Brain Imaging in Catatonia: Current Findings and a Pathophysiologic Model

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ABSTRACT

Karl Ludwig Kahlbaum originally described catatonia as a psychomotor disease that encompassed motor, affective, and behavioral symptoms. In the beginning of the 20th century, catatonia was considered to be the motoric manifestation of schizophrenia; therefore, neuropathologic research mostly focused on neuroanatomic substrates (ie, the basal ganglia underlying the generation of movements). Even though some alterations were found in basal ganglia, the findings in these subcortical structures are not consistent. Recently, there has been a reemergence of interest into researching catatonia. Brain imaging studies have shown major and specific alterations in a right hemispheric neural network that includes the medial and lateral orbitofrontal and posterior parietal cortex. This neural network may be abnormally modulated by altered functional interactions between γ-aminobutyric acid (GABA)-ergic and glutamatergic transmission. This may account for the interrelationship among motor, emotional, and behavioral alterations observed in both clinical phenomenology and the subjective experiences of patients with catatonia. Such functional interrelationships should be explored in further detail in catatonia, which may also serve as a paradigmatic model for the investigation of psychomotor and brain function in general.

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INTRODUCTION

Catatonia was first described by Karl Ludwig Kahlbaum in 1874[1] as a psychomotor syndrome characterized by motor, affective, and behavioral alterations. Later, Kraepelin and Bleuler subsumed catatonia under the heading of *dementia praecox*,[2] considering catatonia to be a subtype of schizophrenia. Because of this characterization, catatonia was predominantly considered to be the motoric manifestation of schizophrenia. In contrast, affective and behavioral alterations were seen to be associated with schizophrenia rather than with catatonia itself. Neuropathologic studies have investigated the role of the basal ganglia in catatonia because these subcortical structures are involved in generating movements. For example, Kleist[2] considered catatonia to be an extrapyramidal disturbance.

In the last 15 years, interest in catatonia has reemerged, and various studies of its pathophysiology have been undertaken. The development of new imaging techniques has allowed the investigation of functional alterations in brain chemistry in this disorder. The purposes of this paper are: 1) to show the pathophysiologic findings in catatonia as seen with various imaging techniques; and 2) to develop a pathophysiologic hypothesis of catatonic motor symptoms based on these findings.

PATHOPHYSIOLOGIC FINDINGS IN CATATONIA

Neuropathologic Findings

The various pathophysiologic findings related to catatonia can be divided into neuropathologic, neurochemical, electrophysiologic, and functional imaging findings (Table 1). Table 2 summarizes the findings in which the neuropathology of the basal ganglia (the caudate nucleus, nucleus accumbens, and pallidum) have predominated.[3-8] Since these early studies yielded rather inconsistent results, they were never pursued. Furthermore, because these findings were made in patients with catatonic schizophrenia, it remains unclear whether these alterations are specifically related to catatonia itself or to schizophrenia. Although there are several case reports with isolated brain lesions in organic catatonia, there are no systematic studies to date that investigate the underlying neuropathology of catatonia in patients without schizophrenia.

Most of the neuropathologic studies cited here were performed on the brains of patients with catatonic schizophrenia who were never exposed to neuroleptics; therefore, these alterations in basal ganglia cannot be related to neuroleptic (antipsychotic) modulation. Nevertheless, findings should be considered rather cautiously, since the methods and techniques available when they were gathered may have produced artifacts.

Neurochemical Findings

Dopamine has been the neurotransmitter of primary interest in catatonia. In early studies, Gjessing[9] found increased dopaminergic (homovanillic acid and vanillic acid) and adrenergic/noradrenergic (norepinephrine, metanephrine, and epinephrine) metabolites in the urine of acute catatonic patients with periodic catatonia. In addition, he found correlations between vegetative alterations and these metabolites. He suggested a close relationship between catatonia and alterations in posterior hypothalamic nuclei.

