). Abnormalities in myelination or other cell-membrane pathology may contribute to these thalamic "Cho" and volumetric abnormalities. Low "NAA" and/or high "Cr" may signal neuronal, glial, and/or energetic dysfunction in this nucleus.

Possible Cellular-Energetic Substrates of ^{18}FDG-PET and ^{1}H MRS Findings in OCD

Here and in the next subsection, we make speculative attempts to link PET and MRS findings in OCD and to relate them to OCD symptomatology. In this subsection, we hypothesize co-occurrence of above-normal GMR and above-normal "Cr" in fronto-basal gangliar loop structures in OCD. This hypothesis derives from the normal flow of energetic metabolism in brain tissue (Siesjö 1978) as follows. ATP is converted to ADP and inorganic phosphate (Eq. 1) yielding immediate energy for metabolic end-processes, such as active transport of ions across cell membranes. When ATP reserves are exhausted, the reversible interconversion of PCr and Cr (Eq. 2; creatine-phosphocreatine buffer, creatine kinase shuttle) provides back-up ATP. Glycolysis (Eq. 3) represents a tertiary ATP source.

(1) $ATP \rightarrow ADP + P_i$ **metabolic end-processes**

(2) $ADP + PCr \leftrightarrow ATP + Cr$ **creatine-phosphocreatine buffer**

(3) $Glc \rightarrow ATP$ **glycolysis**

The creatine kinase shuttle and other phosphoryl relays are sensitive to dynamic fluctuations in cellular ATP supply (Dzeja and Terzic 2003). Therefore, elevated glycolysis may lead to greater throughput of ATP. GMR, as measured by the ^{18}FDG-PET signal, is essentially the local rate of glycolysis (Phelps et al. 1979), while "Cr" area, as mentioned, is proportional to local concentration of Cr + PCr. Conditions such as OCD, manifesting chronically elevated regional GMR, might thus promote enlargement of the Cr-PCr reservoir, i.e., higher concentrations of both Cr and PCr, leading to a larger ^{1}H MRS "Cr" peak as a pathological, adaptive, or compensatory response

Evidence linking glucose metabolism and creatine is at present indirect and cross-sectional. Thus, above-normal "Cr" has been observed in pediatric OCD (Rosenberg et al. 2000, Benazon et al. 2003) in the caudate where above-normal GMR has been seen in adult OCD (Rauch and Savage 2000, Rauch 2003). In childhood autism, a condition with stereotypies that resemble the rituals of OCD (Sears et al. 1999), above-normal "Cr" has been seen in right caudate (Levitt et al. 2003) and in adult autism above-normal GMR has been seen in right caudate (Rumsey et al. 1985). Right caudate "Cr" was significantly lower in medicated than in non-medicated child autistics (Levitt et al. 2003). In different groups of adult Huntington's patients, below-normal "Cr" (Sanchez-Pernaute et al. 1999) and below-normal GMR (Andrews and Brooks 1998) have been observed in striatum. At UCLA, parallel ^{18}FDG-PET and ^{1}H MRS studies are underway in adult OCD patients to test the hypothetical correlation of "Cr" and GMR directly. ^{31}P MRS may also be helpful in distinguishing Cr from PCr contributions to the "Cr" peak in OCD, although even at high field ^{31}P MRS may be limited by low spatial resolution.

Possible Relation of Neuroimaging Findings in OCD and Other Mood Disorders to Neuroglia

Increased "Cr" and GMR in OCD may in part be glial-mediated phenomena. The "Cr" peak from glial extracts is larger than that from neuronal extracts (Urenjak et al. 1992) and the contribution of glycolysis to ATP production in the astrocyte, a species of glia, is appreciable (25-32%; Silver and Erecinska 1997). The Magistretti-Pellerin model of brain energetic metabolism (Magistretti and Pellerin 1996abc, Magistretti et al. 1999) in fact proposes that the ^{18}FDG-PET signal from human brain arises primarily from astrocytes, rather than neurons. Thus, elevated GMR in thalamus, caudate and other fronto-basal gangliar loop components in OCD (Rauch and Savage 2000, Rauch et al. 2003) may reflect glial proliferation and/or hyperactivity in these regions. Glial proliferation may also contribute to thalamic hypertrophy in OCD (Kim et al. 2001, Gilbert et al. 2000) and/or to volumetric abnormalities in striatum or white matter (reviewed in Rauch 2003).

