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Catatonia and neuroleptic malignant syndrome: psychopathology and pathophysiology

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Summary. Catatonia was originally described as a psychomotor syndrome in the 19th century by Kahlbaum including motor, affective and behavioral symptoms. Later, at the beginning of the 20th century, catatonia was rather considered as the motoric manifestation of schizophrenia. Accordingly, neuropathological research focused predominantly on those neuroanatomical substrates, i.e. the basal ganglia being primarily involved in the generation of movements. Even though some authors observed minor alterations in the basal ganglia, consistent findings in these subcortical structures could not be obtained.

Since neuroleptics can induce catatonic-like symptoms i.e. neuroleptic malignant syndrome (NMS), there has been a recent re-emergence in clinical and scientific interest in catatonia. However, exact psychopathological and pathophysiological characterization of both NMS and catatonia remains unclear.

Clinically, catatonia and NMS show more or less similar motor symptoms i.e. akinesia. These may be accounted for by dysregulation in cortical-subcortical circuits between motor/premotor cortex and basal ganglia i.e. the so-called "motor loop". While in NMS the "motor loop" may be dysregulated by neuroleptic blockade of subcortical striatal D-2 receptors one may rather assume cortical gaba-ergic alteration in catatonia. The premotor/motor cortex and consecutively the "motor loop" may be dysregulated by gaba-ergic abnormalities in orbitofrontal cortex. Gaba-ergic cortical dysfunction may account for affective and behavioural abnormalities in catatonia which cannot be observed as such in NMS. Consequently, one may characterize catatonia as a cortical "psychomotor syndrome" while NMS may rather be regarded as subcortical "motor syndrome".

Keywords: Catatonia versus NMS, psychomotor verus motor, cortical versus subcortical, top-down versus bottom-up modulation.

Introduction

Catatonia was first described by Karl Ludwig Kahlbaum (1874) characterizing catatonia as a psychomotor syndrome with motor, affective and behavioral alterations. Later Kraepelin and Bleuler subsumed catatonia under dementia praecox considering catatonia as a motoric subtype of schizophrenia. While its affective and behavioral symptoms were rather neglected. Accordingly, catatonia was regarded as an extrapyramidal motor disorder with consecutive focus on the basal ganglia as the underlying neuropathological substrate (Kleist, 1943).

With the introduction of the neuroleptics, the incidence of catatonia declined (Northoff, 1997). However, neuroleptics are able to induce catatonic-like symptoms i.e. the neuroleptic-malignant syndrome (NMS) (Fink, 1996; Fricchione et al., 2000). Similar to catatonia and Parkinson's disease, the NMS shows strong motor symptoms with akinesia and rigidity. While the most bizarre catatonic motor symptom, posturing, is lacking in both NMS and Parkinson's. Moreover, unlike catatonia, the NMS neither shows affective symptoms with intense and uncontrollable emotions nor behavioural abnormaties like automatic obedience, negativism, stereotypies, etc. (Northoff, 1997).

Due to similarities in motor symptoms, there has been a recent debate whether catatonia and NMS might be regarded as "variants of the same disorder" (Fink, 1996, 2001; Fink and Taylor, 2001). If both NMS and catatonia reflect the same disorder, their respective underlying pathophysiological mechanisms should be more or less identical. In order to reveal the pathophysiological relationship between catatonia and NMS in further detail, we review psychopathology and pathophysiology in both syndromes. The first step consists in review of pathophysiological findings in catatonia and NMS. On the basis of these findings, we focus on the pathophysiological mechanisms potentially underlying the different kinds of symptoms in catatonia and NMS. It is concluded that psychopathological similarities and differences between catatonia and NMS may reflect distinct pathophysiological mechanisms which however strongly overlap with each other.