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Recent investigations of the dopamine metabolite homovanillic acid in the plasma of 32 acute catatonic patients showed increased levels in the acute catatonic state,[10] particularly in those patients who responded well to lorazepam.[11] However, the dopamine agonist apomorphine exerted no therapeutic effect at all in acute catatonia patients.[12] These data suggest that the dopaminergic system may be hyperactive in acute catatonia. Nevertheless, the finding of hyperactivity of the dopaminergic system contradicts the observation that catatonia can be induced by neuroleptic medications (neuroleptic-induced catatonia), which suppress dopaminergic metabolism and, therefore, should be therapeutic. These contradictory data suggest that catatonia cannot be subsumed into one entity with regard to dopaminergic metabolism.

Recent interest in neurochemical alterations in catatonia has focused on γ-aminobutyric acid A ($GABA_A$) receptors because the $GABA_A$ receptor potentiator lorazepam is efficacious in 60% to 80% of all acute catatonic patients.[11,13,14] One study investigated iomazenil binding in 10 catatonic patients with affective or schizophrenic psychosis using single photon emission computed tomography (SPECT) scanning. Since iomazenil is a ligand that binds to the benzodiazepine subunit of the $GABA_A$ receptors without inducing any kind of alteration in the activity of the receptor, iomazenil binding reflects the number and function of $GABA_A$ receptors. The iomazenil binding in these 10 catatonic patients were compared with the iomazenil binding in 10 noncatatonic psychiatric controls with affective or schizophrenic psychosis and 20 healthy controls.[15] The catatonic patients showed significantly lower $GABA_A$ receptor binding and altered right-left relations in the left sensorimotor cortex compared with the two other groups. In addition, the catatonic patients exhibited significantly lower $GABA_A$ binding in the right lateral orbitofrontal and right posterior parietal cortex, correlating significantly with motor and affective (but not with behavioral) catatonic symptoms.

Movement-related cortical potentials (MRCPs) in catatonic patients both before and after lorazepam administration showed abnormal and inverse electrophysiologic reactivity.[16] In addition, all catatonic patients (even those in a postacute state) showed a paradoxical reaction to lorazepam, reacting with agitation rather than with sedation (as was the case in all psychiatric and healthy controls).[16] These studies indicate that catatonia may be associated with abnormalities in the GABAergic system, particularly the $GABA_A$ receptors,[17] and that these abnormalities may be central to the pathophysiology of catatonia.

The glutamatergic system, particularly the *N*-methyl-D-aspartate (NMDA) receptors, may also be involved in catatonia. Some catatonic patients who were nonresponsive to lorazepam have been successfully treated with the NMDA antagonist amantadine. Therapeutic recovery occurred rather gradually.[18] Such gradual improvement suggests that NMDA receptors may be secondarily involved in catatonia, whereas $GABA_A$ receptors appear to be primarily involved. This assumption is speculative, since neither the NMDA receptors nor their interactions with $GABA_A$ receptors have been investigated in catatonia.

In addition, the serotonergic (5-hydroxytryptophan [5-HT]) system may also play a role in the development of catatonia. Catatonia may be characterized by a dysequilibrium in the serotonergic system with upregulated $5\text{-}HT_{1A}$ receptors and downregulated $5\text{-}HT_{2A}$ receptors.[19] However, since there are no imaging studies with regard to the 5-HT system in catatonia, this hypothesis remains speculative.

In summary, neurochemical investigations suggest a central role for $GABA_A$ receptors in ▶

TABLE 1. PATHOPHYSIOLOGIC FINDINGS IN CATATONIA

Neuropathologic
Caudate nucleus
Nucleus accumbens
Pallidum
Substantia nigra pars compacta
Thalamus
Neurochemical
Dopamine
GABA
Glutamate
Serotonin
Electrophysiologic
EEG
Readiness potential
MRCPs
Structural and Functional Imaging
Right prefrontal cortex
Right orbitofrontal cortex
Right parietal cortex

GABA=γ-aminobutyric acid; EEG=electroencephalography; MRCP=movement-related cortical potential.