Other results, however suggest a more complicated picture. For one thing, "Cr" levels from neuronal and glial tissues are close enough to make the "Cr" peak a relatively poor discriminator between the two cell types (Ross and Blüml 2001). One speaks sometimes instead of "Cr" area being proportional to overall cell density. Secondly, cross-sectional *in vivo* ^{18}FDG-PET (Drevets et al. 1997,1998ab; Drevets 1999), and *post-mortem* neuropathology (Öngur et al. 1998) studies of unipolar and bipolar depression suggest that *below*-normal glial numbers (with no equivalent loss of neurons) co-localize with *above*-normal glucose metabolism in the subgenual anterior cingulate. This result may be explicable in terms of the sharing of the metabolic energy burden of the brain between neurons and astrocytes (Magistretti et al. 1999). Astrocytes envelope the brain capillaries with their pseudopodia and thus access incoming glucose before neurons do. Rapid glycolysis in astrocytes then provides energy for short-term demand, passing on lactate to neurons as an energy substrate. Neurons metabolize lactate *via* the Krebs Cycle and oxidative phosphorylation yielding slower, but more

bountiful energy for longer-term needs [altough recent evidence (Kasischke et al. 2004) suggests that neuronal mitochondrial oxidative phosphorylation may procede astrocytic glycolysis]. In human brain, neurons are responsible for 70-80% of total glucose oxidation while glia are responsible for 10-20% (Shen and Rothman 2002). Given the tight regulation of brain energy metabolism, it is likely that the numeric proportions of neurons and glia are balanced in each region of the brain in order to minimize energy consumption, contingent on ready availability. Pathological or compensatory aberrations in relative numbers of glia in either direction could lead to elevated glucose consumption. In particular, a rise in glial numbers would hike the glycolysis rate directly; a dearth of glial cells interposed at the capillaries could expose the glucose supply to neurons with their comparatively greater metabolic appetite for substrate and, thus, also lead to an increase in glucose consumption.

In Baslow's (2002) comprehensive theory, NAA principally functions as an osmolyte that transports the enormous quantities of water generated by neuronal energetic metabolism out of the cell. Baslow's theory incorporates Magistretti-Pellerin implicitly and couples NAA synthesis to glucose metabolism (Moreno et al. 2001). Thus, previous NAA findings in OCD (Ebert et al. 1997, Russell et al. 2003) may also be related to cellular-energetics disturbances in as yet undefined ways.

Excess glucose consumption arising, as outlined above, in consequence of aberrant numbers of neurons and glia could contribute to the characteristic fatigue of OCD, Major Depressive Disorder (MDD), and other mood disorders. Since the human brain is the largest consumer of total body O_2 (20%) and glucose (25%), which are delivered by 15% of total cardiac output (Schurr and Rigor 1998; Magistretti et al. 1993), even regional inefficiencies in brain energetic metabolism, especially when chronic, could have noticeable effects on subjective energy level. This paucity of energy could make tasks subjectively more demanding for the patient, tether him to low-energy rituals, and thus drive the pathological affective behavior.

Functional Neuroimaging in OCD and Free Will

fMRI (Rauch et al. 2001) and functional $H_2{}^{15}O$-PET (Rauch et al. 1997) studies suggest that OCD patients apply fundamentally different strategies than healthy controls in solving certain cognitive tasks. In these experiments, healthy controls and OCD patients were both asked to solve a linguistic and a more automated task (implicit sequence learning) while functional imaging was acquired. Controls showed activation (enhanced BOLD or rCBF) of mesial temporal-lobe structures while they solved the linguistic task and striatal activation while they executed the automated task. OCD patients, in contrast, showed mesial temporal-lobe activation while solving tasks of both types. Performance for the two subjects groups was not significantly different for either task type when the tasks were performed in isolation. When, however, the automated task was executed in parallel with another verbal task, performance for OCD patients was significantly below that of controls. This suggests that part of the symptomatology of OCD consists in a "misapplication" of the will, i.e., the cortical structures normally involved in conscious, willful actions such as those entailed in language processing are also being used to direct normally automatized functions of the basal ganglia. It is assumed this "misapplication" of willful effort is due to a wholly involuntary brain processing deficit in the striatum. Nevertheless, preliminary data obtained at UCLA suggest this information processing defect may be reversible with psycholgical treatment.

