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What catatonia can tell us about "top-down modulation": A neuropsychiatric hypothesis

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Abstract: Differential diagnosis of motor symptoms, for example, akinesia, may be difficult in clinical neuropsychiatry. Symptoms may be either of neurologic origin, for example, Parkinson's disease, or of psychiatric origin, for example, catatonia, leading to a so-called "conflict of paradigms." Despite their different origins, symptoms may appear more or less clinically similar. Possibility of dissociation between origin and clinical appearance may reflect functional brain organisation in general, and cortical-cortical/subcortical relations in particular. It is therefore hypothesized that similarities and differences between Parkinson's disease and catatonia may be accounted for by distinct kinds of modulation between cortico-cortical and cortico-subcortical relations. Catatonia can be characterized by concurrent motor, emotional, and behavioural symptoms. The different symptoms may be accounted for by dysfunction in orbitofrontal-prefrontal/parietal cortical connectivity reflecting "horizontal modulation" of cortico-cortical relation. Furthermore, alteration in "top-down modulation" reflecting "vertical modulation" of caudate and other basal ganglia by GABA-ergic mediated orbitofrontal cortical deficits may account for motor symptoms in catatonia. Parkinson's disease, in contrast, can be characterized by predominant motor symptoms. Motor symptoms may be accounted for by altered "bottom-up modulation" between dopaminergic mediated deficits in striatum and premotor/motor cortex. Clinical similarities between Parkinson's disease and catatonia with respect to akinesia may be related with involvement of the basal ganglia in both disorders. Clinical differences with respect to emotional and behavioural symptoms may be related with involvement of different cortical areas, that is, orbitofrontal/parietal and premotor/motor cortex implying distinct kinds of modulation – "vertical" and "horizontal" modulation, respectively.

Keywords: Bottom-up modulation; catatonia; horizontal modulation; Parkinson's disease; top-down modulation; vertical modulation

> This "new orientation," of which Jellife spoke, and of which he himself was a notable exemplar, did not involve merely combining neurological and psychiatric knowledge, but conjoining them, seeing them as inseparable, seeing how psychiatric phenomena might emerge from the physiological, or how, conversely, they might be transformed into it.
>
> (O. Sacks 1989, p. 157)

Comparison between Parkinson's disease and catatonia reveals distinction between two kinds of modulation, vertical and horizontal. Vertical modulation concerns cortical-subcortical relations and apparently allows for bidirectional modulation. This is reflected in the possibility of both "top-down and bottom-up modulation" and the appearance of motor symptoms in Parkinson's disease as well as catatonia. Horizontal modulation concerns cortical-cortical relations and apparently allows only for unidirectional modulation. This is reflected in one-way connections from prefrontal to motor cortex and the absence of major affective and behavioural symptoms in Parkinson's disease. It is concluded that comparison between Parkinson's disease and catatonia may reveal the nature of modulation of cortico-cortical and cortico-subcortical relations in further detail.

1. Introduction

Differential diagnosis in neuropsychiatry is often rather difficult since similar symptoms may be related to different diseases, being either neurologic or psychiatric. For example, the symptom of akinesia can be caused either by Parkinson's disease (PD), classified as a neurological disease, or by catatonia, usually classified as a psychiatric disease. Moreover, the same symptom, that is, akinesia may be accompanied by different psychological alterations: either depression, as in PD, or uncontrollable anxieties, as in catatonia. Consequently, consideration of both symptomatic origin and complexity makes classification of diseases as either neurologic or psychiatric rather difficult. This is reflected in a so-called "conflict of paradigms" pointing out the inability to draw a clear dividing line between neurologic and psychiatric disturbances (Rogers 1985).

If symptoms of different origin, either psychiatric or neu-

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rologic, show similar clinical appearance, one may assume similar or at least overlapping pathophysiological substrates reflecting functional brain organisation in general. Functional relation between prefrontal/frontal cortex and basal ganglia may account for similarity between PD and catatonia with respect to motor symptoms. Relation between prefrontal/frontal cortex and basal ganglia can be characterized by various "functional circuits" (see Mastermann & Cummings 1997 for a nice overview) allowing for bidirectional modulation with both "top-down and bottom-up modulation" as forms of "vertical modulation." In addition to the cortico-subcortical relation, one may consider the cortico-cortical relation as well reflecting "horizontal modulation," which may be rather unidirectional (see below).

Comparison between pathophysiological mechanisms underlying PD and those subserving catatonia may reveal the nature of these distinct kinds of modulation of cortico-cortical/subcortical relation in further detail. The following hypothesis are postulated: (1) apparent clinical similarity and underlying pathophysiological differences in motor symptoms between PD and catatonia; (2) differences in psychiatric (affective and behavioural) symptoms between PD and catatonia; (3) "double dissociation" between catatonia and PD with respect to underlying pathophysiological mechanisms accounting for clinical differences; (4) opposite kinds of "vertical modulation" between prefrontal/frontal cortex and basal ganglia in PD and catatonia ("bottom-up and top-down modulation") accounting for subtle differences in motor symptoms; (5) presence/absence of alterations in cortico-cortical relation reflecting "horizontal modulation" in catatonia and PD respectively, accounting for major differences in emotional-behavioural symptoms.

First, we describe similarities and differences in clinical symptoms and therapy between PD and catatonia. This is followed by illustration of neuropsychological and pathophysiological findings. Third, we develop pathophysiological hypotheses for the different kinds of symptoms observed in PD and catatonia. On the basis of these pathophysiological hypotheses, a distinction between "horizontal" and "vertical modulation" of cortico-cortical/subcortical relations with respect to directionality is suggested.

2. Catatonia as a psychomotor syndrome: Comparison with Parkinsonism as motor syndrome

2.1. Motor symptoms

Catatonia is a rather rare (incidence: 2%–8% of all acute admissions) psychomotor syndrome. As such it can be associated with psychiatric disturbances such as schizophrenia (one subtype is denoted as catatonic schizophrenia) and manic-depressive illness, as well as with various neurological and medical diseases (Gelenberg 1976; Northoff 1997a; Taylor 1990). Some authors (see Northoff 1997a, for an overview) consider periodic catatonia as an idiopathic disease showing psychomotor characteristics of catatonic syndrome while not being associated with any other kind of disease. Parkinsonism is a motor syndrome which can be either of idiopathic, that is, primary, or of symptomatic, that is, secondary, nature. In the first case one speaks of Parkinson's disease (PD), which may be considered as a nosological analogue of periodic catatonia, whereas in the second case one generally speaks of Parkinsonism which, similar to catatonia, may be associated with various neurological and medical diseases.

The most characteristic feature of catatonia is "posturing," where patients show a specific, uncomfortable, and often bizarre position of parts of their body against gravity, with complete akinesia in which they remain for hours, days, and weeks (and in earlier times even for years; see Fig. 1). If that position is taken actively and internally by the patient himself, one speaks of "posturing"; if such a position can be induced passively and externally by the examiner, one speaks of "catalepsy." Posturing can occur in limbs ("classic posturing"), head ("psychic pillow"), and eyes ("staring").

We saw one patient who postured every morning during shaving. He started to shave himself and then remained, with the razor in his hand and a lifted arm, for hours in that position until his wife came in and "depositioned" him (see Northoff 1997a for detailed description). Another example is a woman who, every morning when opening her wardrobe, remained in a position with a lifted arm keeping the door of the wardrobe open in her hand. Both patients were admitted into the clinic where they neither spoke nor moved at all. On admission, it was possible to "position" their limbs in the most bizarre and uncomfortable positions against gravity without any resistance by the patients themselves. Once the examiner positioned the limbs into one particular position, they remained in that position without showing even the slightest change.

The cases demonstrated in Figure 1 are typical examples of posturing and catalepsy where patients are well able to initiate and execute movements but seem to be unable to return to the initial or resting position in order to start a new movement. Similar to PD, catatonic patients do show akinesia, but, unlike Parkinsonian patients, only in association with posturing and catalepsy. Furthermore, in contrast to PD, catatonic akinesia is not necessarily accompanied by muscular hypertonus, that is, rigidity, since patients may also show muscular normo- or hypotonus (Northoff 1997a). Even if catatonic patients show muscular hypertonus, it is not the kind of rigidity – cogwheel rigidity – that is typical of PD. Instead, they show a rather smooth type of rigidity which is called "flexibilitas cerea" (Northoff 1997a). In addition to hypokinetic features, catatonic patients may show intermittent and fluctuating hyperkinesias like stereotyp-



Figure 1. "Active posturing" in a group of catatonic patients (from Kraepelin 1927).

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ies, dyskinesias, and tics which, unlike in PD, are independent of medication.

Catatonic patients are well able to "plan," "initiate," and "execute" movements which could be demonstrated in ball experiments. We performed systematic ball experiments in 32 catatonic patients in an acute akinetic state before they received any medication (i.e., lorazepam; see Northoff et al. 1995a). To our surprise almost all patients, despite showing concurrent akinesia and posturing, were able to play ball either with the hands or with the legs. Patients were able to catch and throw the ball, doing slightly better during external initiation (i.e., catching) than during internal initiation (i.e., throwing). Most patients, however, remained in a final posture keeping the ball in a position against gravity, apparently unable to change posture and terminate the respective movement. Subjectively, catatonic patients experienced these ball experiments as "funny and relaxing" and as "taking off my inner tension" although they were not aware of their inability to terminate movements, therefore posturing (Northoff et al. 1995a; 1998). Furthermore, in contrast to PD, posturing in catatonic patients cannot be reversed by external sensory stimulation, as for example, drawing a line in front of their feet. Accordingly, catatonic patients did not experience any starting problems or deficits in "internal initiation."

In summary, catatonia and PD can be characterized both by clinical similarities, as reflected in akinesia and rigiditiy, and differences, as reflected in posturing/initiation and cogwheel rigidity/flexibilitas cerea, with respect to motor symptoms.

2.2. Behavioural and affective symptoms

In addition to motor symptoms, catatonia can be characterized by concurrent behavioural and affective anomalies. Behavioural anomalies include mutism (patients do not speak, as was the case in both patients described above), stupor (no reaction to the environment), automatic obedience (patients do everything that they are asked to do), negativism (patients always do the opposite of what they are asked), echolalia/praxia (patients repeat sentences or actions given by other persons several times or even endlessly), perseverative-compulsive behavior (uncontrollable repetitive behavioural patterns), and *mitmachen/mitgehen* (patients always follow other persons and do the same as they do). In contrast to catatonia, such behavioural anomalies cannot be observed in PD, which is characterized predominantly by motor symptoms.

Affective alterations in catatonia include strong anxieties or euphoria/happiness, staring, grimacing, and inadequate emotional reactions. Catatonic patients may show compulsive emotions (involuntary and uncontrollable repetitive emotional reactions), emotional lability (labile and unstable emotional reactions), aggression (often accompanied by extreme emotional states such as anxiety or rage), excitement (extreme hyperactivity with extreme and uncontrollable emotional reactions), affective latence (taking a long time to show emotional reactions), ambivalence (simultaneous presence of conflicting emotions), and flat affect (decreased and/or passive emotional reactivity). Such symptoms are not present in PD. Patients with PD can, rather, be characterized by depression, where they neither show an uncontrollable intensity of emotions nor a comparable variety of emotional reactivity like that of catatonic patients.

In summary, catatonia can be characterized by strong affective and bizarre behavioural anomalies, which do not occur in PD.

2.3. Therapy

Therapeutically, 60%–80% of all acute catatonic patients react to lorazepam, a GABA-A receptor potentiator, either almost immediately within the first 5–10 minutes, or within 24 hours (Bush et al. 1996a; Northoff et al. 1995b; Rosebush et al. 1990), whereas chronic catatonic patients show no improvements on lorazepam (Ungvari et al. 1999). If lorazepam does not work, some catatonic patients show gradual and delayed improvements (within 2 to 4 days) on the NMDA-antagonist amantadine (Northoff et al. 1997; 1999c) and/or on electroconvulsive treatment (ECT) (Fink et al. 1993; Petrides et al. 1997).

Dopaminergic substances like L-Dopa and D1/2 receptor agonists are therapeutically effective in PD. Unlike in catatonia, lorazepam and other benzodiazepines remain therapeutically ineffective in PD. Similar to catatonia, the NMDA-antagonist amantadine is therapeutically effective in PD as well (Merello et al. 1999). In addition to pharmacotherapy, surgical therapies with implantation of either electrodes or fetal tissue in specific structures of the basal ganglia (putamen, caudate, subthalamic nuclei, internal pallidum) may be applied especially in drug-resistant patients with PD.

In summary, treatment in catatonia and PD can be characterized by differences (GABA-ergic agents versus dopaminergic agents) and similarities (NMDA-antagonists).

2.4. Subjective experience

In order to further reveal the nature of psychological alterations and their relation to motor symptoms, we investigated subjective experience in catatonic patients with a self-questionnaire. Due to mutism and akinesia in almost all patients with hypokinetic catatonia, such an investigation remains possible only retrospectively. Catatonic patients were compared with akinetic Parkinsonian patients and noncatatonic depressive and schizophrenic patients (see Northoff et al. 1998, for details).

Parkinsonian patients suffered severely from akinesia; for example, one felt "locked into my body," another "wanted to move but was unable to do so." A catatonic patient, in contrast, did not realize "any alterations in my movements" and said that "they [the movements] were completely normal." When asked why they positioned their limbs in a particular posture, catatonic patients either answered "There was nothing abnormal with my movements," or couldn't say anything. The patient posturing during shaving said, "My movements were completely normal and I could shave in the normal way." No patient said that he subjectively suffered from any changes in his movements. Moreover, no catatonic patient reported any feeling of pain or tiredness even if he postured and remained in the same position for hours (n = 5), days (n = 10) or weeks (n = 5). Instead of changes in their movements, many catatonic patients reported extremely intense emotions, which they experienced as "uncontrollable and overwhelming." Patients "felt totally blocked" by these emotions which "overwhelmed" them and "led to a blockade of [their selves]." The dominating emotion was anxiety (due to para-

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noid delusions, acoustic hallucinations, depressive mood, or traumatic experiences). For example, the patient posturing during shaving as described above, said that "I couldn't control my emotions anymore, they were overflooding me so that I had the feeling that I was just anxiety." Nevertheless, some patients reported positive emotions like euphoria – although, similar to anxiety, they were unable to control this anymore. One patient, for example, became catatonic every time she fell in love (5 times in total), reporting the following: "I am so happy when I fall in love, this feeling really overwhelms me so that I can't control it anymore. Every time I fall in love, I am admitted to clinic. I don't understand this."

Catatonic patients did not subjectively experience any "sensation of effort" during posturing. Although they kept their limbs or head in a position against gravity, where every normal person and patient with PD would feel a "sensation of tiredness or pain," catatonic patients do not experience any "tiredness," pain, or a "sensation of effort" during posturing. For example, catatonic patients lying in bed may keep their head up for hours or even days (i.e., a so-called "psychic pillow") without getting tired and/or reporting any feeling of tiredness. When inquiring after these patients with such a "psychic pillow," they usually answer, "My head was in a completely normal position, I wasn't tired at all"; they seem to, instead, experience a "sense of weightlessness."

No catatonic patient was able to give an account of the position in which he kept his limbs, thus remaining unaware of posturing. It seems as if they have no access to any kind of subjective experience of the actual spatial position during posturing – the "objective position" and the corresponding "subjective experience" of the spatial position seem to be decoupled from each other. Unfortunately, there are no data available whether post-acute patients recognize the posturing characterizing their acute state as their own. Such data could provide information about the exact nature of the deficit in awareness. If they could recognize the posturing as their own, they would show only an alteration in motor awareness but not in self-awareness. However, if they were unable to do so, there would have to be a general deficit in self-awareness. Since, however, catatonic patients are well able to recognize themselves in a post-acute state, one may rather hypothesize a deficit in motor awareness only.

Furthermore, catatonic patients are not aware of the "consequences of their movements" (Snowdon et al. 1998): The patient posturing during shaving claimed that he finished shaving every morning completely without any time delay so that he wasn't aware of the "consequences of posturing." Finally, catatonic patients do not show any objective or any kind of subjective sensory abnormality, so alterations in subjective experience cannot be accounted for by sensory dysfunction.

Almost all catatonic patients reporting strong, intense, and uncontrollable emotions responded well to lorazepam, whereas patients without such emotional experiences did not respond well to lorazepam (Northoff et al. 1998). Nonresponders to lorazepam – for example, the patient described above as posturing in front of her wardrobe – had experiences such as a "blockade of my will with contradictory and ambivalent thoughts about my dresses since I couldn't decide myself." For several days this patient stood in front of her wardrobe remaining in the same quite uncomfortable position with raised arms and standing tip-toe. She wasn't aware of any alterations in her movements, denying any feeling of tiredness during that position ("I wasn't tired at all"). All catatonic patients experienced their admission on a psychiatric ward as terrible ("I thought it was the hell") and/or could not understand it ("I was so happy, there was no reason for admission at this time.") Moreover, they remembered very well the physician and other persons who treated them on admission. Consequently, catatonic patients seem to show neither deficits in memory (except in working memory; see below), nor deficits in general awareness.

In summary, subjective experience differs between catatonic and Parkinsonian patients with respect to motor symptoms (motor anosognosia vs. motor awareness) and psychological state (anxiety vs. depressive reaction).

3. Neuropsychological and pathophysiological findings in catatonia and Parkinson's

Presentation of findings in this section focuses predominantly on comparison between catatonia and PD with respect to distinct kinds of modulation. Therefore the whole variety of differential and subtle pathophysiological alterations obtained especially in PD cannot be considered in the present context. Furthermore, it should be mentioned that systematic pathophysiological investigations with modern techniques are rather rare in catatonia, which is a certain focus within my own studies.

3.1. Neuropsychological findings

We pointed out that the ability to registrate the spatial position of movements, as required for "termination of movements" (see above), involves spatial abilities as potentially related to the right posterior parietal cortical function. We therefore investigated post-acute akinetic catatonic patients with neuropsychological tests for measurement of spatial abilities (Northoff et al. 1999a). Among other measures, we applied the visual-object-space and perception test (VOSP), a test specifically designed for measurement of spatial abilities related to right parietal cortical function. (See Table 1.)

Catatonic patients showed significantly lower performance in VOSP compared to psychiatric and healthy controls (Northoff et al. 1999a). No significant differences between catatonic and noncatatonic psychiatric patients were obtained in any other visuo-spatial test unrelated to right parietal cortical function, or in any other neuropsychological measure such as general intelligence, attention, and executive functions. Furthermore, catatonic patients showed significant correlations between right parietal cortical visuo-spatial abilities (as measured with VOSP) and attentional abilities (as measured with d2 and CWI), which were present neither in psychiatric controls nor in healthy subjects (Northoff et al. 1999a). In addition, motor symptoms in catatonia correlated significantly with both visuo-spatial abilities and attentional function. Catatonia may be characterized by relatively intact psychological functions concerning attention, executive functions, general intelligence, and non-right parietal visuo-spatial abilities. In contrast, visuo-spatial abilities specifically related to right parietal cortex may be altered in catatonic patients, distin-

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Table 1. *Comparison between catatonia and Parkinson's disease*

	Catatonia	Parkinson's
Neuropsychology	Visuospatial attention	Executive functions
	On-line monitoring	
	Emotionally-guided decisions	
Postmortem	Caudate, N. accumbens, Pallidum, Thalamus	Substantia nigra, Putamen, Caudate
Animal models	Bulbocapnine, Stress, GABA	6-OHDH, MPTP
Structural imaging	Prefrontal and parietal cortex	Basal ganglia
Functional imaging	Right prefronto-parietal CBF	SMA/MC
	Right OFC	Lateral prefrontal cortex
	Prefrontal connectivity	Fronto-striatal connectivity
Electrophysiology	Late and postural RP	Early RP
	RP modulation by Lorazepam	RP modulation by dopamine
Neurochemistry	GABA-A receptors	D-2 receptors in striatum
	NMDA receptors	NMDA receptors
	5 HT1a/2a	5 HT2a

Abbreviations:
RP = Readiness Potential
SMA = Supplementary motor area
OFC = Orbitofrontal cortex
MC = Motor Cortex

guishing them from noncatatonic psychiatric controls. Also, catatonic patients show severe deficits in a gambling test (unpublished observations) requiring emotionally guided decisions and intact orbitofrontal cortical function (Bechara et al. 1997).

In contrast, patients with PD show severe neuropsychological deficits in executive functions (Wisconsin Card Sorting test, verbal fluency, etc.). These include, among others, abilities of categorization, shifting, sequencing, and so on, as subserved by dorsolateral prefrontal cortical function. In contrast to catatonia, PD can be characterized neither by deficits in visuo-spatial attention as specifically related to right parietal cortical function, nor by alterations in the gambling test specifically designed for orbitofrontal cortical function.

In summary, catatonia can be characterized by specific deficits in visuo-spatial abilities, related to right parietal cortical function, and by emotionally guided intuitive decisions, related to orbitofrontal cortical function. PD, in contrast, can be characterized by specific alterations in executive functions predominantly related to lateral prefrontal cortical function.

3.2. Postmortem findings

Early postmortem studies in the preneuroleptic time revealed discrete but not substantial alterations in basal ganglia (caudate, N. accumbens, pallidum) and thalamus (see Bogerts et al. 1985 and Northoff 1997a, for an overview). Because these early investigations yielded rather inconsistent results, they were not pursued. Most studies were performed on brains of patients who were never exposed to neuroleptics, implying that these alterations in basal ganglia cannot be related to neuroleptic (antipsychotic) medication. Nevertheless, findings should be considered rather cautiously since the methods and techniques available at that time may have produced artifacts themselves. Furthermore, these findings were obtained in patients with catatonic schizophrenia. Therefore, it remains unclear whether these alterations are specifically related to either catatonia itself or the underlying disease of schizophrenia. Neuropathologic investigations of catatonic syndrome in general, rather than of catatonic schizophrenia in particular, are currently not available.

In contrast to catatonia, substantial alterations in postmortem investigation can be obtained in PD. PD can be characterized by degeneration of dopaminergic cells in substantia nigra pars compacta, leading consecutively to degeneration in striatum (especially putamen and caudate). In many cases of Parkinsonism, vascular or other kinds of alterations may be observed in striatum.

In summary, valid postmortem results in catatonia are currently not available since those obtained showing discrete alterations in basal ganglia relied on insufficient methods. In contrast, PD can be characterized by major degeneration of dopaminergic cells in substantia nigra and its pathways to striatum.

3.3. Animal models

DeJong and Baruk (1930) performed various experiments with the D2-receptor antagonist bulbocapnine. According to DeJong and Baruk, bulbocapnine induced catatonia in animals with a neocortex (mice, rats, cats), whereas in animals without a neocortex, catatonic symptoms could not be induced. Lower (1–2 mg) doses of bulbocapnine lead to catalepsy, whereas higher doses (4–5 mg) induced impulsive and convulsive reactions. As demonstrated by Loizzo et al. (1971), amantadine as an NMDA-antagonist led to reversal of bulbocapnine-induced catatonia; however, relying on my own experiments (unpublished observations), bulbocapnine-induced catatonia rather resem-

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bled haloperidol-induced catalepsy. Furthermore, it could not be determined by lorazepam, as is the case in human catatonia (see above). Bulbocapnine exerts an inhibitory effect on dopamine synthesis (Shin et al. 1998). Consequently, it remains unclear whether DeJong and Baruk really describe catatonia, or, rather, a kind of catalepsy analogous to neuroleptic-induced catalepsy.

Stille and Sayers (1975) induced a catatonia-like reaction in animals using strong sensory stimuli (electric footshock). They postulated an excitement of the ascending arousal system, that is, formatio reticularis with overexcitation of the striatal system via thalamic nuclei. Injection of the GABA-A antagonist bicucullin into dopaminergic cells of the ventral tegmental area (VTA) induced a catatonia-like picture in cats with increased arousal, withdrawal, anxiety, staring, and catalepsy (Stevens 1974). Furthermore, injection of morphine may lead to a so-called "morphine-induced catatonia" (Northoff 1997a). Despite the existence of these various models, none of them has really been established as an animal model of human catatonia.

Freezing as an isolated phenomenon independent from catatonia has been studied in animals and humans. Lesions in amygdala and/or in the periaqueductal gray may induce freezing in animals – whether these results can be extrapolated to humans remains unclear (Fendt & Fansolow 1999).

Animal models of PD focus on specific lesion of nigrostriatal dopaminergic cells and pathways as provided by 6-OHDH in rats and MPTP in nonhuman primates.

In summary, no animal model of human catatonia has yet been established. The ones available focus either on GABA-ergic- or morphine-induced lesions. In contrast, animal models of PD focus on lesions of nigrostriatal dopamine by either 6-OHDH or MPTP.

3.4. Structural imaging

A computerized tomographic (Head CT) investigation of 37 patients with catatonic schizophrenia showed a diffuse and significant enlargement in most cortical areas (see Northoff et al. 1999d). Alterations in temporal cortical areas were present in all three subtypes of schizophrenia, whereas catatonic schizophrenia could be specifically characterized by prefrontal and parietal enlargement. Moreover, prefrontal and parietal enlargement correlated significantly with illness duration in catatonic schizophrenia.

Other authors (Joseph et al. 1985; Wilcox 1991) observed a cerebellar atrophy in catatonic patients, which was investigated neither systematically nor quantitatively. To my knowledge, no study specifically investigating catatonic syndrome (and not only catatonic schizophrenia as a subtype) has been published so far.

In summary, findings in structural imaging in catatonia suggest cortical involvement predominantly in prefrontal and parietal cortex, whereas in PD subcortical structures, that is, the basal ganglia are altered.

3.5. Functional imaging

3.5.1. Regional cerebral blood flow. Investigation of regional cerebral blood flow (r-CBF) in single catatonic patients showed the following findings: (1) right-left asymmetry in basal ganglia with hyperperfusion of the left side in one patient (Luchins et al. 1989); (2) hypoperfusion in left medial temporal structures in two patients (Ebert et al. 1992); (3) alteration in right parietal and caudal perfusion in one patient (Liddle 1994); (4) decreased perfusion in right parietal cortex in six patients with catatonic schizophrenia (Satoh et al. 1993); (5) decreased perfusion in parietal cortex with improvement after ECT in one patient (Galynker et al. 1997). A systematic investigation of r-CBF in SPECT in 10 post-acute catatonic patients showed decreased perfusion in right posterior parietal and right inferior lateral prefrontal cortex compared to noncatatonic psychiatric and healthy controls (Northoff et al. 2000c).

Furthermore, abnormal correlation between right parietal cortical function and visual-spatial and attentional abilities were obtained (Northoff et al. 2000c). In psychiatric and healthy controls, VOSP correlated significantly with right lower parietal and right lower lateral prefrontal cortical r-CBF and iomazenil binding (reflecting the function of GABA-A receptors), whereas in catatonia none of these correlations were found (Northoff et al. 1999e; 2000c). Decreased perfusion in right parietal cortex correlated significantly with motor and affective symptoms. Catatonic motor symptoms correlated significantly with VOSP, right lower parietal r-CBF and iomazenil binding in right lower lateral prefrontal cortex (Northoff et al. 1999e; 2000c).

PD can be characterized by deficits of r-CBF in SMA, motor cortex and caudate, whereas no major alterations in prefrontal and parietal cortex can be observed (see Jahanshahi & Frith 1998).

In summary, investigation of regional cerebral blood flow shows deficits in right lower inferior prefrontal and right parietal cortex in catatonia. PD, in contrast, may rather be characterized by predominant r-CBF deficits in motor cortex, SMA, and basal ganglia.

3.5.2. Motor activation. Functional imaging performed during motor activation (i.e., sequential finger opposition) showed reduced activation of the contralateral motor cortex (MC) in right hand performance. Ipsilateral activation was similar for both patients and (medication-matched) controls (Northoff et al. 1999b). There were no differences in activation of the supplementary motor area (SMA). During left hand performance, right-handed patients showed more activation in ipsilateral motor cortex than in contralateral MC. This must be considered as a reversal in laterality since usually the contralateral side shows four to five times more activation than the ipsilateral side (Northoff et al. 1999b). It should be noted that these results were obtained in only two post-acute catatonic patients. However, assumption of basically intact cortical motor activation (independent from laterality) is further supported by results from an fMRI/MEG study during emotional-motor stimulation in 10 catatonic patients (Northoff et al. 2001a). Cortical motor function showed no alteration in these investigations.

During motor activation, patients with PD show major deficits predominantly in SMA, which receives most afferences from thalamic (motor) nuclei, and the basal ganglia, predominantly the striatum. Furthermore, decreased activation can be observed also in MC though to a lesser degree than SMA. This may be due to the fact that the MC does not receive as many afferences from thalamic (motor) nuclei as SMA does. In contrast to catatonia, no alteration in laterality during motor performance can be observed in PD (Jahanshahi & Frith 1998).

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In summary, catatonia may be characterized by alterations in laterality in the motor cortex during motor performance, while activation in SMA seems to remain basically intact. PD, in contrast, shows major deficits in activation of SMA and, to a lesser degree, in the motor cortex, the latter showing no alterations in laterality.

3.5.3. Emotional-motor activation. Based on subjective experience showing intense emotional-motor interactions, an activation paradigm for affective-motor interaction was developed. This paradigm was investigated in fMRI and MEG (magnetoencephalography) in catatonic patients comparing them with noncatatonic psychiatric and healthy controls (Northoff et al. 2001a). During negative emotional stimulation, catatonic patients showed a hyperactivation in orbitofrontal cortex and a shift of main activation to anterior cingulate and medial prefrontal cortex. Furthermore, catatonic patients showed abnormal orbitofrontal-premotor/motor connectivity (Northoff et al. 2001a). Behavioural and affective catatonic symptoms correlated significantly with reduced orbitofrontal cortical activity, whereas motor symptoms correlated with premotor/motor activity.

PD, in contrast, can be characterized by altered activation in left dorsolateral prefrontal cortex and anterior cingulate during emotional stimulation, whereas orbitofrontal cortical function remained unaffected (see Mayberg et al. 1999).

In summary, catatonia can be characterized by reduced right orbitofrontal cortical activation and abnormal orbitofrontal-premotor/motor connectivity during negative emotional stimulation. PD, in contrast, shows alterations only in left dorsolateral prefrontal cortex and anterior cingulate, not in orbitofrontal cortex.

3.5.4. On-line monitoring. Posturing as an inability to terminate movements may be related with alterations in on-line monitoring. Since on-line monitoring must be considered as an essential part of working memory (Leary et al. 1999; Petrides 1995), we investigated a one-back/two-back task in fMRI in catatonia (Leschinger et al. 2001). Catatonic patients showed significantly decreased activation in right lateral orbitofrontal, including ventrolateral prefrontal cortex (VLPFC), during the working memory task in fMRI (Leschinger et al. 2001). In contrast to orbitofrontal activity, activation in right dorsolateral prefrontal cortex was rather increased. Catatonic behavioural symptoms correlated significantly with activation in right lateral orbitofrontal cortex, whereas motor symptoms showed a significant relationship with right dorsolateral prefrontal activity.