"...the dopamine agonist apomorphine exerted no therapeutic effect at all in acute catatonia patients. These data suggest that the dopaminergic system may be hyperactive in acute catatonia."

"...decreased perfusion in the right parietal cortex correlated significantly with motor and affective symptoms, as well as abnormally with visuospatial and attentional neuropsychological abilities."

the right orbitofrontal, right parietal, and right sensorimortor cortices in catatonia. There is evidence for involvement of the glutamatergic system; in particular, the NMDA receptors may be dysregulated by a primary abnormality in $GABA_A$ receptors. Dopaminergic and 5-HT transmission may be altered in catatonia as well, although there is only indirect evidence for the involvement of both systems in this disorder.

Structural and Functional Imaging Findings

A head computed tomography (CT) investigation of 37 patients with catatonic schizophrenia showed a diffuse enlargement in almost all cortical areas, particularly in frontal cortical regions compared with hebephrenic and paranoid schizophrenic patients.[20] A significant correlation between left frontotemporal areas and illness duration was also demonstrated in this study. Other authors[21] observed a cerebellar atrophy in catatonic patients, but this has been investigated neither systematically nor quantitatively.

Investigations of regional cerebral blood flow (rCBF) in catatonic patients with schizophrenia showed a right-left asymmetry in the basal ganglia with hyperperfusion of the left side in one patient,[22] a hypoperfusion in left medial temporal structures in two patients,[23] an alteration in right parietal and caudal perfusion in one patient,[24] a decreased perfusion in the right parietal cortices in six patients,[25] and a decreased perfusion in the parietal cortex with improvement following electroconvulsive therapy in one patient.[26] In addition, a systematic investigation of rCBF with SPECT imaging in 10 postacute catatonic patients with affective or schizophrenic psychosis showed decreased perfusion in the right posterior parietal and right inferior lateral prefrontal cortices compared with noncatatonic psychiatric controls with affective or schizophrenic psychosis and healthy controls.[27] Furthermore, decreased perfusion in the right parietal cortex correlated significantly with motor and affective symptoms, as well as abnormally with visuospatial and attentional neuropsychological abilities.

Only three functional imaging studies in catatonia have been performed to date due to the rareness of this disorder and difficulty in its investigation. Two catatonic patients with

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TABLE 2. NEUROPATHOLOGICAL FINDINGS
Neuropathologic investigations of the brains of patients with catatonia schizophrenia have shown alterations in the following regions[3-8]:

Caudate Nucleus
- Degeneration of large and small cells
- Lack of large cells
- Atrophied cells, increase of lipofuscin, decrease of cells, increase of Nissl substance
- Decreased diameter of interneurons

Nucleus Accumbens
- Degeneration of large and small cells
- Decrease of cells, increase of lipofuscin and Nissl substance
- Decreased diameter of Golgi type 2 neurons

Pallidum
- Atrophied cells, decreased cells, increase of lipofuscin
- Lack of pyramidal cells, abnormal mineralizations and gliosis
  - -Decreased volume of internal pallidum with normal volume of the external pallidum
  - -Significantly lower number of nerve cells in internal and external pallidum and substantia nigra pars compacta
- Decoloration without degeneration
- Reduced volume of the lateral part with normal cell number

Thalamus
- Decreased cell density in the mediodorsal nucleus

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schizophrenic psychosis were investigated using functional magnetic resonance imaging (fMRI) with a motor activation paradigm.[28] Immediately after receiving lorazepam, both patients were imaged while exhibiting posturing during performance of a motor task (sequential finger opposition). Catatonic patients showed a different pattern of lateralization, with alterations predominantly in the right motor cortex. This contrasts with findings in Parkinson's disease, because no alterations in supplementary motor areas (SMAs) were observed.