Pathophysiological findings

Neuropathological findings

Catatonia: Early postmortem studies in the preneuroleptic area revealed alterations in the basal ganglia (Caudate, N. accumbens, Pallidum). Since these early studies yielded rather inconsistent results, they were never pursued. These findings were made in patients with catatonic schizophrenia so it remains unclear whether these alterations are specifically related to either catatonia itself or schizophrenia. In contrast, neuropathologic investigations of the catatonic syndrome rather than on catatonic schizophrenia are currently not available. It should be noted that most of these studies were performed on brains of patients who were never exposed to neuroleptics. Even if these fndings have not been caused by neuroleptic medication, they

should nevertheless be considered rather cautiously since the methods and techniques available at that time may produce artifacts by themselves.

NMS: In NMS, single cases with alterations in anterior and lateral hypothalamic nuclei were reported (Horn et al., 1988; Jones and Dawson, 1989) whereas systematic postmortem studies about NMS are still lacking.

Structural and functional imaging findings

Catatonia: A computerized tomographic (Head CT) investigation of 37 patients with catatonic schizophrenia showed a diffuse enlargement in almost cortical areas and particular in frontal cortical regions compared to hebephrenic and paranoid schizophrenic patients (Northoff et al., 1999). A significant correlation of left fronto-temporal areas with illness duration could be found in catatonic patients. Other authors (Wilcox, 1991) observed a cerebellar atrophy in catatonic patients which however was neither investigated systematically nor quantitatively.

Investigations of regional cerebral blood flow (rCBF) in catatonia showed the following observations in single patients: (i) right-left asymmetry in basal ganglia with hyperperfusion of the left side in one patient (Luchins, 1989); (ii) hypoperfusion in left medial temporal structures in two patients (Ebert et al., 1992); (iii) alteration in right parietal and caudal perfusion in one patient (Liddle, 1994); (iv) decreased perfusion in the left prefrontal cortex in two patients with simple-sluggish catatonia (Lauer et al., 2001); (v) decreased perfusion in right parietal cortex in six patients with catatonic schizophrenia (Satoh et al., 1993); (vi) decreased perfusion in parietal cortex with improvement after ECT in one patient (Galynker et al., 1997).

A systematic investigation of rCBF in SPECT in 10 postacute akinetic catatonic patients showed decreased perfusion in right posterior parietal and right inferior lateral prefrontal cortex compared to non-catatonic psychiatric and healthy controls (Northoff et al., 2000). In addition, decreased perfusion in right parietal cortex correlated significantly with motor and affective symptoms as well as with visual-spatial and attentional neuropsychological abilities.

Only three functional imaging studies in catatonia have been reported thus far in catatonia.

Two catatonic patients were investigated in functional magnetic resonance tomography (fMRI) with a motor activation paradigm (Northoff et al., 1999). Immediately after receiving lorazepam both patients were imaged while exhibiting posturing during performance of the motor task (i.e. sequential finger opposition). Catatonic patients showed a different pattern of lateralization with alterations predominantly in right motor cortex. While no alterations in supplementary motor area (SMA) were observed.

Based on subjective experiences showing intense emotional-motor interactions (Northoff et al., 1998), an activation paradigm for affective-motor interaction was developed and investigated in fMRI and MEG (magnetoencephalography) in 10 postacute catatonic patients and 10 non-catatonic psychiatric and healthy controls (Northoff et al., 2002). Catatonic patients showed alterations in right medial orbitofrontal/lateral orbitofrontal-

prefrontal pattern of activation and deactivation during negative emotional stimulation. The early magnetic fields could no longer be localized in medial orbitofrontal cortex, as in both control groups, but rather in medial prefrontal cortex. While behavioral and affective catatonic symptoms correlated significantly with reduced orbitofrontal cortical activity motor symptoms were rather related with premotor/motor activity. Moreover, functional connectivity between orbitofrontal and premotor/motor cortex was found to be abnormal in catatonia.

A third study investigated auditory working memory in fMRI in 6 catatonic patients comparing them with psychiatric and healthy controls (Leschinger et al., 2002). Catatonic patients showed worse performance in the working memory task and decreased activity in lateral orbitofrontal and premotor cortex compared to both psychiatric and healthy controls. Behavioral catatonic symptoms correlated significantly with orbitofrontal and premotor cortical activity whereas motor symptoms were rather related to left lateral prefrontal cortical activity.

