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

KJ Peall,[a*] MS Lorentzos,[b*] I Heyman,[c,d] MAJ Tijssen (MD, PhD),[e] MJ Owen,[a] RC Dale,[b+] MA Kurian[d,f+]

[a]MRC Centre for Neuropsychiatric Genetics and Genomics, Hadyn Ellis Building, Heath Park, Cardiff, UK CF24 4HQ

[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

*These authors contributed equally to the manuscript
[+]These authors contributed equally to the manuscript

Corresponding authors:
Dr Kathryn Peall, MRC Centre for Neuropsychiatric Genetics and Genomics, Hadyn Ellis Building, Heath Park, Cardiff, UK CF24 4HQ. Email: PeallKJ@cardiff.ac.uk; Telephone: 029 20 743454
Dr Manju Kurian, Developmental Neurosciences Programme, UCL-Institute of Child Health, London, UK. Email: manju.kurian@ucl.ac.uk; Telephone: 020 7405 9200 ext. 8308

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.

Keywords: Movement Disorders, Genetics, Immune mediated, Psychiatric phenotype.

Introduction

Psychiatric illness is increasingly recognised as a primary phenotypic component of many movement disorders.[1] 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 (Figure 1).[2] 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).[3] 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) (Figure 2).[4, 5]

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 beyond the scope of this review, instead we

have sought to focus on those with and 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.

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 Figure 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).

Parkinsonism

Genetic Parkinsonism

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

(i) Autosomal Dominant Genetic Parkinsonism

The α-synuclein (*SNCA*) gene was the first to be identified in Parkinson's disease (PD).[6] Conflicting evidence has been noted in studies of *SNCA* (PARK1/4) mutation positive cohorts with some observing severe depression, hallucinations and delusions, while case-control comparison found no significant difference in either the reported rate of depression (p=0.7) or lack of motivation (p=0.46).[7, 8] Studies of Leucine-rich repeat kinase 2 (*LRRK2*) (PARK8) mutation positive cohorts have tended to focus on mood disorders with Goldwurm et al (n=19) reporting increased rates of depression (69%), anxiety (62%) and irritability (56%), and a trend towards a pre-motor mood disorder when comparing mutation positive, matched, Ashkenazi Jewish pairs (OR=6.0, p=0.10).[9, 10] Comparison to those with idiopathic Parkinson's disease (iPD) found increased rates of depression amongst those with *LRRK2* mutations (p=0.001), while anxiety levels remain similar (p=0.33).[11, 12] However, a large PD cohort (n=840) with proportionally few *LRRK2* mutation

positive cases (4.8%) identified similar rates of depression when comparing the G2019S *LRRK2* mutation (p=0.90) to the remaining population.[13]

(ii) Autosomal Recessive Genetic Parkinsonism

Early case series of those with *Parkin* (PARK2) mutations found evidence of psychiatric symptoms in 56% of the cohort (n=24), with symptoms including depression, psychosis, and panic attacks. A quarter of cases developed these symptoms >5 years prior to onset of their motor symptoms, while 31% developed psychiatric symptomatology at a later time point.[14] A subsequent case-control study (146 *Parkin* mutation positive, 250 mutation negative controls) found psychiatric symptoms in only 9 cases with *Parkin* mutations, with symptoms spanning psychosis, panic attacks, depression, disturbed sexual behaviour and obsessive-compulsive (OC) symptoms.[15] Several studies have sought to compare early-onset PD (EOPD) cases with and without *Parkin* mutations failing to identify distinct psychiatric markers.[16] Other studies have sought to compare homozygotes, compound heterozygotes, heterozygotes and *Parkin* mutation negative controls using multiple diagnostic tools. Other than a tendency towards higher rates of depression in the relatives of affected heterozygous *Parkin* mutation carriers, these studies have found little between group differences.[17-19]