Based on subjective experiences showing intense emotional-motor interactions, an activation paradigm for affective-motor interaction was developed and investigated using fMRI and magnetoencephalography in 10 postacute catatonic patients with affective or schizophrenic psychosis, 10 noncatatonic psychiatric patients with affective or schizophrenic psychosis, and healthy controls.[29] The catatonic patients showed alterations in the right medial orbitofrontal/lateral orbitofrontal-prefrontal activation/deactivation pattern and in early magnetic fields (which may be localized in the medial prefrontal cortex) during negative emotional stimulation. Behavioral and affective catatonic symptoms correlated significantly with reduced orbitofrontal cortical activity, whereas motor symptoms correlated with premotor/motor activity. Negative emotional processing in the right medial orbitofrontal cortex may be particularly altered in catatonia, with an abnormal functional connectivity to the premotor/motor cortex.

A third study investigated auditory working memory in fMRI in six catatonic patients with affective or schizophrenic psychosis compared with noncatatonic psychiatric patients with affective or schizophrenic psychosis and healthy controls.[30] The catatonic patients showed significantly worse performance in working memory tasks and significantly decreased activity in the lateral orbitofrontal and premotor cortices compared with the other two groups. Behavioral catatonic symptoms correlated significantly with orbitofrontal and premotor cortical activity, whereas motor symptoms were related to left lateral prefrontal cortical activity.

In summary, imaging studies have demonstrated that the parietal cortex, particularly the right parietal cortex, may be involved in catatonia. In addition, the orbitofrontal cortex may be altered, as demonstrated using fMRI during working memory and emotional-motor activation. Imaging studies suggest that the network between the orbitofrontal cortex, premotor/sensorimotor cortex, and posterior parietal cortex in the right hemisphere may be altered in catatonia. This hypothesis remains speculative, since this model is based only on single findings, and the right orbitofrontal-sensorimotor-parietal network has not been investigated in its entirety during functional activation or in the acute catatonic state.

"Negative emotional processing in the right medial orbitofrontal cortex may be particularly altered in catatonia, with an abnormal functional connectivity to the premotor/motor cortex."

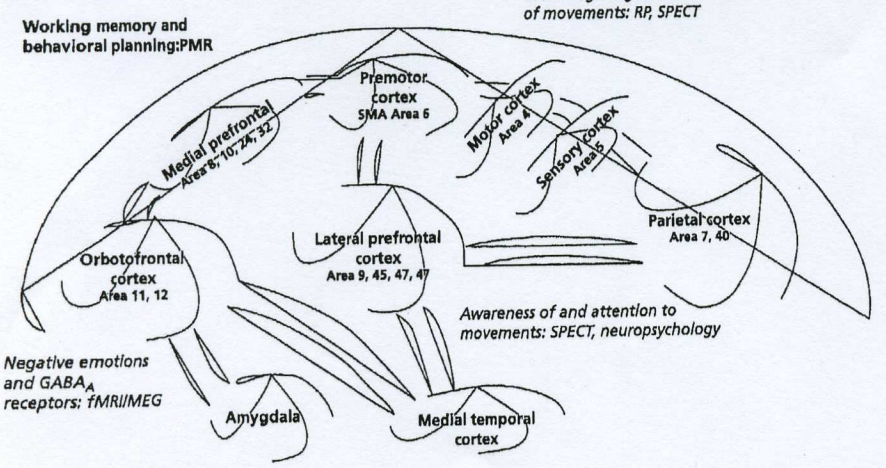

FIGURE 1. Pathophisiological findings in catatonia.
GABA=γ-aminobutyric acid; SPECT=single photon emission computed tomography; SMA=supplementary motor areas; fMRI=functional magnetic resonance imaging; MEG=magnetoencephalography.

"While patients with Parkinson's disease show distinct alterations in MRCPs, reflecting their difficulty in initiation of movements, the alterations in MRCPs of catatonic patients reflect their inability to fully execute and terminate movements."