NMS: Neither structural nor functional imaging results are currently available for NMS.

Electrophysiological findings

Catatonia: Since single catatonic symptoms can be observed in patients with epileptic seizures a relation between catatonia and epilepsy has been postulated (Louis and Pflaster, 1995). Therefore a so-called "non-ictal paroxysmal subcortical dysrythmia" and/or an alteration in alpha-rhythm has been postulated in catatonia. However, systematic investigation of EEG in catatonic patients has not been reported yet. Descriptive observations of EEG in systematic studies did not yield any major or minor abnormalities in EEG (Rosebush et al., 1990; Northoff et al., 1995).

Since catatonic patients show strong motor symptoms, movement-related cortical potentials (MRCP's) have been investigated (Northoff et al., 2000). Ten postacute catatonic patients were investigated and compared with 10 non-catatonic psychiatric and 20 healthy controls. Catatonic patients showed a significantly delayed onset of late readiness and movement potential in central electrodes compared with psychiatric and healthy 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 fronto-parietal electrodes in catatonics than in psychiatric and healthy controls. In contrast, Parkinson's patients show rather alterations in the early readiness potential of the MRCP's (Jahanshahi et al., 1995).

NMS: There are no reports of investigation of MRCP's in patients with NMS. However, due to similarity in motor symptoms between NMS and Parkinson's disease, one would expect similar alterations in MRCP's as in Parkinson's disease. Accordingly, one may hypothesize alterations in the early readiness potential since this part seems to be predominantly determined by dopamine. While the late readiness potential seem to be rather modulated by GABA (Jahanshahi et al., 1995; Northoff et al., 2000).

Neurochemical findings

Catatonia: In early studies, Gjessing (1974), observed 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 reported correlations between vegetative symptoms and altered metabolites. Recent investigations of a 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 catatonic patients responding well to lorazepam (Northoff et al., 1995).

These data suggest hyperactivity in the dopaminergic system in catatonia. Accordingly, dopamine agonists like apomorphine exerted no therapeutic effect at all in acute catatonic patients (Starkstein et al., 1996). However, the assumption of dopaminergic hyperactivity in catatonia may be contradictory with the observation of induction of catatonia by neuroleptics. Neuroleptics, especially typical substances like, for example, haloperidol, can induce catatonic-like pictures, a so-called "neuroleptic-induced catatonia" (see Fricchione et al., 2000; Fink, 2001; Fink and Taylor, 2001). Since neuroleptics block dopaminergic i.e. D-2 receptors one would rather assume hypoactivity in the dopaminergic system. F-18-Dopa PET investigation in two catatonic patients revealed however no major abnormalities in striatum and putamen. Exact functional status of the dopaminergic system in catatonia remains therefore unclear. One may distinguish between the different dopaminergic systems i.e. mesocortical/limbic, nigrostriatal and tubero-infundibular as well as between the distinct dopaminergic receptors (D-1, D-2, D-3, D-4, D-5) which may be affected in different ways respectively.

Since the GABA-A receptor potentiator lorazepam is therapeutically efficacious in 60–80% of all patients (Bush et al., 1996; Rosebush et al., 1990; Northoff et al., 1995), gaba-ergic neurotransmission may be altered in acute catatonia.

One study investigated the density of GABA-A receptors in 10 catatonic patients with 123I-Iomazenil SPECT and compared them with 10 non-catatonic psychiatric controls and 20 healthy controls (Northoff et al., 1999). Catatonic patients showed significantly lower GABA-A receptor binding and altered right-left relations in left sensorimotor cortex compared with psychiatric and healthy controls. In addition, catatonic patients could be characterized by significantly lower GABA-A binding in right lateral orbitofrontal and right posterior parietal cortex correlating significantly with motor and affective catatonic symptoms.