Initial larger case series of those with PTEN-induced putative kinase 1 (*PINK1)* (PARK6) mutations reported symptoms of mood disturbance, depression, anxiety and psychosis.[20-24] Other studies have sought to compare the psychiatric phenotype of those with homozygous mutations to compound heterozygotes with conflicting results. Some found heterozygotes to have a generally milder phenotype,

predominantly involving depression and anxiety, while others have described a broader pattern including schizophrenia spectrum disorder and Obsessive-Compulsive personality disorder.[25-27] Certain psychiatric symptoms may pre-date the movement disorder, with one study reporting initial symptoms of depression (75%) and schizophrenia or affective disorder (55%) (n=20).[28]

iii) Other forms of genetic parkinsonism

Several studies have observed an increased risk of parkinsonism in patients with Gaucher's disease (*GBA* mutation). Results from case-control studies have varied dependent upon the control group to which the cases have been compared. Alcalay and colleagues reported no significant difference in depression scores in 33 *GBA* mutation positive cases compared to 114 mutation-negative EOPD individuals.[29] However, when compared to iPD cases an excess of depressive symptoms ($p=0.05$, $p<0.05$ and $p=0.013$), anxiety ($p=0.007$), apathy and indifference ($p=0.043$) has been observed.[30-32] Psychiatric symptoms in patients with Niemann Pick disease Type C (NPC) are most prevalent in those with the adult-onset form of the disorder, with up to (45% (n=13) reporting symptoms prior to onset of the movement disorder. These symptoms are predominantly psychosis related, with paranoid delusions, behavioural disturbance, auditory and visual hallucinations. [33]

Heredo-degenerative disorders

A full summary of the clinical and genetic features of these disorders can be seen in Table 2.

Huntington's disease

Psychiatric symptoms described in patients with Huntington's disease (HD) include depression, anxiety, irritability, apathy, OCD and psychosis. A large European epidemiological study (n=1766) found psychiatric symptoms to be the presenting feature in 19.6% of patients, with 39.3% developing severe symptoms during the course of the disorder.[34] The severity and likelihood of developing psychiatric symptoms appear independent of the number of trinucleotide repeat expansions, although both cross-sectional and longitudinal studies have noted that proximity to onset of motor symptoms increased the likelihood of developing psychiatric symptoms, particularly affective forms ($p<0.01$).[35-37] A single case series of individuals with juvenile HD (n=12) found depression (n=3), behavioural disorders (n=3) and Obsessive-Compulsive behaviour (n=2) to be most common.[38]

Rates of depression have varied between studies (33-69%), although case-control comparison has found major depressive disorder (MDD) to be significantly increased in both pre-motor symptomatic ($p=0.001$) and symptomatic ($p<0.001$) mutation carriers.[39] Affective symptoms are also likely to present early in the disease course, with increased rates of depression, attempted suicide and irritability scores in those with early HD compared to controls ($p<0.05$).[40]

Anderson et al found >50% of their cohort to demonstrate at least one OCD symptom subtype with aggressive obsessions (26%) and contamination obsessions (22%) being most common (n=1642).[41] Some studies have found that the likelihood of developing OCD-type symptoms increases with disease severity and is linked to a higher level of other psychiatric co-morbidity ($p<0.001$).[42] Others have noted that OCD-type symptoms are more evident in pre-symptomatic mutation carriers

compared to controls (p=0.003), with obsessive worrying and perceived cognitive errors being prominent (p<0.05).[39, 43]

A 9% lifetime risk of schizophrenia has been reported in HD cohorts (n=154), with delusions more common than hallucinations (11% vs. 2%), and a trend towards an increased rate of non-affective psychosis compared to healthy controls (p=0.06).[39] Onset of psychotic symptoms also appears to be linked to onset of motor symptoms, with a younger age at onset observed in those with a higher number of CAG repeats.[44]

Dentatorubral-pallidoluysian atrophy (DRPLA)

Prevalence of psychiatric symptoms in those with *DRPLA* mutations has been reported to be as high as 10%, with larger case series describing psychosis, depression, irritability and anxiety.[45-47] There is also a suggestion that psychotic symptoms, particularly delusions, are more common in those with shorter CAG repeats.[48]

Wilson's disease

A retrospective assessment of 195 cases found 51% to have evidence of psychiatric disturbance during the course of their illness. Presentation with psychiatric symptoms appears to occur in an older age group (mean age 25.3 years), compared to those with initial neurological features, and a gender difference of increased ritualistic behaviour and emotional lability amongst females (p<0.05).[49-51] Comparison with matched healthy controls found significant excesses of lifetime MDD (p=0.001) and bipolar disorder (p=0.001) in those with Wilson's disease, while similar rates of panic

disorder (p=0.922) and total anxiety disorder (p=0.215) were observed between the two groups.[52]