Functional Neuroimaging in Normals and Free Will

Acute functional neuroimaging experiments in healthy subjects suggest that free will does exist and that it exhibits certain brain physiologic manifestations. Beauregard et al. (2001) acquired fMRI of the brain whilst exposing subjects to sexually erotic images. Two conditions were compared. In one, the subject was free to respond "normally" to the image; in the other, the subject was to voluntarily inhibit sexual arousal. The normal viewing condition elicited BOLD activation in right amygdala, right temporal pole, and hypothalamus, one of the few fMRI experiments to date to obtain a functional hypothalamic response. The voluntary inhibition condition markedly attenuated the limbic and diencephalic activation and instead elicited BOLD activation in right superior frontal gyrus and right anterior cingulate gyrus. Thus, the willful restraint on the part of subjects changed the distribution of BOLD Effect in their brains. Similarly, Ochsner et al. (2002) acquired fMRI whilst showing subjects hideous accident photos. In one condition, subjects were given free reign to their spontaneous feelings of horror, revulsion, and disgust. In the other, subjects were to adopt the objective attitude of a paramedic, clinically and rationally evaluating victims' wounds and so on ("cognitive reappraisal"). Cognitive reappraisal yielded increased BOLD activation of lateral and medial prefrontal cortices and decreased activation of amygdala and medial orbitofrontal cortex. In each of the above studies, the mental action of acutely shifting attitude and cognitive perspective, i.e., performing a voluntary cognitive reappraisal of the stimulus configuration presented, led to a measurable, time-correlated change in the BOLD signal in a functionally appropriate brain region. This can be seen as direct empirical evidence that the will influences brain physiology, at least in acute scenarios.

Electrical Motor Potentials of the Brain and Free Will

In the field of cognitive evoked potentials of the brain (EPs), Libet (1983ab) used the celebrated Bereitschaftspotential ("readiness potential"; Kornhuber and Deecke 1965), one of the canonical components of the electrical motor potential of the brain, to characterize free will and its functionality in the human nervous system. Motor potentials were recorded preceding and following self-initiated voluntary movements and analyzed in conjunction with the subjects' introspective sensations of when they initiated the movement. Libet's (1998, 1999) latest analysis of his many years' work in this area concludes that free will takes the form of a

veto power ("free won't") over a given about-to-be-consummated motor action that is positively driven by non-willful, more deterministic factors in the brain. Free won't is exercised on a timescale of ≥100 ms. Libet's work represents strong electrophysiological evidence for the existence of a will and characterizes its dynamic nature. This work is reviewed in in detail in Schwartz and Begley (2002, Chapter 9).

Neuroplastic aspects

This major section concerns neuroplasticity and volition. Some neurophysiological evidence in favor of the existence of plasticity in the adult primate brain is reviewed. Then the anatomy of the fronto-basal gangliar circuits of the brain, sites of pathology in OCD and possibly of plastic transformation in OCD recovery, is reviewed. This includes a discussion of the microanatomy of the caudate nucleus, where emotional and volitional factors may interact to initiate and maintain behavior. The critical role of voluntary effort in rehabilitation is underlined and the mental force concept is discussed.