Furthermore, movement-related cortical potentials in catatonic patients showed abnormal and inverse electrophysiological reactivity to lorazepam (Northoff et al., 2000). Analogously, abnormal orbitofrontal cortical activity during negative emotional stimulation (see above) was "normalized" after stimulation with lorazepam in catatonic patients being similar to the one in healthy controls without lorazepam (Northoff et al., 2002; Richter et al., 2002). While healthy controls with lorazepam showed the same orbitofrontal

pattern as catatonic patients without lorazepam. Clinically, catatonic patients show a "paradoxical" reaction to lorazepam even in the postacute state. Unlike non-catatonic psychiatric and healthy controls, who become sedated, catatonic patients show rather increased agitation. Accordingly, one may assume alteration in the cortical gaba-ergic system in catatonia (see also Carroll, 1999).

In addition to dopaminergic and gaba-ergic transmission, there is some indirect evidence for involvement of glutamatergic and serotoninergic systems in catatonia. The NMDA-receptor antagonist amantadine has been shown to be therapeutically successful in catatonic patients non-responding to lorazepam (Northoff et al., 1997). Due to induction of catatonic syndrome by serotoninergic drugs, involvement of the serotoninergic system with a dysequilibrium between up-regulated 5-HT1a receptors and down-regulated 5-HT2a receptors has been assumed (Lauterbach, 1998; Carroll, 1999). However, exact mechanisms remain unclear.

NMS: There are several lines of evidence for down-regulation of striatal dopamine i.e. D-2 receptors in NMS. First, typical neuroleptics with a high affinity for striatal D2-blockade cause NMS significantly more often than those i.e. atpyical neuroleptics with low affinity to D2-receptors (Mann et al., 2000). Second, systematic studies observed significantly decreased level of homovanillic acid (HVA) in patients with NMS (Nisijima and Ishiguro, 1995). Third, a single case study observed significantly decreased D-2 binding in the striatum (Jauss et al., 1996). One may consequently assume down-regulation of striatal D-2 receptors in NMS. Accordingly, dopaminergic agonists like, for example, apomorphine, have been shown to be therapeutically successful in NMS (Wang and Hsieh, 2001).

While there is strong evidence for involvement of striatal D-2 receptors in NMS neither investigations about the other dopaminergic systems (mesolimbic/cortical, tubero-infundibular) nor on other dopamine receptors (D-1, D-3, D-4, D-5) have not been reported so far.

It should however be noted that atypical neuroleptics, which do not show a strong striatal D-2 blockade, can induce NMS as well (Huang, 2001; Philibert et al., 2001). Accordingly, other transmitter systems like, for example, serotonine, may be involved in NMS as well (see Fink, 2001; Fink and Taylor, 2001; Carroll, 1999). Similar to catatonia, patients with NMS can be treated successfully with lorazepam, ECT and amantadine (Fink, 2001; Fink and Taylor, 2001), suggesting a role for gaba-ergic and glutamatergic transmission in pathophysiology of NMS.

Pathophysiological mechanisms

Motor symptoms

Catatonia: Similar to Parkinson's disease, catatonia can be characterized by akinesia. However, unlike patients with Parkinson's disease, catatonic patients show posturing keeping their limbs and/or head in a position against gravity without being consciously aware of it (Northoff et al., 1998).

Though they show akinesia, catatonic patients are still able to initiate and execute movements. For example, even in the acute akinetic state with mutism and posturing they remain able to play ball both catching and throwing it (Northoff et al., 1995). The supplementary motor area (SMA) being crucially involved in the internal initiation of movements (Jahanshai et al., 1995) may thus be basically intact in these patients. This would be in accordance with imaging findings showing no hypofunction in SMA (Northoff et al., 1999).

In contrast to initiation, termination of movements may be abnormal in catatonic patients. They can initiate and execute the movements necessary for catching or throwing the ball while remaining in that position without returning to the "normal" position (Northoff et al., 1995). The ability to terminate movements may be closely related with the recognition of the actual spatial position from which the respective movement shall be terminated. Spatial coordination of the own body parts is subserved by the right posterior parietal cortex (Pfennig et al., 2002; Jueptner et al., 1997) as can be observed in patients with neglect showing anosognosia of their own body. Catatonic patients do indeed show "motor anosognosia" i.e. they remain unaware of their postures (Northoff et al., 1998) as well as deficits in visual-constructive abilities specifically related with right posterior parietal cortex (Northoff et al., 1999). Moreover, decreased regional cerebral blood flow in right posterior parietal cortex has been observed in catatonia (Northoff et al., 2000). Alteration in right posterior parietal cortical function with consecutive deficits in termination may thus be considered as crucial for posturing as the most bizarre motor symptoms in catatonia.