Neurodegeneration with Brain Iron Accumulation (NBIA)

Psychiatric assessment of a cohort of patients with PKAN (pantothenate kinase associated neurodegeneration), due to *PANK2* mutations (n=16), identified psychiatric symptoms in 50% with behavioural disturbance, OCD, hyperactivity and depression described.[53] A comparison of 66 mutation-positive families with 32 mutation-negative symptomatic families found an overall excess of psychiatric symptoms in the mutation-positive group ($p<0.05$).[54] *PLA2G6*-associated neuro-degeneration (PLAN) describes three over-lapping disorders; classic infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (atypical NAD) and *PLA2G6*-related dystonia-parkinsonism. Psychiatric symptoms are more frequently described in the latter two forms with a case series of atypical NAD describing autistic features, impulsivity, hyperactivity and emotional lability.[55] A larger case series (n=23) of the more recently described Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN), found evidence of inattention, hyperactivity, emotional lability, depression, anxiety, impulsivity and compulsions.[56]

Kufor-Rakeb disease

Psychiatric symptoms have almost exclusively been reported in homozygous *ATP13A2* mutation carriers with Kufor-Rakeb disease. A single case series described six members of the same family where only were two noted to have psychiatric symptoms. Both reported auditory hallucinations, with one additionally being diagnosed with paranoid schizophrenia, and the other with psychosis.[57]

Genetic Dystonia

A summary of the clinical and genetic features of genetically determined dystonic disorders are summarised in Table 3.

DYT1

Systematic psychiatric assessment of motor affected DYT1 mutation carriers identified the risk of recurrent major depression to be greater in non-manifesting carriers (NMC) (RR=4.95) and manifesting carriers (MC) (RR=3.62) compared to controls, with depressive symptoms presenting at an earlier age and independent of motor symptom severity.[58]

DYT3 (X-linked Dystonia Parkinsonism (XDP)/Lubag's disease)

Psychiatric symptoms are well recognised in XDP, with 9% of all mortality attributable to suicide. A single case-control study (n=14 cases, 14 controls) found almost 50% of affected individuals to have symptoms of at least one symptom type, with anxiety related disorders (35.7%), social phobia (28.6%) and agoraphobia (21.4%) being most common. Major depressive symptoms were present in 14.3% with a significantly higher mean depression score in cases compared to controls (p=0.004).[59]

DYT5 dopa-responsive dystonia and other neurotransmitter disorders

GCH1 mutations (Segawa's disease)

Large cohort studies have observed varying frequency of psychiatric symptoms ranging from single cases to lifetime rates of 50% (n=34).[60] Affective disorders,

predominantly MDD, are the most commonly described, typically with onset in the 5th decade of life and a possible female predominance.[61-63] However, the single case-control study to date found no significant differences with either depression (p=0.091) or anxiety scores (p=0.314).[64]

Aromatic L-amino acid decarboxylase (AADC) deficiency

Two studies have examined psychiatric symptomatology in patients with AADC deficiency. The first assessed eleven patients identifying irritability and emotional lability in ten, with single cases of anxiety, panic attacks, ADHD and claustrophobia.[65] A more recent study found 7/8 with symptoms of irritability.[66]

Dopamine Transporter (DAT) Deficiency Syndrome

Several larger case series have identified early evidence of irritability with 6/11 affected in the initial cohort and 3/8 in a more recent study.[67] Genetic association and linkage studies have also suggested a role for DAT in neurodevelopmental disorders, with the SLC6A3 A559V variant having been identified in individuals with ADHD, bipolar disorder and Autistic Spectrum Disorder (ASD).[68]

DYT6

A single case-control study compared eleven *THAP1* mutation positive patients with 82 mutation negative patients with dystonia. No significant difference was identified across a range of non-motor features, with the psychiatric focus being on anxiety (p=0.58) and sadness (p=0.5).[69]

DYT11 (Myoclonus Dystonia)

Psychiatric symptoms have been widely published in *SGCE* mutation positive cohorts with OCD, anxiety, depression and alcohol misuse being the most frequently described.[70] Comparison of several genetically screened cohorts with matched controls have consistently identified an excess of Generalise Anxiety Disorder (GAD), OCD (predominantly compulsivity) and alcohol dependence amongst those with an *SGCE* mutation.[71-73]

