REVIEW

Neurobiology of catatonia

Rajmohan V¹, Mohandas E²

¹MES Medical College, Perintalmanna, Kerala, ²Sun Hospital and Research Centre, Thrissur, Kerala, India

Correspondence to: rajgiggsmohan@yahoo.com

Abstract
The neural underpinnings of this condition despite hundred plus years of research has not revealed a clear picture. Neuroimaging data suggests possible involvement of certain brain areas in catatonic syndromes. Multiple neurotransmitter systems may also be involved as pharmacological agents targeted against specific neurotransmitter systems result in improvement of catatonic symptoms. The orbitofrontal cortex (OFC) is probably the key structure mediating the symptoms of catatonia and its interaction with the dorsolateral prefrontal cortex (DLPFC) and the premotor loop is postulated to cause the affective, behavioural and motor symptoms of catatonia. The neurotransmitter abnormalities in catatonia include the low GABA A activity (in the OFC), low D2 activity (striatal D2), the alterations in NMDA glutamatergic system, (increased posterior parietal glutamate) and a high 5HT1A activity. The neurotransmitter abnormalities in catatonia have provided valuable clues to the effective treatment of catatonia.

Introduction
Catatonia was first described by Kahlbaum in his monograph ‘Die Katatonic oder das Speannahgsirresein’ (Catatonia or Tension Insanity) in 1874. He considered catatonia as a psychomotor syndrome with motor, affective and behavioural features, most
commonly associated with affective disorder. Kraeplin and Bleuler subsequently identified this phenomenon with motor symptoms occurring exclusively in schizophrenia and ignored other dimensions of catatonia especially the affective symptoms. Current concept of catatonia is one of a complex psychomotor syndrome that manifests across a wide range of neuropsychiatric conditions. The neural underpinnings of this syndrome despite hundred plus years of research has not revealed a clear picture. Neuroimaging data suggests possible involvement of certain brain areas in catatonic syndromes. Multiple neurotransmitter systems may also be involved as pharmacological agents targeted against specific neurotransmitter system result in improvement of catatonic symptoms. Despite the progress made in research there is still much debate about the nosologic status, the diagnostic criteria, the assessment methods, the treatment and the neural correlates of catatonia.

**Neuroanatomy**

**Neuropsychological explorations**

Neuropsychological studies have shown involvement of right parietal cortex as catatonics perform poorly in the visual-object-space and perception test (VOSP) compared to psychiatric and healthy controls. This ability to process spatial position of movements is required for termination of movements, a defect of which results in posturing. Orbitofrontal cortical dysfunction has also been suggested by neuropsychological data.

**Electrophysiological evidence**

The generation of movements involves the phases like ‘Plan/strategy’, ‘Initiation’ and ‘Execution’. The investigation using movement related cortical potentials (MRCP) shows that catatonia is characterized by a preserved ability of ‘Plan/strategy’, ‘Initiation’ and ‘Execution’. Further MRCP studies have shown that initiation is normal in catatonics whereas the initiation of termination is delayed. Termination of movements as measured with MRCP in catatonics show a significant delay of MRCP in the parietal electrodes. The termination deficit may reflect a delay in the online monitoring of spatial position of movements by right parietal cortex.

**Neuroimaging in catatonia**

**i) Structural imaging**

Significant cortical enlargement especially the left frontoparietal area has been cited in catatonics. Although temporal cortical enlargement is present in the schizophrenic subtypes, prefrontal and parietal enlargement have been noted in catatonic schizophrenia.

**ii) Functional imaging**

Regional cerebral blood flow (rCBF) studies in catatonia have shown right left asymmetry in basal ganglia, hypoperfusion of left medial temporal area, and hypoperfusion in the right parietal cortex. Further rCBF using SPECT shows
decreased perfusion right posterior parietal and right inferior lateral prefrontal cortex. The right parietal hypoperfusion also correlates significantly with impaired visuospatial ability and the motor and affective symptoms in catatonia. In addition to this, it is observed that isolated lesions of the right parietal cortex result in posturing.  