NMS: Similar to Parkinson's disease, patients with NMS show akinesia and cog-wheel rigidity as well as a deficit in the internal initiation of movements. Unlike catatonia, these patients do neither show posturing nor motor anosognosia. Analogous to Parkinson's disease, one may therefore assume deficits in SMA and striatal dopaminergic receptors while the right posterior parietal cortex may remain intact. Unfortunately, neither systematic imaging studies about cortical motor function in NMS nor about striatal D-2 receptors are available at present.

Despite the lack of direct empirical evidence, there may nevertheless be some indirect empirical support. While inducing NMS, neuroleptics, especially typical neuroleptics, show a strong blockade of striatal D-2 receptors. Analogous to Parkinson's disease (Jahanshahi et al., 1995), blockade in striatal D-2 receptors may consecutively lead to dysregulation in striatal-premotor/motor cortical connections and thus in the "motor loop" (Mastermann and Cummings, 1997). The crucial role of striatal D-2 receptors would be supported by the following: (i) higher incidence of NMS in typical neuroleptics than in atypical neuroleptics the latter inducing less blockade of striatial D-2 receptors; (ii) successful treatment of NMS with the dopamine agonist apomorphin (Wang and Hsieh, 2001).

It should however be noted that even atypical neuroleptics like clozapine or olanzapine (Huang, 2001; Philibert et al., 2001) can induce NMS though with much lower incidence. While atypical neuroleptics show very low or almost absent blockade of striatal D-2 receptors they act predominantly on

other receptor types like, for example, glutamatergic (NMDA, AMPA), serotoninergic (5-HT2a, 5-HT1b) or adrenergic/noradrenergic (alpha/beta) receptors. Accordingly, one may speculate that these receptors may potentially modulate and thus dysregulate the "motor loop" in the same way as striatal D-2 receptors.

In summary, motor symptoms in catatonia may be related with dysfunction in termination of movements and right posterior parietal cortex. While motor symptoms in NMS may rather be accounted for by deficits in the internal initiation of movements and blockade of striatal D-2 receptors with consecutive cortical-subcortical dysregulation in the "motor loop".

Affective symptoms

Catatonia: Catatonic patients show strong, intense and uncontrollable emotions. They often report about anxieties which they are no longer able to control anymore i.e. they are "immobilized by anxiety" (Rosebush et al., 1990; Northoff et al., 1998). Though most often they experience anxieties catatonia may also be induced by experience of uncontrollable joy and happiness. For example, a patient became catatonic each time (3 times) she fall in love (Northoff, 1997). While being unaware of their motor symptoms (see above), catatonic patients are fully aware of their emotional disturbances (Northoff et al., 1998). The crucial role of emotions in catatonia is further underlined by the therapeutic efficacy of gaba-ergic substances like lorazepam showing anxiolytic properties (Rosebush et al., 1990; Northoff et al., 1995). Gaba-ergic involvement in catatonia is further supported by therapeutic efficiacy of electroconvulsive therapy (ECT) which is supposed to affect gaba-ergic transmission (Ungvari et al., 2001; Fink and Taylor, 2001).

The orbitofrontal cortex, especially the medial part, has been shown to be strongly involved in emotional processing (Drevets and Raichle, 1998; Northoff et al., 2000). Moreover, activation and deactivation in medial orbitofrontal cortex during emotional processing may be modulated by gaba-ergic substances like lorazepam (Northoff et al., 2002).