Electrophysiologic Findings

Since single catatonic symptoms can be observed in patients with epileptic seizures, a relationship between catatonia and epilepsy has been postulated.[31] Therefore, a so-called nonictal paroxysmal subcortical dysrythmia and/or an alteration in α-rhythm have been theorized in catatonia. However, no systematic electroencephalographic (EEG) investigations have been performed in catatonic patients. Descriptive observations of EEG in systematic studies have yielded neither major nor minor abnormalities in EEG.[11,13]

Since catatonia is characterized by impressive motor features, MRCPs have been investigated in this disorder.[16] In this study, 10 postacute catatonic patients with affective or schizophrenic psychosis were investigated and compared with 10 noncatatonic psychiatric patients with affective or schizophrenic psychosis and 20 healthy controls. Catatonic patients showed a significantly delayed onset of late readiness and movement potential in central electrodes compared with the noncatatonic psychiatric patients and controls. This delayed onset correlated significantly with catatonic motor symptoms and movement duration. In addition, lorazepam led to significantly stronger delays of late readiness potential in frontoparietal electrodes in the catatonic patients compared with the other two groups.

While patients with Parkinson's disease show distinct alterations in MRCPs, reflecting their difficulty in initiation of movements,[32] the alterations in MRCPs of catatonic patients reflect their inability to fully execute and terminate movements. Therefore, unlike in Parkinson's disease, the primary deficit in catatonia appears to be one of termination rather than one of initiation.

A third study investigated auditory working memory using fMRI in six catatonic patients with affective or schizophrenic psychosis, noncatatonic psychiatric patients with affective or schizophrenic psychosis, and healthy controls.[30] The catatonic patients showed significantly worse performance in working memory tasks as well as significantly decreased activity in the lateral orbitofrontal and premotor compared with the other two groups. Behavioral catatonic symptoms correlated significantly with orbitofrontal and premotor cortical activity, whereas motor symptoms were related to left lateral prefrontal cortical activity.

Imaging studies have demonstrated that the right parietal cortex is altered in catatonia. Functional MRI findings during working memory and emotional-motor activation have demonstrated that the orbitofrontal cortex may also be altered. Thus, the network between the orbitofrontal, premotor/sensorimotor, and posterior parietal cortices in the right hemisphere may be particularly altered in catatonia. This hypothesis remains speculative, since it is based only on a single study finding. To date, the right orbitofrontal-sensorimotor-parietal network has not been investigated fully during functional activation or in the acute catatonic state.

PATHOPHYSIOLOGIC HYPOTHESIS IN CATATONIA

Early studies focused on the basal ganglia in patients without any exposure to neuroleptic medications. Current studies have focused on cortical regions, since the basal ganglia can only be partially visualized in imaging. Most catatonic patients investigated in imaging studies have been medicated. In the studies by Northoff,[15,16,27-29,33] medication use was controlled for by using noncatatonic psychiatric controls who received the same medication. Nevertheless, the suggestion that medication use led to secondary alterations in activation and deactivation patterns cannot be entirely excluded. Most imaging studies have investigated catatonic patients only in a postacute state, not in an acute state; therefore, the findings reflect a trait marker rather than a state marker.

Taking these methodologic limitations into account, the goal should be to develop a pathophysiologic hypothesis for catatonia, relying on clinical phenomenology and pathophysiologic findings. Since catatonic symptoms are quite complex, it must be presupposed that distinct categories of catatonic symptoms are subserved by distinct underlying neural networks. Therefore, it can be assumed that distinct pathophysiologic mechanisms and underlying neural networks exist for motor, affective, and behavioral symptoms in catatonia.[34]

Pathophysiology of Motor Symptoms

Motor symptoms in catatonia have been compared to those in Parkinson's disease. Since akinesia is a prominent symptom shared by both disorders, one expects similar alterations in MRCPs and fMRI findings dur-

ing the generation of movements. However, in contrast to Parkinson's disease,[32] catatonia can be characterized neither by alterations in the SMA nor in the early readiness potential, as related to function of SMA. Since the SMA itself does not appear to be primarily affected in catatonia, there seems to be no primary deficit in internal initiation of movements. This has been shown by the diminished ability of catatonic patients to respond to the ball test, which requires patients to catch, throw, stop, and kick a ball while in the acute catatonic state.[35,36]