Functional imaging during motor activation shows decreased activation of the contralateral motor cortex with normal supplementary motor area activation during performance with right hand (in right handed person). When a right handed person performs actions with the left hand, there is an increased activation of the ipsilateral motor cortex. Imaging studies also show deficits in the orbitofrontal activation during negative emotional states. There is neuroimaging evidence that the orbitofrontal connectivity with the motor/premotor cortex is abnormal in catatonic. The right orbitofrontal activation during negative emotional stimulation is altered and the activation is shifted to the anterior cingulate and medial prefrontal cortex. There is evidence that behavioral and affective symptoms of catatonia correlates with reduced orbitofrontal activity and the motor symptoms correlate with motor/premotor activity. Catatonic patients show a significant decrease in right lateral orbitofrontal (including ventrolateral prefrontal cortex) activation during working memory tasks. This deficit in working memory maybe related to a deficit in the online monitoring of spatial position of movements.  

**Neurochemistry**

*i) GABA*

The efficacy of lorazepam in allaying the symptoms of catatonia has increased the focus of interest on GABA in catatonia. SPECT study of Iomazenil binding which reflects the number and function of GABA-A receptors have been conducted in catatonics. The study shows significantly lower binding of GABA-A in the right orbitofrontal cortex and right posterior parietal cortex. There is also a significantly lesser GABA-A binding in the left sensorimotor cortex in catatonic patients. Study of catatonia with functional magnetic resonance imaging (fMRI) and magnetoencephalogram (MEG) shows that prefrontal cortical activation/deactivation pattern during negative emotion is modulated by GABA-A receptors. It is also noted that lorazepam shortens the MRCP delay during ‘initiation of termination’ in catatonia while it has no influence on initiation. Zolpidem is another agent useful in catatonia and both zolpidem and lorazepam are GABA-Aa agonists. However it is reported that the agonism (stimulation) of GABA-Ab receptor (e.g. valproic acid) in the context of reduced GABA-Aa efficacy can cause catatonia. This has lead to the GABA-Aa versus GABA-Ab hypothesis of catatonia.  

*ii) Glutamate*

The observations that catatonia improves
with the NMDA glutamate antagonist amantidine points to the role of glutamate in catatonia. The therapeutic recovery however was delayed. Therefore it is speculated that the glutamatergic system is secondarily altered in catatonia and that primary alteration is in the GABA-A receptors. The glutamatergic excess seen especially in the posterior parietal areas is speculated to be due to the reduced GABA levels in the orbitofrontal area and supplementary motor area. The role of NMDA glutamate antagonists is further supported by the efficacy of memantine in catatonia.\(^2\)\(^,\)\(^4\)\(^,\)\(^5\)

**iii) Serotonin**

The observation that atypical antipsychotics are associated with catatonia points to a serotonergic role in catatonia. It is proposed that a serotonergic dysequilibrium with an up-regulated 5HT1a receptor and a down-regulated 5HT2a receptor leads to catatonia.\(^4\)\(^,\)\(^6\)\(^,\)\(^7\)

**iv) Dopamine**

Early research into the role of dopamine was by estimation of vanillylmandelic acid (VMA) and homovanillic acid (HVA) in the urine samples of patients with periodic catatonia during an acute episode of catatonia. These studies showed an increase in the levels of dopamine metabolites, suggesting a dopaminergic excess in catatonia. Recent evidence also hints at an increase in dopamine particularly in those patients responding to lorazepam. These findings are however contradictory to the observation that dopamine blockers like antipsychotics induce catatonia. Further there is evidence that dopamine agonist (amantidine) treatment improves catatonia.\(^8\)

The consensus nowadays is that catatonia is characterized by striatal dopaminergic blockade (hypodopaminergic state).\(^4\)

No single neurotransmitter system has been shown to be solely responsible for catatonia. The ‘universal field hypothesis’ of catatonia states that the interaction of these neurotransmitter systems is responsible for catatonia and further points to the fact that the individuals developing catatonia have a neurochemical predisposition for the development of catatonia.\(^4\)

**Pathophysiology of symptoms**

Though there is no clear evidence as to the neural correlates of the symptoms that form the syndrome of catatonia, a tentative hypothesis regarding the possible neuropathology of the symptoms is proposed based on the neuroanatomic and neurochemical explorations.

