Neuroscience and Biobehavioral Reviews 80 (2017) 23–35

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

# A review of psychiatric co-morbidity described in genetic and immune mediated movement disorders

K.J. Peall[a,*,1], M.S. Lorentzos[b,1], I. Heyman[c,d], M.A.J. Tijssen[e], M.J. Owen[a], R.C. Dale[b,2], M.A. Kurian[d,f,**,2]

[a] MRC Centre for Neuropsychiatric Genetics and Genomics, Hadyn Ellis Building, Heath Park, Cardiff, CF24 4HQ, UK
[b] Movement Disorders Clinic, The Children's Hospital at Westmead, University of Sydney, Sydney, NSW, Australia
[c] Department of Psychological Medicine, Great Ormond Street Hospital, London, UK
[d] Developmental Neurosciences Programme, UCL-Institute of Child Health, London, UK
[e] Department of Neurology, University of Groningen, Groningen, The Netherlands
[f] Department of Neurology, Great Ormond Street Hospital, London, UK

ARTICLE INFO

*Keywords:*
Movement disorders
Genetics
Immune mediated
Psychiatric phenotype

ABSTRACT

Psychiatric symptoms are an increasingly recognised feature of movement disorders. Recent identification of causative genes and autoantibodies has allowed detailed analysis of aetiologically homogenous subgroups, thereby enabling determination of the spectrum of psychiatric symptoms in these disorders.

This review evaluates the incidence and type of psychiatric symptoms encountered in patients with movement disorders. A broad spectrum of psychiatric symptoms was identified across all subtypes of movement disorder, with depression, generalised anxiety disorder and obsessive-compulsive disorder being most common. Psychosis, schizophrenia and attention deficit hyperactivity disorder were also identified, with the psychiatric symptoms often predating onset of the motor disorder.

The high incidence of psychiatric symptoms across such a wide range of movement disorders suggests a degree of common or overlapping pathogenic mechanisms. Our review demonstrates the need for increased clinical awareness of such co-morbidities, which should facilitate early neuropsychiatric intervention and allied specialist treatment for patients.

## 1. Introduction

Psychiatric illness is increasingly recognised as a primary phenotypic component of many movement disorders (Lesser and Fahn, 1978). This has led to increased reporting of such symptoms, often resulting in a broad range of psychiatric phenotypes associated with individual movement disorders. Examination of aetiologically homogenous groups provides clear definition when evaluating these symptoms as well as potentially allowing insights into the physiological mechanisms underlying psychiatric disturbance.

The exact mechanisms determining co-occurrence of psychiatric and motor symptoms remain largely unknown. The topographical organisation of sensorimotor, associative and limbic areas of the subthalamic nucleus (STN) and its' interaction with both the direct and indirect pathways of the basal ganglia, provides a potential anatomical explanation for these co-existent symptoms (Fig. 1) (Parent and Hazrati, 1995). Monoamine metabolism is also likely to influence these neural networks with dopaminergic therapy exacerbating Impulse Control Disorders (ICDs) in patients with idiopathic Parkinson's disease (iPD), while loss of GABAergic neurons leads to dis-inhibition of nigral dopaminergic neurons in patients with X-linked dystonia-parkinsonism (DYT3) (Goto et al., 2013). Successful therapeutic use of Selective Serotonin Reuptake Inhibitors (SSRIs) and neuroimaging techniques also signify the importance of serotonin in mental health disorders, most markedly Major Depressive Disorder (MDD), anxiety disorders and Obsessive-Compulsive Disorder (OCD) (Fig. 2) (Mann, 1998; Lin et al., 2014).