Neuroplasticity in Adult Primates and Neurologic Patients

Both the worsening of OCD symptoms through chronic bad cognitive habits and the amelioration of OCD symptoms through CBT are believed to work by inducing neuroplastic changes in the brain (Schwartz 1999, Schwartz and Begley 2002). The plausibility of this proposition is supported by the high degree of neuroplasticity present even in the adult primate brain. Musso et al. (1999), for example, conducted $H_2{}^{15}O$-PET measurements in Wernicke aphasics with left-sided middle cerebral artery infarctions before and after intensive language comprehension training. They found that post-training improvement in verbal comprehension correlated with increased rCBF in right superior temporal gyrus and left precuneus. These results suggest functional plasticity of the adult brain, i.e., that brain regions not normally specialized for language comprehension can take on this function following training. Note that this training is quite effortful for the patient. Some of the best evidence for adult plasticity comes from experiments of Merzenich and co-workers (Jenkins et al. 1990). Using careful single-unit recordings they showed that the specific cortical surfaces encompassed by the motor and sensory homunculi of adult monkeys change radically depending on the recent task experience of the subject. Other evidence comes from the constraint-induced therapies aimed at recovery of motor function developed by Taub and co-workers (Liepert et al. 1998, Kopp et al. 1999). In humans, unilateral loss of motor function, e.g., arm hemiparesis, resulting from stroke is studied; in monkeys, unilateral hemiparesis (perhaps more accurately termed "learned nonuse" by Taub, see Schwartz and Begley 2002, Chapter 4) or other disability is induced surgically through dorsal rhizotomy. In either case, the afflicted primate is treated by binding the unaffected "good" arm to prevent ready use ("constraint") for most hours of the day. Thus, if the primate is to get on with activities of daily living, the human or animal will be inclined to somehow force him- or herself to use the impaired limb. Amazingly, after being bound this way repeatedly and for a duration, the subject slowly reacquires use of the afflicted limb, regaining whole or partial function. The willful effort on the part of the subject to move the afflicted limb (absent when the unafflicted limb is free; highly motivated when it is bound) induces the reestablishment of limb motor function through primary and/or collateral nervous pathways. Notably, constraint-induced therapies usually do not work unless there is some residual function in the afflicted limb.

Neuroplasticity and Fronto-Basal Gangliar Loops in OCD

CBT is hypothesized to induce neuroplastic changes in the brain strengthening volitionally directed circuits and weakening OCD circuits (Schwartz 1999, Schwartz and Begley 2002). The patient becomes more and more able to resist compulsions and eventually the urges subside. The post-treatment neuroimaging changes discussed above suggest that these neuroplastic changes do take place, but their nature is uncertain. The fronto-basal gangliar circuits of the brain are doubtless involved.

Mammalian brains possess five, partly parallel and functionally segregated, cortico-striato-thalamo-cortical circuits ("fronto-basal gangliar circuits"; Alexander et al. 1986,1990; Alexander 1994; Parent et al. 1995; Parent and Hazrati 1995ab). The node structures of each of these circuits are connected by a direct and an indirect pathway. The direct pathways are reentrant positive-feedback neural network loops involving frontal cortex, striatum, pallidum, thalamus, and return to frontal cortex and are listed as follows. The motor loop direct pathway runs from supplementary motor (+ primary motor + premotor + sensory) cortex to putamen to globus pallidus interna to ventrolateral thalamus (*pars medialis* and *pars oralis*) back to supplementary motor cortex. This loop has to do with voluntary movements of somatic musculature. The oculomotor loop runs from frontal eye fields (+ dorsolateral prefrontal + posterior parietal) cortex to the caudate body to the caudomedial globus pallidus interna to the lateral ventroanterior thalamus back to the frontal eye fields. This loop has to do with eye movements. The dorsolateral prefrontal loop runs from the dorsolateral prefrontal (+ premotor + posterior parietal) cortex to the dorsolateral caudate head to the laterodorsal and medial globus pallidus interna to the dorsomedial and ventral anterior thalamus back to the dorsolateral prefrontal cortex. Functions of this loop may include spatial working memory. The lateral orbitofrontal loop runs from the lateral orbitofrontal (+ anterior cingulate + superior temporal + inferior temporal) cortex to the ventromedial caudate head to the dorsomedial and medial globus pallidus interna to the dorsomedial and medial ventral anterior thalamus back to the lateral orbitofrontal cortex. The functions of this loop may include shifting of attention and divided attention, especially concerning reward-based and aversive contingencies. Finally, the limbic loop runs from anterior cingulate (+ hippocampal + entorhinal + infe-

rior temporal + superior temporal) cortex to the nucleus accumbens to the rostrolateral globus pallidus interna and ventral pallidum to the dorsomedial and medial ventral anterior thalamus back to the anterior cingulate. The functions of this loop may include motivation. The prefrontal and limbic loops are critical in OCD pathology; the dorsolateral loop is believed to be active in OCD rehabilitation with CBT (Schwartz 1999, Schwartz and Begley 2002).