Catatonic patients showed significantly worse behavioural performance in both one-back and two-back tasks, and their deficit seems not to be limited to active storage/retrieval. In the latter case one would have expected worse performance in the two-back task only. Instead, catatonia may rather be characterized by principal problems in on-line processing and monitoring, which accounts for bad performance in both one-back and two-back task.

Investigation of working memory in PD revealed alteration in lateral prefrontal cortex, especially in left dorso-lateral prefrontal cortex (DLPFC), whereas orbitofrontal cortical function, including the ventrolateral prefrontal cortex, remained intact (Jahanshahi & Frith 1998).

In summary, catatonia can be characterized by major deficits in on-line monitoring and right lateral orbitofrontal, that is, ventrolateral prefrontal cortical (VLPFC) function, whereas PD shows deficits in left dorso-lateral prefrontal cortical (DLPFC) function.

3.6. Electrophysiological findings

3.6.1. Initiation in catatonia and Parkinson's disease. Generation of "willed action" can be characterized by "Plan/Strategy," "Initiation," and "Execution," which are supposed to be reflected in movement-related cortical potentials (MRCP) (see Northoff et al. 2001b).

We investigated MRCPs during finger tapping in 10 post-acute akinetic catatonic patients, 10 noncatatonic psychiatric controls (same underlying diagnosis, same medication, same age and sex), and 20 healthy controls (Northoff et al. 2000a; Pfennig 2001; Pfennig et al. 2001). We found no significant differences in amplitudes between catatonic and noncatatonic subjects in early MRCPs; that is, in early readiness potential (early RP) reflecting "Plan/Strategy" and "Initiation" of movements in DLPFC and anterior SMA. Amplitudes in late MRCPs, that is, in late readiness potential (late RP) and movement potential (MP) reflecting "Execution" of movements in posterior SMA and motor cortex, revealed differences.

Patients with PD show reduction of amplitude in early and late MRCPs, which can be modulated by dopaminergic agents resulting in an increase of amplitude (Dick et al. 1987; 1989; Jahanshahi et al. 1995; Jahanshahi & Frith 1998).

In summary, catatonia can be characterized by intact early and late readiness potentials, reflecting the apparently preserved ability of "Plan/Strategy," "Initiation," and "Execution" of movements in these patients. In contrast, patients with PD show severe deficits in "Initiation" and "Execution" as electrophysiologically reflected in alterations in early and late readiness potentials.

3.6.2. Termination in healthy subjects. Phenomena like posturing and catalepsy can be observed in patients with right parietal cortical lesions, although they do not show any deficits in "Initiation" and "Execution" (Fukutake et al. 1993; Saver et al. 1993). This suggests that visuo-spatial attention and right parietal cortical function may be necessary for on-line monitoring and consecutive termination of movements. In a first step, we therefore investigated termination of movements in healthy subjects with electrophysiological measurements of movement-related cortical potentials (MRCP) (Northoff et al. 2001a; Pfennig 2001).

We compared "normal" MRCP as obtained by finger tapping with MRCP for simple lifting. The finger had to be kept up without going back into the initial position (MRCP 1) reflecting "Plan"/"Strategy," "Initiation," and "Execution" of finger tapping with exclusion of "Termination." "Termination" of movements was measured by lowering of the finger after some seconds of posturing (MRCP 2), reflecting "initiation of termination" and "execution of termination" (see below). MRCP 1 and 2 differed significantly in various onsets and amplitudes from MRCP, so that neither MRCP 1 nor MRCP 2 can be equated with MRCP for simple finger tapping. In addition, we obtained significant differences between MRCP 1 and MRCP 2, the latter showing significantly lower amplitudes in early parietal MRCPs, earlier onset of movement potential and more posterior

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parietal localization of underlying dipoles, than the former (Northoff et al. 2001b; Pfennig et al. 2001).

Lorazepam as a GABA-A potentiator had a differential influence on early and late components of MRCPs during "Initiation" and "Termination." During "Initiation," lorazepam led to a delay in onsets of late MRCPs in frontal electrodes (MRCP 1), whereas during "Termination" (MRCP 2), early onsets in parietal electrodes were delayed. These results were further supported by dipole source analysis. MRCP 1 reflecting "Plan"/"Strategy," "Initiation," and "Execution" showed dipole sources in anterior/posterior SMA and motor cortex. In contrast, MRCP 2 reflecting "Termination" was characterized by initial location of the early dipole in right posterior parietal cortex, later shifting to posterior SMA and motor cortex (Pfennig et al. 2001).

The following conclusions with respect to "Termination" of movements can be drawn. First, some kind of initiation must be involved, because otherwise there would have been no readiness potential – we call this the "initiation of termination." Second, the "initiation for execution" (i.e., MRCP 1) and the "initiation for termination" (i.e., MRCP 2) can apparently be distinguished from each other, since otherwise there would have been no differences in amplitudes between MRCP 1 and MRCP 2 in early MRCPs. Third, MRCPs during Termination could be characterized by right posterior parietal localization. In order to avoid terminological confusion, we reserve the term "Initiation" for the "Initiation of Execution," whereas the "initiation of Termination" will be subsumed under the term "Termination." Fourth, "Execution" and "Termination" involve different movements (lifting and lowering), which is reflected in distinct movement potentials in MRCP 1 and MRCP 2. Fifth, the "Termination" of movements seems to be particularly related with right parietal cortical function and GABA-ergic neurotransmission. Otherwise, there would have been no differences between MRCP 1 and MRCP 2 in parietal cortical dipole source location and reactivity to lorazepam.

In summary, "Termination" of movements may be characterized by two distinct aspects, initiation and execution. These may be subserved by involvement of right parietal cortical function and GABA-ergic neurotransmission. Neuropsychologically, on-line monitoring of the spatial position of the ongoing movement, as related to right parietal cortical function, may be considered as crucial for "Termination," distinguishing it from "Plan"/"Strategy," "Initiation," and "Execution."

3.6.3. Termination in catatonia. Kinematic measurements during "Initiation" and "Termination" of finger tapping revealed that catatonic patients needed significantly longer for "Termination" than psychiatric and healthy controls. In contrast, no deficits were observed in "Initiation" (Pfennig 2001; Pfennig et al. 2001). These results contrast with those in patients with PD who needed significantly longer time duration for "Initiation," but not for "Termination."

Catatonic patients showed no abnormalities in MRCPs of "Initiation," that is, lifting (MRCP 1). Instead, they showed significantly delayed onsets in early MRCPs in central and parietal electrodes during "Termination," that is, lowering (MRCP 2), compared to psychiatric and healthy controls (Pfennig et al. 2001). The fact that the early onset was altered only in MRCP 2 but not in MRCP 1, indicates a delay specifically in "initiation of termination," while "Initiation" itself seems to remain principally intact. This is further supported by results from dipole source analysis showing decreased source strength in right posterior parietal cortex in catatonic patients, while sources in SMA showed no abnormalities. In addition, catatonic motor and behavioural symptoms correlated significantly with delayed early onset in MRCP 2 in parietal electrodes.

In summary, posturing in catatonia may be characterized by a specific deficit in "Termination" of movements while "Plan"/"Strategy," "Initiation," and "Execution" seem to remain basically intact. Such an assumption is supported by observation of alterations in temporal duration, onset of early MRCPs, right parietal cortical localization and GABA-ergic reactivity in MRCPs specifically related to "Termination" of movements.

3.7. Neurochemical findings

3.7.1. GABA. Recent interest in neurochemical alterations in catatonia has focused on GABA-A receptors. The GABA-A receptor potentiator lorazepam is therapeutically effective in 60–80% of all acute catatonic patients (Bush et al. 1996a; Northoff et al. 1995b; Rosebush et al. 1990). One study investigated iomazenil-binding, reflecting number, and function of GABA-A receptors in 10 catatonic patients in single photon emission computerized tomography (SPECT) and compared them with 10 noncatatonic psychiatric controls and 20 healthy controls (Northoff et al. 1999e). Catatonic patients showed significantly lower GABA-A receptor binding and altered right-left relations in left sensorimotor cortex. In addition, catatonic patients could be characterized by lower GABA-A binding in right lateral orbitofrontal and right posterior parietal cortex, correlating significantly with motor and affective (but not with behavioural) catatonic symptoms.

Furthermore, emotional-motor stimulation in fMRI/MEG (see above) was performed after neurochemical stimulation with lorazepam (see Northoff et al. 2001d; Richter et al. 2001). After lorazepam, healthy subjects' activation shifted from orbitofrontal cortex to medial prefrontal cortex, resembling the pattern of activity from catatonic patients before lorazepam. Catatonic patients, in contrast, showed a reversal in activation/deactivation pattern after lorazepam: Activation in medial prefrontal cortex was replaced by deactivation, and deactivation in lateral prefrontal cortex was transformed into activation. It was concluded that prefrontal cortical activation/deactivation pattern during negative emotional processing may be modulated by GABA-A receptors.

In addition to fMRI and MEG, kinematic measurements and movement-related cortical potentials were investigated in catatonic patients before and after lorazepam (Northoff et al. 2000a; Pfennig et al. 2001). After injection of the GABA-A potentiator lorazepam, time duration for "Termination" reversed between groups and was now significantly shorter in catatonic patients than in psychiatric and healthy controls. In contrast, no influence of lorazepam was observed on temporal duration of "Initiation" in either group. After lorazepam, the early onset in parietal electrodes in MRCP 2 was reversed between groups, being now significantly earlier in catatonics than in psychiatric and healthy controls. Lorazepam thus "normalized" – that is, shortened – delayed early onsets in MRCPs during "Termination" in catatonia. In contrast, it delayed early onsets in both psychiatric and healthy controls. In contrast to MRCP 2, lo-

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razepam had no abnormal influence on MRCP 1 in catatonic patients (Pfennig et al. 2001). Moreover, it should be noted that, psychologically, lorazepam induced a "paradoxical" reaction in all catatonic patients. Instead of reacting with sedation, as was the case in psychiatric and healthy controls, they became rather agitated.

In contrast to catatonia, GABA-ergic transmission in orbitofrontal and prefrontal cortex, does not seem to reveal any abnormalities in PD, whereas there are subcortical GABA-ergic alterations in basal ganglia.

In summary, catatonia can be characterized by major alterations and abnormal reactivity of GABA-A receptors in right orbitofrontal, motor cortex, and right parietal cortex. In PD, in contrast, no such orbitofrontal cortical GABA-ergic abnormalities can be observed.

3.7.2. Dopamine. In early studies, Gjessing (1974) found increased dopaminergic (homovanillic acid and vanillic acid) and adrenergic/noradrenergic (norepinephrine, metanephrine, and epinephrine) metabolites in the urine of patients with periodic catatonia. In addition, he obtained correlations between vegetative alterations and these metabolites. He suggested a close relationship between catatonia and alterations in posterior hypothalamic nuclei. Recent investigations of the dopamine metabolite homovanillic acid in the plasma of 32 acute catatonic patients showed increased levels in the acute catatonic state (Northoff et al. 1996), particularly in those responding well to lorazepam (Northoff et al. 1995b). Accordingly, the dopamine agonist apomorphine exerted no therapeutic effect at all in acute catatonic patients (Starkstein et al. 1996). Instead, one would expect therapeutic efficacy of dopamine-antagonists like neuroleptics. However, neuroleptics such as haloperidol may rather induce a catatonia, that is, so-called "neuroleptic-induced catatonia" (Fricchione et al. 2000). Involvement of the striatal dopaminergic system, especially of D-2 receptors in catatonia, therefore remains controversial. No systematic studies investigating D2 receptors in catatonia have been reported so far.

In contrast to catatonia, dopamine is the major transmitter affected in PD. Several studies showed decreased striatal D2-receptor binding in patients with PD.

In summary, exact involvement of the dopaminergic system in catatonia remains unclear. In contrast, PD can be characterized by reduction of striatal D-2 receptors.

3.7.3. Glutamate. The glutamatergic system, in particular the NMDA-receptors, may be involved in catatonia as well. Some catatonic patients being nonresponsive to lorazepam have been treated successfully with the NMDA-antagonist amantadine. Therapeutic recovery occurred rather gradually and delayed (Northoff et al. 1997; 1999c). Such gradual and delayed improvement suggests that NMDA-receptors may be involved only secondarily in catatonia, whereas GABA-A receptors seem to be primarily altered. Such an assumption remains rather speculative, since neither the NMDA-receptors nor their interactions with GABA-A receptors have been investigated in catatonia.

In PD, a modulation of glutamatergic-mediated cortico-striatal pathway by NMDA-antagonists has been suggested as a model for explanation of therapeutic efficacy of amantadine/memantine (Merello et al. 1999). Alternatively, modulation of glutamatergic pathways within basal ganglia themselves, that is, between subthalamic nuclei and internal pallidum, has been discussed.

In summary, both catatonia and PD may be characterized by glutamatergic abnormalities especially in NMDA-receptors. Amantadine as a NMDA antagonist is therapeutically effective in both diseases and may modulate glutamatergic-mediated cortical and subcortical connectivity.

3.7.4. Serotonin. The serotonergic system has been assumed to be involved in catatonia. Atypical neuroleptics that have serotonergic properties may induce catatonic features (Carroll 2000). Therefore, it has been hypothesized that catatonia may be characterized by a dysequilibrium in the serotonergic system with up-regulated 5-HT1a receptors and down-regulated 5-HT2a receptors (Carroll 2000). However, no investigations of the serotonergic system in catatonia have yet been reported, so that this hypothesis remains speculative.

Similar to catatonia, the serotonergic system may be involved in PD, which may be related to dopaminergic abnormalities.

In summary, the serotoninergic system seems to be involved in both catatonia and PD. This may reflect secondary modulation by another primarily altered transmitter system, that is, GABA in catatonia and dopamine in PD.

4. Pathophysiological hypothesis

The present hypothesis focuses predominantly on similarities and differences between PD and catatonia with respect to distinct kinds of modulation. Similar to the presentation of data (see sect. 3), various subtle aspects of pathophysiology, especially in PD, will therefore not be discussed in detail. In addition, the present hypothesis primarily focuses on catatonic responders to lorazepam. This is important to mention, since responders and nonresponders may be characterized by distinct underlying pathophysiological mechanisms (Northoff et al. 1995b; 1998; Ungvari et al. 1999). Instead of giving an overview of the pathophysiology in its entirety, the focus will be on the distinct kinds of modulation.

4.1. Pathophysiology of motor symptoms

4.1.1. Deficit in "Execution" of movements: Akinesia. Both catatonia and PD can be characterized by akinesia which may be related to functional alterations in the so-called "direct motor loop." The "motor loop" includes connections from MC/SMA to putamen, from putamen to internal pallidum, and from there via mediodorsal thalamic nuclei back to MC/SMA (Masterman & Cummings 1997). Decrease in striatal dopamine leads to down-regulation of the "direct motor loop" (exclusion of external pallidum) and concurrent "up-regulation" of the "indirect motor loop" (inclusion of external pallidum), resulting in a net effect of decreased activity in premotor/motor cortex.

In contrast to PD, functional imaging studies during performance of movements yielded no alterations in SMA and MC in catatonia. However, effective connectivity ranging from orbitofrontal cortex to premotor/motor cortex was significantly reduced during emotional-motor stimulation in catatonic patients. Premotor/motor cortical function re-

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Table 2. *Pathophysiological correlates of symptoms in catatonia and Parkinson's disease*

		Catatonia	Parkinson's
Motor symptoms	Akinesia	Cortico-cortical GABA-ergic	Subcortico-cortical Dopaminergic
	Starting problems	Top-down-regulation of SMA/MC	Deficit in SMA/MC in relation to altered bottom-up modulation
	Posturing	Right orbitofrontal Right posterior parietal	
	Rigidity	Top-down modulation of striatal D-2 receptors	Deficit in striatal D-2 receptors
Behavioural symptoms	Motor anosognosia	Network between ventrolateral, dorsolateral, and parietal cortex	
	Mutism and stupor	Anterior cingulate and medial prefrontal cortex	
	Preservative-compulsive behavior	Concomitant dysfunction in dorso- and ventrolateral prefrontal cortex	
Affective symptoms	Anxieties	Medial orbitofrontal cortex Unbalance between medial and lateral prefrontal cortical pathway	
	Inability to control anxieties	Unfunctional relation between medial and lateral orbitofrontal cortex	
	Depression		Anterior cingulate
Therapeutic agents	GABA (lorazepam)	GABA-ergic mediated neuronal inhibition in medial orbitofrontal cortex Modualtion of functional and behavioural inhibition	
	NMDA (amantadine)	Down-regulation of glutamatergic-mediated overexcitation in prefrontal and orbitofrontal-parietal pathways	Down-regulation of glutamatergic-mediated overexcitation in subcortical pathways
	dopamine	Top-down modulation of striatal D-2 receptors predisposing for neuroleptic-induced catatonia	Compensation for striatal D-2 receptor deficit with "normalization" of "bottom-up modualtion"

mains apparentely intact during isolated motor stimulation, whereas it seems to become dysregulated during emotional stimulation via cortico-cortical connectivity in orbitofrontal/prefrontal cortex. Consequently, the "motor loop" itself seems to remain intact in catatonia, whereas it is dysregulated by orbitofrontal and prefrontal cortex via "cortico-cortical, that is, horizontal modulation."

In summary, akinesia is closely related to down-regulation of the "motor loop." This down-regulation may be caused either by dopamine and subcortical-cortical "bottom-up modulation," as in PD, or by GABA and cortico-cortical, that is, "horizontal modulation" with consecutive "top-down modulation," as in catatonia.

4.1.2. Deficits in "Initiation" of movements: Starting problems. Parkinsonian patients could be characterized by deficits in initiation, which may be considered as one essential component of the "willed action system."

Movements have to be planned and a strategy formed, to get an idea what kind of movement shall be performed which may be closely related to lateral orbitofrontal cortical function (Deecke 1996). This aspect is referred to as the "Plan/Strategy" of movements, later in this article. There must be an idea of how to move, including a decision to perform a movement, which can be initiated either internally (i.e., voluntary) or externally (i.e., involuntary). Internally initiated movements can be considered as willed movement/actions, which may be subserved by a so-called "willed action system" involving the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate, the anterior supplementary motor area (SMA), and fronto-striatal circuits (Deecke 1996; Jahanshahi et al. 1995; Jahanshahi & Frith 1998, pp. 494, 517–99.). This aspect is referred to as "Initiation" in the further course of the article. Once a movement is initiated, it can be executed – which probably is closely related to function of posterior SMA and the motor cortex (Deecke 1996; Jahanshahi & Frith 1998); this is referred to as "Execution" in the rest of this article. The executed movement can be characterized by dynamic and kinematic properties. Dynamic properties refer to force and velocity of the movements that may be encoded primarily in neurons of the motor cortex (Dettmers et al. 1995). Fronto-mesial structures such as the SMA, as well as the putamen and the ventrolateral thalamus, may be im-

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portant for coding of temporal properties, that is, the "timing" of movements (Deecke 1996, Jahanshahi & Frith 1998, p. 493). Kinematic properties describe spatial characteristics of movements such as angles, and so on, which may be encoded by neurons in parietal cortex (areas 5, 39, 40) (Jeannerod 1997, pp. 57–58, 72–73; Kalaska 1996.). Finally, the movement must be terminated, which is referred to as "Termination," implying postural change with on-line monitoring of the spatial position of the movement.

PD can be characterized by severe deficits in SMA, which, as part of the "willed action system," is closely related to the ability of "Initiation." Parkinsonian patients do indeed show severe deficits in internal initiation, although they are well able to execute them once they have overcome their initiation problems. Consequently, PD may be characterized by disturbance in the "willed action system" with problems in the voluntary generation of movements by itself (Jahanshahi & Frith 1998).

In contrast to PD, catatonia cannot be characterized by primary alterations in the "willed action system," since both "Initiation" and the function of SMA seem to remain more or less intact in these patients. Therefore, voluntary generation and "initiation" imply that the "willed action system" itself remains basically intact. Instead, the "willed action system" becomes dysregulated by cortico-cortical connectivity so that it only appears as if there is a deficit in "Initiation" in catatonia.

In summary, "initiation" as part of the "willed action system" is disturbed in PD, clinically accounting for starting problems. Whereas, in catatonia, the intact functioning "willed action system" becomes dysregulated by cortico-cortical modulation, resulting in motor similarity between catatonic and Parkinsonic patients.

4.1.3. Deficit in "Termination" of movements: Posturing. In order to terminate a movement, on-line monitoring of the spatial position of the respective movement is necessarily required. Neuropsychologically, such on-line monitoring may be subserved by visuo-spatial attention, as closely related to function of the right posterior parietal cortex.

The posterior parietal cortex has been shown to be specifically involved in location and direction of the spatial position of movements and limbs in relation to intrapersonal space of the body (Anderson 1999; Colby & Duhamal 1996; Roland et al. 1980.). On the basis of spatial attention with a redirection to extrapersonal or sensory space, movements will be selected in orientation on the respective spatial context. Providing the spatial frame of reference, the posterior inferior parietal cortex, as contrasted to the posterior superior parietal cortex, is specifically involved in abstract spatial processing and exploration (Karnath 1999). As such, the right posterior inferior parietal cortex may provide the intrapersonal "spatial frame of reference of the body necessary for the conscious organization of movements thus making spatial codes available for prefrontal cortical representation" (Vallar 1999, p. 45). In addition to spatial monitoring, the posterior inferior parietal cortex seems to be specifically involved in early initiation of movements (Castiello 1999; Desmurget et al. 1999; Driver & Mattingley 1998; Mattingley et al. 1998; Snyder et al. 1997), which, in the present context, may be interpreted as a specific relationship between "initiation of Termination" and posterior inferior parietal cortical function. Consequently, posterior inferior parietal cortical function may provide the linkage between spatial registration as "internal spatial monitoring," and "initiation of Termination" as necessarily required for postural change and consecutive "execution of Termination."

In catatonia, alterations in right parietal cortical function were found in neuropsychology and SPECT. Neuropsychologically, catatonic patients showed deficits in visuo-spatial abilities correlating with attentional function. SPECT results revealed decreased r-CBF in right parietal cortex and abnormal correlations with visuo-spatial abilities. Involvement of right posterior parietal cortex in pathophysiology of catatonia is further supported by consideration of anatomo-functional parcellation in this region. Distinct areas representing eye movements, arm movements, and head movements may be distinguished within posterior parietal cortex (Anderson 1999; Colby & Duhamel 1996). Such distinct representational areas for eyes, head, and arm coincide with clinical observations that posturing in catatonia can occur in eyes, arms, and/or head. Posturing of eyes may be reflected in staring, posturing of head is reflected in "psychic pillow," and posturing of arm is the classical type of posturing (see above). All three kinds of posturing can occur simultaneously, but they may also dissociate from each other, so that, for example, patients may show only the "psychic pillow" without staring and posturing of limbs. It is therefore postulated that such a clinical dissociation between these three kinds of posturing may have its physiological origin in anatomo-functional parcellation in posterior parietal cortex.

It may be hypothesized that the deficit in right parietal visuo-spatial attention in catatonic patients leads to an inability in "initiation of Termination." The spatial position of the ongoing movement can no longer be registrated in an appropriate way, resulting in an impossibility to initiate the terminating movement. This may result in an inability of "execution of Termination" with a consecutive blockade in postural change, which clinically is reflected in posturing. Assumption of relation between posturing and right parietal cortical dysfunction is supported by electrophysiological findings during termination (Pfennig 2001; Pfennig et al. 2001). Furthermore, patients with lesions in right parietal cortex show posturing as well (Fukutake et al. 1993; Saver et al. 1993).

Due to additional disturbances in orbitofrontal cortex, catatonia has to be distinguished from disorders related to isolated lesions in right parietal cortex as, for example, neglect showing the following differences: (1) patients with neglect do not show posturing; (2) unlike patients with neglect, catatonic patients neither deny the existence of limbs or parts of their body, nor overlook these body parts in relation to the environment, so that they do not strike with these body parts against walls, doors, and so on; (3) patients with neglect show attentional deficits, whereas in catatonic patients no such deficits could be found; (4) patients with neglect do often show sensory deficits which cannot be observed in catatonia; (5) unlike patients with neglect, catatonic patients do not show a right-left pattern with respect to their symptoms, that is, posturing; (6) unlike patients with neglect, catatonic patients do not suffer from alterations in peripersonal and extrapersonal space (as reflected in successful ball experiments; Northoff et al. 1995), whereas they may be characterized by alterations in personal space, being unable to locate the position of his/her own limbs in relation to the rest of the body. Since personal

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and peri/extrapersonal space may be subserved by distinct neural networks (Galati et al. 1999), distinction between both kinds of spaces may be not only phenomenologically relevant but physiologically as well. Hence, catatonia cannot be compared with neglect as an attentional disorder, so that posturing cannot be accounted for by disturbances in attention, which is further supported by neuropsychological findings showing no specific alterations in attentional measures (see above).

Other disorders related to right posterior parietal cortical dysfunction must be distinguished from catatonia as well. Patients with Balint Syndrome show symptoms like an inability to fixate objects and an optic ataxia, neither of which can be observed in catatonia. Since Balint Syndrome and especially optic ataxia indicate involvement of right posterior superior parietal cortex, differences between catatonia and Balint Syndrome do further underline the particular importance of the right posterior inferior parietal cortex in catatonia.

In contrast to catatonia, Parkinsonian patients show neither posturing nor alterations in right parietal cortex.

In summary, catatonia can be characterized by specific deficits in "initiation of termination," while PD shows deficits in "initiation of execution," implying functional dissociation between both diseases with respect to initiation of movements. Whereas the deficit in "initiation of termination" seems to be related with dysfunction in right posterior inferior parietal cortex, lack of "initiation of execution" seems to be accounted for by functional deficits in SMA.

4.1.4. Alteration in tonus of movements: Cogwheel rigidity and flexibilitas cerea. Parkinsonian patients could be characterized by muscular hypertonus with a so-called "cogwheel rigidity" which may be accounted for by a deficit in striatal D2-receptors and consecutive dyscoordination of activity in internal pallidum.

Catatonic patients may show muscular hypertonus but without "cogwheel rigidity" – instead, they show a smooth kind of rigidity, a so-called flexibilitas cerea. Since there is no primary, that is, direct deficit of striatal D2-receptors in catatonia, dyscoordination of the internal pallidum may be not as strong as in PD, implying that there may be some kind of smooth muscular hypertonus without cogwheel rigidity. Assumption of discrete down-regulation of striatal D2-receptors may be supported by symptomatic overlap between catatonia and neuroleptic malignant syndrome, possibility of "neuroleptic-induced catatonia," and central role of striatum in animal models of catatonia (see Carroll 2000).

Origin of down-regulation in striatal D2-receptors in catatonia remains, however, unclear. Down-regulation of striatal D2-receptors may be related to cortical alterations: Orbitofrontal cortical alterations may lead to down-regulation in D2-receptors in caudate via "top-down modulation" within the "orbitofrontal cortical loop" (see Fig. 4 below). Or striatal D2-receptors may be top-down modulated within the "motor loop," which by itself may be dysregulated by cortico-cortical connectivity. However, due to lack of specific investigation of basal ganglia in catatonia, both assumptions remain speculative.

In summary, rigidity may be related to alterations in internal pallidum as induced by down-regulation of striatal D2-receptors. Abnormal modulation of D2-receptors may be due to alterations in either subcortical-subcortical connectivity, as in PD, or abnormal cortico-cortical connectivity with consecutive "horizontal modulation" and concurrent cortico-subcortical "top-down modulation," as may be the case in catatonia.

4.2. Pathophysiology of behavioral symptoms

4.2.1. Deficit in on-line monitoring: Motor anosognosia. Subjective experience in catatonic patients could be characterized by unawareness of posturing and movement disturbances in general, whereas Parkinsonian patients were well aware of their motor deficits. This raises the question of difference between catatonic and Parkinsonian patients with respect to "internal monitoring" of the movement. It should be noted that catatonic patients showed unawareness only with respect to their motor disturbances, since they were well aware or even hyperaware of emotional alterations, which excludes the possibility of a deficit in general awareness.

Awareness of movements is closely related to the ability of on-line monitoring as an "internal monitoring," which by itself necessarily requires generation of an "internal model" of the respective movement. According to Miall and Wolpert (1996), distinct kinds of models can be distinguished (see Fig. 2). There is a causal representation of the motor apparatus that can be described as a "Forward dynamic model." The model of the behavior and the environment can be called "Forward output model." Finally, an "Inverse model" can be assumed where the causal flow of the motor system is inverted by representing the causal events that produced the respective motor state (for more detailed discussion, see Miall & Wolpert 1996).

In orientation on the model by Miall and Wolpert (1996), "predicted" and "actual state" are compared with each other, necessarily presupposing the estimation of the actual spatial position. Both estimation of spatial position and comparison between actual and predicted state seem to be disturbed in catatonia, as indicated by quadrats with crosses leading consecutively to alterations in "initiation and execution of Termination," and finally resulting in posturing, which is the most bizarre symptom in catatonia. Parkinson's disease, in contrast, may rather be characterized by deficit in "Initiation" leading to difficulties in "Execution" whereas, unlike in catatonia, estimation of spatial position and comparison between actual and predicted spatial state remain intact by themselves.

Note that there is double dissociation between catatonia and Parkinson's disease with regard to feedforward and feedback: Feedback is disturbed in catatonia and feedforward seems to be preserved by itself, whereas in Parkinson's disease, feedforward is disturbed with feedback remaining intact.

The "internal monitoring" of movements could itself be either "implicit" or "explicit." Following Jeannerod (1997), only certain aspects of movements are internally monitored in an "explicit" mode of processing. "Plan/Strategy" and, to some extent, "Initiation" are accessible to consciousness and can be characterized by "explicit internal monitoring." In contrast "Execution" by itself is not accessible to consciousness and can be related only with "implicit internal monitoring" (Jeannerod 1997). Accordingly, Jeannerod distinguishes between an "implicit How system" and an "explicit Who system" of movements/action, the former being responsible for "Execution," whereas the latter includes "Plan/Strategy" and "Initiation."

