

Movement disorders in psychiatric patients

Laura Perju-Dumbrava,¹ Peter Kempster^{1,2}

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ABSTRACT

The observability of movement gives it advantages when trying to draw connections between brain and mind. Disturbed motor function pervades schizophrenia, though it is difficult now to subtract the effects of antipsychotic treatment. There is evidence from patients never exposed to these drugs that dyskinesia and even parkinsonism are to some degree innate to schizophrenia. Tardive dyskinesia and drug-induced parkinsonism are the most common movement disorders encountered in psychiatric practice. While D2 dopamine receptor blockade is a causative factor, both conditions defy straightforward neurochemical explanation. Balanced against the need to manage schizophrenic symptoms, neither prevention nor treatment is easy. Of all disorders classified as psychiatric, catatonia sits closest to organic neurology on the neuropsychiatric spectrum. Not only does it occur in the setting of unequivocally organic cerebral disease, but the alterations of consciousness it produces have 'organic' qualities even when the cause is psychiatric. No longer considered a subtype of schizophrenia, catatonia is defined by syndromic features based on motor phenomenology. Both severe depression and obsessive-compulsive disorder may be associated with 'soft' extrapyramidal signs that resemble parkinsonian bradykinesia. As functional neuroimaging studies suggest, movement and psychiatric disorders involve the same network connections between the basal ganglia and the cerebral cortex.

INTRODUCTION

Movement, David Marsden once wrote, is one of the robust bridges between neurology and psychiatry.¹ Its observability gives it special advantages when trying to draw connections between brain and mind. Movement disorders are encountered widely in psychiatric practice, often as side effects of psychotropic medication. This brief overview will highlight ways in which psychiatric diseases show convergence with the motor system.

MOVEMENT DISORDERS OF SCHIZOPHRENIA

Disturbed movement pervades schizophrenia, though it is difficult now to subtract the effects of antipsychotic treatment. There is evidence from patients never exposed to these drugs that dyskinesia and even parkinsonism are to some degree innate to schizophrenia. Anomalous

movements such as mannerisms, stereotypies and tics were well documented in the preneuroleptic era, and the postural and behavioural disturbances of chronic catatonic states were then quite common in psychiatric institutions (figure 1). Kraepelin, who delineated schizophrenia in his nosological writings (he called it dementia praecox), recorded a variety of hyperdynamic movements in his patients.² It is possible to observe motor features of preneuroleptic schizophrenia in historical documentary footage. The 1938 silent film production *Symptoms in Schizophrenia* depicts stereotypy, catalepsy, echopraxia, but also orofacial movements that resemble tardive dyskinesia.^{3 4}

More recent research supports a fundamental link between schizophrenia and movement disorder. In a cohort of never-treated Indian schizophrenic patients, McCreadie *et al* found more than half exhibiting spontaneous dyskinesia.⁵ They suggested that tardive and spontaneous dyskinesias, although aetiologically different, are phenomenologically similar. A review of 13 studies looking at antipsychotic-naïve patients with a first episode of psychosis concluded that the median rate of spontaneous dyskinesia is 9%.⁶ Adolescents with prodromal psychotic symptoms showed subtle hyperkinetic movement abnormalities, particularly of the facial region, in a carefully controlled observational study.⁷

Patients with schizophrenia who have never had antipsychotic drugs score significantly higher for parkinsonism than age-matched controls.^{6 8} The observant Kraepelin had already remarked this tendency in his patients—'the face vacant, immobile, like a mask...'; 'simple movements are stiff, slow, forced...'.² Subtle parkinsonism is seen both in newly diagnosed and in chronic but never-medicated schizophrenia.³ Of the mild extrapyramidal signs documented in these studies, rigidity and poverty of movement were most apparent. Meta-analysis also showed a smaller but significant excess of mild



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¹Neurosciences, Monash Medical Centre Clayton, Clayton, Victoria, Australia

²School of Clinical Sciences of Medicine, Monash University, Clayton, Victoria, Australia

Correspondence to

Dr Laura Perju-Dumbrava; laura.perju-dumbrava@calvarycare.org.au



Figure 1 A group of schizophrenic men in manneristic poses, from Kraepelin's textbook.² The text states: 'They were put without difficulty in the peculiar positions, and kept them, some with a sly laugh, others with rigid seriousness'.