In accordance with their strong emotional symptoms, catatonia can indeed be characterized by major deficits in medial orbitofrontal cortex during negative emotional processing (Northoff et al., 2002). Furthermore, lorazepam "normalizes" these deficits so that orbitofrontal cortical activity in catatonic patients after lorazepam resembles the one of healthy subjects without lorazepam (Richter et al., 2002). The crucial role of gaba-ergic transmission is further supported by findings of decreased density in gaba-ergic binding in right orbitofrontal cortex in catatonia (Northoff et al., 1999).

The orbitofrontal cortex is closely and directly connected with the premotor/motor cortex. Functional connectivity between orbitofrontal and premotor/motor cortex was found to be significantly changed i.e. decreased in catatonic patients compared to psychiatric and healthy controls (Northoff et al., 2002). One may characterize catatonia therefore by altered cortico-cortical interaction. Accordingly, one may assume alteration in transformation between emotional and motor function with secondary dysregulation

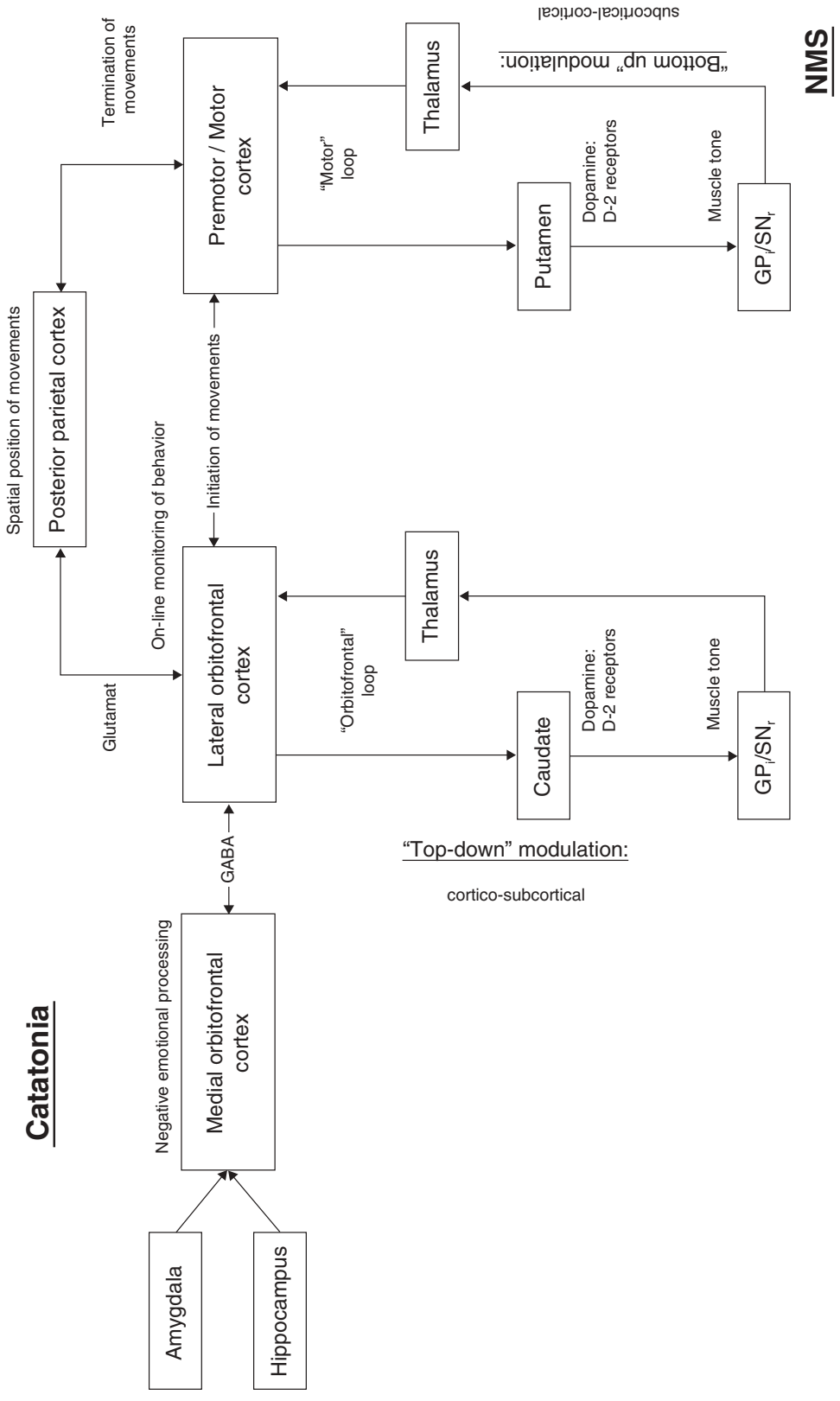

Fig. 1. Pathophysiological mechanisms in catatonia and Neuroleptic Malignant Syndrome (NMS)

of the latter by the former. As such catatonia may be accounted for as a cortical "psychomotor disease" (Homburger, 1932) which would be in full accordance with the original description by Kahlbaum (1878).

NMS: Unlike catatonic patients, anxiety in patients with NMS is not as intense and uncontrollable. It may rather be regarded as a reaction to the awareness about their motor immobility. Being aware of their akinesia and immobility the patients become anxious as it can also be observed in Parkinson's disease (Northoff et al., 1998).

Accordingly, no observation of alterations in cortical regions involved in emotional processing like, for example, the orbitofrontal cortex, has been reported so far in NMS. While the striatum and other basal ganglia may modulate emotional processing they are apparently not primarily involved in emotional processing by themselves. Via their subcortical-cortical connections (Mastermann and Cummings, 1997) they may nevertheless secondarily modulate prefrontal cortical regions and other non-dopaminergic transmitter systems (serotonine, glutamate, etc.) participating in emotional processing. "Bottom-up modulation" may thus potentially account for emotional reactions accompanying akinesia and immobility in NMS.