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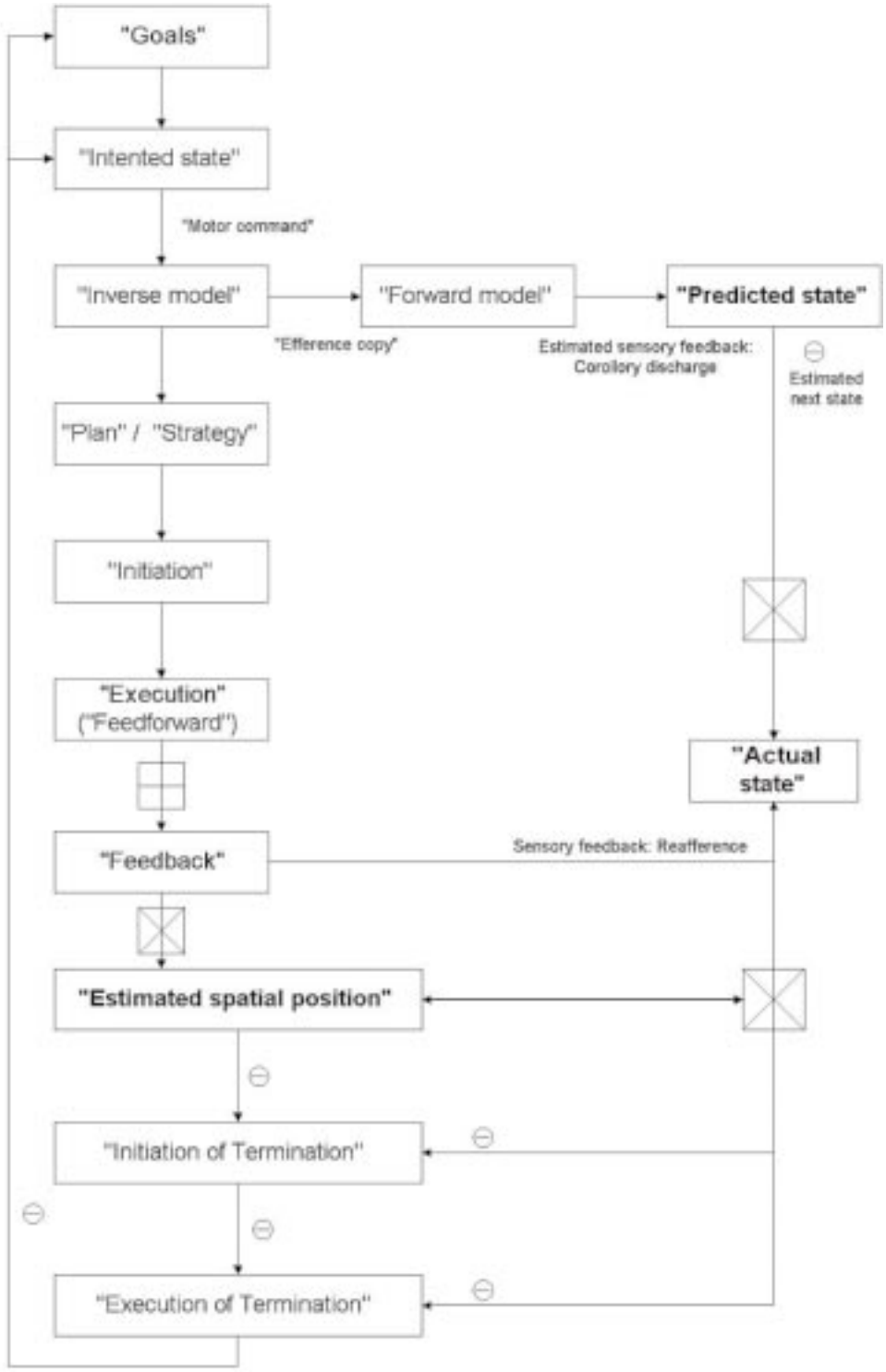


Figure 2. "Forward model" (in orientation on Miall and Wolpert 1996) of physiological motor control in catatonia and Parkinson's disease

Legend

⊞ = Disturbance in Parkinson's disease

⊠ = Disturbance in catatonia

⊖ = Hypofunction in catatonia

The figure shows the "forward model" as established by Miall and Wolpert (1996) supplemented by the distinct aspects of movements "Plan"/"Strategy," "Initiation," "Execution." In addition distinct processes involved in "Termination" of movements, feedback, "estimated spatial position," "initiation and execution of Termination" are included. In orientation on the model by Miall and Wolpert (1996) "predicted" and "actual state" are compared with each other necessarily presupposing the estimation of the actual spatial position. Both estimation of spatial position and comparison between actual and predicted state seem to be disturbed in catatonia as indicated by quadrats with crosses leading consecutively to alterations in "initiation and execution of Termination" finally resulting in posturing as the most bizarre symptom in catatonia. Parkinson's disease in contrast may rather be characterized by deficit in "Initiation" leading to difficulties in "Execution" whereas, unlike in catatonia, estimation of spatial position and comparison between actual and predicted spatial state remain intact by themselves.

Note that there is double dissociation bewteen catatonia and Parkinson's disease with regard to feedforward and feedback: Feedback is disturbed in catatonia while feedforward seems to be preserved by itself whereas in Parkinson's disease feedforward is disturbed with feedback remaining intact.

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Empirically, such an assumption is further supported by a study from Grafton et al. (1995) investigating whether persons were conscious or unconscious of a particular order of sequences of movements they performed – consciousness of the order of sequence necessarily presupposing an "explicit internal monitoring" of "Plan/Strategy." Subjects showing consciousness of the order of sequence could be characterized by activation in right dorsolateral prefrontal cortex (Area 9), right posterior parietal cortex (Area 40), and right premotor cortex (Area 6), compared to those subjects who were unconscious. Increasing demand of "explicit internal monitoring," as induced by mirror experiments, led to activation in right lateral dorsolateral prefrontal cortex (Area 9 and 46) and right posterior parietal cortex (Area 40) (Fink et al. 1999).

Following distinction between "implicit" and "explicit" internal monitoring, an analogous hypothesis shall be developed for "Termination." "Initiation of Termination" and "execution of Termination" can be distinguished from each other, emphasizing the particular importance of internal spatial monitoring for "initiation of Termination." Following phenomenological accounts of movements, one may well be conscious about the spatial position from which one "initiates" the "terminating movement" – "initiation of Termination" may be characterized by "explicit internal monitoring." In contrast, "execution of Termination" may be associated only with "implicit internal monitoring." Hence, the spatial position from which the "Termination" is initiated may be accessible to consciousness, that is, "explicit internal monitoring," whereas execution of the terminating movement itself may rather remain unconscious, because it may be characterized only by "implicit internal monitoring."

"Internal monitoring" of the spatial position of movements may be regarded as a subset of on-line monitoring in general and can be considered as an essential component of working memory. On-line monitoring in general is closely related to functional activity in ventrolateral and dorsolateral prefrontal cortex (i.e., VLPFC and DLPFC) (see Leary et al. 1999; Petrides 1995). Therefore, it may be hypothesized that on-line monitoring of the spatial position of their respective movements, may be subserved by a right-hemispheric network between VLPFC, DLPFC, and posterior parietal cortex (i.e., PPC). Consequently, functional connections between right posterior parietal, right dorsolateral prefrontal, and right lateral orbitofrontal/ventrolateral prefronal cortex may be of crucial importance for "implicit" and "explicit internal monitoring" of the spatial position of movements. As based on the above-mentioned studies of motor awareness, the VLPFC seems to be related to "implicit internal monitoring," whereas the DLPFC may be involved in "explicit internal monitoring."

The lateral orbitofrontal/ventrolateral prefrontal cortex shows similar cytoarchitectonic subdivisions as the posterior parietal cortex (Carmichael & Price 1994), and receives reciprocal connections from both posterior parietal and dorsolateral prefrontal cortex that project to similar areas (Cavada & Goldman-Rakic 1989; Morecraft et al. 1992; 1998; Selemon & Goldman-Rakic 1988). In accordance with such reciprocal connectivity, co-activation of these three regions has been demonstrated in tasks requiring behavioral flexibility and "implicit and explicit spatial monitoring" (Athwal et al. 1999; Meyer-Lindenberg et al. 1999; Nobre et al. 1999; Quintana & Fuster 1999; Stephan et al. 1999). The orbitofrontal cortex may modulate activity in dorsolateral and posterior parietal cortex, which has already been demonstrated in both animals (Quintana et al. 1989) and humans (Büchel et al. 1997; Drevets & Raichle 1998; Mayberg et al. 1999). Furthermore, the right orbitofrontal cortex shows a higher density of neurons and neuronal connections, which may account for predominance of right hemispheric activation (see below). Consequently, the right hemispheric neural network between posterior parietal, dorsolateral prefrontal, and lateral orbitofrontal/ventrolateral prefrontal cortex may be crucially involved in "implicit" and "explicit internal monitoring" of the spatial position of movements, resulting in updating of spatial location and representation of movements (Colby 1999).

Catatonia can be characterized by major deficits in on-line monitoring and alterations in right ventro/dorsolateral prefrontal cortex (i.e., VLPFC, DLPFC) and right posterior parietal cortex (PPC) as has been demonstrated in SPECT and fMRI (see above). This right hemispheric network between VLPFC, DLPFC, and PPC may be altered in catatonia, which may account for deficit in on-line monitoring of the spatial position of movements, consecutively leading to posturing. One may assume that both kinds of on-line monitoring – "implicit" and "explicit internal monitoring" – may be deficient in catatonia: Catatonic patients are neither able to terminate their movements requiring "implicit monitoring," nor are they aware of their motor disturbances requiring "explicit internal monitoring," resulting in concurrent posturing and motor anosognosia.

Furthermore, one may hypothesize that primary involvement of GABA-ergic transmission may be somehow related to motor anosognosia. Similar to catatonia patients with movement, disturbances with primary alteration in GABA, such as Huntington's chorea and Parkinsonian dyskinesia, do show unawareness of their motor anomalies, that is, motor anosognosia (Snowdon et al. 1998). However, the exact relationship between GABA-ergic transmission and motor anosognosia remains unclear.

In contrast to catatonia, Parkinsonian patients show deficits neither in on-line monitoring in general, nor in "implicit and explicit internal monitoring" of movements in particular. Physiologically, this may be reflected in the absence of major deficits of function in VLPFC and GABA-ergic transmission, implying that these patients remain fully aware of their motor disturbances.

In summary, catatonia can be characterized by ventrolateral prefrontal cortical dysfunction with consecutive deficits in on-line monitoring in general. This deficit may lead to dysregulation of the right-hemispheric network between VLPFC, DLPFC, and PPC, resulting in lack of "implicit and explicit internal monitoring" of the spatial position of movements. Clinically, such a dysregulation is reflected in concurrent occurrence of posturing and motor anosognosia in catatonic patients.

4.2.2. Deficit in verbal and nonverbal contact: Mutism and stupor. One of the most impressive clinical features in catatonic patients is mutism or even stupor, implying that there is no longer any kind of verbal contact (mutism) and/or nonverbal contact (stupor) with other persons – neither mutism nor stupor occur in PD.

Catatonia could be characterized by alterations in medial and lateral orbitofrontal cortex during negative emotional processing. These alterations shift the patterns of activity

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towards anterior cingulate/medial prefrontal cortex and lateral prefrontal cortex, resulting in functional lack of balance between medial and lateral pathway in prefrontal cortex (see sect. 3).

The anterior cingulate (areas 24 and 32, according to Brodmann) shows anatomical, cytoarchitectonic, connectional, and functional subdivision into an affective (area 24a), cognitive (area 24b), and motor (area 24c) part. Relation between these three subdivisions may be characterized by reciprocal suppression (Devinsky 1997): For example, strong emotional processing leads to activation in the affective part and concurrrent suppression of the cognitive part, and vice versa (see Bush et al. 2000).

Because the patterns of activity shifted from orbitofrontal cortex to anterior cingulate/medial prefrontal cortex, there may be extremely strong and high activity in the affective part (i.e., 24c) of the anterior cingulate. Via reciprocal suppression, one may assume almost complete down-regulation of functional activity within the motor part of the anterior cingulate. Down-regulation of the motor part in the anterior cingulate may account for mutism as an inability to speak (that is, making verbal contact with other persons). Such an assumption would be supported by observation of mutism in patients with isolated lesions in the anterior cingulate. In addition, these patients can be characterized by a combination of akinesia and mutism – akinetic mutism, which, of course, is in full accordance with catatonia. However, comparison between catatonia and akinetic mutism should be restricted to concurrent occurrence of akinesia and mutism. Unlike in catatonia, patients with akinetic mutism show neither hyperkinesias nor other behavioral anomalies (like negativism, perseverative and compulsive behavior, etc.).

In addition to anterior cingulate alterations, catatonic patients showed functional alterations in medial prefrontal cortex during negative emotional processing. The medial prefrontal cortex is involved in social cognition as well as in perception of movements and mental states of other persons (see Castelli et al. 2000). Shift of pattern of activity from orbitofrontal to medial prefrontal cortex may lead to dysfunction of the latter. Medial prefrontal cortical dysfunction may in turn result in deterioration of the ability to perceive movements and mental states from other persons. Clinically, this may be reflected in stupor, or the inability to make either verbal or nonverbal contact with other persons at all.

In summary, deficit in orbitofrontal cortical activation during negative emotional processing in catatonia leads to a shift of patterns of activity towards anterior cingulate and medial prefrontal cortex. Clinically, dysfunction in anterior cingulate and medial prefrontal cortex may be reflected in mutism and stupor.

4.2.3. Deficit in inhibitory control and planning of behaviour: Perseverative-compulsive behaviour. In contrast to PD, catatonia can be characterized by bizarre behavioural anomalies including negativism, stereotypies, perseverations, echolalia/praxia, and so on (see above), which may be classified as perseverative and compulsive behaviour. These bizarre perseverative and compulsive behavioural anomalies may be closely related with dysfunction in the orbitofrontal cortex.

The orbitofrontal cortex, and especially the lateral part including the ventrolateral prefrontal cortex (VLPFC), may be associated with control and monitoring of complex behaviour (Deecke 1996), whereas planning of its details seems to be subserved rather by the dorsolateral prefrontal cortical function (DLPFC) (Jahanshahi & Frith 1998). Control and monitoring of complex behaviour may be exerted by inhibition (Dias et al. 1996; 1997) realized by suppression as an inhibitory control. Similar to VLPFC, the DLPFC shows reciprocal connections with posterior parietal cortex (PPC) (Cavada & Goldman-Rakic 1989; Selemon & Goldman-Rakic 1988). Therefore, control and monitoring of behaviour may be closely associated with registration of the spatial position of the respective movement. It is the neural network between VLPFC, DLPFC, and PPC which may consequently subserve the control and monitoring of complex behaviour.

Due to deficits in medial and lateral orbitofrontal cortical activation in catatonia, the VLPFC may be unable to exert inhibitory control and monitoring of complex behaviour. Behaviour can no longer be controlled by inhibition, resulting in lack of suppression of once started behavior with consecutive perseverations. It is this inability to suppress once started behaviour that may account for perseverative symptoms like stereotypies, echolalia/praxia, perseverations, and so on. Furthermore, alterations in lateral orbitofrontal cortex are closely associated with compulsive behaviour, for example, in obsessive-compulsive disorder. This may further support our assumption of a relation between perseverative-compulsive behavioural anomalies and dysfunction in VLPFC in catatonia.

Dysfunction in VLPFC may lead to functional alteration in DLPFC as well, because both regions are reciprocally connected. In addition to the inability to suppress once started behavioural patterns, as related to dysfunction in VLPFC, functional alterations in DLPFC may lead to a deficit in planning the details of new behaviour: If one is unable to plan one's own behaviour, one has to take over behavior from other persons by either imitating or negating them. This may be reflected in bizarre symptoms like automatic obedience, negativism, echolalia/praxia, *mitgehen/machen,* and so on. However, assumption of dysfunctional cortico-cortical relation between VLPFC and DLPFC in catatonia remains speculative. It is, nevertheless, supported by findings of significant correlations between behavioural symptoms and lateral orbitofrontal/ventrolateral prefrontal dysfunction during on-line monitoring in catatonia (see Leschinger et al. 2001). Though in some instances, patients with PD may show palilalia, they do nevertheless not show the whole spectrum of behavioural anomalies as observed in catatonia. Accordingly there is no evidence for major dysfunction in lateral orbitofrontal and ventrolateral prefrontal cortex in PD.

In summary, deficit in orbitofrontal cortex may lead to concurrent dysfunction in inhibitory control of behaviour and deficit in planning of new behaviour as related with VLPFC and DLPFC, respectively. Dysfunction in cortico-cortical relation between VLPFC and DLPFC may account for perseverative-compulsive behavioural anomalies observed in catatonia.

4.3. Affective symptoms

4.3.1. Alteration in negative emotional processing: Anxiety. In contrast to PD, catatonia can be characterized by strong and intense anxieties, so that catatonic patients are

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"paralyzed by fear" or "immobilized by anxieties" (Northoff et al. 1998; Rosebush et al. 1990). Based on such phenomenology, a paradigm for emotional-motor stimulation was developed showing a major deficit of activation in medial orbitofrontal cortex during negative emotional processing in catatonia.

The medial orbitofrontal cortex is reciprocally connected with the amygdala, that is, the basal nucleus, which is closely related to processing of negative emotions (see Drevets & Raichle 1998, Northoff et al. 2000b). Amygdala and medial orbitofrontal cortex have been shown to be activated particularly during negative emotions, whereas both are either less activated or not activated at all during positive emotional processing (see Northoff et al. 2000b for an overview).

Processing of negative emotions in medial orbitofrontal cortex seems to be altered in catatonia, characterized by a shift of activation from medial orbitofrontal cortex to anterior cingulate/medial prefrontal cortex (see above). Unfortunately, there are no data available yet concerning the function of the amygdala in catatonia, which could potentially further reveal the origin of functional deficit in medial orbitofrontal cortex.

The occurrence of catatonic syndrome in patients with major depression may give some further ideas in this respect. Major depression can be characterized by alterations in subgenual anterior cingulate (see Drevets & Raichle 1998; Mayberg et al. 1999). Via asymmetric amygdalo-prefrontal cortical connectivity (see LeDoux 1996, p. 287), this part of the anterior cingulate is closely connected with both medial orbitofrontal cortex and supragenual anterior cingulate/medial prefrontal cortex. If dysfunction in the subgenual area surpasses a certain threshold, as may be clinically reflected in strong depressive symptoms, effective connectivity to medial orbitofrontal cortex may be altered. Clinically, such a process may be reflected in gradual development of catatonic syndrome in severely depressive patients (see Starkstein et al. 1996). Furthermore, the amygdala may be affected as well in depression, implying that alteration in the amygdala could potentially lead to dysregulation in medial orbitofrontal cortex via modulation of asymmetric connectivity (see sect. 5.1). Consequently, there would be at least two other areas – the subgenual area and the amygdala – which could dysregulate medial orbitofrontal cortical function, accounting for occurrence of catatonia in depression. However, such a hypothesis remains speculative since, currently, there are no data available about subgenual and amygdala function in catatonia.

Deficit in medial orbitofrontal cortical activation during negative emotional processing leads to alteration in balance between medial and lateral pathways in the prefrontal cortex. Analysis of structural, functional, and effective connectivity demonstrated division of the prefrontal cortex into medial and lateral pathways (Kötter & Northoff 2001; Northoff et al. 2000b): The medial pathway starts from medial orbitofrontal cortex, continues to anterior cingulate and medial prefrontal cortex, and ends in medial premotor cortex (SMA). The lateral pathway starts from lateral inferior prefrontal cortex, including lateral orbitofrontal cortex and VLPFC, continues to dorsolateral and upper lateral prefrontal cortex, and ends finally in lateral premotor cortex. The premotor/motor cortex can consequently be regarded as a common final functional output station for both pathways. Relying on imaging results and analysis of effective connectivity (Kötter & Northoff 2001; Northoff et al. 2000b), negative emotions seem to be processed predominantly in the medial pathway in prefrontal cortex, whereas positive emotional processing seems to be subserved by the lateral pathway.

It is the balance between medial and lateral pathway in prefrontal cortex that seems to be altered in catatonia. Catatonia can be characterized by down-regulation of effective connectivity in medial pathway with consecutive up-regulation of the lateral pathway. Dysfunction in medial prefrontal pathway includes alteration in effective connectivity between medial orbitofrontal cortex and premotor cortex, which may account for concurrent occurrence of emotional and motor symptoms. Due to unbalance between medial and lateral pathways in prefrontal cortex, negative emotions may no longer be processed in an appropriate way, clinically resulting in an overflow of anxiety; though such an assumption remains rather speculative. Nevertheless, it is supported by findings of highly significant correlations between affective and motor disturbances, on the one hand, and orbitofrontal and premotor cortical activity, on the other (Northoff et al. 2001a; 2001c).

In summary, anxiety in catatonia may be accounted for by alteration in negative emotional processing in medial orbitofrontal cortex and medial pathway in prefrontal cortex. As connections from the orbitofrontal to premotor cortex are affected, that may account for concurrent occurrence of emotional and motor disturbances in these patients.

4.3.2. Deficit in emotional control: Inability to control anxieties. In addition to deficit in medial orbitofrontal cortex during negative emotional processing, catatonia can be characterized by functional alterations in lateral orbitofrontal cortex during both negative emotional processing and on-line monitoring (as part of working memory).

Whereas the medial orbitofrontal cortex seems to be closely related to emotional processing, the lateral orbitofrontal cortex has, rather, been associated with cognitive control of emotional processing, thereby linking emotional functions with behaviour (Carmichael & Price 1994; Damasio 1997; Dias et al. 1996; 1997; Drevets & Raichle 1998; Morecraft et al. 1992; 1998; Shore 1996). Interaction between medial and lateral orbitofrontal cortex provides an "internal model of the social and emotional context" (Bechara 1997; Rolls 1998; Shore 1996). Such a controlling function in emotional-behavioral processing would be in full accordance with involvement of VLPFC in on-line monitoring in general (see above). Consequently, negative emotional processing in medial orbitofrontal cortex may be controlled by on-line monitoring in lateral orbitofrontal cortex, implying reciprocal dependence between medial and lateral orbitofrontal cortical function. Such reciprocal dependence between medial and lateral orbitofrontal cortical function may be reflected in the pattern of activation and deactivation obtained in fMRI (see Baker et al. 1997; Drevets & Raichle 1998; Mayberg et al. 1999; Northoff et al. 2000b). Activation (i.e., positively activated activity) in medial orbitofrontal cortex was accompanied by deactivation (i.e., negatively correlated activity) in lateral orbitofrontal cortex, whereas activation in lateral orbitofrontal cortex was accompanied by deactivation in medial orbitofrontal cortex (see also Raichle et al. 2001).

It is this pattern of activation and deactivation in medial and lateral orbitofrontal cortex that was found to be altered

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in catatonia, as has been revealed in fMRI. If reciprocal dependence between medial and lateral orbitofrontal cortex is altered, functional balance between negative emotional processing and emotional control may be altered as well, as is clinically reflected in the uncontrollability of anxieties. If the ability of on-line monitoring as a kind of cognitive control of negative emotions is disturbed, catatonic patients have to rely on other less sophisticated forms of emotional control, for example, involvement of the motor system (see Northoff et al. 2001c). The cognitive control of emotional processing is replaced by motor control, which, psychodynamically, may be regarded as a "sensorimotor regression" (Northoff et al. 2001c). Such a shift from cognitive control to motor control of negative emotional processing may be subserved by dysfunctional regulation of the network between medial orbitofrontal cortex, lateral orbitofrontal cortex, and premotor/motor cortex (see Fig. 3). An analogous shift from cognitive control to motor control of emotional processing may be observed in hysterical paralysis. Accordingly, patients with hysterical paralysis show dysfunction in right orbitofrontal cortex and anterior cingulate (Marshall et al. 2000).

The lateral orbitofrontal cortex can be characterized by close and reciprocal connections with medial temporal lobe comprising ento/perirhinal structures (Morecraft et al. 1992; 1998; Zald et al. 1998), which may account for occurrence of catatonic syndrome in schizophrenia. Schizophrenia can be characterized by alterations in ento/perirhinal structures (Bogerts et al. 1985; Gray 1995), and if they surpass a certain degree of severity, that is, a certain threshold, they may lead to alterations in temporal-lateral orbitofrontal connectivity. Modulation of temporal-lateral orbitofrontal connectivity may account for clinical observation of occurrence of catatonic syndrome in severely affected schizophrenic patients (see Northoff 1997a; Northoff et al. 1999d).

Dysfunction in balance between medial and lateral orbitofrontal cortex may lead to functional alteration in the network between VLPFC, DLPFC, and PPC (see above and Fig. 3) which, clinically, may account for a close relationship between affective and behavioral anomalies in catatonia. Furthermore, dysfunction in lateral orbitofrontal cortex may lead to alteration in basal ganglia. As part of the "orbitofrontal loop" (see Fig. 3), the lateral orbitofrontal cortex is closely connected with the ventromedial caudate, which then via pallidum and thalamus connects back to lateral orbitofrontal cortex (see Mann et al. 2000; Mastermann & Cummings 1997). Alteration in lateral orbitofrontal cortex may lead to abnormal top-down modulation of activity in caudate and other basal ganglia. Such a top-down modulation may potentially account for discrete postmortem findings in basal ganglia (see above) and alterations of r-CBF in caudate in single catatonic patients.

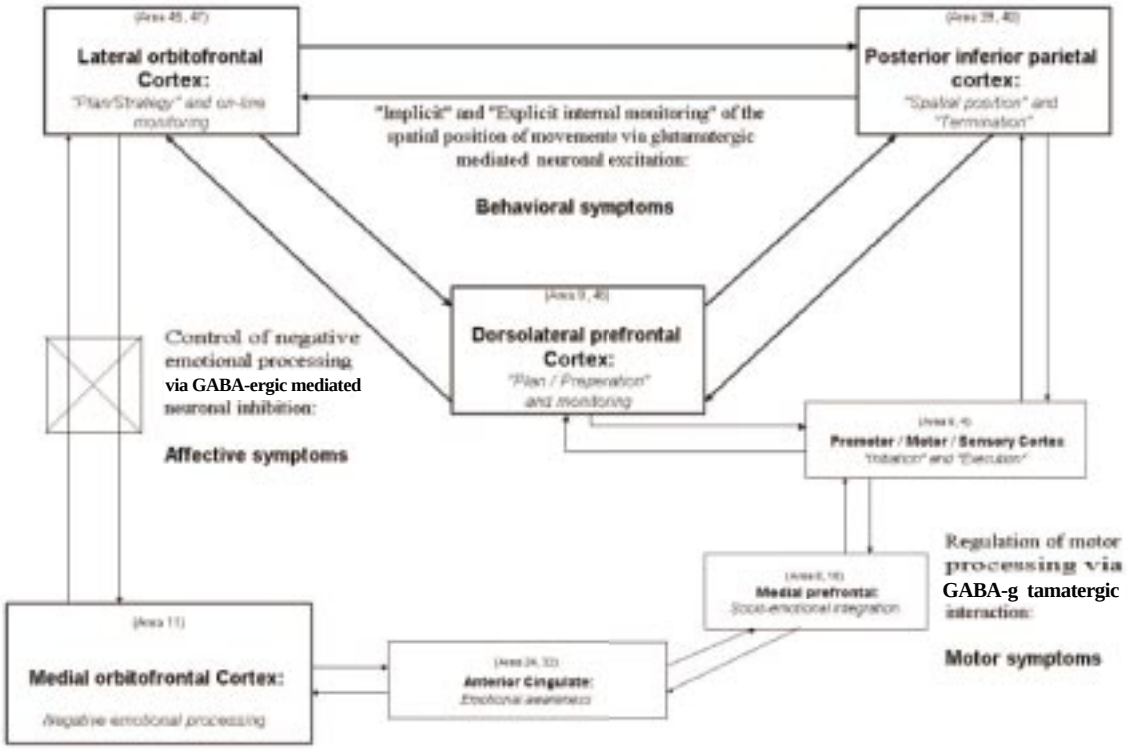


Figure 3. Pathophysiological model of cortico-cortical interactions as forms of "horizontal modulation" in catatonia
Legend
☒ = Disturbance
The figure shows cortico-cortical networks hypothetically underlying catatonic symptoms. Dysfunction in GABA-ergic mediated balance between medial and lateral orbitofrontal cortex may lead to alteration in medial prefrontal cortical pathway, potentially accounting for concomittant emotional and motor symptoms, and in network between lateral orbitofrontal, dorsolateral prefrontal, and posterior parietal cortex, potentially accounting for behavioral symptoms. Consequently catatonic symptoms may be closely related to alterations in cortico-cortical interactions as forms of "horizontal modulation."

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Investigations showed that the VLPFC-DLPFC-PPC network in the right hemisphere and not the left hemisphere is altered in catatonia. Since this is based on various neuropsychological and neurophysiological findings, there seems to be solid evidence for such a right hemispheric preference. Reasons for such a right hemispheric preference remains, however, unclear. The predominance of alterations in the right hemisphere (Devinsky 1997) may be accounted for by density of connectivity. Orbitofrontal connections with prefrontal and parietal cortex, as well as with basal ganglia and the limbic system, are much stronger and more expanded in the right cortex than in the left one (Shore 1996, p. 67). Whether or not this may account for right hemispheric preference must remain an open question. The example of catatonia does nevertheless clearly demonstrate that right hemispheric function cannot be transferred to or replaced by left hemispheric function. Furthermore, right hemispheric predominance seems to account for both the right and left sides of the body since, unlike symptoms in neglect (see above), no lateralization of posturing can be observed in catatonia (Northoff 1997a; Taylor 1990). Finally, as has been demonstrated in recent imaging studies, right hemispheric predominance in orbitofrontal and prefronto-parietal cortical function seems to be associated with motor attention (Binkowski et al. 1999) and motor inhibition (Strik et al. 1999), which would be in full accordance with both pathophysiological findings and clinical symptoms in catatonia.

In summary, deficit in emotional control with the inability to control anxieties in catatonia may be related to dysfunction in reciprocal dependence between medial and lateral orbitofrontal cortex with respect to activation and deactivation. In addition, orbitofrontal cortical dysfunction may lead to deregulation of both the VLPFC-DLPFC-PPC network and "orbitofrontal loop." Clinically this may be reflected in concurrent occurrence of emotional and behavioral disturbances in such patients.

4.3.3. Dysfunctional regulation of mood: Depression. The mood can be altered in both catatonia and PD: Catatonic patients may develop catatonic syndrome on the basis of pre-existing depression, whereas Parkinsonic patients may develop depression either before (especially in the case of older patients) or after manifestation of motor symptoms. Depression as a dysfunctional regulation of mood has been related to alterations in dorsolateral prefrontal cortex and anterior cingulate in PD (Mayberg et al. 1999). Both anterior cingulate and DLPFC are involved in the "willed action system" accounting for planning of movements in detail (see above). Down-regulation in anterior cingulate and DLPFC may affect regulation of both mood and movements, which potentially may account for concurrent occurrence of depressive and motor features in PD. Such an assumption is further supported by consideration of "medial prefrontal loop" and "dorsolateral prefrontal loop" connecting anterior cingulate and DLPFC with basal ganglia, which may be altered in depressive PD patients (Masterman & Cummings 1997). Reduction in striatal dopamine may down-regulate both anterior cingulate and DLPFC via "bottom-up modulation" within "medial prefrontal and dorsolateral prefrontal loop." Such an assumption is supported by dopaminergic dependency of depression in PD.