parkinsonism in healthy first-degree relatives of patients with schizophrenia.⁸

Reserpine, first isolated from the Indian snakeroot plant (*Rauwolfia serpentina*), and chlorpromazine, a spin-off of antihistamine research by the pharmaceutical company Rhône-Poulenc, revolutionised the treatment of schizophrenia when both were introduced in the early 1950s. Though reserpine's action as an irreversible inhibitor of the vesicular monoamine transporter was not then known, the motor behavioural effects of the drug were a key to Arvid Carlsson's discovery of the role of dopamine as a neurotransmitter, for which he won the Nobel Prize, and then to understanding the chemical defect of Parkinson's disease (PD). Carlsson showed in 1963 that chlorpromazine blocked dopamine receptors, and this realisation led to the development of a dopamine hypothesis of schizophrenia.⁹

The original supposition that hyperactive dopamine neurotransmission equates with psychotic symptoms was later refined with knowledge about regional dopaminergic pathways and receptor subtypes. Thus, hallucinations and delusions were linked to subcortical release of dopamine, increased D2 receptor activation and disturbed cortical transmission through the nucleus accumbens. Negative symptoms of schizophrenia (apathy, anhedonia, social withdrawal) could, on the other hand, be explained by reduced D1 receptor activation in the prefrontal cortex, decreased activity of the caudate nucleus and possible additional D3 receptor changes.¹⁰ Despite shortcomings, these dopamine hypotheses do support the concept of a motoric schizophrenia phenotype. As with the positive-negative dichotomy of schizophrenic symptoms, different aspects of dopaminergic dysfunction might explain the presence of both hyperkinetic and hypokinetic features. A more recent iteration

considers dopamine dysregulation as a final common pathway, allowing for upstream contributions from other neurotransmitters—glutamate, gamma aminobutyric acid, serotonin—through which schizophrenia's predisposing genetic and environmental factors might be acting.¹¹

SCHIZOPHRENIA AND FUNCTIONAL MOVEMENTS

Functional (psychogenic) movement disorders are incongruous with the motor abnormalities of neurological diseases and show attention dependency, with distractibility, during clinical examination. Psychological models of functional neurological disorders have, in recent years, given way to more biologically orientated ones that emphasise disturbed higher level sensorimotor processing. In fact, surveys show that psychopathology in these patients is not greatly over-represented.¹² Although uncommon, functional movements do occur in schizophrenia.¹³ This is of interest in relation to another characteristic of functional motor syndromes—the lack of sense of agency (control over one's actions) that attends them.¹⁴ Passivity phenomena of psychosis result in perceptions of external control of movement.¹⁵ It is possible that the undermining of agency in functional movement disorders and schizophrenic passivity have a common pathophysiological basis.

TARDIVE MOVEMENT DISORDERS

Once dopamine receptor blocking agents (DRBAs) were in wide usage, tardive movement disorders appeared as a 'new' problem in psychiatric practice.¹⁶ The definition of tardive dyskinesia in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) recognises that long exposure to neuroleptics is not always required: 'involuntary athetoid or choreiform movements lasting at least a few weeks, developing in association with the use of a neuroleptic medication for at least a few months, and persisting beyond 4–8 weeks'.¹⁷ Older age, acquired brain damage, first generation antipsychotics, cumulative antipsychotic dosage, and duration of schizophrenia are all risk factors.¹⁸ Case-controlled research has identified a number of possible genetic predispositions. Polymorphisms in the dopamine D2 and D3 receptors are examples. Some of these associations, though, have not been as strong after further study or meta-analysis.¹⁹ Typical tardive dyskinesia has an orobuccolingual topography, producing repetitive licking, lip smacking and chewing movements. Variations include torsional movements of the tongue inside of the mouth, quick tongue protrusions (flycatcher tongue), and pushing of the tongue against the inner cheek creating a bulge (bonbon sign).²⁰ Tardive dyskinesia commonly worsens temporarily on cessation of the causative DRBA. In one study, about 30% of treated patients with schizophrenia without tardive

dyskinesia developed withdrawal-emergent dyskinesia when their antipsychotic medication was stopped.²¹

The explanation of a persistent dopamine hypersensitivity state from D2 receptor adaptation to chronic blockade is both a truism and a simplification. A more recent account of tardive movements invokes synaptic plasticity. Chronic blockade of D2 receptors and their resultant hypersensitisation induces a maladaptive adjustment in corticostriatal transmission, resulting in imbalance between direct and indirect basal ganglia motor pathways.²²