In summary, strong, intense and uncontrollable emotional symptoms in catatonia may be accounted for by dysfunction in medial orbitofrontal cortex and gaba-ergic neurotransmission. In contrast, emotional reactions in NMS may rather be related with altered "bottom-up modulation" dopaminergic striatal deficits modulating subcortical-cortical connections in an abnormal way. While catatonia may be regarded as a cortical "psychomotor syndrome" NMS may rather be characterized as a cortical "motor syndrome".

Behavioral symptoms

Catatonia: Catatonia can be characterized by bizarre behavioural abnormalities including perseveration, stereotypies, mitmachen/gehen, automatic obedience, negativism, etc. Many of these behavioural symptoms may functionally be related with a lack of inhibition of either internally initiated (perseveration, stereotypies) or externally observed (mitmachen/gehen, automatic obedience) behavioural patterns.

The lateral orbitofrontal cortex has been shown to be closely related with behavioural inhibition and affective control (Dias et al., 1996; Drevets and Raichle, 1998). In accordance with lack of both behavioural inhibition and affective control (see above), catatonic patients show major deficits in lateral orbitofrontal cortical activity during working memory (Leschinger et al., 2002). Since working memory requires on-line monitoring and manipulation of behavioural patterns its dysfunction may be somehow related with behavioural symptoms. Accordingly, significant correlations between behavioural symptoms, working memory deficits and decreased lateral orbitofrontal cortical activity were observed (Leschinger et al., 2002).

The lateral orbitofrontal cortex is closely connected with the posterior parietal cortex which by itself may be associated with motor symptoms in catatonia (see above). Since cortico-cortical connections are glutamatergic

therapeutic efficacy of glutamatergic substances like amantadine, an NMDA-antagonist (Northoff et al., 1997, 1999), may be accounted for by modulation of these connections. Moreover, the lateral orbitofrontal cortex is closely connected with the ventral striatum being part of the "orbitofrontal loop" (Mastermann and Cummings, 1997). Even if neuroleptics may predominantly block striatal D-2 receptors they may nevertheless indirectly modulate neural activity in orbitofrontal cortex via the "orbitofrontal loop". Clinically, this may be reflected in the symptomatic overlap between catatonia and NMS as well as in possibility of induction of catatonia by neuroleptics i.e. so-called neuroleptic-induced catatonia (Koch et al., 2000; Fink, 2001; Fink and Taylor, 2001).