The DLPFC can be characterized by asymmetric connectivity with strong (feedforward) connections towards premotor/motor cortex and rather weak or even absent (feedback) connections towards orbitofrontal cortex (Kötter & Northoff 2001). This may account for the absence of major emotional and behavioral abnormalities in PD as they can be observed in catatonia. Due to asymmetric connectivity, the DLPFC can exert predominantly feedforward effects, resulting in modulation of movements. In contrast, feedback effects with potential modulation of orbitofrontal cortical function and consecutive alteration in behavior and emotions remain rather weak or even absent. Note that the same principle, that is, asymmetric connectivity may account for concurrent occurrence of behavioural, emotional, and motor symptoms in catatonia, though in a reversed way. Due to the strong feedforward connections, premotor/motor cortical function becomes apparently deregulated by orbitofrontal cortical dysfunction.

In summary, depression in PD may be accounted for by down-regulation of DLPFC. Due to asymmetric connectivity, the altered DLPFC may affect only premotor/motor cortical function, whereas orbitofrontal cortical function may remain unaffected. This may potentially account for the absence of major emotional-behavioural anomalies in PD.

4.4. Therapeutic agents

4.4.1. GABA-ergic agents: Lorazepam. Most (60–80%) catatonic patients show the almost dramatic and immediate therapeutic efficacy of the GABA-A potentiator lorazepam, as well as abnormal orbitofrontal cortical reactivity to lorazepam (see above).

Activity in orbitofrontal cortex during emotional processing may be strongly modulated by GABA-A receptors. This is supported by findings of dense GABA-ergic innervation in orbitofrontal cortical neurons (Carmichael & Price 1994; Davis 1994) and alteration in emotionally induced orbitofrontal cortical activity during stimulation with lorazepam in humans (Northoff et al. 2001d).

Relationship between emotional processing, orbitofrontal cortical function, and GABA-A receptors is supported by several investigations. In an animal model, Crestani et al. (1999) showed that GABA-ergic substances, that is, benzodiazepines, lead to reversal of anxiety-driven behavior and modulation of activity in GABA-A receptors in prefrontal, amygdala, and hippocampal areas. In healthy humans, lorazepam leads to alteration in subjective experience and perception of emotions (Ferrara et al. 1999; Garcia et al. 1997). Benzodiazepines show dramatic therapeutic effects in neuropsychiatric diseases characterized by orbitofrontal cortical dysfunction and strong anxieties such as obsessive-compulsive disorder (Coplan & Lydiard 1998) and panic disorder (Gorman et al. 2000). Physiologically, it has been demonstrated that GABA-ergic agents lead to alterations in neural activity and r-CBF in rats (Forman et al. 1998) and humans (Mathew et al. 1995; Spanaki et al. 1999; Wang et al. 1996).

Dysfunction in orbitofrontal cortical GABA-A receptors may lead to regulatory and compensatory changes in sensitivity of GABA-A receptors in VLPFC-DLPFC-PPC network and orbitofrontal-premotor/motor connections (see above). Since GABA-ergic deficits in orbitofrontal cortex seem to alter prefronto-parietal cortical networks, one may characterize orbitofrontal cortical function as a "gating function." Such a "gating function" may exert inhibitory control on prefrontal and posterior association cortical function.

The orbitofrontal cortex seems to function predomi-

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nantly via neural inhibition (Dias et al. 1996; 1997; Kiefer et al. 1998; Shore 1996; Strik et al. 1999; Zubicaray et al. 1999). Thereby, inhibition may be understood in different senses. First, inhibition may be understood in a behavioural sense implying, for example, suppression and inhibition of once started behaviour or emotions. Such a behavioural inhibition may certainly be deficient in catatonia as it is reflected in perseverative-compulsive behaviour and uncontrollable emotions. Second, inhibition may be understood in a functional, that is, connectional sense. For example, orbitofrontal cortical activity may lead to suppression and inhibition of activity in parietal cortex as it is reflected in disinhibition and increased activity of the latter in case of orbitofrontal cortical lesions (Jahanshahi & Frith 1998). Since we observed alterations in both orbitofrontal and parietal cortex, one may assume alterations of such functional, that is, connectional inhibition in catatonia as well. Third, inhibition may be understood in a neuronal sense as opposed to excitation. GABA-A receptors are inhibitory, leading to hyperpolarization of nerve cells, thus making induction of action potentials and neuronal excitation less likely. Such a neuronal inhibition may be altered in catatonia as well, since lorazepam is quite effective. It is important to note that only inhibition in a neuronal sense may be directly related to GABA-A receptors, whereas both functional and behavioural inhibition may potentially be mediated by glutamatergic or other transmitter systems.

One may assume that local and autoregulatory GABA-ergic mediated neuronal inhibition may be deficient in orbitofrontal cortex in catatonia. This in turn may modulate glutamatergic-mediated connections from orbitofrontal cortex to VLPFC, DLPFC, PPC, and premotor/motor cortex. Such an altered functional (connectional) inhibition may be accompanied by alteration in behavioural and emotional inhibition accounting for catatonic symptoms. This assumption does remain speculative, however, since studies investigating modulation of effective connectivity by different transmitter systems are still lacking.

In summary, GABA-ergic potentiation by lorazepam may compensate for deficit in GABA-ergic mediated orbitofrontal cortical "gating function." This may lead to consecutive "normalization" in cortico-cortical connectivity via "horizontal modulation" and cortico-subcortical connectivity via "top-down modulation." Clinically, such a restoration of "vertical and horizontal modulation" may account for almost immediate resolution of emotional, behavioural, and motor symptoms.

4.4.2. Glutamatergic agents: Amantadine. Amantadine is a NMDA-antagonist leading to a down-regulation of glutamatergic-mediated excitation that is therapeutically effective in both catatonia and PD.

Catatonia could be characterized by a deficit in local GABA-ergic mediated inhibition in orbitofrontal cortex. Via "horizontal modulation" and "top-down modulation" GABA-ergic mediated orbitofrontal cortical dysfunction may induce glutamatergic-mediated hyperexcitation in both prefronto-parietal network and premotor/motor-basal ganglia network. Cortico-cortical association fibers can be characterized by excitatory, that is, glutamatergic transmission and are therefore dependent on NMDA-receptors. If these long fibers are no longer inhibited by GABA-ergic mediated neuronal inhibition, they become disinhibited resulting in hyperexcitation. Amantadine as a NMDA-antagonist may indirectly compensate for lack of GABA-ergic mediated neuronal inhibition by blocking glutamatergic overexcitation in prefronto-parietal network. Instead of direct increase in GABA-ergic mediated neuronal inhibition, amantadine does rather indirectly increase neuronal inhibition by down-regulation of neuronal excitation. In contrast to the almost immediate reaction to lorazepam, the therapeutic effects of amantadine may therefore be rather delayed (Northoff et al. 1997; 1999c).

The motor cortex seems to be of crucial importance. SPECT investigation showed significantly reduced benzodiazepine binding in catatonia (see above). Such an apparent deficit in GABA-A receptor functions may be related with dysregulation of the "motor loop." The motor cortex shows a high density of GABA-ergic neurons and thus of GABA-A receptors. This is supported by findings of major reduction in amplitude of movement-related magnetic fields in MEG after application of lorazepam in healthy subjects (Northoff et al. 2001d). Assumption of GABA-ergic dependency of cortical motor function is further supported by findings of modulation of movements after application of GABA-ergic agents into primate motor cortex (Hikosaka et al. 1985; Kubota et al. 1996; Kurata & Hoffman 1994). Furthermore, there seems to be strong and direct interference between GABA-A receptors and NMDA receptors in motor cortex. Ketamine as a NMDA-antagonist lead to strong and highly significant alterations in benzodiazepine binding in this region in healthy controls (see Northoff et al. 2001e). Consequently, one may speculate that amantadine as a NMDA-antagonist may interact with GABA-A receptors in motor cortex leading to down-regulation of glutamatergic-mediated overexcitation with consecutive resolution of motor symptoms in catatonia.

Schizophrenia may be characterized by glutamatergic alterations in NMDA-receptors and consecutive overexcitation in prefrontal cortical and medial temporal areas (Abi-Saab et al. 1998; Olney & Farber 1995). Due to glutamatergic-mediated connections from medial temporal areas, activity in lateral orbitofrontal/prefrontal cortex may be deregulated in schizophrenia. If these changes are strong enough, glutamatergic overexcitation may spread to other cortical areas such as, for example, the posterior parietal cortex and premotor/motor cortex. Clinically, such a cortico-cortical spread of glutamatergic-mediated overexcitation may be reflected in the occurrence of catatonic syndrome in schizophrenia.

In addition to glutamatergic mediated cortico-cortical connections, amantadine may modulate cortico-subcortical and subcortico-subcortical connections that are mediated by NMDA-receptors as well. Cortico-subcortical connections from premotor/motor cortex to striatum, that is, putamen and subcortical-subcortical connections from subthalamic nucleus to internal globus pallidus, are modulated by glutamate and NMDA-receptors. In PD, either of these connections or both are modulated by the NMDA-antagonist amantadine leading to gradual resolution of Parkinsonian symptoms. It should be noted that, in addition to NMDA-antagonism, amantadine has weak dopamine release and agonist properties, which could account for therapeutic efficacy as well (see Carroll 2000).

In summary, amantadine may be therapeutically effective in catatonia via down-regulation of glutamatergic-mediated overexcitation in both cortico-cortical and cortico-subcortical connectivity. In PD, amantadine may lead to

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top-down modulation of glutamatergic mediated cortico-striatal connectivity and/or modulation of subcortical connectivity within the basal ganglia themselves.

4.4.3. Dopaminergic agents: L-Dopa and neuroleptics. PD can be characterized predominantly by the deficit and/or down-regulation of D-2 receptors in striatum which therapeutically may be compensated for by dopaminergic agents such as L-Dopa. Functional compensation of decreased striatal D-2 receptor function restores functional balance between "indirect and direct motor loop" (see Mastermann & Cummings 1997). The "direct motor loop" is weakened, whereas the "indirect" one is reinforced, resulting in a netto-effect of increased excitatory activity in premotor and motor cortex via "bottom-up modulation." In addition to the "motor loop," which is regulated by the nigrostriatal dopaminergic system, "medial prefrontal and dorsolateral prefrontal loops" – as regulated by the mesocortical dopaminergic system – may be restored by dopaminergic agonists as well.

Typical neuroleptics like haloperidol lead to blockade and down-regulation of striatal D-2 receptors, which may worsen Parkinsonian symptoms; so they should be avoided in patients with PD.

Furthermore, typical neuroleptics may induce catatonia, which is why some authors speak of a so-called "neuroleptic-induced catatonia" (Fricchione et al. 2000). Combination of deterioration in cortical function and concurrent subcortical D-2 blockade may induce alterations in cortico-cortical and cortico-subcortical connectivity via "horizontal modulation" and "vertical modulation." It should, however, be noted that, in addition to D-2 receptors, other dopaminergic receptors such as D1 and D4/5 may be involved in catatonia as well.

In summary, dopaminergic agonistic agents such as L-Dopa compensate for deficiency in striatal D-2 receptors in PD, leading to "normalization" of functional activity in premotor/motor cortex via "bottom-up modulation." D-2 receptor antagonists such as typical neuroleptics may worsen Parkinsonian symptoms and induce a so-called "neuroleptic induced catatonia."

5. Conclusion

We compared clinical symptoms, neuropsychology, and pathophysiology between PD and catatonia, both revealing similarities and differences. From this, PD may be characterized as a motor disorder and catatonia, rather, as a psychomotor disorder. In addition, comparison revealed the importance of the possibility of bi-directional modulation between cortical and subcortical structures reflecting "vertical modulation" with "bottom-up and top-down modulation." In contrast, cortico-cortical relations could be characterized only by unidirectional modulation implying that such "horizontal modulation" has to be distinguished from "vertical modulation." In the following, these distinct kinds of modulation shall be discussed in further detail.

5.1. What is "top-down modulation"?

Top-down modulation may be described as a modulation of subcortical structures by cortical areas as reflected, for example, in the modulation of caudate and other basal ganglia by lateral orbitofrontal cortex (see the "orbitofrontal loop" in Fig. 4). Such a top-down modulation has to be distinguished from bottom-up modulation as a modulation of cortical areas by subcortical structures, as reflected, for example, in the modulation of premotor/motor cortical areas by basal ganglia (see the "motor loop" in Fig. 4). Cortico-subcortical relations may consequently be characterized by the possibility of bidirectional modulation with both "top-down and bottom-up modulation."

The figure shows cortico-subcortical loop involved in catatonia and Parkinson's disease. In catatonia, GABA-ergic mediated deficit in orbitofrontal cortex may lead to alteration in "top-down modulation" of caudate and other basal ganglia via the "orbitofrontal loop," whereas in Parkinson's dopami-n-ergic mediated deficit in striatum may lead to alteration in "bottom-up modulation" of premotor/motor cortex via the "motor loop."

In addition to "top-down and bottom-up modulation" as forms of "vertical modulation" one may describe cortico-cortical (and subcortico-subcortical) modulation as forms of "horizontal modulation" (see Hurley 1998, p. 421; Juarrero 1999; pp. 197–99).

It should be noted that cortico-cortical connectivity is sometimes one-way, implying absence of reciprocal connectivity between two cortical areas. For example (see Edelman & Tononi 2000, p. 180), pyramidal neurons in layer V in posterior SMA and motor cortex are directly or indirectly related to motor effectors via long-range axons traveling through the spinal cord. These neurons are directly connected with neurons in layer VI in anterior SMA and other prefrontal cortical areas, which are predominantly related with the thalamo-cortical loop as the main feedback loop. However, interaction between neurons in layer V and VI is one-way – there is interaction from layer VI to layer V, but no reciprocal interaction from layer V to layer VI. Consequently, the thalamo-cortical loop as the main feedback loop may modulate cortical activity in SMA/MC via connections from layer VI to layer V, whereas an inverse modulation from layer V to layer VI remains impossible. Therefore, cortico-cortical relations as a form of "horizontal modulation" remain unidirectional, implying that prefrontal cortical activity may modulate activity in SMA/MC but not vice versa. This is also reflected in the absence of direct connections from premotor/motor cortex to dorsolateral and orbitofrontal cortex, whereas both orbitofrontal and dorsolateral cortical areas are directly connected with SMA/MC (see Kötter & Northoff 2001; Northoff et al. 2000b). Another example of such connectional asymmetry would be the connectivity between amygdala and prefrontal cortex, which is much stronger in direction from amygdala to prefrontal cortex than from prefrontal cortex to amygdala (LeDoux 1996, p. 287). Such connectional asymmetry may prevent short-circuiting, thereby providing the anatomo-connectional substrate for output orientation. Therefore, the premotor/motor cortex may be regarded as the common final output area for the various prefrontal cortical areas and pathways.

Due to such one-way connectivity, cortical-cortical relations may be modulated only unidirectionally, which may be reflected in difference between PD and catatonia. PD can be characterized by alterations in striatal dopamine which, via "bottom-up modulation" within the "motor loop," leads to down-regulation of activity in SMA/MC, accounting for akinesia as the predominant motor symptom.

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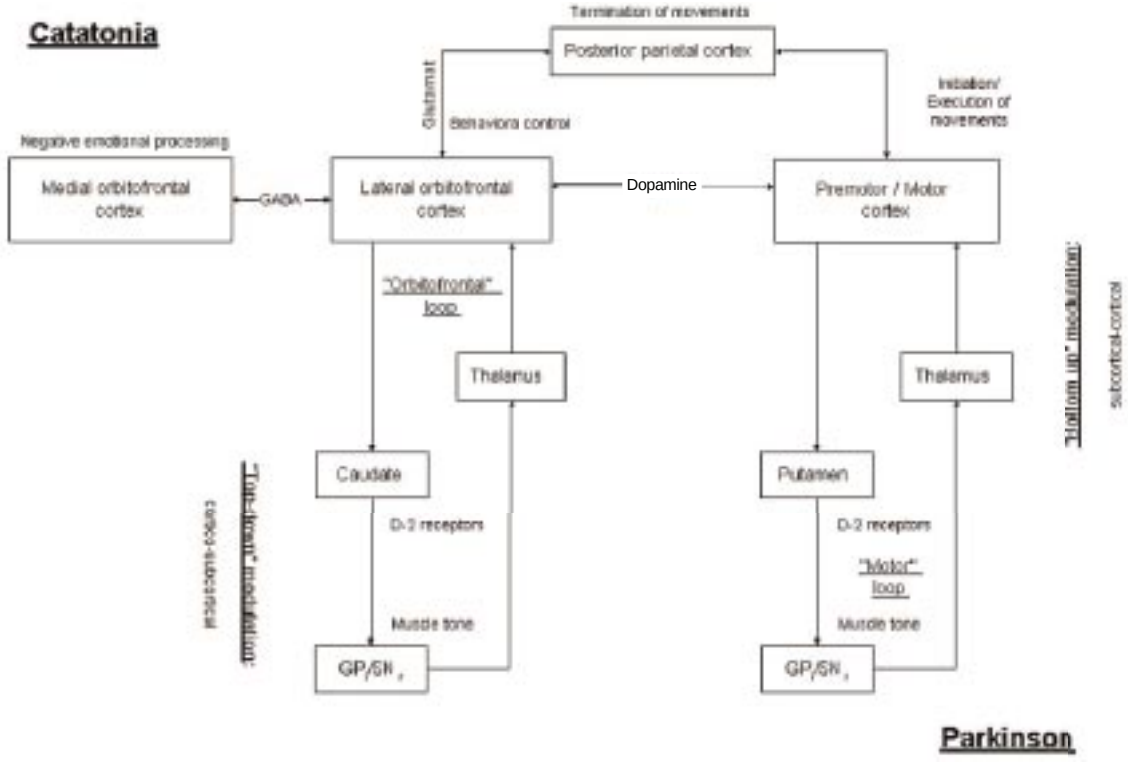


Figure 4. "Top-down modulation" and "bottom-up modulation" as forms of "vertical modulation" in catatonia and Parkinson's
The figure shows cortico-subcortical loop involved in catatonia and Parkinson's. In catatonia GABA-ergic mediated deficit in orbitofrontal cortex may lead to alteration in "top-down modulation" of caudate and other basal ganglia via the "orbitofrontal loop" whereas in Parkinson's dopaminergic mediated deficit in striatum may lead to alteration in "botton-up modulation" of premotor/motor cortex via the "motor loop."

However, PD shows major alterations neither in orbitofrontal and prefrontal cortex, nor in behavioural (and affective) functions – as is, for example, the case in catatonia. This may be related to the impossibility of modulation of orbitofrontal and prefrontal cortex by SMA/MC, which in turn may be due to one-way connectivity between both, as described above. Catatonia, in contrast, can be characterized by concurrent motor and affective-behavioural symptoms. Motor symptoms may be accounted for by "top-down modulation," whereas affective-behavioural alterations may, rather, be related with abnormal "horizontal modulation." Clinical differences between PD and catatonia, and thus, between motor and psychomotor disorders, may consequently be accounted for by difference between "vertical modulation" and "horizontal modulation" with respect to directionality (i.e., uni- or bi-directional).

Functionally, such an assumption of "horizontal modulation" characterizing cortico-cortical relationship by unidirectionality and asymmetry may be related with the concepts of "reentrant circuitry" (Edelman & Tononi 2000) and feedback modulation (Lamme 2001). Similar to these concepts, it should be noted that unidirectional character in "horizontal modulation" concerns only modulation via direct pathways without any intermediating connections. If one considers indirect pathways with intermediating connections, there is of course bi-directional modulation possible in cortico-cortical relations. However, the exact criteria by means of which "horizontal modulation," "reentrant circuitry," and feedback modulation can be detected, remain unclear (Lamme 2001). Currently, there is not much knowledge available about functional interactions in cortico-cortical relations in humans. The present distinction between "vertical and horizontal modulation" with respect to directionality remains, therefore, limited in its connection with physiological principles (see also Northoff 2001c).

In summary, difference between PD and catatonia with respect to involvement of affective and behavioural symptoms may be associated with difference between bidirectional and unidirectional modulation characterizing "vertical modulation" and "horizontal modulation," respectively.

5.2. Where can "top-down modulation" be located?

Both "top-down and bottom-up modulation" can be located within functional systems which can be described in the following way (see also Northoff 1999):

> according to this view, a function is, in fact, a functional system (. . . .) directed towards the performance of a particular biological task and consisting of a group of interconnected acts that produce the corresponding biological effect. The most significant feature of a functional system is that, as a rule, it is based on a complex dynamic "constellation" of connections, situated at different levels of the nervous system, that, in the performance of the adaptive task, may be changed with the task itself remaining unchanged. (Luria 1966, Preface)

For example, the "motor loop" allowing for both "top-down and bottom-up modulation" can be considered as an essential part of the "willed action system" (see Jahanshahi & Frith 1998), which may be regarded as a functional system in the sense suggested by Luria. The "willed action system" can

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be characterized by "functional circuits" allowing for "top-down and bottom-up modulation." PD can be characterized by a disturbance in the "willed action system." This is reflected in alteration of "vertical modulation" with abnormal "bottom-up modulation" accounting for the deficit in initiation of movements. In contrast to PD, catatonia cannot be characterized by disturbance in the "willed action system." Instead, the "willed action system" itself remains intact but becomes dysregulated by cortico-cortical connectivity with abnormal "horizontal modulation." GABA-ergic disturbance in orbitofrontal cortex seems to lead to dysregulation in SMA/MC activity via "horizontal, that is, cortico-cortical modulation." This, in turn, seems to dysregulate the "willed action system," accounting for concurrent occurrence of motor and affective-behavioural symptoms in such patients.

In contrast to "vertical modulation," which takes place within one particular functional system, "horizontal modulation" can be located between different functional systems. "Vertical modulation" can be located within the functional system for "willed action." "Horizontal modulation" may rather be located between the functional systems subserving emotions, behaviour, and "willed action," with the possibility of dysregulation of the latter by the former. To put it in different terms: "Vertical modulation" modulates within one particular loop (i.e., within motor or orbitofrontal loops, respectively) as is the case in PD; whereas "horizontal modulation" modulates between different loops (i.e., between orbitofrontal and motor loops) as is the case in catatonia.

In summary, the difference between PD as a motor disorder and catatonia as a psychomotor disorder may be related to the difference between "vertical modulation" and "horizontal modulation" with respect to location. "Vertical modulation" can be located within one particular functional system, whereas "horizontal modulation" intermediates between different functional systems.

5.3. When does "top-down modulation" become visible?

Both "top-down and bottom-up modulation" become clearly visible in the case of alteration of the respective functional systems. In the case of PD, the dopaminergic deficit in striatum makes adjustment in activation of SMA/MC via "bottom-up modulation" within the "motor loop" necessary. As long as it can fully compensate for striatal deficits, alteration in "bottom-up modulation" does not become visible (up to 80% reduction of striatal dopamine), which, however, changes with the appearance of the first clinical symptoms. In the case of catatonia, alteration in "top-down modulation" becomes visible only if catatonic patients show motor symptoms more or less similar to the ones in PD, as is clinically reflected in manifestations of akinesia. Functionally, such similarity in motor symptoms may be reflected in alteration of the same "functional circuit" – the "motor loop" in both diseases: The "motor loop" may either be abnormally "top-down modulated" by cortico-cortical relation, that is, "horizontal modulation" alterations, as is the case in catatonia. Or it may be abnormally "bottom-up modulated" by subcortical alterations, that is, "vertical modulation," as is the case in PD. Functionally, the "motor loop" can consequently be modulated by both "top-down and bottom-up modulation." This comes close to what P. Schilder called the "principle of double way":

> The fact that function of the same anatomical apparatus may be disturbed by both organic lesions and psychological alterations can be described as the "principle of double way." (Schilder 1925, p. 81; my translation)

Clinically the "principle of double way" may be reflected in the "double-facedness of psychomotor function" ("Doppelgesichtigkeit der Psychomotorik"; Homburger 1932, p. 261), implying that motor symptoms, such as akinesia, for example, may either be of neurologic or psychiatric origin.

However, from a functional point of view, "top-down modulation" cannot be considered as exactly the same as "bottom-up modulation." The former is primarily of cortical origin, whereas the latter reflects rather predominant subcortical sources. Functional difference between "top-down" and "bottom-up" modulation may be reflected in subtle differences with respect to motor symptoms: Akinesia in PD is accompanied by deficits in initiation, whereas akinesia in catatonia is closely related with a deficit in termination. The same sign, that is, akinesia may be accompanied by different symptoms in both diseases, respectively, such as starting problems and posturing. Another example would be rigidity describing muscular hypertonus: Typically patients with PD show cogwheel rigidity, whereas catatonic patients can rather be characterized by a smooth kind of rigidity, that is, flexibilitas cerea. Though exact pathophysiological mechanisms underlying both kinds of rigidity remain unclear, it may nevertheless be speculated that symptomatic differences could potentially be due to functional difference between "top-down modulation" and "bottom-up modulation."

In summary, occurrence of "top-down" and "bottom-up" modulation within the same functional system may account for apparent similarities between PD and catatonia with respect to motor symptoms. Subtle differences in motor symptoms between both disorders may be accounted for by functional differences between both kinds of modulation.

5.4. How is "top-down modulation" implemented?

Both "vertical and horizontal modulation" are implemented in functional and effective connectivity reflecting feedforward and feedback connections. These connections regulate and modulate functional relations between cortical areas and cortical areas/subcortical structures, which in turn may be determined by particular "thresholds" for activation/deactivation. Relying on such "thresholds," certain patterns of activity across different cortical/subcortical regions, that is, so-called "functional clusters" may be generated (see Edelman & Tononi 2000, p. 146, for the use of the terms "thresholds" and "functional clusters" in the present sense). These "thresholds" may be modulated by different transmitter systems. For example, dopamine and especially D-2 receptors seem to be essential for modulation and "thresholding" of anatomical structures subserving the "willed action system." In PD, deficits in striatal dopamine lead to disturbance in functional balance between basal ganglia and premotor/motor cortex. Application of dopaminergic agents does apparently alter the "threshold" for "bottom-up modulation" between basal ganglia and premotor/motor cortex, which is clinically reflected in the

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resolution of motor symptoms. In catatonia, GABA-ergic deficits in orbitofrontal cortex seem to modulate the "threshold" for "horizontal modulation" of "functional clusters" in prefronto-parietal cortical networks. Application of GABA-ergic substances does apparently restore "horizontal modulation" and prefronto-parieto cortical "functional clusters," resulting in the consecutive resolution of catatonic symptoms.

In both cases, local changes in specific transmitters/receptors do apparently lead to alterations in functional/effective connectivity. These connections may be modulated by "vertical and/or horizontal modulation" which in turn may be determined, at least partially, by "thresholding" as related to transmitters/receptors. In addition to dopamine and GABA, other transmitter/receptors like serotonin, glutamate, and so on, may be involved. Since, for example, the long fibers, which connect different cortical and cortical/subcortical areas, are primarily mediated by excitatory glutamatergic transmission, the latter may be altered as well in both diseases. This is supported by the therapeutic efficacy of the NMDA-antagonist amantadine in both catatonia and PD.

In summary, differences and similarities in therapy between PD and catatonia may be accounted for by alterations in "thresholds" for "vertical and horizontal modulation" which are apparently determined by different though overlapping transmitter systems.

5.5. Why is there "top-down modulation"?

"Vertical modulation" with "top-down and bottom-up modulation" can be located within a particular functional system apparently subserving adjustment between distinct functional components within the respective functional system. For example, the "willed action system" can be characterized by distinct components, such as "Plan/Strategy," "Initiation," "Execution" (and potentially "Termination"), with "Initiation" being especially affected in PD. Adjustment by "bottom-up modulation" serves for compensation of the dopaminergic-induced deficit in "Initiation." Considering the fact that Parkinsonian symptoms appear first after 80% reduction of nigrostriatal dopamine, functional compensation by "bottom-up modulation" seems to be quite effective and successful.

In contrast to "vertical modulation," subserving adjustment of distinct components within one particular functional system, "horizontal modulation" may rather subserve adjustment between different functional systems. For example, relation between functional systems subserving behavioural planning/control, negative emotional processing, and "willed action" seems to be altered in catatonia. Despite their apparently strong and abnormal emotions, catatonic patients do not show motor symptoms. Only when the emotions can no longer be controlled cognitively, do motor symptoms become visible. Cognitive control of emotions may be subserved by "horizontal modulation" adjusting the emotional and cognitive systems to each other. The moment such "horizontal modulation" between emotional and cognitive systems breaks down, may be considered as the onset of motor symptoms.

Adjustment within and between functional systems characterizing "vertical" and "horizontal modulation, respectively, may be subserved patterns of activation and deactivation. Both "vertical" and "horizontal" modulation may reinforce particular components within functional systems, while concurrently and reciprocally suppressing others (Shulman et al. 1997). For example, "horizontal modulation" may lead to concurrent activation and deactivation in medial and lateral orbitofrontal cortex, implying reciprocal regulation between affect and cognition (see above and also: Northoff et al. 2000b; 2001d; Drevets & Raichle 1998; Raichle et al. 2001). Alteration in "horizontal modulation" may disrupt this pattern of concurrent activation and deactivation, as is, for example, the case in catatonia (Northoff et al. 2001a). Similar observations of activation/deactivation patterns were made in the different cortical and subcortical anatomical structures subserving the "motor loop," which are altered in PD.

Ultimately, "vertical and horizontal modulation" generating such patterns of cortical and subcortical activation/deactivation may serve for specific and individual adjustment of the organism to its respective environment. Adjustment of the organism to its environment may be reflected in representation and maintenance of environmental events within certain patterns of activation and deactivation in cortical and subcortical structures. Environmental events may be coded as such within neuronal organisation. "Vertical and horizontal modulation" may allow for modulation of both distinct subcomponents within functional systems and relations between different functional systems in orientation on the respective environmental event. The various internal and external stimuli are therefore not coded in isolation from each other. Instead, they can be coded in relation to each other, thus reflecting the respective environmental event. One may consecutively speak of a so-called "event coding" (Hommel et al. 2001), as distinguished from "stimulus coding" (Northoff 2001c). "Vertical and horizontal modulation" may allow for "event coding"; whereas, in the absence of both kinds of modulation only "stimulus coding" would be possible, which, in addition to neuropsychiatric consequences, would have major epistemological implications (Northoff 2001c). PD and catatonia may be regarded as clinical examples where alterations in "vertical and horizontal modulation" result in neuronal reorganisation of "event coding" with consecutive problems in environmental and epistemological adaptation (see Northoff 1999; 2001c).

In summary, "vertical modulation" serves for adjustment between distinct components within one particular functional system, whereas "horizontal modulation" seems to account for adjustment between different functional systems. Ultimately, both "vertical" and "horizontal" modulation may serve for neuronal coding of internal and external stimuli in orientation to the respective environmental event, implying a so-called event coding.