Balanced against the need to manage schizophrenic symptoms, neither prevention nor treatment of tardive dyskinesia is easy. Use of an atypical antipsychotic agent at the lowest effective dose is advisable, though these drugs, with the exception of clozapine, have stronger associations with tardive dyskinesia than was previously thought.²³ There is little evidence that switching to an atypical antipsychotic improves established tardive movements.²⁴ Tetrabenazine, which depletes dopamine by inhibiting vesicle monoamine transporter-2, has a long record and is moderately effective. Trials of valbenazine, a related compound, have recently shown promise of efficacy with a better side-effect profile.²⁵ Deep brain stimulation appears to be beneficial and fairly safe in severe, refractory tardive dyskinesia.²⁶

Tardive dystonia, different from tardive dyskinesia in its predilection for younger schizophrenic men after relatively short duration antipsychotic treatment, targets cervical and truncal muscles resulting in extensor or torsional fixed postures.²⁷ Other drug-induced movement disorders are often present. It can also more closely resemble idiopathic focal dystonia, including the occurrence of 'sensory trick' alleviating phenomena.²⁸ While anticholinergic drugs worsen tardive dyskinesia, they can diminish tardive dystonia.²⁹

Other tardive syndromes such as akathisia, chorea, myoclonus, stereotypy, tics, tremor and pain are generally less well defined. Tardive tremor is an uncommon and puzzling disorder. The original 1992 publication described 5 cases of rest and postural tremor between 3 and 5 Hz without other signs of parkinsonism. There were tardive dyskinesic movements as well, and both tremor and dyskinesia improved on tetrabenazine.³⁰ A later study of 10 patients diagnosed with the disorder did not support a major diagnostic criterion of the original article—response to tetrabenazine.³¹ Three other single case reports exist.

Tardive pain in the oral or genital region has been associated with the use of DRBAs. Tetrabenazine and antidepressant treatment appear to be beneficial.³²

ACUTE ANTIPSYCHOTIC DRUG-RELATED MOTOR SYNDROMES

With the acute motor syndromes caused by antipsychotics—akathisia and acute dystonic reactions—the relationship to D2 dopamine receptor blockade is clearer.

Akathisia, with an incidence ranging from 21% to 75%,³³ is a sensorimotor syndrome consisting of inner restlessness, an urge to move, an objective component of restless movement and, sometimes, prominent dysphoria. It usually occurs acutely and improves with drug withdrawal, though it has a chronic or tardive counterpart that may worsen with cessation of dopamine receptor blockade.³⁴

Acute dystonic reactions are seen predominantly in younger patients, males being more susceptible. They are reportedly more likely to occur with the injectable DRBAs or with higher doses. While akathisia may develop within minutes of a first dose of antipsychotic treatment, acute dystonic reactions are usually delayed by at least 12 hours.³⁵ This may relate to the drop in blood level of the medication.³⁶ Ninety per cent of reactions begin within 3–5 days. The prevalence of acute dystonia has been estimated to range from 2.3% to 60% of patients treated with conventional antipsychotics,³⁷ and from 2% to 3% with atypical ones.³⁸ The usual manifestations are orofacial dystonia, back arching, neck extension and occasionally laryngospasm. Pisa syndrome, characterised by tonic lateroflexion of the trunk, may occur as subacute dystonic reaction 3–10 days after starting a DRBA, or as a form of tardive dystonia.³⁹

Pharmacologically, the responsiveness of acute dystonic reactions to anticholinergic agents suggests that early cholinergic overactivity in response to a dopamine receptor antagonist is an important factor.⁴⁰

DRUG-INDUCED PARKINSONISM

Drug-induced parkinsonism is at first face the easiest of these movement disorders to understand, with blockade of nigrostriatal dopaminergic transmission mimicking the effects of nigral cell degeneration in PD. Yet the situation is not so straightforward. Once the causative agent has been stopped, clinical improvement occurs with a lag time of months, well after the pharmacological dopamine receptor block should have disappeared. Marsden thought that patients sometimes took as long as 18 months to start to improve, and as long as 5 years to recover completely.⁴¹

Estimates of the prevalence of drug-induced parkinsonism vary. One population study detected it in 36% of subjects treated with neuroleptic drugs for more than 6 months.⁴² Then, there are observations that can be made in any inpatient psychiatric service. Most patients presenting with psychotic illness, once titrated to an effective dose of antipsychotic treatment, develop a degree of blankness of facial expression, woodenness of movement or dampening of arm swing when walking. These impressions support the notion that D2 dopamine receptor blockade is an important determinant of the effectiveness of this drug therapy.