Interwoven into each of the five circuits is also an indirect pathway that runs from cortex to striatum to globus pallidus externa to the subthalamic nucleus to the globus pallidus interna to the thalamus back to the cortex (Rauch and Savage 2000). The indirect pathways are negative-feedback reentrant loops and thus work in opposition to the auto-excitatory direct pathways. Direct pathway activation is thought to be important for initiating and sustaining, indirect pathway activation for halting or modulating a given basal ganglia-related behavioral routine (Baxter et al. 2000). Balanced neurotransmitter tone between the two pathways is considered crucial for normal cognitive and motor functioning and imbalances have been implicated in OCD, Parkinson's disease, Huntington's disease, and other neurologic and psychiatric conditions (Swerdlow 1995, Baxter et al. 2000). The direct pathways of the orbitofrontal and limbic circuits are thought to promote OCD symptoms, the corresponding indirect pathways to relieve them (Baxter et al. 2000).

Microanatomy of the Caudate Nucleus

The microanatomy of the caudate nucleus in its relation to functional localization of volition in the brain, OCD symptomatology, and CBT intervention has been reviewed by Schwartz (1999).

The striatum contains neuronal modules called striosomes dispersed within a larger compartment called the matrix (Graybiel et al. 1994). Striosomes are believed to be involved in modulation of emotional arousal (Graybiel 1995) and receive dense projections from orbitofrontal and anterior cingulate cortices (Eblen and Graybiel 1995) and the amygdala (Gerfen 1992), brain regions implicated in OCD pathology (Rauch and Baxter 1998) and pharmacological (Saxena et al. 1998) and CBT treatment response (Schwartz 1998). The striatal matrix in turn is organized into modules called matrisomes (Flaherty and Graybiel 1994), consistently found in close proximity to striosomes. Matrisomes receive projections from lateral prefrontal cortex, which plays a key role in higher-order cognitive functions such as anticipation and planning (Stuss and Benson 1986, Fuster 1989), functions exploited in CBT for OCD. Tonically Active Neurons (TANs) localize at striosome-matrix borders (Aosaki et al. 1995). TAN activity is modified by behaviorally meaningful stimuli and TANs may participate in "gating" or re-directing information through the striatum during preparation for and initiation of behavior (Baxter 1995, Swerdlow 1995). Functional re-gating of neuronal activity could be important for acquisition of behavioral skills in the course of CBT, which requires applied behavioral planning to modulate responses to powerful emotions mediated by the limbic brain.

Gating of information through the basal ganglia helps determine whether signals received by the thalamus result in subsequent excitation or inhibition of behaviorally critical cortical areas. Imbalances in gating cortical output can affect levels of cerebral excitation and inhibition in ways that influence an organism's conscious experience. In OCD, for example, rapid hyperactivation of orbitofrontal and cingulate cortices, caudate, and thalamus is observed upon symptom provocation (Rauch 2003, Mataix-Cols et al. 2004). These structures also exhibit chronically increased metabolic activity in OCD (Rauch and Baxter 1998). Damage to orbitofrontal and anterior cingulate cortices can lead to perseverations, repetitive performance of behaviors no longer serving a useful function. Single-unit recordings from these structures in non-human primates (Niki and Watanabe 1979, Rosenkilde et al. 1981, Thorpe et al. 1983) indicate that these structures generate "error detection" signals, when a reward is no longer forthcoming subsequent to a cue in violation of contrary expectation. Hyperactivity of orbitofrontal and cingulate cortex and concomitant excess generation of error signals are thought to underlie the pathological intrusions into consciousness, the sense of dread, and the intractable feeling that "something is wrong" (error signal) that are characteristic of the internal state in OCD.