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Top-down modulation, emotion, and hallucination

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Abstract: We argue that the pivotal role assigned by Northoff to the principle of top-down modulation in catatonia might successfully be applied to other symptoms of schizophrenia, for example, hallucinations. Second, we propose that Northoff's account would benefit from a more comprehensive analysis of the cognitive level of explanation. Finally, contrary to Northoff, we hypothesize that "top-down modulation" might play as important a role as "horizontal modulation" in affective-behavioral alterations.

In a thought-provoking tour de force, incorporating notions from psychoanalysis, neuropsychology, and pharmacology, but firmly grounded in neuroscience, Northoff's target article attempts to provide an integral account of catatonia. More specifically, alterations in interactions between prefrontal cortex and parietal and subcortical areas are implicated in the neural basis of catatonia. Consistent with this hypothesis, fMRI evidence reported by Northoff and associates points to an important role for top-down modulation in catatonia. Crucially, this is not observed in the motor disorders associated with Parkinson's disease, which lends the model considerable specificity. Top-down modulation is defined as "a modulation of subcortical structures by cortical areas as reflected, for example, in the modulation of caudate and other basal ganglia by lateral orbitofrontal cortex" (target article, sect. 5.1). We will adhere to this definition, and use the term accordingly, although it should be noted that "top-down processing" in the cognitive experimental literature refers to the modulation of modality-specific perceptual processing by higher-order processing (e.g., initiated in prefrontal areas) (Kosslyn 1994). We propose that the notion of top-down modulation might not only have explanatory power for neuropsychiatric symptoms such as catatonia, but also for other symptoms such as hallucinations.

Recent theoretical accounts of hallucination have implied that alterations in information processing in which the system assigns a decisive priority to top-down factors in determining the final percept, at the expense of bottom-up information, might contribute to the genesis of hallucinations (Behrendt 1998; Grossberg 2000). With regard to the visual system, evidence from functional neuroimaging indicates that attentional modulation does not only influence processing in sensory areas, but may also affect subcortical processing, that is, activation of the lateral geniculate nucleus (O'Connor et al. 2002). A study of top-down modulation in the auditory modality also observed activation of the thalamus (Frith & Friston 1996). Considering that activation of subcortical structures has been consistently observed in neuroimaging studies of auditory hallucination (Shergill et al. 2000), we hypothesize that altered activation of frontal and subcortical (thalamic) areas might lead to activation of the temporal auditory association cortex, giving rise to the phenomenal experience of hallucination.

In the "levels of explanation" approach to the study of schizophrenia (Mortimer & McKenna 1994), it is assumed that the cognitive level is intermediate between symptoms and neuropathology, and that a detailed cognitive analysis of specific information processing abilities in patients might enable one to connect neuroscience with phenomenology. As an example, a recent cognitive neuropsychological case-study of a continuously hallucinating patient contrasted performance of this patient with that of nonhallucinating control patients on a number of cognitive tasks targeted at measuring visual and auditory mental imagery and perception (Aleman et al. 2002). Evidence was found for an increased role of auditory imagery over perception in information processing for the hallucinating patient, as compared to the control patients. Such findings can fuel further neuroimaging research into the neural underpinnings of putative cognitive mechanisms underlying a particular symptom, which in turn will provide data that constrains the psychological models. We would be keen to learn more about this cognitive level in catatonia.

Finally, contrary to Northoff, we hypothesize that "top-down modulation" might play as important a role as "horizontal modulation" in affective-behavioral alterations. Notably, a recent study reported that, contrary to the prevailing view, all brain regions, including the amygdala, responding differentially to emotional faces, did so only when sufficient attentional resources were available to process the faces (Pessoa et al. 2002). The authors concluded that, similar to the processing of other stimulus categories, the processing of facial emotional expression is under top-down control. Given the evidence of alterations in orbitofrontal cortex activation associated with emotional processing in catatonia, and the fact that the orbitofrontal cortex is intimately connected to the amygdala, the hypothesis of altered top-down modulation of the amygdala gains plausibility. We concur, therefore, with Northoff's assertion that more data are needed concerning the function of the amygdala in catatonia, specifically in relation to the medial orbitofrontal cortex (target article, sect. 4.3.1). Research aimed at elucidating the role of top-down modulation in different neuropsychiatric conditions will undoubtedly further our understanding of these conditions and, ultimately, yield new avenues for treatment.

Nonconscious processing, anterior cingulate, and catatonia

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Abstract: A composite cognitive model of a neuropsychiatric condition should integrate clinical symptoms with the impairments of cognitive information processing. A model of catatonia, for example, should emphasize deficits of nonconscious information processing that impair a patient's ability to use implicit motor feedback for execution and termination of a voluntary motor activity.

Our understanding of the pathophysiology of neuropsychiatric disorders is limited by the lack of composite cognitive models that could integrate clinical symptoms with the impairments of cognitive information processing. The models that are based only on clinical symptoms imply that the disorders manifesting similar cognitive deficits have similar neural deficits. This implication, obviously, is misleading because it ignores the fact that a cognitive function involves a number of processing steps, and that each step is mediated by distinct cortical areas. Impairment at any of these areas could theoretically cause similar overt cognitive deficits. Therefore, the strategy that is most likely to provide deeper understanding of the nature of a neuropsychiatric condition involves delineation of underlying deficits of cognitive information processing.

An increasing amount of evidence suggests that impairments in the processing of nonconsciously acquired and stored (implicit) information profoundly affect overt cognitive processes (for discussion see Badgaiyan 2000a and b; Schacter & Badgaiyan 2001). In fact, findings from our recent experiments have indicated that

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efficient execution of a conscious (explicit) action depends heavily on the efficiency of implicit processing (Badgaiyan 2000b; Badgaiyan & Posner 1997; Badgaiyan 1999). These observations have suggested that prior to the initiation of a conscious action, relevant information is implicitly retrieved, and that this information plays a critical role in the formulation and execution of a conscious action (Badgaiyan 2000 a and b). It is therefore evident that our ability to perform a conscious action is limited if implicit information is either unavailable or is somehow altered. Catatonia is an example of such a limitation. In this condition, nonconscious information regarding the body position and motor activity is either altered or is unavailable to conscious awareness (motor anosognosia). This limits the ability of a patient to formulate and execute a conscious action, resulting in premature termination of the action, and the consequent "catatonic posture." Thus, even though the deficit in catatonia appears overtly to be an impairment of conscious action, the underlying cause may be the alteration of nonconscious information processing, which results in inappropriate motor action.

Cognitively, motor actions are described either as "willed" or "automatic" actions (Norman and Shallice 1986). While willed actions are voluntary, automatic actions are thought to be carried out nonconsciously. Norman and Shallice (1986) suggested that willed actions are performed by voluntary selection of one or another available alternatives of activity (schema), and that when the activity requires a complex action, selection and coordination between different actions is facilitated by a supervisory system. The automatic action, according to this model, is carried out by a "contention-scheduling" mechanism, which selects an action by lateral inhibition of competing action sequences. Northoff's hypothesis (Northoff 2003) supports the concept of lateral inhibition by arguing that the catatonic motor impairments are due to altered "horizontal processing."

Norman and Shallice's (1986) model assumes that nonconscious actions are not complex, and therefore do not require a supervisory system (Badgaiyan 2000a). Because the supervisory function is carried out by a central executive system, by inference, nonconscious actions should not engage this system. Neuroimaging studies (Berns, Cohen & Mintun 1997; Badgaiyan & Posner 1998), however, have shown that the anterior cingulate, which is a part of the central executive (Badgaiyan 2000a), is involved in a variety of nonconscious actions, including response selection and error monitoring. These findings support the author's earlier suggestion that nonconscious actions are also regulated by the supervisory function of the central executive system (for discussion see Badgaiyan 2000a).

It is possible that a disruption of this supervisory function at the anterior cingulate is responsible for the catatonic symptoms. Studies suggest that reciprocally connected (Devinsky 1997) discrete regions of the cingulate support either cognitive, affective, or motor function (Badgaiyan & Posner 1998; Bush, Lun & Posner 2000). Because catatonic episodes are often triggered by emotional stimuli, it appears that due to the activation of the affective part of the cingulate, its motor part is excessively inhibited, resulting in the arrest of a motor activity. Further, since the cingulate is involved in the response selection process (Berns et al. 1997; MacDonald et al. 2000; Pardo et al. 1990; Berns et al. 1997) an inhibition of its motor function may interrupt an ongoing motor activity. Excessive inhibition of the motor part in catatonia could possibly be a result of failure, or alteration, of the supervisory regulation. Northoff's hypothesis (Northoff 2003) suggests that the reciprocal inhibition of groups of cingulate neurons explains some of the behavioral symptoms of catatonia. This suggestion supports the idea that a failed supervisory system could be one of the underlying deficits in catatonia. Such a failure would explain both the behavioral and the motor symptoms of catatonia.

As argued in the beginning, a cognitive model of a neuropsychiatric disorder should ideally emphasize impairments of cognitive information processing and not the symptoms, because symptom-based models can be misleading. For example, catatonia and an injured peripheral nerve could overtly present with a similar symptom (lack of motor activity), despite the fact that the neural bases of impairments in the two conditions are entirely different. This underscores one of the problems with Northoff's hypothesis (Northoff 2003). The idea of drawing parallels between catatonia and the akinesia of Parkinson's disease (PD) indicates the hypothesis' emphasis on the symptom, rather than on cognitive information processing. Even though both conditions clinically present as a paucity of motor activity, the deficits in these conditions are a result of entirely different neurocognitive impairments. In catatonia, the deficit is mainly cognitive, whereas it is primarily motor in Parkinsonian akinesia. The fact that motor cognition is severely impaired in catatonia, but remains relatively intact in PD, suggests that altered implicit information processing is a characteristic of catatonia, but not of Parkinsonian akinesia.

Because of their distinct cognitive identities, drawing parallels between these two conditions can be misleading. The hypothesis, however, acknowledges that the altered nonconscious processing may be responsible for the overt motor deficits of catatonia. This makes it an interesting and promising hypothesis that could be a good starting point for the formulation of a composite cognitive model of catatonia.

Catatonia isn't ready for a unified theory

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Abstract: Northoff's target article presents a unifying theory of the pathophysiology of catatonia, as compared to Parkinson's disease. We address two arguments in particular that do not appear justified by available evidence: (1) The physiological basis of catatonia is the breakdown of right hemisphere prefrontal-parietal cortical connectivity, and (2) Dysfunction in this system results in specific deficits in termination of action.

In the target article, Northoff proposes that the distinction between cortico-cortical modulation ("horizontal") and cortical-subcortical modulation ("vertical") may serve to clarify the heretofore hazy separation between "neurologic" and "psychiatric" disorders. Unfortunately, the argument is made in the context of a novel and, we believe, untenable unified theory of catatonia. Northoff's theory of catatonia holds that right parietal dysfunction is critical to the pathology, and that catatonia can be functionally characterized as a deficit specifically in the termination of action. It is to these claims that we direct our comments.

The multiple and varied etiologies of catatonia pose a challenge for any attempt to relate it to a particular underlying pathology. Catatonic symptoms may arise from various psychiatric conditions (schizophrenia, major depression, bipolar disorder), or any number of neurologic and medical etiologies, including epilepsy, posterior fossa atrophy, and Wernicke's encephalopathy (e.g., Realmuto & August 1991). Lesions of diverse etiology, including the frontal lobe, limbic system, diencephalon, and basal ganglia have also been reported to produce catatonia (Saver et al. 1993). Rosebush et al. (1990), on whose study Northoff et al. (1999a) base several of their diagnostic criteria for catatonia, reported that 10 out of 15 catatonic patients had "evidence of pre-existing CNS vulnerability for their catatonia" (p. 358), including hydrocephalus, lacunar infarction, and generalized cerebral atrophy. Further, in this study CNS abnormality was evident in 8 of 12 responders to lorazepam, suggesting that the effects of lorazepam may be highly nonspecific, and that distinctions between "psychogenic" and "nonpsychogenic" catatonia may not be functionally meaningful. The fact that these "organic" catatonic syndromes may account for a significant proportion of catatonic cases – and that very few result from specific deficits in the circuitry that Northoff proposes to be dysfunctional in catatonia – appears to pose a significant problem for the theory.

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More specifically, consider the lesion literature; if the localization of symptoms to the right parietal cortex is valid, we might expect to find cases in which patients with right parietal lesions exhibit catatonia. Indeed, Northoff cites two such cases (cf. Fukutake et al. 1993; Saver et al. 1993). However, one of these reported asymmetric symptoms (more prominent on the left), was accompanied by left hemineglect, and this patient's lesion also included the occipital and temporal lobes, the insula, and caudate. The other case (Fukutake et al. 1993) reported unilateral symptoms, affecting only the left upper extremity. Thus, there is no clear lesion-based support for the theory that right parietal lobe dysfunction can lead to the bilateral symptoms of posturing and akinesia seen in catatonic patients. Furthermore, patients with right parietal lesions typically show a host of more common deficits, such as apraxia, left hemineglect, and tactile impairment (e.g., Portnoff et al. 1983)), that are presumably not present in catatonic patients. If dysfunction in the right-parietal lobe underlies catatonia, wouldn't we expect frequent co-occurrence of these symptoms?

Next, consider the neuropsychological evidence garnered in support of the right-parietal localization hypothesis. Northoff states that catatonics, as compared to normal and psychiatric controls, showed deficits on a neuropsychological measure of right parietal cortical function (the Visual Object and Space Perception Battery; VOSP), but not on "any other visuo-spatial test unrelated to right parietal cortical function" (sect. 3.1, para. 2). This is a potentially important finding, which, if robust, may inform theories about catatonia. However, the VOSP was designed to discriminate patients with nonspecific right hemisphere lesions from those with left-hemisphere lesions (Warrington & James 1991, p. 7). While Northoff may argue, based on other data, that these tests are specifically tapping parietal function, the battery was not normed on parietal patients, and so conclusions should be tentative. Moreover, catatonic patients performed worse on only one of the two VOSP subtests (Objects, but not Silhouettes) (Northoff et al. 1999a), leading to some question as to the robustness of the effect. Finally, the theoretical implications of neuropsychological testing done in remitted catatonics are not well specified. Northoff implies that catatonia is more than a state. But what precisely should we expect the relationship to be between the functioning of the catatonic patient in the acute, as compared to the remitted, state? For instance, if patients recently, but not currently, catatonic did not show right parietal dysfunction, would this count as evidence against the claim that right parietal dysfunction underlies the catatonic state?

This brings us to the imaging support for the right-parietal localization hypothesis. Although the author's own data (Northoff et al. 2000b) may be encouraging, the other studies cited provide little support; Luchins et al. (1989) find basal ganglia asymmetry, Ebert et al. (1992) report left temporal hypoperfusion, and Liddle's (1994) primary finding was underactivity in the dorsolateral prefrontal cortex. Although Satoh et al. (1993) do report reduced regional cerebral blood flow (r-CBF) in frontal and parietal regions in six catatonic schizophrenics, Northoff fails to mention that this reduction was bilateral and most marked on the left. Similarly, Galynker et al. (1997) report the most dramatic decreases in perfusion in the left parietal and left motor cortices, when comparing a single catatonic patient to controls. In addition, studies which rescanned patients in a remitted state, found improved perfusion (Ebert et al. 1992; Galynker et al. 1997; Luchins et al. 1989), suggesting that localized blood flow changes may be highly state-specific. Thus, it is unclear how such findings relate to tests done in remitted patients (i.e., neuropsychological findings). Further, with regard to structural imaging findings in catatonia, it is curious that Northoff characterizes his finding of significant sulcal enlargement "in almost all cortical areas" (Northoff al. 1999b) as "prefrontal and parietal enlargement." At odds with Northoff's theory, the data are at present difficult, if not impossible, to fit together.

Our second concern, briefly, relates to the functional characterization of catatonia as a deficit specifically in the termination of behavior. It is difficult to see how several of the symptoms reported to be most common in catatonia – mutism, stupor, and refusal to eat/drink, which may develop gradually over time (Rosebush et al. 1990) – are deficits of termination, rather than initiation. This conclusion also seems inconsistent with Northoff et al.'s (1995) own ball experiments, in which significantly more catatonics were able to perform externally guided (catching, stopping) than internally guided tasks (throwing, kicking). In that article, Northoff concluded that catatonic patients show a "deficit of internal initiation, as in Parkinsonism, as well as a dysfunction in the generation of voluntary movements" (p. 589). It appears that Northoff's electrophysiological experiments, in which he reportedly found intact "early readiness potentials" (RPs) in catatonics, may have compelled him to abandon this earlier position. Unfortunately, only one of the three papers cited is published (Northoff et al. 2000a), and this paper reports data only on late RPs and movement potentials (both of which were delayed in catatonics). Hence, we cannot evaluate this claim.

Given the heterogeneity of catatonia (in terms of etiology, consistent diagnostic criteria, and state at time of testing), it would be quite surprising if a unique neural and functional substrate could be identified. The development of a coherent category is a necessary preliminary step. With respect to the current literature, Northoff's attempt at unification seems premature.

Does catatonia have a specific brain biology?

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Abstract: Dr. Northoff's comprehensive comparison of clinical symptoms and neurobiological findings in catatonia with that of Parkinson's disease through integration of various levels of investigation, from neurochemistry up to the subjective experience, is a good example of the new strategies we need to improve our understanding of psychiatric disorders. His multimodal approach, leading to the hypothesis that different pathophysiologies of transcortical "horizontal modulation" and "bottom-up/top-down" – orbitofrontal/basal ganglia – "vertical modulations," may explain many clinical aspects of catatonia and Parkinson's disease, and thereby fills an important gap in current theories of psychomotor syndromes. However, to analyze more specifically the pathophysiology of catatonia, comparison not only with Parkinson's disease, but also with schizophrenia and anxiety disorders would be helpful. As long as the pathohistological and molecular basis of catatonic syndromes is unknown, theories based mainly on functional considerations remain preliminary.

Catatonia and Parkinson's disease: More differences than similarities. Northoff's approach, which integrates very different levels of research, such as motor, behavioral, and affective symptoms, psychopharmacology, subjective experience, neuropsychology, electrophysiology, and postmortem as well as structural and functional imaging findings, to create a new type of neuropsychiatric hypothesis, can be taken as an example of the new strategies we need for a better understanding of mental disorders in general. Several conceptual problems, however, remain unanswered in his article.

After reading Northoff's article it remains unclear whether he regards catatonia as a disease entity, that is, a syndrome separate from schizophrenia or affective disorder, or whether he defines it as an extreme end of other neuropsychiatric disorders, such as schizophrenia, major depression, anxiety disorders, and organic brain diseases.

Although catatonic syndromes can sometimes be observed in severe forms of major depression and after brain lesions, catatonia is regarded by most psychiatrists as a subtype of schizophrenia. According to *DSM IV* and *ICD-10* criteria, this syndrome is usually listed as "catatonic schizophrenia" (e.g., in *ICD-10:* F20.2). This is because of the many attributes catatonia has in common with the psychopathology, clinical course, and "positive" and "negative" forms of the group of schizophrenias, as well as with schiz-

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ophrenic "psychomotor poverty" or "disorganized" or "reality distortion" subtypes. Besides the psychomotor symptoms, such as mutism, posturing, negativism, and catalepsy, catatonic patients frequently experience paranoid symptoms, often combined with extreme states of anxiety and even hallucinations. All of these symptoms are quite uncommon in Parkinson's disease, which shares essentially the "psychomotor poverty" or akinesia symptoms with catatonia. Moreover, there are considerable differences in the long-term course of both syndromes: Although the frequency of typical idiopathic Parkinson's disease increases with age and the disease follows a chronic progressive course, catatonia usually occurs during the course of schizophrenia in young or middle adulthood. The long-term course of catatonia is quite unstable, and in many patients it is characterized by exacerbations and remissions, often followed by long intervals without symptoms. Some patients recover completely. The most common psychopathological symptoms in Parkinson's disease are depression and "bradyphrenia" (slowing of thinking). These considerable differences in long-term course, outcome, and psychopathology suggest that, in spite of some psychomotor similarities, the underlying brain pathologies of Parkinson's disease and catatonia must be totally different (although this might not be the case for neuroleptic-induced Parkinsonism), and cannot simply be explained by opposite disturbances of top-down or bottom-up modulations.

More information on the neuropathology of catatonia is needed. Despite the considerable recent interest in the neuropathology of schizophrenia and affective disorder, nearly no studies in the pathomorphology of catatonic syndromes are available. Very few carefully controlled postmortem studies that were not mentioned by Northoff are available, however. Already several decades ago, Hopf (1954) described cytopathological changes in the internal and external pallidum of catatonic schizophrenics that were not observed in paranoid patients or normal controls. All brains were collected before the introduction of neuroleptic drugs. Stevens (1986) found in the same brain collection reduced volumes (measured by planimetry of serial sections) of the pallidum and striatum of catatonics, as compared to controls, while paranoid schizophrenics had smaller temporolimbic structures, but normal basal ganglia. Both studies indicate that parts of the basal ganglia, regarded to be important components of the extrapyramidal system, are affected in catatonic schizophrenia. Dom et al. (1981) investigated the thalamus of catatonics and normal controls by applying cytometric methods and found a significant reduction of small neurons in the pulvinar, suggesting a loss of inhibitory interneurons in this association nucleus of the thalamus. These findings, which fulfilled modern quantitative statistical criteria, never were reinvestigated and, of course, need replication. Unfortunately, none of the many postmortem studies of schizophrenia published in the last 20 years specifically addressed the catatonic syndrome; thus the question of pathohistological changes in those cortical areas that play an essential role in Northoff's theory, remains open.

As far as I know, the only structural imaging study in catatonic patients was published by Northoff's group (Northoff et al. 1999b). But surprisingly, some very impressive results in that paper, which give important additional information on brain biology in catatonia, are clearly underemphasized in his theory. In this CT scan study (Northoff et al. 1999b), sophisticated regional morphometry of internal and external CSF spaces revealed that catatonic schizophrenics ($n = 37$) had by far the highest extent of lateral and third ventricular enlargement, as well as of frontal interhemispheric fissure and Sylvian fissure enlargement, and bilateral frontal and temporal sulcal widening, as compared to hebephrenic schizophrenics ($n = 28$), paranoid schizophrenics ($n = 39$), and normal controls ($n = 37$). Thus, at least in terms of pathomorphology, catatonia seemed to be the most severe subtype of schizophrenia. There were significant positive correlations between the size of left hemispheric CSF spaces and disease duration, indicating that structural changes in the left hemisphere of catatonics are progressive. Fronto-orbital sulcul widening was most significant in hebephrenics, not in catatonics, suggesting that orbitofrontal dysfunction might be more relevant in hebephrenia than in catatonia.

The few existing postmortem and structural imaging studies of catatonics suggest that there is primary pathology in many cortical and subcortical structures, and argue against a more or less selective dysfunction of orbitofrontal/parietal and premotor cortical areas. By contrast, Parkinson's disease has a very well known primary pathology in the brain stem monamonergic cell groups, by which most of the pathophysiology and clinical symptoms can be explained; and it is easy to describe here a disturbance of bottom-up modulation. Because of the immense lack of knowledge of the brain biology in catatonic syndromes, it may be premature to postulate similar simple pathophysiological models. Since extreme anxiety is a central pathophysiological feature of hypokinetic catatonia, pathology of the amygdala may play a central role; however, neither postmortem nor structural or functional imaging data are available from this limbic key structure in catatonia.

Similar defects of neuronal inhibition in catatonia and schizophrenia? Northoff could show by a number of elegant experiments that catatonics fail to terminate adequately their movements, whereas planning, initiation, and execution are relatively intact. This observation, as well as the fact that the GABA agonist lorazepam improves catatonic symptoms in most cases, led him to hypothesize that cortical neuronal inhibition is deficient. Similar inhibitory deficits can be postulated for paranoid schizophrenia in sensory cortical association areas. That these patients show reduced prepulse inhibition and latent inhibition, hallucinations, delusions, and reduced sensory gating, commonly seen in paranoid schizophrenia, can well be explained by reduced neuronal inhibition (possibly caused by pathology of GABA-ergic interneurons) in the higher sensory and limbic cortical association areas. It is tempting to speculate that similar deficits in neuronal inhibitory functions occur in catatonic and paranoid schizophrenia; the difference being that in catatonics the orbitofrontal brain regions responsible for internal monitoring of motor actions are affected, whereas in paranoid-hallucinatory patients the sensory and limbic association areas are more affected.

Northoff's hypothesis gives considerable impetus for further comparative investigations of intracerebral inhibitory mechanisms in different neuropsychiatric syndromes. Such studies could answer the question of whether differences in regional distribution of similar types of pathology can explain various aspects of the clinical features.

What medical catatonias tell us about top-down modulation

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Abstract: Catatonia resulting from a general medical condition (as defined in the *DSM-IV*) seems to account for a large percentage of patients presenting with catatonia in psychiatric settings. In view of Dr. Northoff's hypothesis, it is important to emphasize that medical catatonias provide additional information to support his neuropsychiatric hypothesis of the anatomical and biochemical mechanisms of catatonia.

There have been several reviews of catatonia and the ascribed causative medical illnesses. Lohr and Wisniewski (1987) reviewed the literature on medical causes of catatonia and observed that neuroleptic-induced catatonias seem to occur in patients already at risk for development of catatonia.

Catatonia resulting from a general medical condition was added to the *DSM-IV,* making the identification and study of medical catatonia easier for clinicians and researchers (APA, 1994). In a literature analysis by Carroll et al. (1994), levels of evidence were

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Table 1 (Carroll). *Most likely etiologies of medical catatonia (Carroll et al. 1996)*

CNS structural damage
Encephalitis and other CNS infections
Seizures or EEG with epileptiform activity
Metabolic disturbances
Phencyclidine exposure
Neuroleptic exposure
Systemic lupus erythematosus, usually with cerebritis
Corticosteroids
Disulfiram
Porphyria and other conditions

used to determine the relative strength of the association between the putative medical illness and medical catatonia. In many instances, there was only a weak association between the condition (e.g., diabetes mellitus) and catatonia, or the association was multifactorial (e.g., cerebritis + corticosteroids + neuroleptics). We were able to create a hierarchy of medical conditions that are most likely to cause medical catatonia, allowing the clinician to coordinate the diagnostic work-up for the most likely and fulminant etiologies. For instance, encephalitis would be considered before porphyria in the hierarchy of likely causes of medical catatonia (see Table 1).

It is difficult to determine the frequency of medical catatonias relative to psychiatric catatonias, because the initial published reports on catatonia tend to have small sample numbers and the medical catatonias are not always clearly identified. Among the larger studies of catatonia conducted after 1985, the relative percentages of medical catatonias are as follows: Barnes et al. (1986) – 20%, Rosebush et al. (1990) – 25%, and Bush et al. (1996a) – 21%. The setting appears to have an effect on the observed frequency of medical catatonia, in that the percentages listed come from inpatient psychiatric units, whereas the relative frequency of medical catatonias might be expected to be higher in medical units and consultation-liaison services. Although it remains difficult to determine an accurate frequency of medical catatonia in our institution, the Chillicothe VA Medical Center, which is a neuropsychiatric facility, the frequency of medical catatonias is 30% among all of our patients with catatonia (Carroll & Graham, unpublished data). Therefore, it appears that in most settings the relative frequency of medical catatonia is 10% to 30% of all patients presenting with catatonia.

Despite the limited number of cases of medical catatonia, a comparison with cases of psychiatric catatonia described in the literature has been performed using a retrospective chart review and a prospective study (Carroll et al. 2000). Although there were some differences in some individual catatonic signs in medical catatonias, no consistent pattern emerged that would allow one to conclude that medical catatonias are indistinguishable from psychiatric catatonias. Because no single catatonic sign, or set of signs, could be found to differentiate medical from psychiatric catatonias, clinicians should consider medical etiologies in all patients presenting with catatonia, regardless of their ascribed psychiatric diagnosis.

Kahlbaum stressed the importance of the clinico-anatomic study of catatonia and performed autopsies on his patients in an effort to isolate a causative lesion (Kahlbaum 1887/1973). Kahlbaum's (1887/1973) and subsequent studies have failed to identify a single common lesion associated with medical catatonias (Northoff 2000a). Multiple focal sites are associated with medial catatonias: (1) the anterior cingulate gyrus, (2) the thalamus (mediodorsal), (3) the basal ganglia (specifically globus pallidus interna), (4) the medial frontal cortex, (5) the inferior orbital frontal cortex, (6) the parietal cortex, (7) the pons and upper brainstem, and (8) abnormalities of the cerebellum. Because focal lesions in these regions only rarely cause catatonia, medical catatonias probably result from dysfunction in neural pathways that include these structures.

In contrast to focal lesions, diffuse central nervous system (CNS) etiologies, such as encephalitis and seizures, are responsible for a significant number of the cases of medical catatonias discussed in the literature. Diffuse disease processes associated with medical catatonia support the hypothesis that medical catatonias are caused by pathway dysfunction rather than focal (site-specific) dysfunction and may arise from lesions at one or more points along these pathways, as outlined by Northoff's hypothesis.

Neurochemistry studies supported by functional brain imaging have also provided insight into types of cerebral dysfunction responsible for producing the catatonic syndrome. Possible neurochemical etiologies for medical catatonias include glutaminergic antagonism, GABA antagonism, serotonergic actions, and dopamine antagonism (Carroll 2000). The relationship between D2 blockade and NMS has been a focus of more intense study (Mann et al. 2000), and both catatonia and NMS have been reported in response to both standard and novel antipsychotic medications. Recently, the identification of D2 blockade in all novel antipsychotics (Kapur & Seeman 2001) and identification of the TaqI A polymorphism of the D2 receptor gene has provided additional support for this dopamine-based hypothesis (Suzuki et al. 2001).

The treatment of psychiatric disorders resulting from general medical conditions focuses on treating the presenting psychiatric syndrome in the same way one would treat the confirmed psychiatric disorder that it most resembles (Carroll et al. 1996): by treating identified co-morbid conditions and also by treating the causative medical condition. Medical catatonias tend to be multifactorial (Carroll et al. 1994), and all three of these approaches to treatment should be considered in most cases (Bush et al. 1996b).

In conclusion, studies of medical catatonia lend support to "top-down modulation" of psychiatric catatonia.

Catatonia: A window into the cerebral underpinnings of will

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Abstract: The will is one of the three pillars of the trilogy of mind that has pervaded Western thought for millennia, the other two being affectivity and cognition (Hilgard 1980). In the past century, the concept of will was imperceptibly replaced by the cognitive-oriented behavioral qualifiers "voluntary," "goal-directed," "purposive," and "executive" (Tranel et al. 1994), and has lost much of its heuristic merits, which are related to the notion of "human autonomy" (Lhermitte 1986). We view catatonia as the clinical expression of impairment of the brain mechanisms that promote human will. Catatonia is to the brain systems engaged in will, as coma is to the reticular ascending systems that promote sleep and wakefulness (Plum 1991).