This review seeks to better define the psychiatric phenotype associated with aetiologically homogenous movement disorders of both adult and paediatric onset. Discussion of all movement disorders is

* Corresponding author.
** Corresponding author at: Developmental Neurosciences Programme, UCL-Institute of Child Health, London, UK.
*E-mail addresses:* PeallKJ@cardiff.ac.uk (K.J. Peall), manju.kurian@ucl.ac.uk (M.A. Kurian).
[1] These authors contributed equally to the manuscript.
[2] These authors contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.neubiorev.2017.05.014
Received 21 March 2017; Received in revised form 10 May 2017; Accepted 12 May 2017
Available online 18 May 2017

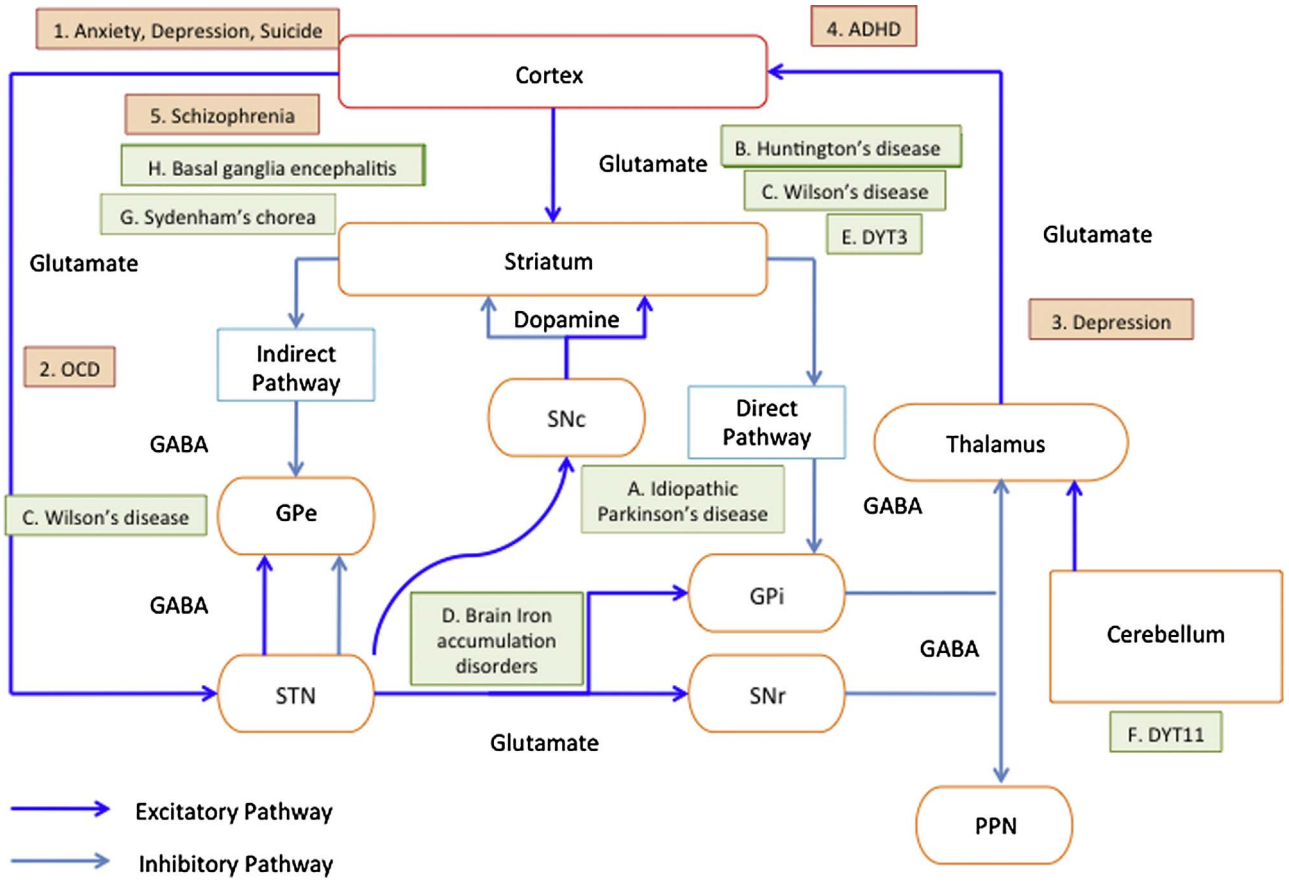


**Fig. 1.** Proposed main mechanisms and hypothesised neural pathways involved in movement and psychiatric disorders.
Key: 1: Cortico-limbic pathways are thought to be involved in anxiety, depression and suicide, 2: For OCD, an imbalance between direct and indirect basal ganglia pathways is thought to contribute to OCD with direct pathway activity increased over that of the indirect pathways, 3: A role for the thalamus has been suggested in depression, 4: Altered networks between the cortex, striatum and cerebellum have been proposed for ADHD, 5: Schizophrenia: altered processing by the cortex, thalamus and basal ganglia of sensory information has been proposed as a substrate for hallucinations. A: Idiopathic Parkinson's disease, degeneration of dopaminergic neurons predominantly seen in the SNc, B: Degeneration of striatal-cortical projections and caudate atrophy observed in the early stages of Huntington's disease, C: Wilson's disease; copper deposition in the putamen and globus pallidus, D: PKAN, PLAN, BPAN and Kufor Rakeb - brain iron accumulation in the globus pallidus and substantia nigra, E: DYT3, early loss of striosomal GABAergic projections re proposed to cause disinhibition of nigral dopaminergic neurons leading to the hyperkinetic dystonic disorder followed by later involvement of the matrix resulting in parkinsonism, F: Impaired saccadic adaptation observed in DYT11 cases. In addition brain-specific isoforms of the epsilon-sarcoglycan protein are differentially expressed in the brain with the highest levels observed in the cerebellum, G: Sydenham's chorea: autoantibodies are targeted towards basal ganglia structures disrupting basal ganglia-cortical circuits, H: Antibodies targeted towards D2 receptors, predominantly in the putamen, are observed in basal ganglia encephalitis. GPi: Globus Pallidus internus, GPe: Globus Pallidus externus, PPN: Pedunculopontine nucleus, SNc: Substantia nigra pars compacta, SNr: Substantia nigra pars reticulate, STN: Subthalamic nucleus. Psychiatric symptoms are annotated in red boxes and movement disorder subtypes in green boxes.