*Mutism and stupor:* The neuroimaging studies have shown that the orbitofrontal connectivity with the motor/premotor cortex is abnormal in catatonics. The right orbitofrontal activation during negative emotional stimulation is altered and the activation is shifted to the anterior cingulate and medial prefrontal cortex. This shift in function especially to the anterior cingulate, probably results in a heightened activity of the affective division of the anterior
cingulate. This then leads to an almost complete down-regulation of the motor portion of the anterior cingulate which may account for mutism. The shift of function to the medial prefrontal cortex an area involved in social cognition and the perception of movements and mental states of others, may lead to an altered function of this area. The medial prefrontal dysfunction may result in total inability of verbal and non verbal contact with others resulting in stupor.¹ ²

**Posturing:** In catatonia, the maintainace of postures is hypothesized to be due to a failure in the termination of movements. It involves the interaction of areas involved in spatial attention and the ‘initiation of termination’ of movements. The right inferior parietal cortex is proposed to be the structure involved in these functions and dysfunction here possibly results in posturing.²

**Waxy flexibility and rigidity:** There is a striatal especially globus pallidus internum dysfunction leading to the rigidity and waxy flexibility in catatonia. This however is not as robust as in Parkinson’s disease and catatonia is probably characterized by a kind of smooth muscle hypertonus without rigidity causing the characteristic catatonic rigidity and waxy flexibility. This hypertonus is due to a striatal D2 down-regulation. The orbitofrontal top-down regulation of the D2 loop in the caudate in the orbitofrontal loop is a possible way of D2 down-regulation. It is also speculated that the orbitofrontal connectivity to the motor cortex (horizontal or cortico-cortical regulation) may down-regulate the striatal D2 within the motor loop and result in hypertonus.²

**Perseverative behaviour:** Catatonia has behavioral features like negativism, stereotypies, perseveration, echolalia and echopraxia. These are posited to be the result of a defect in the lateral part of the orbitofrontal cortex including the ventrolateral prefrontal (VLPFC) cortex, the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC). The lateral part of the orbitofrontal cortex including the VLPFC is related to control of complex behavior while the DLPFC is involved in planning of complex, it has reciprocal connection with PPC, so registration of spatial position is also needed to control and monitor complex behaviours. The VLPFC deficit leads to lack of suppression of behaviors once they have started leading to perseveration. The DLPFC defect leads to an inability to plan and an inability to plan ones behavior forces the person to take behavior from another either by negating them or imitating them.²

**Affective symptoms:** The affective symptomatology of catatonia possibly results from a defect in the balance between lateral and medial orbitofrontal cortex. The medial orbitofrontal cortex area via the amygdala especially its basal nucleus has rich limbic connections and is involved in the
Review - Neurobiology of catatonia

The preliminary explorations into the neuroanatomy and neurochemistry of catatonia have revealed some data in terms of the mechanisms mediating this phenomenon and the possible treatment targets. The OFC is probably the key structure mediating the symptoms of catatonia and its interaction with the DLPFC and the premotor loop is postulated to cause the affective, behavioural and motor symptoms of catatonia.\(^1\) (Figure 1) The neurotransmitter abnormalities in catatonia include the low GABA A activity (in the OFC), low D2 activity (striatal D2), the alterations in NMDA glutamatergic system, (increased posterior parietal glutamate) and a high 5HT1A activity. The neurotransmitter abnormalities in catatonia have provided valuable clues to the effective

**Figure 1: Neural Circuit of Catatonia**

(Modified version of original)  

**Conclusion**

The preliminary explorations into the neuroanatomy and neurochemistry of catatonia have revealed some data in terms of the mechanisms mediating this phenomenon and the possible treatment targets. The OFC is probably the key structure mediating the symptoms of catatonia and its interaction with the DLPFC and the premotor loop is postulated to cause the affective, behavioural and motor symptoms of catatonia.\(^1\) (Figure 1) The neurotransmitter abnormalities in catatonia include the low GABA A activity (in the OFC), low D2 activity (striatal D2), the alterations in NMDA glutamatergic system, (increased posterior parietal glutamate) and a high 5HT1A activity. The neurotransmitter abnormalities in catatonia have provided valuable clues to the effective
treatment of catatonia. Future research is needed to elucidate the exact neuroanatomic and neurochemical abnormalities associated with catatonia.

References