Northoff's article is a timely effort to view catatonia as a natural model for the understanding of crucial aspects of human behavior. The ideas put forth in the article might become clearer if, the neurobehavioral systems that are impaired in catatonia, as indicated by clinicoanatomic studies, as well as the neuropsychiatric concept of will, were taken into account. Moreover, given the multiplicity of its semantic affiliations, the author should state what he has in mind when he talks about catatonia. The diagnoses of the

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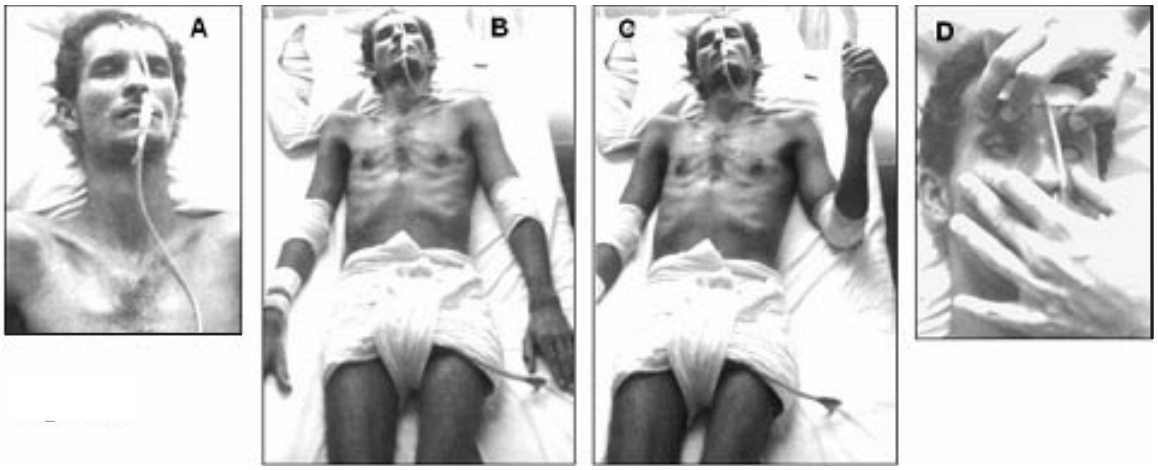


Figure 1 (de Oliveira-Souza et al.). Catatonia in a patient with bipolar mood disorder.

patients he dealt with in his research would be particularly instructive in this regard. In our comment, we use the term "catatonia" as epistemologically analogous to other syndromes in medicine, such as fever or coma (Barnes et al. 1986).

In current usage, "catatonia" (from the Greek, *kata,* meaning abnormality; *catatonia,* meaning abnormality of muscle tone) encompasses three distinct conditions (Magrinat et al. 1983): a disease, a subtype of schizophrenia, and a syndrome defined by its psychomotor features. As originally described, catatonia followed a characteristic cyclical course, with an orderly progression through discrete stages consisting of melancholy, elation, stupor, confusion, and eventual recovery (Kahlbaum 1874/1973). It is easy to recognize in this pattern the essential features of what was known later as the untreated course of manic-depressive illness (Kirby 1913). The disease catatonia derives its name from the psychomotor symptoms that immediately preceded or accompanied the stage of stupor. In psychiatry, stupor means stupefied or dull, without implying a decrease of wakefulness as it does in current neurology. The major symptoms of catatonia can be broadly categorized in passivity and negativism phenomena. Whereas passivity indicates an abnormally low compliance with outside influences (catalepsy, waxy flexibility, *mitgehen,* automatic obedience, echolalia, and echopraxia), negativism (mutism, blepharospasm, pouting of the lips, *gegenhalten,* refusal to cooperate) implies an abnormally high resistance to external influences. Patient 1 was admitted in a febrile comatose state of unexplained origin. For several weeks he lay unresponsive in bed with his eyes shut (Fig. 1, A and B). He was then found to show waxy flexibility (Fig. 1C) and blepharospasm at the slightest attempt to passively open his eyes (Fig. 1D). He recovered fully after eight sessions of electroconvulsive therapy (ECT) and was discharged with a diagnosis of bipolar disorder. The coexistence of passivity and negativism in different body segments is highlighted by this case.

Patient 2 is a dramatic instance of passivity. Previously successful as an administrator, this patient was brought to consultation by his sister, who said he had developed a pervasive lack of interest and a decline in occupational level after a traffic accident years before. Although cognitively intact (MMSE = 28/30), he tamely complied with all the requests of the examiner, even if potentially harmful (Fig. 2). Thus, *even when told that he needed not to,* he would not hesitate to put his finger (A) or tongue (B) in the flame of a cigarette lighter, to go under a small desk (C and D), copy meaningless gestures performed before him (E and F), and lie quietly in uncomfortable molded positions for several minutes (G and H). MRI revealed extensive damage to the right orbitofrontal (I) and left inferior temporal gyri (H).

After Kraepelin included it as one of the fundamental subtypes



Figure 2 (de Oliveira-Souza et al.). Catatonia in a patient with traumatic brain injury.

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of dementia praecox, catatonia became firmly entrenched with the concept of schizophrenia (Kraepelin 1896/1971). As passivity and negativism were described in disorders other than manic-depressive illness and schizophrenia, however, the label "catatonia" gradually expanded to encompass a nonspecific syndrome common to a variety of medical disorders (Gelenberg 1976).

Patients with focal brain injury constitute another important source of knowledge on the anatomical correlates of catatonia (Beversdorf & Heilman 1998; Fisher 1989; Saposnik et al. 1999). Four syndromes are relevant in this respect: environmental dependency (Lhermitte et al. 1986), avoidance behavior (Mori & Yamadori 1989), some types of the alien hand (Kertesz 2000), and the autoactivation deficit syndrome (Laplane & Dubois 2001). They suggest that discrete sectors of the dorsolateral frontal and parietal cortex mediate the outward expression of behavior in terms of fundamental patterns of approach-avoidance based on the exteroceptive and proprioceptive senses (Denny-Brown 1952; Eslinger 2002). The appropriateness and selectivity of such action-patterns to behavioral context is probably furnished by the orbitomedial divisions of the frontal lobes and certain hypothalamo-basal prosencephalic structures with which they are profusely interconnected (Groenewegen & Uylings 2000; Yamanaka et al. 1996).

Catatonia implies that normal people are distributed around the middle of a theoretical continuum representing the construct of will, on the ends of which fall the syndromes of passivity and negativism. This formulation is in accord with recent attempts to revitalize the neuropsychiatry of will after nearly a century of unwarranted oblivion (Berrios & Gili 1995). From a neuropsychiatric standpoint, the will can be conceived of as a vector that shapes the transactions of the individual with the social and physical *milieu* according to a delicate balance between approach and avoidance mechanisms (Metcalfe & Mischel 1999). It expresses the degree to which the individual resists, counteracts, or complies with the challenges, demands, and influences of both the external (e.g., a phone call) and internal (e.g., hunger) environments (Brown & Pluck 2000). The will provides the necessary directionality and intensity ("willpower") to the operational dimensions of behavior, which have been under continuous scientific inquiry during the past decades (Lent 2002).

When patients or normal subjects agree to participate in a given treatment or research protocol – that is, when they become "volunteers" – their will is already implicit in their behaviors. Studies on "voluntary behavior" usually deal only with its cognitive and operational aspects. Novel and ingenious experimental paradigms are needed to tap the "preoperational" aspects of voluntary behavior, so that the subject is forced to do what he does not feel like doing, or conversely, is prevented from acting as he feels like. Until such extra-cognitive aspects of willful behavior are recognized as a legitimate object of empirical investigation, a critical piece of the puzzle of the neuropsychiatry of will, shall remain missing. Catatonia opens a window into this, as yet obscure, landscape of the human mind.

Catatonia: A disorder of motivation and movement

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Abstract: Georg Northoff employs a comparison with Parkinson's disease in an effort to tease apart the underlying pathophysiology of psychogenic catatonia. Northoff's extensive treatment of the subject is abetted by his own research as well as the research of others. Nevertheless, a number of points concerning basal ganglia/thalamocortical processing need to be raised, some adding support to his hypothesis and others detracting from it.

In psychogenic catatonia, as Northoff points out, there are horizontal, unidirectional cortico-cortical effects on the motor cortex and subsequent cortico-striatal changes. In Parkinson's disease, there are vertical, bidirectional effects from basal ganglia to the motor cortex. In essence, psychogenic catatonia is a top-down modulated disorder beginning with horizontal cortico-cortical effects, with the secondary vertical effects from motor cortex down to basal ganglia accounting for similarities with Parkinson's disease. Parkinson's disease on the other hand is a bottom-up disorder without cortico-cortical influences, and as such, many of the behavioral characteristics of psychogenic catatonia are missing in Parkinson's disease.

Northoff enlists much data, often from the neuroimaging field, on behalf of this hypothesis. Nevertheless, there are the following points to make in regard to the article: First of all, he ignores the primary work of Garrett Alexander and his colleagues at Johns Hopkins, in establishing the structural loop circuitry of the brain – the basal ganglia thalamocortical circuitry (Alexander et al. 1986; 1990). One of the key findings in the work of the Johns Hopkins team was that these overlapping basal ganglia thalamocortical loops are connected up cortico-cortically, cortico-striatally, and, through the activity of the brain motivation circuitry, travelling in the medial forebrain bundle (MFB). The MFB carries serotonin from the nucleus raphe, dopamine from the ventral tegmentum, and norepinephrine from the locus ceruleus, and distributes these neurotransmitters to important terminal zones along this reward superhighway.

It is also important to note that Alexander loop circuitries take advantage of what Edelman and Tononi described as neural complexity (Tononi et al. 1994). These circuits are both segregated, according to their special functional responsibilities, and integrated by virtue of the three approaches mentioned above. In large part, the Northoff article is really seeking to refine this understanding of the brain by focusing on psychogenic catatonia and Parkinson's disease and their relationship, but surprisingly, not much is discussed about the brain motivation circuitry and its ability to link up basal ganglia and ventral tegmentum with paralimbic and prefrontal cortices.

Northoff also does not mention other potential basal ganglia modulatory effects on the cortex. In a very interesting hypothesis, Brown and Marsden in 1998 suggested that the basal ganglia, in addition to being a major center for motor functioning, might be of prime importance for EEG desynchronization in the executive forebrain, which in turn may allow response selection and movement to ensue (Brown & Marsden 1999). They base their hypothesis on clinical evidence that basal ganglia dysfunction allows slow idling cortical rhythms to predominate. Normal EEG desynchronization correlates with local circuit neuron gamma frequency synchronizations. When the basal ganglia are dysfunctional, as they are in Parkinson's disease, the surface EEG desynchronization is faulty. Thus, Parkinson's patients with low basal ganglia dopamine flow will have impaired desynchronization, with a corresponding loss of the normal Piper rhythm in muscle. They may also become depressed and show signs of frontal network dysfunction (Litvan et al. 1998). Treatment with levodopa as a dopamine agonist can restore EEG desynchronization and the Piper rhythm.

Akinesia, abulia, and bradyphrenia are characterized by impaired desynchronization with a corresponding reduction in local circuit neuron 30–50 Hz synchronization. Akinesia, as a slowing of movement, and bradyphrenia, as a slowing of thought processes, reflect the fact that the basal ganglia may be able to affect different frontal regions, resulting in changes both in movement and in thought. Thus, it can be hypothesized that psychogenic catatonic withdrawal might be the product of a faulty frontal desynchronization related to primary basal ganglia dysfunction. Could it be that in certain cases of psychogenic catatonia the medial orbital frontal dysfunction, thought to be primary by Northoff, is really secondary to faulty local circuit neuron activity, which is reflected in diminished desynchronization of the surface EEG?

Of course, we are dealing with loop circuits so we cannot say

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that the basal ganglia are "in charge," but neither can we say that the medial orbital frontal cortex or the anterior cingulate area is in charge.

There is also lack of attention paid to an important GABA-A interneuron that sits in the ventral tegmentum and the substantia nigra on a GABA-B neuron with connections to the dopamine cell body (Carlsson & Carlsson 1990). Northoff does do an excellent job of discussing the GABA-A systems in the orbital frontal cortex. But, it is also important to understand the basal ganglia GABA-A interneuron to get a complete picture of both catatonia and Parkinson's disease. It is essential for setting the gain on the important dopamine flow in the medial forebrain bundle; thus, one might view the effectiveness of lorazepam on GABA-A neurons, not only in a frontal cortical regions, but also in the basal ganglia, as being of therapeutic importance.

There is an animal model that is mentioned by Northoff which seems to suggest how important the GABA-A-dopamine system in the basal ganglia is in terms of catatonia. Janice Stevens applied bicuculline, a GABA-A antagonist, into the ventral tegmentum of cats (Stevens et al. 1974), and the catatonic presentation ensued. Picrotoxin, an antagonist of the fluoride channel of the benzodiazepine GABA-A recognition site, was also able to create a catatonic presentation when administered in the ventral tegmentum. Smaller doses led to fear and staring, whereas larger doses produced prolonged severe dystonia, especially after haloperidol.

The focus of the target article is purely on psychogenic catatonia, and therefore the need to understand catatonic presentations in the face of multifocal neuromedical origins is circumvented. Nevertheless, one must wonder whether a model that would include the potential not only for strong top-down modulation, but also bottom-up modulation under certain circumstances, might be better able to describe the multifactorial etiologies of the catatonic syndrome.

In summary, I commend Northoff for his exhaustive research on psychogenic catatonia and its brain underpinnings. He provides us a primer on movement dynamics and motor-related cortical potentials. He also provides an intensive examination of the interaction of the lateral orbital frontal, medial orbital frontal, anterior cingulate, and dorsal lateral prefrontal cortical areas, with the premotor and motor cortices. Such intricate cortico-cortical connections are certainly of major importance in the top-down modulation that results in a catatonic state; but, as in depression, there is the potential not only for top-down control, but also for bottom-up influence in catatonia.

As Helen Mayberg has pointed out in her neuroimaging work on depression, it may be that modulators flow up from the midbrain nuclei and feed terminal zones off the medial forebrain bundle, as well as flow down from the anterior cingulate and medial orbital frontal and prefrontal cortices, to influence the amygdala, hippocampus, ventral tegmentum, and substantia nigra (Mayberg et al. 2002). In catatonia, our medications (GABA-A and dopamine agonists in particular) may be working from the bottom-up as well as, as Northoff suggests in the case of GABA-A agonists and NMDA antagonists, from the top-down.

Top-down versus bottom-up is not the same thing as psychological versus biological

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Abstract: While there may be interesting theoretical differences between cortical and subcortical malfunctions, it is not a difference that is going to separate the psychological from the biological. For, the distinctions we draw between the "psychological" and "biological" turn on our assessments of others' conscious experiences, and not on anything deeper or more profound.

In his discussion of top-down modulation (sect. 5.3), Northoff makes some perhaps throw-away comments regarding the connection between top-down versus bottom-up modulation and psychological versus neurological disorders. He implies here, and throughout his discussion, that we can ally cortical modulation with psychological control of a behavior and subcortical modulation with neurological control. I wish to worry some about this taxonomy.

The long and the short of it is that this division is way too simple. I agree that, intuitively speaking, we would want to say that catatonia is a mental disorder while Parkinson's disease seems more "physical" somehow. Why do we think this? It isn't because we can trace catatonia to disturbed cortical processing and Parkinson's disease to subcortical lesions. We believe that catatonia is a problem with the mind because of how catatonic patients describe what their symptoms feel like, and we believe that Parkinson's disease is a problem with the body because of how those patients describe their disorder. Catatonic patients by and large are not aware of their difficulties, while Parkinson's patients are all too aware. In general (though I don't want to make this principled criteria), when someone is not aware of some personal or bodily malfunction that the rest of us believe should be patently obvious, we think that the person is crazy-in-the-head. When someone can't make his or her body move in ways that the rest of us can easily move, then we believe that that person has some sort of physical malady. And we believe these things independently of what is going on inside the brain. Were we to learn that catatonia is caused by subcortical mechanisms, even then, I maintain, we would still believe that it is a mental disorder of some sort.

We can see examples of what I am talking about when we consider the various fear and anxiety disorders. As Northoff himself discusses, we can trace many of these to abnormal amygdala functioning, which is subcortical. Yet, for the most part, we think of people with phobias and other anxieties as having a mental difficulty. Similar remarks hold for Obsessive-Compulsive Disorder (OCD). That too appears to have subcortical origins, yet it seems to us to be a mental phenomenon. And we believe these to be mental disturbances, given how those afflicted talk about them. Fear and anxiety patients are all too aware of their affective disturbances. Were they not aware, it is not clear that we would think them as having any disorder at all. (What would the symptoms be of an unconscious anxiety disorder? What would bring the patients in for treatment?) OCD patients, too, are upset by their compulsive behavior, the recurring worries that drive the behavior, and their inability to control their own reactions. They, like the anxiety patients, don't like how their disorder feels; they don't like what their disorders do to their conscious experiences. Because they don't like the way they feel, people suffering from anxiety disorders, OCD, phobias, and so forth, realize they have some problem or other. And because of what these patients report about their own internal states and how these states affect their behavior, we believe that their problem is with their minds.

My point is that whereas there may be interesting theoretical differences between cortical and subcortical malfunctions, it is not a difference that is going to separate the psychological from the biological. There, too, might be interesting theoretical distinctions to be drawn between those who are not aware of their deficits and those who are frustrated by them – I am dubious that there are any interesting distinctions to be drawn about how we think others should feel – but again there is no reason to assume that these distinctions are going to be related to cortical versus subcortical processing. For the moment, the distinctions we draw between the "psychological" and "biological" turn on our assessments of others' conscious experiences and not on anything deeper or more profound. (In the end, though, we will not be able to maintain a psychological/biological distinction successfully, since both our psychologies and our neurobiologies are housed in our brains – it is all biological.) To relate any sort of folkish psychological/biological distinction to the brain is first going to require at least a vague theory of consciousness, since at bottom

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this is a distinction that reflects what makes it into conscious awareness.

Dopamine, Parkinson's disease, and volition

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Abstract: Disruptions in dopamine transmission within the basal ganglia (BG) produce deficits in voluntary actions, that is, in the interface between cortically-generated goal representation and BG-mediated response selection. Under conditions of dopamine loss in humans and other animals, responses are impaired when they require internal generation, but are relatively intact when elicited by external stimuli.

Jahanshahi and Frith (1998) suggested that striatal dopamine activity plays a role in the "willed action system," and that Parkinson's (PD) patients, suffering nigrostriatal dopamine (DA) loss, exhibit symptoms that reflect an inability of the will to influence motor response systems. Northoff extends this notion in his persuasive counter-example of the catatonic patient who shows motor symptoms superficially similar to the PD patient, but whose symptoms (1) do not reflect an impairment in the interface between the "will" (goal representation) and action (response selection systems), and (2) do not arise from nigrostriatal DA loss.

Northoff describes the PD patient who feels "locked in his body" (sect. 2.4). Yet, this sensation apparently does *not* reflect failure of motor neurons to transmit signals to muscles, or of muscles to cause limb movements. I believe that Northoff is correct in describing PD (i.e., nigrostriatal DA loss) as an inability to access motor acts under conditions of voluntary action. Apparently immobile PD patients have been observed to walk or run in response to a fire alarm. PD locomotor deficits are attenuated when the patient is provided the opportunity to step over salient lines on the ground (Martin 1967). PD motor deficits appear to be greatest when the response requires internal generation, and are reduced in the presence of external response-eliciting stimuli. Similarly, we find that rats under DA-antagonist challenge show deficits in internally-generated response execution, but not in the execution of the identical response when it is elicited by a well-acquired conditioned stimulus (Horvitz & Eyny 2000). A role for DA in the interface between goal representation and behavioral response systems is further supported by the work of Salamone and colleagues, which showed that ventral striatal DA depletion in rats impairs the exertion of "effort" to achieve goals, but does not disrupt execution of the required response per se, or diminish the animal's goal-seeking behavior when effort requirements are low (Salamone et al. 1997).

Northoff provides an informative account of the cognitive and movement deficits seen in PD, and also points to areas of cortex and basal ganglia implicated in these deficits. However, in his more mechanistic descriptions of how DA loss produces Parkinsonian motor symptoms, Northoff states that "PD can be characterized predominantly by the deficit and/or down-regulation of D-2 receptors in striatum" and alludes to DA's opposing roles in direct versus indirect basal ganglia loop activity (sect. 4.4.3). It is not quite clear what Northoff means by a deficit of D-2 receptors in striatum in PD; perhaps he is referring to reduced DA binding to these receptors following nigrostriatal DA loss. With respect to opposing DA effects on direct and indirect pathways, I believe that this remains an interesting theoretical perspective, rather than an established fact.

Recent evidence suggests that DA may act within the striatum to "select" appropriate corticostriatal glutamate inputs for further basal ganglia processing, essentially by permitting the throughput of strong corticostriatal inputs while filtering-out weaker inputs (Hernandez-Lopez et al. 1997; Horvitz 2002; Kiyatkin & Rebec 1996). From this theoretical perspective, under conditions of DA loss, strong corticostriatal glutamate input signals fail to receive the normal DA-mediated amplification, and weak glutamate input signals that would normally be attenuated by DA activity are instead permitted to access BG output structures and influence motor activity (Horvitz 2002). It is possible that PD rigidity reflects, in part, the abnormal collective activity of groups of motor neurons, whose simultaneous activation is incompatible with normal response production. As a result, the PD patient does not lack muscle tone, but shows muscle rigidity, reflecting simultaneous activation of opposing muscle groups.

One of the major conceptual distinctions offered in this article is that of "horizontal versus vertical" disruptions in neural transmission. By horizontal and vertical deficits, Northoff refers to those primarily involving dysfunction between cortical regions (horizontal deficits in catatonia) and those involving disruption of information flow from subcortical to cortical structures, or vice versa (vertical ascending deficits for PD; vertical descending deficits for catatonia). A key question is the extent to which the differing symptoms of PD and catatonia can be explained by the distinction between "horizontal and vertical" disruptions in neural information flow. Northoff notes that catatonic patients often show abnormalities in affect (sect. 2.2), which may include aggression, excitement, or euphoria. Is the author suggesting that such affective abnormalites will be seen only following "horizontal" disruptions, and not in disorders involving only vertical (or ascending vertical) disturbances? Should we assume that behaviors such as perseveration and echolalia, typical of catatonia, will only be seen in disorders that involve horizontal dysfunction? Nigrostriatal DA degeneration does not produce these types of affective or behavioral anomalies. Is this because PD involves a "vertical" disruption of information flow from subcortical to cortical structures, and not a horizontal impairment? Or, is it because the particular subcortical and cortical structures impaired after "vertical" nigrostriatal DA loss are not those that mediate the behavioral and affective functions disrupted in catatonia?

Does the form of akinetic mutism linked to mesodiencephalic injuries bridge the double dissociation of Parkinson's disease and catatonia?

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Abstract: Northoff provides a compelling argument supporting a kind of "double dissociation" of Parkinson's disease and catatonia. We discuss a related form of akinetic mutism linked to mesodiencephalic injuries and suggest an alternative to the proposed "horizontal" versus "vertical" modulation distinction. Rather than a "directional" difference in patterned neuronal activity, we propose that both disorders reflect hypersynchrony within typically interdependent but segregated networks facilitated by a common thalamic gating mechanism.

The very interesting comparison developed in the target article effectively enlarges the clinical symptom of akinesia and its identified variations in Parkinson's disease (PD) and catatonia. The comparison points out the often artificial separation of psychiatric and neurological disorders. Northoff convincingly links important differences in the relative contribution of emotional and behavioral symptoms in catatonia to altered function of orbitofrontal-prefrontal and parietal networks through the use of modern neuroimaging techniques; these networks are not typically identified with the pathophysiological mechanisms of PD. (However, see Mentis et al. 2002 for a demonstration of abnormal visuospatial functioning in PD patients associated with a parietal lobe net-

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work.) Although only briefly discussed in the target article (sect. 4.2.2), a related disorder that appears to bridge many of the common aspects of PD and catatonia is the form of akinetic mutism seen with bilateral injuries to the paramedian thalamus and midbrain (mesodiencephalon) first described by Segarra et al. (1970) (see Schiff & Plum 2000 for a review). Patients suffering from this form of akinetic mutism may demonstrate behaviors quite similar to the catatonic patients carefully described in the target article.

For example, unlike the motionless hypervigilant form of akinetic mutism associated with direct injury of the mesial frontal cortices, these patients typically exhibit a "slow syndrome" in which responses (that may be quite accurate) come after a very long time delay. The patients may also demonstrate a waxy flexibility. They do not relate evidence of emotional overflow, but typically exhibit rather flat emotional tone. The response of this disorder to medication overlaps PD and catatonia: amantadine, traditional dopaminergic agonists, and occasionally ECT may improve this condition (Burruss & Chacko 1999; Fleet et al. 1987); in addition, although not well-documented in the medical literature, lorazepam and midazolam may also on occasion briefly reverse these conditions (unpublished case reports).

Bilateral paramedian injuries to the mesodiencephalon typically arise from vascular disease in the setting of variant blood supply that innervates both paramedian thalami and often one side of the medial mesencephalon (Castaigne et al. 1981). Damage to these regions produces injury typically to the posterior intralaminar nuclei of the thalamus (centromedian-parafasicularis complex) and the medial portions of the midbrain and pretectum, including the mesencephalic reticular formation. A similar syndrome demonstrating less akinesia is identified with injury to the anterior paramedian thalamus (Castaigne et al. 1981; Katz et al. 1987) involving the rostral intralaminar nuclei (central lateral, paracentralis, and central medial). These nuclei receive, among many other inputs, strong innervation from the periaqueductal gray matter, providing a potential explanation for the emotional flatness seen in patients with damage to these structures (cf. Panksepp 1998; Watt 1998).

The anatomical connectivity of these paramedian thalamic nuclei suggests a potential substrate for interaction of the likely interdependent but segregated networks identified for PD and catatonia. The centromedian-parafasicularis complex provides a critical thalamostriatal and thalamocortical relay for the direct "motor" loop discussed in the target article. This nuclear complex, in fact, undergoes marked degeneration (40–55%) in most PD patients (Henderson et al. 2000). The rostral intralaminar nuclei, however, have strong connectivity with the networks identified by Northoff in catatonia, including the anterior cingulate and parietal cortex (central lateral), and orbitofrontal cortices (paracentralis, central medial) (Macchi & Bentivoglio 1985). Groenewegen and Berendse (1994a; 1994b) proposed that, as a group, the thalamic intralaminar nuclei gate the interactions of the parallel "loops" through the prefrontal cortex and basal ganglia. A direct link between the anterior and posterior intralaminar groups, through the thalamic reticular nucleus, has been recently demonstrated, providing a mechanism for normal and abnormal cross-talk between these nuclear groups and their projection targets (Crabtree & Issac 2001).

Direct injury to these thalamic nuclei associated with akinetic mutism may also produce hypersynchronous epileptiform activity (von Domberg et al. 1996), which is not always demonstrated on the surface electroencephalogram (Williams & Parsons-Smith 1951). Of note, these thalamic nuclei underpin the distribution of hypersynchronous discharges in absence seizures (Seidenbecher & Pape 2001), a disorder with somewhat similar clinical features, but transient in nature, and with clear cortical spike activity. The rapidity of the response of most catatonia patients to lorazepam, a standard antiepileptic agent, supports the interpretation of hypersynchronous activity possibly restricted within thalamostriatal loops.

Recent studies in PD and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate models indicate that abnormal stabilization of intrinsic network rhythms may underlie important aspects of the pathophysiology of PD, including the mechanism of response to dopaminergic agents and deep brain stimulation (Farmer 2002; Levy et al. 2002). We are therefore led to a slightly different interpretation of the mechanism than that proposed in the target article; we suggest that both disorders may reflect relatively restricted hypersynchrony within distributed networks, organized by similar principles of discrete parallel cortico-striatopallidal-thalamocortical "loop" schemes (Alexander et al. 1986). Both may involve hypersynchrony in the intralaminar thalamic projections to the basal ganglia and cortex, with the symptoms of catatonia referred primarily to the rostral intralaminar group, producing relatively segregated hypersynchrony in orbitofrontal and anterior cingulate cortices (along with their parietal connections).

The normal state of these networks, however, presumably involves continuous selective integration of emotional tone, behavioral goals, and motor program selection, possibly facilitated by the intralaminar thalamic nuclei (Groenewegen & Berendse 1994a). Selection of modes of integration of these activities within the prefrontal cortex may depend on regulation by thalamic and other subcortical inputs (Kötter et al. 2001). This view does not require special directional aspects of neuronal activation for the expression of the disorders; rather, it suggest a differential basis in terms of subcortical regions, which may undergo neurodegeneration in catatonia and schizophrenia compared to PD. Such variations may provide for different vulnerabilities to hypersynchronous activity.

Catatonia, motor neglect, and hysterical paralysis: Some similarities and differences

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Abstract: We outline some ways in which motor neglect (the underutilization of a limb despite adequate strength) and hysterical paralysis (failure to move a limb despite no relevant structural damage or disease) may throw light on the pathophysiology of catatonia. We also comment on the manifold inadequacies of distinguishing too firmly between symptoms of "neurologic origin" and of "psychiatric origin."

Only a two-substance dualism, in which the world consists of mutually exclusive (albeit mysteriously interactive) mental and material events, allows that a given pathology is of either organic or functional origin. If dualism is rejected, then all diseases (and indeed all normal states) will have both physical and psychological aspects. This was clearly stated some centuries ago by Hippocrates (in his treatise *On the Sacred Disease*). Whether we are much closer than was Hippocrates to understanding exactly how material and mental manifestations of one reality fit together, is debatable. But Northoff is clearly looking in some of the right places in his "neuropsychiatric" comparison of the differing akinesias of catatonia and Parkinson's disease.

With respect to Northoff's dis-analogies of catatonia with spatial neglect, two issues stand out: First, what exactly are the "specific deficits in visuo-spatial abilities" that patients with catatonia manifest? Merely to note that they have lower scores than psychiatric and normal controls on a visual object and space perception battery (VOSP) is not very informative. Second, a reasonable guess is that motor neglect (not personal, peripersonal, or extrapersonal neglect) may be related to catatonia. In motor neglect, patients fail to spontaneously move the limb contralateral to the lesion, although there is no primary loss of strength or sensorimotor control: Patients can move the limb appropriately when specifically required to do so by the examiner.

This underuse of a nonparetic limb can dissociate from spatial

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neglect in any or all modalities (Laplane & Degos 1983). Many different lesion sites have been associated with motor neglect, but right parietal and right prefrontal damage are certainly frequent correlates (Vallar 1993). Patients with motor neglect have not been reported to show bizarre "posturing," and it is perhaps unlikely that they would show "catalepsy" if the limb were put in an uncomfortable position. It might nonetheless be worthwhile to investigate these issues: Patients with anosagnosia for hemiplegia do sometimes leave the affected limb in what would in a normal person be a highly uncomfortable or even painful position. More detailed comparisons between motor neglect and catatonia may yet reveal as many similarities as differences. Certainly, the reports that Northoff quotes, of reduced regional cerebral blood flow in right prefrontal and right parietal regions, would support the analogy.