The applied use of anticipation and planning to alter behavioral responses to the powerful intrusive thoughts and urges of OCD is the key element to success in overcoming the symptoms of this condition. In addition, circuits within lateral prefrontal cortex, and projecting into the caudate to the matrisomes, are likely involved in the thought processes required for the execution of CBT strategies. These neuronal elements exist in close juxtaposition to highly specialized TAN cells in the caudate which appear to be sensitive to changes in the perceived relevance of sensory inputs and are well positioned to alter the gating of information needed to alter behavioral responses to those inputs. These represent the necessary neural ingredients to elucidate the cerebral mechanism of CBT response in OCD (Schwartz 1999), except for the element of subjective effort which is critical to driving treatment forward in a real-life situation.

Force Mentale: The Role of Effort in Neuroplasticity

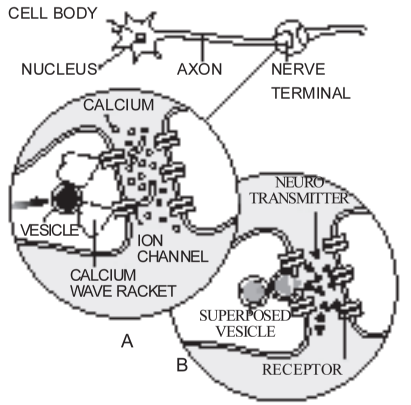
It appears that neuroplastic changes in OCD accompanying successful treatment only take place or take place to a greater extent, if the patient exerts considerable *effort* to overcome his compulsions and to direct him or herself to alternative adaptive behaviors. William James (1892/1992) wrote "volitional effort is effort of attention". In contemplation of this, Schwartz (1999) adopted the concept of "mental force". This concept is based on the common-sense introspective experience that mental exertion (for example, effortful recall of memories, resistance to distractions in keeping the mind focused on a single line of thought, keeping the mind a blank…) is subjectively rather like physical exertion (lifting a heavy weight, staying in a footrace without collapsing…). The neurophysiological correlates or consequences of mental force are thought to act

Quantum Effects of Attention

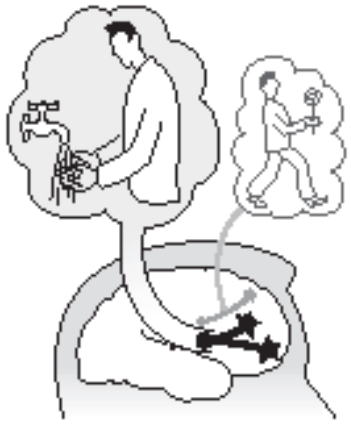
The rules of quantum mechanics (QM) allow attention to influence brain function. Neurotransmitter release requires calcium ions to pass through ion channels. Since ion channels are extremely narrow, the QM rules and the Uncertainty Principle must be applied to calcium migration. The very small uncertainly in position of the ion in the channel causes a rapid spreading of its associated probability cloud. Because of this the release/non-release of transmitter has a significant quantum probabilistic component. This is true even for a single vesicle.

1 In obsessive-compulsive disorder the brain circuit representing “wash your hands” fires again and again and again. This involves overactivity in the orbital cortex/anterior cingulate-caudate nucleus circuit.

2 In therapy, a new insight, “go to the garden”, is introduced. This new thought requires activation of the “planning” area of the brain in the prefrontal cortex, but it is still new and therefore less likely to occur.



3 A vesicle that releases its contents can exist in a superposed state with another version of itself in which its contents are not released. This quantum probabilistic process requires application of the rules of QM which causes “quantum splitting” to occur in human brain circuitry.



4 According to the rules of quantum mechanics, these two circuits will coexist in superpositions - “quantum splitting” of the brain will cause both possibilities simultaneously to exist. Early in therapy though the OCD circuit will be much stronger.

5 By expending mental effort (thus unleashing mental force) and focusing attention on the “garden” thought, the “therapy” circuit is held in place by the Quantum Zeno Effect and can temporarily displace the OCD circuit.

6 Once this is accomplished, the patient can act on this thought and can actually go to the garden - this makes the “therapy” circuit stronger.

7 By going to the garden regularly instead of washing hands, neuroplasticity causes brain changes that continue to strenghten the “therapy” circuit. This increases the probability of displacing the OCD circuit at any given moment in time.

within fronto-basal gangliar loops of the brain, perhaps influencing gating of information flow by the TAN cells of the caudate nucleus as described above.