NMS: Unlike catatonia, patients with NMS do not show major behavioural abnormalities. Accordingly, deficits in lateral orbitofrontal cortex in NMS have not been reported so far. However, similar to lethal catatonia (Fink, 2001; Fink and Taylor, 2001; Mann et al., 2001), NMS can be characterized by strong vegetative abnormalities.

Dopamine receptors regulate function in midbrain (hypothalamus) and brainstem nuclei subserving regulation of vegetative function like, for example, temperature. Blockade of these dopamine-receptors by neuroleptics may thus induce vegetative alterations including malignant hyperthermia as they can be observed in NMS. Moreover, midbrain and brainstem nuclei are directly connected with the medial orbitofrontal cortex the latter top-down-modulating the former. Dysfunction in medial orbitofrontal cortex may thus induce alteration in top-down modulation of midbrain/brainstem resulting in vegetative abnormalities like, for example, malignant hyperthermia, as it can be observed in lethal catatonia.

In summary, bizarre behavioural abnormalities in catatonia may be related with deficits in behavioural inhibition and lateral orbitofrontal cortical activity. Vegetative abnormalities may be related with alteration in midbrain and brainstem nuclei. These may be either abnormally regulated by blockade of dopamine receptors as in NMS. Or these subcortical structures may become abnormally top-down modulated by medial orbitofrontal cortical dysfunction as it may be the case in lethal catatonia.

Conclusion

Catatonia was originally described in the 19th century by Kahlbaum as a psychomotor disease with a peculiar constellation of motor, affective and behavioral symptoms. Early in the 20th century catatonia was often reduced to motor symptoms so that research focused predominantly on basal ganglia associated with generation of movements. Introduction of neuroleptics led to a yet unexplained decline in the incidence of catatonia while neuroleptic malignant syndrome (NMS) emerged. Relationship between catatonia and NMS remains however unclear in both regards psychopathologically and pathophysiologically.

Recently, catatonia and NMS have been regarded as "variants of the same disorder" (Fink, 1996, 2001; Fink and Taylor, 2001; Fricchione et al., 2000).

However, consideration of both psychopathology and pathophysiology reveals rather differences between catatonia and NMS though there are some clinical similarities as well.

Motor symptoms reflecting akinesia with posturing in catatonia may be accounted for by right posterior parietal cortical dysfunction. While akinesia without posturing in NMS may rather be related to blockade of D-2 receptors in striatum with consecutive dysregulation of subcortical-cortical connections in the "motor loop".

Intense and uncontrollable affective symptoms in catatonia may be accounted for by deficits in medial orbitofrontal cortical activity and gaba-ergic transmission. While in NMS affective symptoms must rather be regarded as an emotional reaction to akinesia which may be subserved by abnormal subcortical-cortical modulation.

Bizarre behavioural symptoms in catatonia may be related with dysfunction in lateral orbitofrontal cortex. Lateral orbitofrontal cortical dysfunction may induce abnormal top-down modulation in both ventral striatum and midbrain/brain stem nuclei potentially accounting for vegetative alterations in neuroleptic-induced catatonia and lethal catatonia respectively. While in NMS blockade of dopamine receptors in midbrain/brainstem may account for vegetative alterations.

These psychopathological and pathophysiological differences should be taken into account in consideration of catatonia and NMS. Accordingly, catatonia may be characterized as cortical "psychomotor syndrome" while NMS may rather be regarded as a subcortical "motor syndrome". Despite these differences there may nevertheless be some clinical similarities as, for example, both showing akinesia, vegetative symptoms and therapeutic efficacy of lorazepam and ECT. These clinical similarities may potentially be accounted for by functional overlaps between "top-down modulation" and "bottom-up modulation" reflecting interaction between prefrontal cortex and basal ganglia. In addition to elucidation of pathophysiology in NMS and catatonia, comparison between both syndromes may therefore contribute to our knowledge about the various kinds of modulation between cortical and subcortical structures.

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