It might also be useful to pursue more vigorously potential parallels between catatonia and "hysterical" paralysis (although in the latter condition the passive limb does not usually assume a bizarre position). The patient with hysterical paralysis reported by Marshall et al. (1997) showed anomalous activation of known negative motor areas (orbitofrontal cortex and anterior cingulate) when attempting to move her paralyzed leg. The "will to move" seemed relatively intact, as inferred from normal patterns of activation (in the left dorsolateral prefrontal cortex and the cerebellar hemispheres) when "preparing" to raise the paralyzed left leg. It was, we argued, as if between the "willing" and the execution of the willed action, an involuntary process of active inhibition took place. Whether, in some cases, an analogous neurophysiological inhibition prevents the limbs of patients with catatonia from returning to a resting position remains to be determined (Kahlbaum 1874). Functional neuroimaging might be particularly revealing in the large proportion of catatonic patients in whom there are no relevant neurological or psychiatric findings (Barnes et al. 1986).

One should not, however, assume that there is a single pathophysiology for all cases of catatonia-like symptoms. As Northoff points out, recent papers have discussed catatonia in the context of an extremely wide range of general medical (Carroll et al. 1994), neurological (Saver et al. 1993; Scheepers et al. 1995), and psychiatric conditions (Shiloh et al. 1995). Likewise, the status of associated symptoms remains questionable even within a diagnostic category. Northoff describes in the target article how a variety of "concurrent behavioral and affective anomalies" can be associated with the "posturing" of catatonia. Are the emotional reactions seen in catatonia (including aggression, excitement, ambivalence, flattened affect, and anxiety) the cause, the effect, or a tightly coupled consequence of an underlying impairment, or mere correlates of posturing? Are the associated behavioral patterns (including mutism, automatic obedience, negativism, and chopraxia) variations on a basic theme or indicants of quite distinct pathologies that it would be a mistake to conflate? Is "catatonia" in the context of schizophrenic signs and symptoms (Kraepelin 1920) the same type of "catatonia" that Baillarger (1843) first described as "melancholie avec stupeur"?

Answers to such questions may in turn depend on a much more richly specified description of catatonic patients. Do the patients recognize, for example, that a fellow patient's posture is abnormal? Do they recognize in a mirror that their own movements and postures might be odd? If there is no awareness of their "inability to terminate movements," what is the pathophysiology of that failure in conscious monitoring (Fink et al. 1999)? Do the patients have above average muscle strength (in order to sustain uncomfortable positions)? If so, the patients may be similar to yet another group of people. Half way across the Pont Neuf in Paris one often sees immobile "living statues" holding strange positions for considerable lengths of time. These are not catatonic patients, just street artists earning a living the hard way.

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Catatonia in Alzheimer's disease: The role of the amygdalo-hippocampal circuits

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Abstract: The intrinsic merit of Northoff's model lies primarily in the fact that it integrates data concerned with different levels of organization of the brain. This approach implicitly argues against reductionism, although, apparently, its rather simplistic assumption gives too many degrees of freedom. In considering that a symptom from two different syndromes indicates a common neural alteration, we grossly disregard neural plasticity.

Although not explicit, Northoff's article argues against two traditional schools of thought, which are still strongly defended by some contemporary neuroscientists: *the reductionistic approach,* which has tried to explain a behavior or a symptom as the [dys]function of an "isolated" neural circuit, and *the traditional dissociation* between nonfunctional psychiatric and neurological symptoms. Both ideas have been representative for the neuroscientists' community. In the pre-paradigmatic period, when there were very few methods to study the brain, localizationism was psychologically fulfilling for the neuroscientist, who had to explain something as sophisticated as behavior, or a neuropsychiatric symptom, after having studied only a small piece of brain tissue. Back then, this was the only way by which neurologists were able to trade their knowledge with the powerful psychiatrists. The oversimplified image of the brain and the redundant psychiatric descriptions were compatible at that time. What happens now, after the rich harvest of the decade of the brain? Many medical practitioners agree with the fact that what happens in the brain is important for behavior and that the reverse is as true, but they still dissociate some nonfunctional symptoms in psychiatric and neurological categories. Our view is that neurology has grossly ignored the fundamental research in neuroscience, and that psychiatry has ignored cognitive psychology. Their common reason is that we still do not know enough about the brain and behavior. In this context, there is a growing trend to integrate results from neuroscience and try to correlate them with today's clearer psychiatric classifications. The target article is such an attempt.

The fundamental premise of the target article is that clinical similarities, for example, between akinesia that occurs both in Parkinson's disease and in catatonia, are indicative of pathophysiological substrates which could offer insight into the functional organization of the brain. Instead of directly commenting on some of the arguments brought by Northoff, we will discuss a third case in which catatonia is often a symptom – that is, Alzheimer's disease (AD). Recent experiments with animal models of Alzheimer-like encephalopathy have shown that one of the most striking behavioral modifications is an original hypokinesia that progresses to akinesia. This akinesia is very similar to catatonia because it is a noxious-driven behavior, and it cannot be explained by severe sensory-motor deficits resulting from global neurodegeneration (see for details: Miu et al. 2002). In AD, catatonia can be correlated mainly with the functional isolation of the hippocampal formation, determined by the extensive degeneration of CA1 pyramidal and subiculum neurons and the profound loss of layers II and IV entorhinal cortex neurons (e.g., Gómez-Isla et al. 1996; Tomlinson & Kitchener 1972). There have also been reports of significant decreases in the packing density of neurons in the cortical and medial nuclei, and also in the lateral and basal nuclei of the amygdaloid complex (Herzog & Kemper 1980). Some of these nuclei project to the hippocampal formation through the entorhinal cortex and receive a reciprocal connection from cells along the border of the subiculum and CA1 (see for details: Amaral et al. 1992). In the case of AD catatonia, the motor symptoms associated with anxiety are often explained by an alteration of the amygdalo-hip-

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pocampal and amygdalo-striatal projection to the ventral striatum and also to the putamen and caudate nucleus.

Where the emotional dysfunctions in the catatonic syndrome are concerned, Northoff mainly refers to an alteration of the reciprocal connections between the medial and lateral orbitofrontal cortex. The malprocessing of negative emotions subserved by the medial prefrontal pathway is associated with motor symptoms, that is, deficits in the initiation of termination, which are considered indicative of a lateral pathway dysfunction through which the lateral orbitofrontal cortex is connected with motor structures such as the ventromedial caudate. One way to describe this lack of balance is an alteration of the horizontal prefrontal modulation, followed by an alteration of the top-down prefrontal-striatal modulation. Another psychomotor deficit that occurs in catatonia is that of online monitoring of movements, which means that the catatonic patients are not aware of their motor disturbances. Northoff argues that this can be correlated with prefronto-parietal dysfunction. If this were the case, the patient should display deficits in general awareness. But, in catatonia, the motor unawareness is accompanied by an emotional hyperawareness, a condition that could be more reliably associated with an alteration of the amygdalo-hippocampal system. This specific corticosubcortical dysfunction could explain the co-occurrence of catatonia in AD and the catatonic syndrome. In summary, our amendment emphasizes the role of the amygdalo-hypocampal system in catatonia, which seems to be underscored by Northoff's model.

Taking clinical similarities as a criterion to infer relationships among common pathophysiological substrates is rather promising. It is clear that a priority of contemporary neuroscience is to explain behavior by integrating data from studies that target different levels of organization of the brain, and to rectify the simplistic ideas about the brain, which sometimes govern the medical practice in neurology and psychiatry. Starting from a clinical symptom, that is, catatonia, we have tried to trace common themes between the catatonic syndrome and AD. An example of such a common theme is the alteration of the amygdalo-hippocampal system. Through this comparison between AD and the catatonic syndrome, we have followed the basic assumptions of Northoff's reasoning. Our point is that a striking, though subtle, aspect of such an exercise is the lack of difficulty of the comparison between two rather different syndromes. This could indicate that the clinical similarity criterion could be regarded as insufficient. In this context, the efforts of Northoff and others are noteworthy, but if one makes a rapid screening of the literature, one can conclude that there are too many alternative explanations for a syndrome such as catatonia. This could imply that we must be careful not to overtake the existent empirical evidence in our efforts at integration. In case it is too early for this kind of synthesis, which we think it is not, any such attempt could be accused of being greedy reductionism, perhaps more, but still insufficiently, informed than localizationism. Moreover, what about plasticity?

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A self frozen in time and space: Catatonia as a kinesthetic analog to mirrored self-misidentification

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Abstract: Aspects of Northoff's argument lend themselves to the ongoing investigation of localizing the self in the brain. Recent data from the fields of neuropsychology and cognitive neuroscience provide evidence that the right hemisphere is a candidate for localization of self. The data on catatonia further that proposition and add insight into the continuing investigation of self in the brain across sensory and motor domains.

Recent data from the fields of neuropsychology and cognitive neuroscience implicate the right hemisphere as the likely candidate substrate for self in the brain (see Gallup & Platek 2002). For example, Craik et al. (1999; see also Platek et al., in press) have shown that when thinking about self-describing adjectives, the right hemisphere is differentially activated. Consistent with the hypothesis originally formulated by Gallup (1982) that self-awareness is what makes mental state attribution possible, Baron-Cohen et al. (1994) provided data suggesting that when individuals think about mental state terms (e.g., intention, belief) the right hemisphere (i.e., right orbital frontal cortex) becomes activated. There is also convergent data linking the ability to model the mental experience of another individual (same or different species; i.e., anthropomorphism) and episodic memory to activation in the right prefrontal cortex (e.g., Nyberg et al. 1995; Stone et al. 1998; Stuss et al. 2001; Vogeley et al. 2001; but see also Fletcher et al. 1995, who argue for left prefrontal localization of theory of mind).

In addition, the ability to recognize one's face, which is the most common feature of self-recognition, may be lateralized to the right hemisphere. As an extension of earlier research conducted on callosotomy patients (see Preilowski 1977; Sperry et al. 1979), Keenan et al. performed several psychophysical experiments (Keenan et al. 1999; 2000) in which subjects were asked to respond to images of their own face and the faces of either familiar or strange people, and found that subjects were faster at responding to their own face with their left-hand, which, assuming contralateral motor control, suggests right hemisphere dominance when responding to self-faces. Keenan et al. (2001) recently utilized the WADA (named after John A. Wada) sodium pentobarbital hemispheric anesthetization test to further determine whether self-face recognition may be lateralized to the right hemisphere. Patients who were candidates for temporal lobectomy because of intractable epilepsy were asked to identify a morphed (computerized combination) of their own face and that of a famous person. Upon recovery of right hemisphere anesthetization, subjects were more likely to report having seen the face of a famous person. However, upon recovery of left hemisphere anesthetization, they were more likely to report that they saw their own face.

Breen et al. (2001) present data on patients with highly localized right prefrontal lesions who exhibit a unique mirrored self-misidentification syndrome whereby they can no longer recognize themselves in the mirror, but the ability to recognize other people and inanimate objects using mirrored space is intact. In addition, several disorders of frontal functioning (e.g., schizophrenia and autism) have been associated with deficits in self-face processing (e.g., Dawson & McKissick 1984; Orbach et al. 1966; Platek & Gallup 2002), theory of mind (see Baron-Cohen et al. 1985; 2000; Frith & Corcoran 1996; Langdon & Coltheart 1999, Sarfati & Hardy-Bayle 1999), and episodic memory (Nyberg et al. 1995).

The study of catatonia as a disorder of self-processing may expand the notion of prefrontal localization to include a more distributed network for self-processing. For example, recent data

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from our laboratory show that self-information from various sensory domains can produce cross-modal facilitation of self-face responding (Platek & Gallup, under review). In fact, catatonia may represent a motoric/kinesthetic analog to mirrored self-misidentification in that the patients have lost an explicit sense of relation between their limbs and body.

Catatonic patients experience a loss of awareness of movement termination; that is, they do not realize that their movement has changed or been altered while in a state of akinesia. Some patients report not being aware of the change in movement, but do report an overwhelming feeling of being controlled by emotions such as extreme anxiety/elation. Furthermore, Northoff describes catatonia as a deficit in the processing of online and internal spatial monitoring of one's own limbs in relation to the rest of the body, which suggests that the individual can no longer instantiate the limbs as an extended portion of their body. He notes that this ability seems to be localized to the right posterior parietal cortex (Pfennig 2001).

These data, along with the neglect syndrome in which an individual believes that limbs contralateral to brain trauma (usually left limbs as a consequence of damage to the right hemisphere, see Feinberg 2001) are not his/her own and should not be attached to their body, suggest that part of the self-concept may include a representation of the body as an extended portion of the self. This relation between the posterior parietal cortex and kinesthetic self-awareness, and its relationship with the prefrontal cortex, might be part of a distributed network involved in processing various properties associated with self-awareness. It is well know that the prefrontal/orbitofrontal regions maintain connections with posterior parietal cortex (e.g., Binkowski et al. 1999, Strik et al., in press). Furthermore, the idea that catatonia results from intense feelings of fear and/or anxiety also lends itself to this network hypothesis, because the amygdala is heavily connected to both the posterior parietal cortex and the orbitofrontal cortex; hence, uncontrollable emotional feelings could serve to dysregulate or over-regulate other portions of a distributed self-network. Interestingly, the amygdala is also related to self-processing and the ability to follow someone's gaze, engage in appropriate empathic responding, and understand the meanings of mental state terms (see Baron-Cohen et al. 2000).

The comparison of akinesic states associated with Parkinson's disease and catatonia, and the hypothesis comparing cortico-cortical horizontal modulation and cortico-subcortical vertical modulation, lead not only to new understanding of these disorders, but also suggest that the neuropsychology of self-awareness may involve a horizontal cortico-cortical modulatory loop containing multiple cortical substrates.

The disease status of catatonia

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Abstract: Georg Northoff encounters a problem regarding the logical status of "catatonia." Whereas Parkinson's disease (PD) is a disease on the basis of Virchowian criteria, catatonia is not. PD is associated with pathognomonic neurological lesions. Catatonia does not require any such association. The diagnosis is rendered using social criteria rather than neuropathological ones. Therefore, Northoff is not comparing two disease states at all.

A basic problem with Georg Northoff's fascinating comparison between PD and catatonia is that PD is a disease and catatonia is not. Admittedly, in some circumstances, a neurological lesion may produce the latter. For instance, Joseph notes that lesions in the amygdala can result in complete cessation of movement, what he calls "catatonic-like frozen states" (Joseph 1996). The amygdala produces such a state through its interconnections with the basal ganglia and medial frontal lobes. Though Joseph states that the problem is an inability to initiate a movement, and Northoff makes the important point that the actual defect in catatonia is the failure to terminate an action, the results appear to be similar enough to warrant mention. In the case of medial frontal lobe lesions, flexibilitas cerea and *gegenhalten* occur as part of the catatonic syndrome (Joseph 1996). By contrast, a patient of mine with Parkinson's disease had the interesting problem of experiencing enormous difficulty walking through a doorway, a dramatic example of impaired movement initiation in PD as opposed to the catatonic problem of movement termination. Ordinarily, however, catatonia is not associated with a neurological lesion.

In comparing the neurophysiology of PD patients with that of catatonic ones, Northoff provides a probing analysis, but appears to glide over this important difference between the two conditions. Parkinson's disease is a much-discussed topic in neuroscience and clinical neurology. Kandel has 19 separate citations for the disease and spends 21 pages discussing various aspects of it. When it comes to catatonia, however, the only mention of this entity is part of a discussion of schizophrenia and consists in its entirety of the following fragment: "and catatonic schizophrenia, a rare form in which mutism and abnormal postures predominate" (Kandel & Jessel 2000). This dearth of references reflects the attitude that pathologists and neuroscientists do not regard catatonia as a disease. Clearly, Northoff offers numerous illuminating distinctions regarding the difference between the two states, but these distinctions are neurological, not conceptual, and there is a good deal of conceptual work to be done.

Northoff's thesis that the basic difference between PD and catatonia has to do with the kind of disruption in top-down and bottom up modulation between the orbitofrontal cortex and the basal ganglia (in catatonia) and the basal ganglia and premotor cortex (in PD), respectively, is important to our understanding of the functional anatomy of the human brain. However, we must ask what the cause of this dysregulation is in each case. In PD, we know that there is a loss of dopamine producing neurons of the substantia nigra in the midbrain. Therefore, PD conforms to Virchow's requirement that there be a lesion for every pathological process. In the case of catatonia, however, aside from the occasional medial frontal or amygdaloid abnormality, there is no pathognomonic lesion to consider. Northoff makes the point that the problem in catatonia has to do with the manner in which functional groups are modulated, not with anything to do with cellular pathology. Thus, by his formulation (a formulation that makes a great deal of sense), there is no basis for regarding catatonia as a disease.

What then is catatonia, if not a disease? It is nothing more than a social construct. That is, the criteria that identify this state as "pathological" are the same sort of standards that define interpersonal propriety. Northoff's Figure 1 makes the point very well by showing six men standing rigidly in place for an extended period of time, something we would commonly frown upon in ordinary social settings. In other words, such behavior is obnoxious, subject to public criticism, and relegated to physicians who provide a "diagnosis" for it. The understanding of problematic behavior, then, is transformed into a diagnostic/therapeutic exercise as a way of dealing with its troubling aspects.

The obvious rejoinder is that, at least in some cases, catatonia must be a disease because it is associated with lesions in the medial frontal cortex and amygdala. In these cases, the Virchowian criterion requiring cellular pathology as the basis for any disease appears to be satisfied. The problem, though, is deeper than this single standard. In psychiatric diagnosis, unlike the rest of medicine, it is behavior of one sort or another that is deemed pathological. Standing with a pair of shoes held above one's head for several hours is regarded as diseased, perhaps part of a schizophrenic syndrome. The attribution of pathology does not depend at all on the identification of an underlying lesion. It has only to do with the behavior itself. Nowhere in the rest of medicine can such a pattern of identification and diagnosis be found. Writhing in pain be-

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cause of an inflamed appendix is symptomatic of a disease process, but is not in itself the disease. We require something like a disruption in the normal biological functioning of the organism (in the case of appendicitis, infection) to be correlated with the lesion. Altered social behavior is not sufficient.

It is perhaps because of such considerations that Northoff refers to PD as a motor disorder and catatonia as a psychomotor disorder. Similarly, he speaks of functional systems in the sense that Luria intends. The cause of behavioral pathology in this instance is the result of altered top-down and bottom-up modulation within the same functional system. The problem that persists, however, is that Northoff could just as well be providing a schema for understanding why some people are Dodger fans and others root for the Yankees. His very fine work in neurophysiology would be greatly enhanced if his distinction between motor and psychomotor disorders rested on firmer ground.

Do neurodegenerative cascades in Parkinson's disease really reflect bottom-up processing?

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Abstract: The target article suggests that the neurological disorders catatonia and Parkinson's disease share similar behavioral features that nevertheless reflect different forms of abnormal information processing. However, emerging research on Parkinson's disease and related age-dependent neurodegenerative disorders suggests that no simplistic notions about processing will be correct for all stages of the disease.

The article by Northoff suggests that neurological disorders sharing apparently similar behavioral symptoms can arise as a result of quite differing stages and levels of neural (mis)processing. Northoff uses the examples of catatonia and Parkinson's disease to distinguish "bottom-up" forms of processing from "top-down" and "horizontal" processing, the latter two presumably being key distinctions in catatonia.

There are two main critiques that can be directed against the hypothesis, which I will address in this commentary. A final comment will address Northoff's use of the terms "up-" and "down-regulation."

The author begins his review by stating that differential clinical diagnoses of catatonia versus Parkinson's disease are somehow an issue for neurology, with confusion arising in some cases. The author documents similar features that superficially make initial symptoms appear to be of identical origin. However, by the author's own detailed survey, the distinctions between these two disorders far outweigh the similarities. Not only are the time frames of these disorders vastly different, but so too are ages of onset, responses to medication based on effects on very different neurotransmitter systems, and, for Parkinson's disease, "progression" as additional neural damage occurs. In fact, the only real surprise is that the disorders are ever confused in current practice. Problems in diagnosis might have been more crucial 50 or more years ago, but with better understanding of disease history, the advent of brain imaging techniques, and so forth, the "problem" Northoff seeks to remedy is a nonproblem. If for no other reason, the issue is moot simply because Parkinson's disease is not curable in any sense, and palliative dopamine replacement strategies are only moderately successful – and then only for a time. Catatonia may be different, but this difference may reside primarily in the fact that it is not neurodegenerative, whereas Parkinson's disease is.

Northoff then uses the extensive differences between the disorders to argue that these reflect major differences in processing (more appropriately, abnormal processing) pathways within the brain. This hypothesis may be correct in a general sense, but the conclusion cannot be supported, at least in the case of Parkinson's disease, for many reasons. A brief review of some of the more salient features of Parkinson's disease will help make these reasons clear.

First, Parkinson's disease is progressive, that is, neural degeneration continues until the majority of dopaminergic neurons in the substantia nigra (s.n.) have been destroyed. The disease is then clinically manifested by its behavioral symptoms. Preclinical stages of the disease are largely unknown, except for the familial early onset form; notably, the latter is only a small fraction of all Parkinson's cases (Tanner et al. 1999), and it will be clear that whatever genetic abnormality is causal to early Parkinson's likely bears little relation, except in outcome, to the likely environmental factors causing the sporadic form.

Second, while conventional views of Parkinson's disease suggest that it arises as a result of simple loss of the dopamine-containing neurons of the s.n, leading to "bottom-up" failures of information transmission, the emerging view of the disease is vastly more complex. Specifically, considerable overlap has now been described with other neurological disorders, including the presence of traditional markers of Alzheimer's disease in the central nervous system of Parkinson's patients (Eisen & Calne 1992), and the observation that variants of Parkinson's/Alzheimer's can occur in the same individual (Calne & Eisen 1989). As an example of the latter, the ALS-Parkinsonism dementia complex of Guam perfectly illustrates this point (Kurland 1988). Therefore, in advanced Parkinson's disease (and maybe preclinically as well), not only is the striatal system affected, but significant parts of higher cognitive structures are also impacted. Once the latter are involved, it becomes difficult to describe Parkinson's disease as a pure case of bottom-up abnormal processing.

Third, examining Parkinson's patients after diagnosis affords only a late stage "snap shot" of the disease, with little or no insight to be gained about how the damage arose. Simply put, we still have no clear idea of what environmental/genetic factors are causal to the initiation of the disease, no idea of what the stages of neuronal degeneration are happening in different brain regions, and no understanding of the pathological biochemical cascade leading to neuronal death. Even if we could know all the molecular and circuit changes that have occurred through post-mortem examination, there is no way, theoretically or experimentally, to distinguish from this stage alone those events that are causal, those that are "co-incidental," and those that may be compensatory (failed or successful). Given the above, any depiction of Parkinson's disease as a bottom-up process is, at best, a statement, even if true, about a particular late stage of the disease.

Finally, I note that the author frequently refers to "up-regulation" and "down-regulation" in relation to changes in neural circuit function and to alterations in behavior. One presumes that this terminology arises from the well-documented cases of neurotransmitter receptor regulation (for review, see Shaw & Pasqualotto 2000), in which various biochemical reactions, notably phosphorylation, lead to loss of functional receptor number. Down-regulation refers to a process that begins with phosphorylation of some amino acid sequence of the receptor, followed by an internalization of the protein. Up-regulation refers to an increased transcription and trafficking (Shaw & Pasqualotto 2000) of receptor proteins back to the cell surface. Both processes are dynamic and occur in response to stimulation of various kinds. The question that arises is this: Does the author mean that the circuits themselves have been physically removed or regrown? Or does he mean to imply that the neurotransmitter receptors underlying circuit-firing activity have been regulated? The former, if this is the intent of the use of the term "regulation," would have to be justified by reference to such modification occurring at the circuit level. In contrast, if the latter is meant, then it should be so stated.

In conclusion, whereas it might serve heuristic purposes to distinguish the abnormal forms of information processing in Parkinson's disease and catatonia, the failure to address the dynamic nature of the underlying pathology of the former does not allow the current hypothesis to be evaluated.

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Table R1 (Northoff). *Problems and issues raised by the different commentators*

Neuroanatomy and neurophysiology of catatonia	Anterior cingulate (**Badgaiyan**), Orbitofrontal cortex (**de Oliveira-Souza et al.**), Parietal cortex (**Bearden & Monterosso**), Negative motor areas (**Marshall et al.**), GABA and inhibition **Bogerts**), Amygdala-hippocampus (**Bogerts**, **Miu & Olteanu**, **Savodnik**), Thalamus and hypersynchronous activity (**Kamal & Schiff**, **Fricchione**), Subcortical GABAergic mechanisms (**Fricchione**), Striatal dopamine-glutamate interaction (**Horvitz**), Multiple regions (**Bearden & Monterosso**, **Bogerts**, **Carroll**)
Cognitive-motor deficits in catatonia	Supervisory system and lateral inhibition (**Badgaiyan**), Cognitive deficits in catatonia (**Aleman & Kahn**), Relation between initiation and termination (**Bearden & Monterosso**), Motor neglect (Marshall et al.), Role of inhibition (**Badgaiyan**, **Bogerts**, **Marshall et al.**)
Conceptual issues	Distinction between vertical and horizontal modulation (**Horvitz**), as well as between "top-down" and "bottom-up modulation" (**Shaw**), Definition and level of "top-down modulation" (**Aleman & Kahn**), Linkage between top-down and bottom-up modulation (**Fricchione**), Anatomical structures vs. functional modulation (**Kamal & Schiff**), Definition of "lesion" (**Savodnik**), Distinction between cause and symptoms of disease (**Bogerts**, **Shaw**), "Biological" vs. "psychological" (**Hardcastle**, **Marshall et al.**, **Miu & Olteanu**, **Savodnik**)
General methodology in neuropsychiatric research	Cognitive models as a starting point (**Badgaiyan**), Description and phenomenology of symptoms (**Marshall et al.**), State vs. trait (**Bearden & Monterosso**), Distinction between cause, compensation, cooccurrence and consequences (**Savodnik**, **Shaw**), Definition of "disease" and "syndrome" (**Savodnik**, **de Oliveira-Souza et al.**), Too premature for hypothesis (**Bearden & Monterosso**, **Bogerts, Marshall et al.**, **Miu & Olteanu**)
Neurophilosophical implications	"Psychological" vs. "biological" (**Hardcastle**), Role of consciousness (**Hardcastle**), Neurobiology of self and relation to body (**Platek & Gallup**), Neurobiology of will (**de Oliveira-Souza et al.**), Monism vs. dualism (**Hardcastle**, **Marshall et al.**)

Author's Response

Neurophysiology, neuropsychiatry and neurophilosophy of catatonia

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Abstract: The excellent and highly interesting commentaries address the following concerns: (1) neuroanatomy and neurophysiology of catatonia; (2) cognitive-motor deficits in catatonia; (3) conceptual issues; (4) general methodology in neuropsychiatric research; and (5) neurophilosophical implications. The specific problems, issues, and aspects raised by the different commentators are grouped under these categories in Table R1 presented below. These five areas of concern are then discussed in the order listed in the five sections of the Response.

R1. Neuroanatomy and neurophysiology of catatonia

Badgaiyan suggests the involvement of the anterior cingulate, including its distinct motor, affective, and cognitive parts, in catatonia.

Involvement of the anterior cingulate is strongly supported by our imaging results acquired during emotional stimulation (Northoff et al. 2002a). Post-acute catatonic patients showed altered, that is, decreased signal intensity in medial orbitofrontal and ventromedial prefrontal cortex; the latter includes the subgenual and pregenual, that is, the affective part of the anterior cingulate. Moreover, abnormalities in medial prefrontal cortex, including the supragenual anterior cingulate (i.e., its motor and cognitive part) were observed.

The exact functional mechanisms and the interregulation between the different parts of the anterior cingulate, however, remain unclear. **Badgaiyan** offers an interesting explanation by hypothesizing that the motor part may be inhibited, and thus, suppressed by overactivity in the affective part. Such a hypothesis seems to be of particular interest considering the fact that akinetic mutism, which shows similar motor features, may be caused by lesions in the motor part of the anterior cingulate. However, to my knowledge, there is, so far, no direct empirical evidence for his hypothesis.

The excellent case descriptions from **de Oliveira-Souza et al.** suggest involvement of the orbitofrontal cortex especially the medial and right part. They nicely describe the behavioral anomalies which are so prominent and bizarre in these patients. They unfortunately do not describe the affective status of their patients. The medial orbitofrontal cortex might play a crucial role in catatonia as based on imaging findings and deficits in the Gambling task. These deficits might deregulate the functional balance between medial and lateral orbitofrontal cortex, which, psychologically, might be reflected in an abnormal emotional control of behavior. This remains purely speculative, however, and awaits further empirical confirmation.

Bearden & Monterosso point out the crucial role of the right parietal cortex in my hypothesis, and argue that, if this

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is indeed the case, catatonic patients should show similar symptoms (apraxia, hemineglect, tactile impairment) to those with lesions in this region. This is a question that occurred to me, as well. However, it should be noted that they refer to patients with exclusive lesions in the right parietal cortex, which, unlike catatonia, do not show deficits in the orbitofrontal cortex. It may therefore be hypothesized that the co-occurrent involvement of right parietal and orbitofrontal cortex may lead to a different pattern of symptoms than isolated lesions in the right parietal cortex. Moreover, a recent study demonstrated that patients with hemineglect showed lesions in the right superior temporal cortex, rather than the right posterior parietal cortex (Karnath et al. 2001). Accordingly, exact localization of lesions may differ between catatonia and hemineglect.

Marshall, **Gurd & Fink** (**Marshall et al.**) suggest the involvement of so-called negative motor areas, like the orbitofrontal cortex and the anterior cingulate. As already pointed out in both the target article and these commentaries, there is strong evidence for involvement of these regions in catatonia. Because of overlap in symptoms, it may well be imaginable that these regions could be involved in both hysterical paralysis and catatonia – although, in contrast, there is no direct evidence for alterations in active inhibition. However, there may be some indirect evidence. Behavioral inhibition may be reflected in posturing and its release by external stimuli, as, for example, when catching a ball (see Northoff et al. 1995). Physiological inhibition may be reflected in the good therapeutic efficacy of lorazepam, a GABA-A potentiator, which enhances neuronal inhibition. This is supported by abnormal (i.e., paradoxical) clinical responses to lorazepam (Northoff et al. 1999a), as well as abnormal changes in readiness potential (Northoff et al. 2000a) and orbitofrontal cortical fMRI signals (unpublished observation) after application of lorazepam in catatonic patients

Bogerts refers to the process of neuronal inhibition and potentially GABAergic mechanisms by assuming that there may be a principal deficit in neuronal inhibition underlying both schizophrenia and catatonia. His hypothesis, that deficits in neuronal inhibition are basic to the principal disease process in both schizophrenia and catatonia though manifest in different regions, is appealing, especially from a clinical point of view. As he points out, catatonia occurs often as the most severe and extreme manifestation of paranoid schizophrenia – the same underlying pathophysiological mechanisms (i.e., altered neuronal inhibition) may account for this co-occurrence.