To bolster the status of the mental force concept within physical theory, Schwartz and Stapp (Schwartz 1999, Stapp 1999) introduced a further development of the von Neumann interpretation of Quantum Mechanics (1932). Von Neumann argued persuasively that the conscious observer is an inseparable and mathematically explicitly accountable part of any quantum mechanical depiction of physical reality. Schwartz and Stapp have proposed the von Neumann-consistent and empirically validated Quantum Zeno Effect (QZE; Itano et al. 1990) as a physical basis for the manifestation of free won't (as discussed above) in the brain (Stapp 2001, Schwartz et al. 2004). QZE is an effect whereby an observed particle fails to change its present quantum state (though it is energetically capable of doing so) based solely on the fact that the particle is *being repeatedly observed* by an experimenter. In other words, the act of repeated observation by a conscious experimenter "freezes" the objective particle in its present quantum state. When observation is relinquished, the particle may spontaneously transition to another quantum state. Stapp (2001) and Schwartz et al. (2004) have devised a model whereby human free will is exercised through the QZE acting via quantum rules. The application of the quantum rules is necessitated in the case of neurotransmission by the fact that Ca^{2+} ions transitioning through extremely narrow presynaptic plasma membrane channels are a *sine qua non* for neurotransmitter vesicle release. The Ca^{2+} channel lumen is sufficiently narrow (<1 nm) that a quantum description is required. The requirement of using quantum rules allows for the application of QZE to brain states, such that attention focused on an experience can hold the associated brain state in place. Thus focusing attention away from an intrusive urge brought to consciousness by maladaptive brain circuits such as those in OCD can prevent the urge from being acted on. (See Figure. For details of the model see Stapp 2001, Schwartz et al. 2004).

The above von Neumann-Schwartz-Stapp quantum model is presented to indicate that there are hard physics arguments in favor of the existence of the will. The Reader, of course, need not necessarily endorse this particular model with its application of QZE to brain states and so on in order to accept the will as a neurophysiologically and neurocognitively valid concept or to appreciate its utility in OCD therapy.

Conclusions

The foregoing has been a survey of the role of volition in the treatment of Obsessive-Compulsive Disorder (OCD) in Cognitive-Behavioral Therapy (CBT). Volition is intimately involved with the symptomatology of OCD and its remediation with CBT. The highly intuitive concept of a signal role for volition in OCD and recovery therefrom is strongly supported by clinical experience. Nonetheless, formal trials of Mindfulness-Based Cognitive Therapies (MBCBT), the CBT approach that relies most directly on exploiting and building patient volition, are relatively scarce. Results of such trials would put clinicians in a better position to assess the powers and limitations of MBCBT as an adjunctive and primary therapy for OCD. This is important as MBCBT has the potential to reach many patients who do not tolerate ERP or other therapies and may yield added benefit when combined with these other therapies.

Well done, though isolated fMRI studies reveal that normal subjects can induce changes in their acute BOLD responses with willful shifts of attitude (Beauregard et al. 2001, Ochsner et al. 2002). The EEG Bereitschaftspotential also indicates that willful decision on the part of normals subjects is an intrinsic element in voluntary motor action (Libet 1999). Many neuroimaging studies document pathologic elevation of GMR, rCBF, and/or fMRI BOLD response in fronto-basal gangliar loop structures in OCD. A number of them show reductions in these functional-metabolic endpoints in response to SSRI treatment, a few show such reductions in response to CBT. Thus, consistent application of willpower resulting in successful CBT is accompanied by chronic, presumably salutory, changes in the ^{18}FDG-PET signal of the brain. These chronic changes suggest that subjective volition, consistently applied, induces neuroplastic changes in the brain. This notion is supported by the efficacy of constraint-induced therapies for recovery of motor function in stroke patients. Due to their therapeutic and basic research relevance, more neuroimaging investigations of normal volition and response of OCD and other mood disorders to CBT should be conducted. In particular, we have recommended the symptom provocation reversal paradigm in OCD as one next step.

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