Clinically, drug-induced parkinsonism is a little less likely to be asymmetrical than the idiopathic disease. Normal dopamine transporter scans discriminate

drug-induced parkinsonism from idiopathic PD, and this accounts for 60% of cases. The other 40% appear to have some sort of presynaptic dopamine deficiency.⁴³ Unmasking of incipient idiopathic PD by pharmacological dopamine receptor antagonism is one explanation, yet this subgroup of drug-induced parkinsonism seems to exceed the natural prevalence of PD, and limited clinicopathological studies do not disclose a great deal of Lewy body pathology.⁴⁴ Chronic dopamine receptor blockade increases the firing rate and metabolic activity of dopaminergic nigral neurons. Consequent depolarization block⁴⁵ or structural neuronal damage⁴⁶ are possible reasons for delayed recovery after drug withdrawal. Despite theoretical risks of exacerbating psychosis, levodopa is generally well tolerated as a treatment when cessation of antipsychotic medication is impractical. Patients with abnormal dopamine transporter scans may be more responsive.⁴⁷

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome is perhaps the most serious movement disorder encountered by psychiatrists. Schizophrenia is a strong risk factor; a typical case would be a younger male with relatively drug-resistant psychosis requiring multiple or high-dose antipsychotic drug treatment.⁴⁵ In its fully developed form, fever, rigidity with rhabdomyolysis, autonomic instability and altered mental state have life-threatening potential. There are milder versions, with a continuum that extends from pronounced drug-induced parkinsonism. Dopaminergic D2 receptor blockade is likely to be the primary cause, and peripheral explanations around skeletal muscle fibre toxicity are less satisfactory. The breakdown in regulation of muscle energy expenditure in neuroleptic malignant syndrome underlines one important purpose of the basal ganglia—to optimise energy efficiency in motor control.

A neuroleptic malignant-like syndrome may also occur in patients with PD who have had sudden reductions in dopaminergic medications.⁴⁷ It has also been described with drugs that do not interact directly with dopamine receptors.⁴⁸

CATATONIA

Of all disorders classified as psychiatric, catatonia sits closest to organic neurology on the neuropsychiatric spectrum. Not only does it occur in the setting of unequivocally organic cerebral disease,⁴⁹ but the alterations of consciousness it produces have ‘organic’ qualities even when the cause is primarily psychiatric. With its peculiar mental withdrawal conjoined with degrees of mutism, the challenge for the clinician is to identify behavioural and motor features that set catatonia apart from other causes of stupor and coma. Its motor signs, while distinctive, bear resemblances to those of organic basal ganglia disease—dystonia-like sustained abnormal postures; the hypertonia of waxy flexibility. It used to be said that catatonia’s

incidence had greatly fallen in Western countries over the last hundred years, and perhaps this is true. But a recent meta-analysis of 74 studies of psychiatric inpatients and outpatients found a prevalence of 9%, with no consistent national or geographical trend.⁵⁰ Kraepelin regarded catatonia as a subtype of schizophrenia.² Although associations with severe depression and organic neurological disease were subsequently recognised, his view largely held sway through to the DSM-4. The DSM-5, though, concentrates on catatonia’s syndromic rather than disease character, with diagnostic features weighted towards motor abnormalities (table 1). Of these, the two postural maintenance criteria—*catalepsy*, the induction by an examiner of a posture that persists against gravity; and *posturing*, spontaneously adopted then retained against gravity—are least likely to be encountered in other clinical situations. The DSM-5 definition also takes in forms with retained alertness and echo-phenomena, agitated states and less specific motor findings of mannerism, stereotypy and grimacing.