Catatonic patients are well able to initiate movements, but they are apparently unable to terminate the movement once initiated in an appropriate way. In contrast to initiation neural networks, the study of underlying termination of movements has been neglected in the research to date. In healthy individuals, termination of movements is believed to involve the right posterior parietal cortex, because the registration and on-line monitoring of the respective spatial position of the movement may be of central importance for an appropriate termination.[33] Since findings in imaging and neuropsychology indicate a relationship between deficits in visual-constructive functions and decreased rCBF in the right posterior parietal cortex, alterations in the right posterior parietal cortical function may account for the deficit in termination of movements in catatonia that result in the motor symptom of posturing. This assumption is further supported by our findings in late MRCPs as well as fMRI, reflecting alterations in termination rather than initiation. If registration and on-line monitoring of the spatial position of movements (as related to right posterior parietal cortical function) are deficient in catatonia, this should lead to an unawareness of the respective spatial position. This is indeed the case since catatonic patients (unlike Parkinson's disease patients) suffer from anosognosia of posturing.[37]

This model of motor symptoms may explain the finding by Saponik et al[38] of catalepsy in 2.3% of patients with stroke. Catalepsy was demonstrated in the nonparetic side, and head CT scanning revealed ischemic infarcts in the middle cerebral artery territory in most cases.[38]

In summary, alterations in the right posterior parietal cortex—related to registration and on-line monitoring of the spatial position of movements and, thus, of termination—and GABAergic neurotransmission may be of primary importance in the pathophysiology of motor symptoms in catatonia (Figure 1). Involvement of the basal ganglia, as indicated by earlier neuropathologic findings remains unclear, since these are difficult to visualize in functional imaging.

Pathophysiology of Affective Symptoms

There are strong affective alterations in catatonia that cannot be associated entirely with an underlying affective psychosis.[1] This observation is supported by the therapeutic effectiveness of the anxiolytic lorazepam, as well as the subjective experiences of these patients who report strong, intense, and uncontrollable anxieties that make them immobilized by anxiety.[13,37] Consequently, the affective dimension should be included as one symptomatic category in catatonia,[34] although it may be difficult to distinguish it from the affective alterations related to the underlying diseases of either affective or schizophrenic psychosis.

Based on subjective experiences of the strong interrelationship between affective and motor symptoms, an emotional-motor activation paradigm has been developed and investigated in catatonia. In this paradigm, catatonic patients showed an abnormal activation/deactivation pattern in the medial orbitofrontal and lateral orbitofrontal/prefrontal cortices during negative emotional stimulation, exhibiting deactivation in the medial orbitofrontal region and activation in the lateral orbitofrontal/prefrontal cortex. This pattern is almost inverse to that observed in healthy controls. Since the medial orbitofrontal cortex is reciprocally connected with the amygdala, it is strongly involved, particularly in negative emotional processing.[39,40] Reduced and altered activation in the orbitofrontal cortex may account for affective alterations in catatonia as reflected by patients' inability to control and reduce negative emotional experiences.

In addition, we have found alterations in functional connectivity between the medial orbitofrontal and premotor/motor cortices in catatonic patients with affective or schizophrenic psychosis compared with noncatatonic psychiatric patients with affective or schizophrenic psychosis and healthy controls.[29] These findings suggest that a disturbed functional connectivity between the orbitofrontal and premotor/motor cortices may ▶

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be closely related to the generation of motor symptoms. The origin of motor symptoms in catatonia may stem from an alteration in the relationship between emotional and motor functions (ie, between the medial orbitofrontal and premotor/motor cortices). This hypothesis corresponds with the early characterization of catatonia as a psychomotor disease by Homburger,[41] as well as with the subjective experiences of these patients.