Bogerts, **Miu & Olteanu**, and **Savodnik** argue for the potential involvement of the amygdala-hippocampal complex in the pathophysiology of catatonia. Bogerts (see also Savodnik) points out the similarity between catatonia and anxiety disorder with regard to strong and uncontrollable emotional symptoms (i.e., anxieties). Since the amygdala may be crucially involved in anxiety disorder, it should play a role in catatonia, as well. This is certainly right, and strongly supported by the existence of strong and reciprocal connections between the amygdala and the orbitofrontal cortex. Although the latter is altered in catatonia, one may assume that the former (i.e., the amygdala) is also involved. Miu & Olteanu point out the potential relevance of the hippocampus by drawing on the occurrence of catatonia in Alzheimer's disease. It is true, indeed, that many of the catatonic features, and catatonia as a whole, can be observed in dementia, Alzheimer's, and frontal lobe dementia in particular. Moreover, there is reciprocal and strong connectivity between the medial orbitofrontal cortex and the hippocampus (Barbas 2000), which makes involvement of both regions in catatonia rather likely. Finally, both schizophrenia and depression, the diseases in which catatonia most often occurs, can be characterized by abnormalities in the hippocampus (Bogerts 1997; Liotti & Mayberg 2001). Accordingly, there is some, albeit rather indirect, evidence for potential involvement of the hippocampus in catatonia.

Kamal & Schiff shift the attention to the thalamic nuclei and hypersynchronous neural activity. Rather than considering this as contradictory to my hypothesis, I would regard their comments as complementary. The cortico-subcortical loops described certainly involve the thalamic nuclei, which, in turn, may alter the neuronal pattern, consecutively leading to hypersynchronization. Hypersynchronous neural activity may account for the "deadlock" that can be observed in catatonia. However, this remains purely speculative, because there are no data at all to support such an assumption. The same remains true with regard to **Fricchione**'s suggestion of impaired desynchronization in the basal ganglia. There are no EEG data so far which have been shown any abnormalities in catatonic patients.

The problem remains, to establish a solid animal model that really mirrors catatonia as observed in humans. Although DeJong (see Northoff 1997a) claimed to have established an animal model of bulbocapnine-induced catatonia, application of the same agent led, rather, to a kind of neuroleptic-induced catalepsy, which did not react at all to GABAergic agents like lorazepam (my own unpublished observations). **Fricchione** points out the animal model by Stevens where a GABA-A antagonist was injected into the ventral tegmentum of cats and induced a catatonic-like state in cats. This may point out the relevance of subcortical GABA-ergic mechanisms which, on account of methodological reasons, have not been investigated in human catatonia so far.

The same problem arises if one wants to investigate the exact interaction between cortical glutamatergic projections and dopaminergic nigrostriatal neurons in the striatums. As claimed by **Horvitz**, the interaction between both kinds of neurons may be altered in Parkinson's disease, which consecutively may account for muscle rigidity accompanying akinesia. It is one of the most distinguished features of akinesia in catatonia, in that it is not accompanied by an increase in muscle tone, which, in contrast, may be either on a normal or even lower (i.e., decreased) level. One may subsequently assume that the glutamatergic-dopaminergic interaction in the striatum may be different in catatonia from Parkinson's disease.

Finally, it should be pointed out that several authors (**Bearden & Monterosso**, **Bogerts**, **Carroll**) support the assumption of diffuse and multiple lesions in catatonia. This was the reason why I put the emphasis on a network model, involving several regions and circuits, rather than on a single and particular anatomical location.

R2. Cognitive-motor deficits in catatonia

Badgaiyan makes the interesting assumption that the supervisory system and lateral inhibition may be disturbed in

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catatonia. The selection of action from among competing action sequences may be disturbed. Clinically, the inability to select appropriate action from among different kinds of actions may be reflected in both hypokinetic and hyperkinetic symptoms. In hypokinetic symptoms, no further action can be selected, whereas in hyperkinesias the switch between different actions is disturbed. Accordingly, there is clinical evidence for a deficit in the selection of action. Whether this is caused by alteration in lateral inhibition, however, remains unclear. Nevertheless, as already pointed out, assumption of altered inhibition (i.e., lateral inhibition) seems rather likely. Neuroanatomically, this is supported by potential involvement of the ventrolateral prefrontal cortex, which may be related to inhibitory functions.

Neuropsychological results show a cognitive deficit in decision-making in catatonia as investigated with the Gambling task (own data, not published yet). This answers the question for cognitive deficits raised by **Aleman & Kahn**. However, the exact relationship of these cognitive deficits to catatonic symptoms remains unclear. One may speculate that the behavioral symptoms in particular may be related with these deficits in decision-making.

Bearden & Monterosso raise the issue of the relation between initiation and termination of movements in catatonia. There is, apparently, a deficit in the termination of movements, because otherwise, patients would be able to complete their movements. However, initiation and termination are closely linked with each other. For example, terminating a movement presupposes an initiation for termination. Accordingly, initiation and termination cannot really be separated from each other. Because of their close linkage, catatonic patients show deficits in the internal initiation of movements, as observed in my ball experiments (Northoff et al. 1995). However, unlike patients with Parkinson's disease, catatonic patients also show deficits in the termination of movements, resulting in posturing. These deficits were also observed in the ball study and were described as a deficit in the "voluntary generation of movements." Accordingly, the present assumption of alteration in termination is not contradictory to my earlier statement of deficits in the initiation of movements.

Marshall et al. raise the comparison between motor anosognosia in catatonia and motor neglect. They are certainly right in doing so, and support their claim by neuroanatomical evidence. I fully agree with them. However, as also pointed out by them, motor neglect does not lead to posturing. Accordingly, motor neglect may account for the lack of awareness of posturing, rather than for posturing itself. Instead of equating catatonic symptoms with motor neglect, I would suggest that catatonia might reflect a higher (i.e., cognitive) form of motor neglect. However, at present, this claim remains purely speculative. It is certainly true, as they state, that further phenomenological and psychological information is necessary in order to elucidate the exact nature of the motor deficits.

Badgaiyan, **Bogerts**, and **Marshall et al.** point out the crucial role of inhibition in catatonia. It should be noted, however, that the exact meaning and level of inhibition should be defined: Do they mean behavioral inhibition? Psychological inhibition? Physiological inhibition, as it might be reflected in GABA-ergic mechanisms? All of these different levels of inhibition might dissociate from each other. For example, behavioral inhibition might be subserved by physiological (i.e., neuronal) excitation. Accordingly, the meaning of the term "inhibition" should be specified and discussed in full detail. With regard to catatonia, the exact relationship between the different kinds of inhibition remains unclear and can only be speculated about.

R3. Conceptual issues

The first conceptual issue concerns the distinction between vertical and horizontal modulation. **Horvitz** raises two questions: first, the exact relation between a particular kind of modulation (i.e., vertical or horizontal) and symptoms; and second, the relationship between anatomical structures and functional modulation. There is certainly no exclusive relationship between particular symptoms and a specific kind of modulation (i.e., horizontal and vertical). Catatonia, for example, may eventually involve vertical modulation as well, with top-down modulation of subcortical nuclei involved in affective regulation (locus coeruleus, raphe nuclei). Parkinson's disease, on the other hand, may involve horizontal modulation, as, for example, dysregulation of prefrontal cortical areas, accounting for emotional processing by motor/premotor cortical areas. Accordingly, it is not a matter of "All-or-Nothing," but rather a matter of "More or less," with regard to the kind of modulation involved. The same remains true for the distinction between "bottom-up" and "top-down" modulation, which, rather than being absolute, must be considered as "relative," as pointed out by **Shaw**. Because of the widespread, and often strong and reciprocal, cortical-subcortical and cortico-cortical connectivity, a sharp and exclusive distinction between the distinct kinds of modulation remains impossible. This is probably reflected in relative, rather than absolute, differences between clinical symptoms, like, for example, akinesia. Catatonia seems to be dominated by alterations in horizontal modulation, whereas Parkinson's disease may rather be characterized by predominant changes in vertical modulation.

Aleman & Kahn raise the question for the definition of "top-down modulation." They contrast the anatomo-connectional cortico-subcortical definition with a rather psychological definition by cognitive-sensory interaction. They are right in emphasizing the distinction, since both cases do not necessarily fall together. This, for example, is the case in visual attention, where prefrontal cortical areas top-down modulate sensory cortical regions. This cortico-cortical modulation might be subsumed under the term "horizontal modulation" in the anatomo-connectional sense. There is apparently some confusion and rather unclear definition of the various kinds of modulation. To clarify these issues must be considered an important task which might contribute substantially to a better understanding of the pathophysiological mechanisms in psychiatric disorders. Aleman & Kahn have pointed out hallucinations and affective-behavioral alteration as other examples where altered top-down modulation may be crucial. As they describe, cortico-cortical and cortico-subcortical modulation might go together, resulting, neuropsychologically, in top-down modulation. Consequently, top-down modulation and horizontal modulation might be regarded as equally important and should be seen to be complementary rather than exclusive, because they describe different levels of operation – that is, anatomo-connectional as well as neuropsychological.

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My emphasis was on pointing out these distinct kinds of modulations and the different levels they were operating on. It is not that I forgot the loops and circuitry by Alexander et al., as is suggested by **Fricchione**. Rather, my concept of the distinct kinds of modulation, which point out the functional level rather than the structural anatomy, must be regarded as complementary. Fricchione is certainly right in noting the neglect of subcortical regions – the basal ganglia, in particular – which resulted in a lack of discussion of the neuromedical origin of catatonia. My focus was concentrated on the cortical-cortical interactions and the distinct kinds of modulations as these are questioned in the consideration of psychogenic catatonia. However, these kinds of modulation do not necessarily exclude subcortical-cortical modulation, that is, bottom-up modulation. Fricchione's suggestion, for linking top-down and bottom-up modulation in order to account for both psychogenic and organic catatonia, might therefore be considered as a good model for further investigation.

This leads us to the second question, the relation between functional modulation and anatomical structures. I would claim that the clinical symptoms themselves, in both disorders, cannot be directly related to particular deficits in specific anatomical structures, but rather, are related to particular alterations in functional modulations (i.e., circuits and loops). For example, the nigrostriatal dopaminergic deficit is the cause of the dysregulation in the "motor loop" in Parkinson's disease, which then accounts for the motor symptoms. Accordingly, anatomical structures can be regarded as a necessary, but not sufficient, condition for generation of clinical symptoms. For example, a particular anatomo-structural lesion may predispose and increase vulnerability to a certain dysregulation in functional modulation, as pointed out by **Kamal & Schiff**. However, there may also be anatomo-structural lesions without dysregulation in functional modulation, which may be reflected in an absence of clinical symptoms. Functional modulation, which operates on and across different anatomical structures, may therefore be regarded as a sufficient condition. This is, for example, reflected in psychogenic disorders. Despite the absence of a particular anatomo-structural lesion, psychogenic disorders show alterations in functional modulation, whereas their clinical symptoms resemble the diseases having lesions in those anatomical structures on which the loops and circuits operate. Accordingly, the relations between anatomical structures and functional modulation can be manifold. Different constellations can be possible and may account for major and minor differences in clinical symptoms.

Closely related to the difference between structure and function, is the concern raised by **Savodnik**, regarding the definition of a "lesion." He argues that catatonia cannot be characterized by lesions in the Virchowian sense, because no anatomo-cellular correlate has been detected so far. However, within the present framework, the concept and definition of a "lesion" should be extended to include not only anatomo-structural lesions, but also alterations in functional modulation (i.e., loops and circuits). These may, for example, concern alterations in vertical and horizontal modulation, as is the case in catatonia. Moreover, this extended definition of "lesion" could then also account for psychogenic disorders, and would therefore bridge the "old" gap between the structural and functional level, and thus between "organic" and "psychogenic" disorders. Presupposing this definition of a "lesion," catatonia, too, can be regarded as a "disease," which makes its characterization as a "social construct," as suggested by Savodnik, superfluous.

Moreover, the distinction between the cause of a disease and the symptoms of a disease should be considered. The present hypothesis aims at pointing out the pathophysiological correlates underlying the different kinds of symptoms in catatonia. Although, in contrast, it does not say much about the pathophysiology related to the cause of these changes. Because the hypothesis focuses predominantly on the pathophysiological correlates of symptoms, it rather neglects the dynamic nature and course of catatonia, as has been noted by **Bogerts** and **Shaw**. Both these commentators are certainly right that, in order to obtain a full and complete pathophysiological account of catatonia, its dynamic nature and course should be taken into account. However, focus on the symptoms themselves, with neglect of the dynamic course, does not make the comparison with Parkinson's disease worthless (see Shaw's commentary in this regard), as long as it does not claim to be a comparison between both diseases (but rather, between their symptoms). Shaw is certainly right, however, in pointing out the necessity of giving the exact stage of the disease (early or late) to which the motor symptoms in Parkinson's refer.

The difference between pathophysiological correlates of the disease cause and the disease symptoms is nicely reflected in Parkinson's. The nigrostriatal dopaminergic deficit may somehow be regarded as the correlate of the disease cause (although the cause for the degeneration of these neurons remains unclear), whereas the changes in the "motor loop" are instead the correlate of the motor symptoms. As pointed out by **Bogerts**, the disease cause remains unclear in catatonia, and it may be of anatomo-structural nature. Accordingly, the distinction between disease cause and disease symptoms may reflect the distinction between the anatomo-structural and functional level. Although – as, for example, in psychogenic disorders – this is not necessarily the case.

The term "cause" of particular symptoms may be further specified and may refer either to a particular disease or a syndrome. **Bogerts** remarks that there is a lack of clear specification as to whether catatonia is a syndrome, or a disease by itself. As pointed out in my studies, I regard catatonia as being a syndrome (see also **Carroll**). As a result, catatonia can be associated with a variety of different diseases, from which it may turn out to be a "common functional final pathway." For example, fever can be associated with a variety of different diseases. Nevertheless, there is a specific pathophysiological correlate of fever that remains absent in patients with the same disease, but without fever. Fever may therefore be regarded as an analogous model syndrome for catatonia. Considering fever, which is the extreme manifestation of an underlying disease, catatonia may indeed be regarded as the "extreme end" of certain neuropsychiatric diseases, such as, for example, affective and schizophrenic disorders. In contrast to Bogerts' implicit assumption, the syndrome character of catatonia and its characterization as an "extreme end" are not mutually exclusive.

As pointed out by **Bogerts**, **Miu & Olteanu**, **Carroll**, and **Bearden & Monterosso**, catatonia can apparently be related, not to one particular anatomical structure, but rather, to multiple and different ones. It therefore defies strict localizationism. However, this does not mean that

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catatonia can be related to the whole brain, as presupposed in holism. The present concept of description of loops and circuits, which operate across several but specific anatomical structures, defies and undermines the exclusive and opposite distinction between localizationism and holism. The term "up- and down regulation" does, therefore, refer primarily to specific circuits, rather than to transmitters as suggested by **Shaw**. However, transmitters should not be neglected entirely, because the functional output of the circuits may essentially depend on the kinds of transmitters. Instead, the present hypothesis can be regarded as an attempt to provide the groundwork for a more dynamic approach and to move beyond or undermine the classical distinction between localizationist and holistic approaches, which are still quite prevalent in neuropsychiatry, either explicitly or implicitly.

Finally, the distinction between "biological" and "psychological," which reflects the distinction between "psychogenic" and "organic" catatonia, is raised by several commentators, either implicitly or explicitly (**Hardcastle**, **Marshall et al.**, **Miu & Olteanu**, **Savodnik**). I do not intend to say that "psychogenic" disorders are cortical and "organic" disorders are subcortical. Instead of making an "absolute" difference, I would rather call for a "relative" distinction with matters of degree. The loops and circuits cross the boundary between cortical and subcortical regions and, therefore, "relativize" this distinction. **Hardcastle** is subsequently right in claiming that this "division" is "too simple." However, it may reappear in a "relativized" form within the terms "top-down" and "bottom-up" modulation, and thus in the direction of the modulation within one particular cortical-subcortical loop/circuit. It is this characterization of the different directions of the modulation within the same loops/circuits that may account for the subtle and minor differences in otherwise almost similar clinical symptoms of organic and psychogenic disorders. For example, detailed and exact clinical observation reveals subtle differences between hysterical paralysis and organic paralysis. The regions, pointed out by **Marshall et al.** (orbitofrontal, anterior cingulate) in hysterical paralysis, are usually not affected in the case of organic paralysis. However, they may lead to abnormal top-down modulation of those regions usually affected and lesioned in organic paralysis. Hysterical paralysis can thus neither be "localized" in cortical regions nor in subcortical areas, whereas the direction of modulation may be specified in this regard.

R4. General methodology in neuropsychiatric research

Badgaiyan emphasizes the need for consideration of cognitive models as a starting point for psychiatric research by "delineating the underlying deficits of cognitive information processing," which should replace the focus on symptoms. The commentator replaces symptoms with cognitive models, because the same symptoms, as for example akinesia, may show different underlying neurocognitive disturbances. Drawing parallels between symptoms may therefore be problematic. However, in addition to similarities, we pointed out subtle differences between catatonic and Parkinsonic akinesia, which concerned not only subtle motor features (muscle tone), but also the predominantly subjective experience of akinesia. Total replacement of symptoms by cognitive models as a starting point, as implicitly suggested by Badgaiyan, should therefore be rejected, because then the subjective experience would be neglected. Especially in psychiatric disturbances, the role of subjective experience (i.e., phenomenology) is often neglected and regarded as superfluous in the search for a neurobiological substrate.

The present hypothesis of catatonia, in contrast, aims to demonstrate the necessity of considering subjective experience as a starting point for the generation of a neurobiological hypothesis (see Northoff et al. 1998; 2002b). Differences and/or special features of subjective experience must have a specific underlying physiological substrate. Accordingly, subjective experience and phenomenology may serve as a starting point for the generation of a neurobiological hypothesis. Cognitive models may thereby serve as an intermediate step, which may bridge the gap between subjective experience and symptoms, on the one hand, and physiological and anatomical substrates, on the other. In the present case of akinesia in catatonia, this intermediate position is supposed to be filled by reference to the model of Miall and Wolpert (1996).

In addition to their subjective experience in the first-person perspective, the symptoms themselves should be described objectively as accurately as possible from a third-person perspective. This point is raised by **Marshall et al.** Their question of recognition of other postures in other persons by catatonic patients is an interesting one and probably aims at the function of the observation system. Is there a specific dissociation between observation and awareness of one's own and other's movements in catatonia? Unfortunately, no data have been reported yet. Are catatonic patients "living statues," holding strange postures like the artists in Paris? Yes, they are "living statues," but they are not like these artists. These artists probably do show increased muscle tone and muscle strength to hold their postures. This is not the case in catatonic patients, who often show either normal or even decreased muscle tone. Moreover, they do not show abnormal muscle strength. Finally, moreover, unlike those artists in Paris, catatonic patients are not able to deliberately and voluntarily start and stop their postures, because they remain unaware of them. Accordingly, it seems rather unlikely that the artists in Paris, as observed by Marshall et al., may be "hidden and nondetected" catatonic patients that need lorazepam.

Moreover, complementing subjective experience and objective symptoms, the exact characterization of their occurrence should be considered. Are the symptoms state or trait markers? This point is raised by **Bearden & Monterosso**, and they are completely right in emphasizing it. As a result of the fact that imaging of patients in an acute catatonic state remains (practically and ethically) almost impossible, most pathophysiological findings concern the post-acute state, and therefore may be considered to be "trait markers" rather than "state markers." One may therefore concede that dysfunction in the reported regions may predispose a person for the development of catatonic symptoms, whereas they may not be considered as the anatomofunctional substrate of the symptoms themselves. Total dissociation between "state- and trait markers" with regard to their respective pathophysiological substrates subsequently cannot be excluded. The best way to generate a pathopysiological hypothesis about the symptoms themselves (i.e., "state markers") probably would be the development of an

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animal model. This also would allow for a distinction between the cause, compensatory mechanisms, co-occurrence, and consequences of the disease, as emphasized by **Savodnik** and **Shaw**, which, due to lack of available knowledge, is rather underemphasized or neglected in my hypothesis. Moreover, the meaning of the term "syndrome," as raised by **de Oliveira-Souza et al.** should be considered. I fully agree with their definition of catatonia as a syndrome as analogous to other syndromes in medicine such as fever or coma. Catatonia as a psychomotor syndrome may consequently be regarded as the "common final functional pathway" of various different causes which reflect the different (psychogenic and organic) origins of catatonia.

These considerations lead us to two more basic questions, the first one regarding the definition of a disease, and the second one regarding the time point, or timing, of a neuropsychiatric hypothesis.

The question regarding the definition of disease is raised by **Savodnik** and has long been debated in psychiatry. Can behavioral symptoms, as observed in psychiatry, be defined as a disease in the absence of a pathophysiological substrate providing the unifying umbrella? Or are they mere social constructs, as suggested by Savodnik? How shall the search for pathophysiological substrates proceed methodologically? Or does a neurobiology of psychiatry remain impossible altogether? Considering the recent advances in our understanding of higher brain function, the last question can almost certainly be denied. My own position on this issue is that an accurate and detailed account of both subjective experience and objective symptoms may serve as the starting point for the development of a pathophysiological hypothesis as intermediated by cognitive models (see also above). Such an approach presupposes a so-called first-person neuroscience (see Lutz et al. 2002; Northoff 2003), where first-person perspective data from subjective experience are directly included in analysis of third-person perspective data about physiological processes.

Instead of being considered as a "unified theory," the present hypothesis about catatonia rather may be regarded from a heuristic point of view, which may guide and focus neurobiological investigation. One may subsequently start with an often observed and preliminarily defined constellation and co-occurrence of specific symptoms and subjective experiences. Although the definition of a disease can be put on hold, this, however, does not prevent neurobiological research. Once pathophysiological data are obtained, the definition of these symptoms as a disease entity may ultimately be decided.

The question of the timing of the present hypothesis about catatonia has been raised by several authors: Isn't it too premature to develop a hypothesis about catatonia? **Bearden & Monterosso** mention the complexity of catatonia; **Bogerts** raises the problem of the lacking pathohistological correlate; **Marshall et al.** bring up the lack of detailed clinico-phenomenological knowledge; and **Miu & Olteanu** note the possibility of too many alternative explanations as obstacles to a hypothesis or theory of catatonia. Therefore, they argue, it is premature to develop such a hypothesis.

I agree with all commentators with regard to the points they raise, as already discussed above. However, I think that they may potentially presuppose a different and much stronger meaning of the term "hypothesis" than I originally intended. "Hypothesis" in the present sense points out a preliminary character, rather than a fixed and definitive character as, for example, in a "unified theory." Moreover, hypothesis in the present sense remains very much open to modification in the process of acquisition of further data. The hypothesis in the present sense can subsequently be regarded only as a starting point rather than an end point. As such, it serves as a coherent conceptualization of present and available data, which then may guide, focus, and restrict further neurophenomenological and neurobiological investigation, the results of which, in turn, may make modification of the initial hypothesis necessary. Accordingly, the present hypothesis may not be regarded as a "unified theory," which can be either verified or falsified. Instead, it may rather be modified, specified, and complemented in the course of further investigation.

The complexity of catatonia, as demonstrated nicely by **Bearden & Monterosso**, makes the development of a hypothesis, in this sense, necessary, because otherwise, the lack of any kind of conceptualization of the complexity of catatonia could make any further neurobiological approach doomed to failure. Moreover, the hypothesis may serve as a guide for restricting and limiting the focus of the search for a pathohistological correlate, as emphazised by **Bogerts**. In addition, the hypothesis may serve to raise novel clinico-phenomenological questions, as pointed out by **Marshall et al.**, which may provide us with a "new look" on "old and well known" clinical symptoms. Finally, the hypothesis attempts to reduce the number of alternative explanations, although, because of its preliminary character (being a starting point rather than an end point, see above), it remains unable to reduce them down to the possibility of either verification or falsification, as implicitly suggested by **Miu & Olteanu**. Accordingly, it may be too early and premature to formulate a "unified theory" of catatonia with consecutive verification and falsification. However, it may not be premature or too early to generate a hypothesis for focusing and guiding further and future neurobiological research into catatonia.

R5. Neurophilosophical implications

Hardcastle points out the importance of consciousness in the distinction between "psychological" and "biological," which, according to her, cannot be related to the distinction between cortical/top-down and subcortical/bottom-up. I certainly agree that consciousness (i.e., conscious experience) may be crucial to the distinction between "biological" and "psychological," at least at present. However, she neglects two other factors. First, conscious experience changes with dependence on the respective environment, and thus, on our state of knowledge. For example, diseases nowadays classified as "biological" (e.g., epilepsy) were regarded as "psychological" before their underlying neurobiological substrate had been revealed. Accordingly, the distinction between "biological" and "psychological" does not depend only on our conscious experience, but also on our environment.

Second, "experience" includes not only conscious experiences but also unconscious ones. There may be much more unconscious experience than conscious experience, that is, the latter may be only the "tip of the iceberg" (see also Northoff 2003). This is reflected in the relevance of psychodynamics as a method for the description and reve-

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lation of these unconscious experiences, which may be manifest in a variety of different clinical symptoms like, for example, hysterical paralysis. If these unconscious processes are so abundant and may even determine conscious experience, the search for their underlying neurobiological substrate may be at least as important as the one for conscious experience. One may consequently speak of an attribution of "overimportance" to consciousness as compared to unconsciousness (Northoff 2003). This "overimportance" may be reflected in the focus of both neuroscience and philosophy on consciousness, which, in part, may be a result of the methodological difficulty of getting access to unconsciousness. Any "theory of consciousness" should consequently be accompanied by a "theory of unconsciousness" with respect to both the underlying neurobiological substrate and the philosophical implications.

Platek & Gallup point out the implications of the present hypothesis for the neurobiology of the self. There are indeed disturbances of the self in catatonic patients, which we investigated in a separate study. We used the Repertory-Grid test, which asks for characterization and description of the person (i.e., self) and then allows for semiquantitative analysis (see Northoff et al. 2002b). The catatonic patients indeed showed severe alterations in their "self-constructs" as compared to noncatatonic depressive, manic, and schizoaffective patients, which, in addition, correlated significantly with alterations in orbitofrontal cortical signal intensity during emotional stimulation. These results, therefore, lend strong support to the assumption of alterations of the "self" in catatonic patients. Moreover, they point out the relevance of both the body and the right orbitofrontal cortex for the self. Platek and Gallup cite additional support for involvement of the right orbitofrontal cortex in the self by referring to studies of self-face recognition by Keenan et al. (2000). Moreover, they emphasize the role of the body and a kinaesthetic model and relate this to an orbitofrontal-parietal loop. There is further strong support for involvement of the body in the generation of the self. Disturbances in the body image may also lead to disturbances in the self (see Northoff 2001b; 2003). The body may consequently be regarded as a constitutive and necessary (though not sufficient) condition for the self of a person. It is this crucial role of the body for the self that may shed new perspectives on both the neurobiology and the philosophy of the self. Neurobiologically, it may guide further studies in the search for a correlate of the self. Catatonia, with its apparent alteration in the orbitofrontal-parietal connections, may serve here as a paradigmatic example for the close linkage between body and self. Although, philosophically, it may counter-argue models of the self, which, as derived from Descartes, are purely mental and consequently non-bodily. As a result, empirically more realistic and plausible models of the self may be developed in philosophy.

de Oliveira-Souza et al. suggest that the behavioral anomalies in catatonia reflect disturbance of the will in these patients – the symptoms of passivity and negativism oscillating between the two extremes of free or nonfree will. This is a very interesting suggestion and might shed some light on the neurobiological mechanisms underlying the will. Considering the findings in catatonia, the orbitofrontal cortex might play a crucial role in generating behavioral choices and alternatives which, on a phenomenal level, may be related with the will. One may distinguish the possibility of behavioral choices from the subjective experience or feeling of having a choice. The possibility of the latter is raised by the findings from Libet. Both components may not necessarily be subserved by the same neural correlates. Oliveira-Souza et al.'s suggestion might concern the behavioral choices rather than the subjective experience itself, but it might nevertheless be regarded as a good starting point into the neurobiological exploration of our will. I consequently fully agree with them that "catatonia opens a window into this as yet obscure landscape of the human mind."

Finally, the old issue of monism versus dualism is raised by **Marshall et al.** and **Hardcastle**. Marshall et al. speak of a "rejection of two-substance dualism," with the consequence being that all diseases display both physical and psychological symptoms; while Hardcastle rejects the distinction between "biological" and "psychological," because in the end, everything will be "housing in the brain" and thus be "biological" anyway. Aren't these two positions rather contradictory?

Before arguing in further detail, I would like to introduce a distinction that is often rather neglected in the current discussion. One should distinguish between the ontological, the epistemic, and the empirical level, which do not necessarily have to be in full accordance with each other; that is, they may dissociate from each other (see also Northoff 1999c; 2003). For example, **Marshall et al.** reject ontological dualism, though on an empirical level they still maintain some sort of dualism by claiming the co-occurrence of physical and psychological symptoms. In contrast, **Hardcastle** refers exclusively to the ontological level when she speaks of "biological" versus "psychological." Accordingly, both positions are not incompatible, because they both refer to different levels (i.e., ontological and empirical) while ostensibly rejecting any form of ontological dualism.

I agree with the rejection of ontological dualism, but I also accept empirical dualism. This empirical dualism may potentially be traced back to some sort of epistemic dualism. I already mentioned above that both first- and third-person perspective accounts should be considered in the exploration of neuropsychiatric diseases. At this point, I want to go even one step further by claiming that first- and third-person perspectives may have distinct (although potentially overlapping) neurobiological substrates (see Northoff 2003, for further details). Epistemic dualism leads subsequently to empirical dualism. However, since both perspectives may be related to the anatomo-functional (and nonmental) substrates of the brain, both epistemic and empirical dualism remain compatible with ontological monism (see Northoff 2000b; 2001a; 2003).

The conjunction between ontological monism, on the one hand, and epistemic and empirical dualism, on the other, may be well reflected in catatonia as a psychomotor syndrome (see also Northoff 1999). The most strange and bizarre forms of objective behavior in the third-person perspective can be related to the brain, and to the corresponding subjective experience in the first-person perspective which also may be related to the brain, but through different loops and circuits (i.e., lateral orbitofrontal-parietal circuit, medial orbitofrontal-striatal-pallidal circuit). Epistemic dualism between first- and third-person perspectives may thus be reflected in empirical dualism. However, both behavior and experience can be related principally to the same underlying ontological substrate (i.e., the physical stuff of the brain), which implies ontological monism. Catatonia may consequently be regarded as a paradigmatic example of

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the mind-brain relation, empirically, epistemically, and ontologically (see Northoff 1997b; 1999c).

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Letters "a" and "r" appearing before authors' initials refer to target article and response, respectively.

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