beyond the scope of this review, instead we have sought to focus on those with an underlying genetic or immune-mediated aetiology with movement disorders as the dominant feature. An evaluation of the quality of the evidence is also included with emphasis on that from larger cohort and case-control studies.

## 2. Methods

We performed a systematic literature search of the PUBMED database using the key words "psychiatry"; "psychiatric"; "alcohol abuse/dependence"; "schizophrenia"; "psychosis"; "major depressive disorder"; "bipolar disorder"; "generalised anxiety disorder"; "agoraphobia"; "specific phobia"; "social phobia"; "obsessive compulsive disorder"; "post-traumatic stress disorder"; "anorexia nervosa" and "bulimia nervosa" in combination with each of the genetic or immune-mediated disorders. All those published in English and in peer-reviewed journals until March 2017 were included. Additional inclusion criteria were 1) identification of a genetic aetiology or immunological syndrome and 2) where the movement disorder was a predominant disease feature. Publications were excluded if the genetic or immunological testing was negative; not performed or movement disorder was not described in the clinical phenotype. Studies identified were divided according to the size of the cohort and whether there was comparison to a control group (Supplementary Fig. 1): Case Reports (n = 1) (Supplementary Table 1); Small Case Series (n < 5) (Supplementary Table 2); Larger Case Series (n > 5 patients) (Supplementary Table 3) and Case-Control Studies (Supplementary Table 4). All evidence from larger case series (+) and case-control studies (++) are summarised in Tables 1–4. The (+) marker denotes features described in larger case series; but with no control groups and no statistical comparison of significance; (++) indicates a statistically significant elevation of psychiatric comorbidity compared to a control group. The key publications from these tables are discussed below. Population prevalence estimates for all major psychiatric disorders in adults and children are available for comparison (Supplementary Table 5).

## 3. Parkinsonism

### 3.1. Genetic parkinsonism

The clinical and genetic features of genetic parkinsonian disorders with evidence of psychiatric symptoms are summarised in Table 1.