The activation/deactivation pattern in the medial and lateral orbitofrontal cortices during emotional stimulation appears to be modulated by GABAergic transmission, since use of the GABAergic agent lorazepam in healthy controls leads to a reversal of the activation/deactivation pattern in exactly the same way as has been observed in catatonic patients not taking lorazepam.[29] Alterations in the activation/deactivation pattern in the medial and lateral orbitofrontal cortices in catatonia may be related to GABAergic dysfunction. This accords with findings in SPECT imaging of benzodiazepine receptors, which show reductions in the right inferior prefrontal (ie, the orbitofrontal) cortex. In catatonia, decreased inhibition (reduced GABAergic transmission) renders the orbitofrontal cortex unable to exert its "gating" function on further prefrontal and frontal cortical areas so that prefrontal activity becomes dysregulated in its entirety. This may account for alterations in orbitofrontal-premotor/motor cortical connectivity. However, the assumption of a relationship between alterations in the activation/deactivation pattern in the medial and lateral orbitofrontal cortices (and reduced $GABA_A$ receptors) remains speculative, since there is no direct evidence for bilateral dependency.

Catatonia may be characterized by alterations in the medial and lateral orbitofrontal activation and deactivation patterns during emotional-motor stimulation. This extends to affective symptoms and (via a disturbance in orbitofrontal-premotor/motor functional connectivity) to motor symptoms. In addition, alterations in the activation/deactivation pattern in the medial and lateral orbitofrontal cortices may be closely related to alterations in GABAergic transmission. (Direct evidence for this, however, is still lacking.) Catatonia may be regarded as a true psychomotor disturbance, where alterations in neural networks underlying emotional functions are transformed into abnormal movements. Alterations in the amygdala and medial temporal structures may be of central importance in catatonia; however, the origin of disturbed activity patterns in the orbitofrontal cortex remains unclear (Figure 1), and their respective roles may differ depending on the primary psychiatric illness (affective or schizophrenic psychosis).

Pathophysiology of Behavioral Symptoms

In addition to motor symptoms, catatonic patients often show bizarre behavioral alterations. These predominantly include repetitive phenomena, such as echolalia, stereotypies, perseverations, etc. They may also exhibit disturbances of will, such as automatic obedience, negativisms, etc. Such phenomena imply that catatonic patients are no longer able to control their behavior either involuntarily or voluntarily in an appropriate manner.

Control of behavior implies on-line monitoring, which is usually regarded as a part of working memory. Behavioral investigation of working memory has shown severe deficits in catatonic patients that cannot be related to a reduced ability of storage but rather to severe deficits in on-line monitoring, since catatonic patients may be characterized by significantly more mistakes in both one-back and two-back tasks compared with noncatatonic psychiatric patients and healthy controls.[30]

In addition, fMRI has shown that catatonic patients may demonstrate significantly decreased activation in the lateral orbitofrontal and premotor cortices predominantly on the right side, correlating significantly with behavioral symptoms. Behavioral alterations in catatonia may be related to dysfunction in the lateral orbitofrontal cortex. Lesion studies in patients with orbitofrontal cortical lesions show repetitive phenomena and disturbances of will that are similar to those observed in catatonia. The medial and lateral orbitofrontal cortex may be subject to inverse and reciprocal kinds of activity (either activation or deactivation); these appear to be mutually dependent on each other.[39,40]

In addition, dysfunction in the lateral orbitofrontal cortex may be closely related to alterations in negative emotional processing in the medial orbitofrontal cortex, which may account for the close relationship between behavioral and affective symptoms in catatonia. Furthermore, the lateral orbitofrontal cortex is reciprocally connected anatomically

with the posterior parietal cortex via long association fibers. This relationship between the lateral orbitofrontal and posterior parietal cortices may account for the deficit in on-line monitoring of the spatial position of movements, which may be a central factor in the pathophysiology of posturing (characterized by an inability to terminate movements). In the working memory study,[30] lateral orbitofrontal cortical function is closely related to the ability of on-line monitoring, whereas posterior parietal cortical function accounts for spatial registration. Consecutive tasks requiring both on-line monitoring and spatial registration/spatial attention lead to coactivation in both the right lateral orbitofrontal/lower lateral prefrontal cortices, as well as the right posterior parietal cortex.[42]

Based on the author's findings, it appears that the alterations that are predominantly present in the right medial/lateral orbitofrontal and right posterior parietal cortices invoke dysfunction in the right medial/lateral orbitofrontal-posterior parietal cortical neural network during on-line monitoring of the spatial position of movements. This hypothesis remains speculative, since neither region (orbitofrontal or parietal) has been investigated within the same session in functional imaging or during termination of movements.