With modern supportive care and treatment, lethal catatonia no longer has its dire connotation although patients with this variant develop prolonged depression of conscious state with fever and autonomic instability. There are parallels between severe catatonia and neuroleptic malignant syndrome, and the two disorders can be hard to differentiate when intermediate syndromes occur in psychiatrically ill patients on antipsychotic drugs. Both conditions may be worsened by dopamine receptor antagonists, whereas electroconvulsive treatment is effective in catatonia and in selected cases of neuroleptic malignant syndrome.⁵¹ A prior or family history of catatonia is a risk factor for neuroleptic malignant syndrome.⁵² Both conditions produce alterations in alertness that are likely to be neurochemically mediated yet are poorly understood. Serotonin syndrome, which shares a number of clinical signs with neuroleptic malignant syndrome and catatonia, enters the differential diagnosis when there is additional exposure to serotonergic agents. Typically, serotonin syndrome has more mental agitation, with more excitatory motor features such as tremor, myoclonus, clonus and hyperreflexia.⁵³

MOVEMENT DISORDERS IN OTHER PSYCHIATRIC CONDITIONS

There are subtle disturbances of movement in other psychiatric disorders that hint at basal ganglia abnormality. The psychomotor retardation of severe depression has superficial similarities to non-tremor dominant PD—impassive face, global slowness, flexed upright posture. These subjects do have reduced finger-tapping speed and defective postural control which, in contrast to PD, improve with dual task activity.⁵⁴ It has been theorised that depressive rumination interferes with movement control, and that concentration on

Table 1 Clinical features of catatonia

Clinical feature	Phenomenology	DSM 5	Bush-Francis
Catalepsy	Passive induction of postures held against gravity	•	
Posturing	Spontaneous postures maintained against gravity	•	•
Waxy flexibility	Slight, even resistance to passive movement	•	•
Stupor	Hypoactivity, minimal response to stimuli	•	•
Agitation/excitement	Hyperactivity, non-purposeful and not influenced by external stimuli	•	•
Mutism	No or minimal verbal response	•	•
Negativism	Resistance to instructions without obvious motive; tendency to contrary responses	•	•
Mannerisms	Odd, exaggerated caricatures of purposeful movement; abnormality inherent in act itself	•	•
Stereotypies	Repetitive, non-goal directed movements; abnormality not inherent in act but in its frequency	•	•
Grimacing	Maintained odd facial expressions	•	•
Echolalia	Repeating of words spoken by an examiner	•	
Echopraxia	Mimicking of movements made by an examiner	•	•
Staring	Fixed gaze, reduced environmental scanning, decreased blinking		•
Verbigeration	Meaningless repetition of words and phrases		•
Withdrawal	Refusal to eat, drink and make eye contact		•
Impulsivity	Inappropriate behaviour without provocation		•
Automatic obedience	Exaggerated cooperation with an examiner's instructions		•
Mitgehen (facilitatory paratonia)	Patient allows an examiner to induce a change in limb position with only light pressure, despite instruction to resist		•
Gegenhalten (oppositional paratonia)	Patient resists passive movement of a limb to a new position		•
Rigidity	Closely related to <i>Gegenhalten</i> , since recognisably extrapyramidal hypertonia is excluded		•
Ambitendency	Indecisive, hesitant patterns of movement		•
Perseveration	Of speech or actions		•
Combativeness	Undirected and apparently without motivation		•
Grasp reflex	Resembles the palmar grasp reflex of neurological disease states		•
Autonomic abnormality	Cardiovascular, respiratory or thermoregulatory		•

Three or more of the 12 features listed as Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria are required for a diagnosis of catatonia. The Bush-Francis Catatonia Rating Scale⁵⁷ comprises 23 items, though posturing and muscle tone features show some overlap.

a second task may be helping by drawing attentional resources away from it.

Motor abnormalities occur in obsessive-compulsive disorder. Obsessive-compulsive and tic disorders overlap, with roughly 30% in each category fulfilling the DSM-5 criteria for the other.⁵⁵ About a quarter of patients with obsessive-compulsive disorder have degrees of obsessional slowness. This probably relates to poorly suppressed intrusive and perseverative behaviours. It may be accompanied by 'soft' parkinsonian findings—impaired initiation and fluency of movement, subtle speech and gait abnormalities, cogwheel rigidity.⁵⁶

CONCLUSION

In the same way that 'non-motor' profiles of many movement disorders are now recognised, this essay has really been about the 'non-psychiatric' profiles of psychiatric illnesses. These clinical features blur the demarcation between neurology and psychiatry, and may represent clues to pathophysiology. As functional neuroimaging studies suggest, movement and psychiatric disorders involve the same network connections between the basal ganglia and the cerebral cortex.

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