In contrast to the relationship between the medial and lateral orbitofrontal cortices, which appears to be primarily modulated by GABAergic (ie, inhibitory) transmission, the relationship between the lateral orbitofrontal and posterior parietal cortices must be primarily modulated by glutamatergic (ie, excitatory) transmission, since long association fibers are excitatory. The relationship between GABAergic and glutatamergic transmission may be altered in catatonia, which may account for the therapeutic efficacy of both lorazepam (a $GABA_A$ potentiator) and amantadine (an NMDA antagonist). Nevertheless, the exact mechanisms involved in catatonia remain unclear and cannot be supported by direct empiric evidence.

Since the orbitofrontal cortex has direct connections to the basal ganglia, particularly to the caudate nucleus, alterations in the orbitofrontal cortex may lead to consecutive modulation in the function of the basal ganglia. This direct orbitofrontal-caudate relationship may account for the generation of abnormal movements in relation to behavioral alterations as well as for earlier neuropathologic findings in the basal ganglia. Since the basal ganglia are difficult to investigate in functional imaging, this assumption remains to be proven.

In summary, behavioral alterations in catatonia may be closely related to deficits in behavioral controls, as reflected in a reduced capacity for on-line monitoring. This deficit in on-line monitoring may be subserved by altered and reduced activation in the lateral orbitofrontal and premotor cortex, as demonstrated in working memory during fMRI. Since the lateral orbitofrontal cortex is reciprocally connected to the posterior parietal cortex, right-hemispheric dysfunctional connections between both regions may account for deficits in on-line monitoring of the spatial position of movements and for deficits in the posterior parietal cortex (as observed in SPECT imaging) (Figure 1). Furthermore, the dysfunctional lateral orbitofrontal-posterior parietal connection may be modulated by interactions between GABAergic and glutamatergic transmission.

CONCLUSION

Catatonia was originally described by Kahlbaum as a psychomotor disease with a peculiar constellation of motor, affective, and behavioral symptoms. Early in this century, the conceptualization of catatonia was reduced to motor symptoms, and research focused consecutively on the corresponding anatomic structures of the brain (ie, the basal ganglia). In the following decades, research into catatonia decreased considerably. However, in the past 10–20 years, interest in catatonia has reemerged. It became clear that catatonia can neither be equated with motor symptoms, nor be subsumed exclusively under schizophrenia. Therefore, catatonia is currently considered to be a "psychomotor syndrome as a final common functional pathway of affective and schizophrenic psychosis" (and other medical and psychiatric diseases).[35]

Despite methodologic problems, modern imaging techniques allow for imaging of the neural networks that potentially underly catatonic symptoms. Brain imaging results indicate functional alterations in the neural network between the right medial and lateral orbitofrontal cortices and the right posterior parietal cortex. This may account for the close interrelationship between emotional and motor symptoms, as well as for the interrela-

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tionship between affective and behavioral symptoms observed in clinical symptoms reported in the subjective experience of these patients. This right hemispheric medial/lateral orbitofrontal-posterior parietal cortical network may be modulated by interactions between GABAergic and glutamatergic transmission. Consequently, research into the pathophysiology of catatonia should return to Kahlbaum's initial description of catatonia as a psychomotor disorder.

Investigation of such functional interrelationships may be of interest not only for catatonia itself, but because it also may provide a better understanding of the healthy brain. In this way, catatonia may be considered a paradigmatic model for psychomotor and brain research in general. CNS

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