DYT12 (Rapid-onset Dystonia Parkinsonsim)

Longitudinal and cross-sectional studies have consistently identified symptoms of depression and social phobia. Comparison of 29 mutation positive individuals and 27 familial controls found significantly higher anxiety ($p=0.025$) and depression ($p=0.025$) scores, together with increased rates of psychosis (19% vs 0%) in motor affected individuals compared to controls. Mean age at onset of these symptoms was lower than is usually seen with more typical psychosis (15-24 years), with psychiatric symptom onset preceding development of the movement disorder in several cases.[74]

DYT28

Heterozygous variants in the KMT2B gene have recently been described in individuals with a complex progressive childhood-onset dystonia. Two case series have been reported to date with the larger of the two (n=27) describing symptoms of anxiety, ADHD, obsessive-compulsive traits and self-harm behaviour.[75]

Genetic Chorea

Mutations in two distinct genes have been identified to cause genetically determined forms of chorea: NK2 homeobox 2 gene (*NKX2.1*), causing Benign Hereditary Chorea (BHC), and Adenylate cyclase 5 (*ADCY5*) involved in *ADCY5*-related dyskinesias. Three larger cohort studies of patients with the *NKX2.1* mutation have identified relatively low rates of psychiatric symptomatology with 7/28 meeting diagnostic criteria for ADHD in a recently French study, while others have described single cases each of psychosis and OCD.[76-78] To date only a single cohort study (n=19) has reported psychiatric symptoms in those with *ADCY5* mutations. Here psychosis and auditory hallucinations were identified in two cases, one of whom had recurrent episodes of psychosis with delusions and auditory hallucinations.[79]

Immune-mediated Movement Disorders

The clinical characteristics of immune-mediated movement disorders with psychiatric co-morbidity are summarised in Table 4.

Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS)

The PANDAS concept has remained controversial, reflected in diagnostic difficulties in reported studies. This has been further augmented by the recent introduction of paediatric acute neuropsychiatric syndrome (PANS), a modified diagnosis involving development of an infection associated neuropsychiatric syndrome, but not specifically post-streptococcal. Examination of a large PANDAS cohort (n=50), identified ADHD (40%), oppositional defiant disorder (40%) and major depression (36%) as the most common forms of psychiatric symptoms. However, symptomatology may fluctuate, with emotional lability (66%), changes in personality

(54%) and bedtime fears/rituals (50%) described most frequently during subsequent episodes.[80] Other studies have identified high levels of OCD, with obsessions principally focused on the fear of harm to self or others (5/12) and compulsions predominantly hygiene related.[81] The relationship with OCD however, may be more complex with increased rates of OC personality disorder (11%), subclinical OCD (8%) and OCD (26%) amongst 1st-degree relatives (n=157) of those with PANDAS.[82]

Results from case-control studies have varied with several studies observing no difference between PANDAS cases and controls.[83] In contrast, Murphy and colleagues found that those with PANDAS were more likely to have a dramatic onset of psychiatric symptoms ($p<0.05$) and clear periods of remission ($p<0.05$), particularly during treatment with antibiotics ($p<0.01$).[84] Others have found that rates of psychiatric symptoms may differ dependent on the methods of assessment, and that PANDAS-associated psychiatric symptoms are likely to vary in conjunction with the symptomatic fluctuation observed with the disorder.[85]

Sydenham's Chorea

Case-control analyses have identified increased rates of ADHD ($p<0.01$) and MDD ($p<0.01$) amongst those with Sydenham's chorea when compared to patients with Rheumatic fever, while comparison to matched healthy controls has found little difference in the rates of anxiety and depression.[86, 87] A similar case-control comparison reinforced an increased rate of ADHD ($p=0.001$), identified an excess of OCD ($p=0.003$) and found only those with persistent motor symptoms had an excess of ADHD compared to controls.[88] In contrast, a more recent study identified an

increased rate of depression amongst those with persistent motor symptoms (p=0.03) but no significant difference in the rates of ADHD or OCD.[89] Longitudinal observation of a single cohort (n=28) provides a potential explanation, describing temporal variation in the psychiatric phenotype with depression (69%) and anxiety (78%) highest during the episodes of chorea, and ADHD most pronounced following resolution of the movement disorder (36%).[90] However, a recent case-control comparison of standard treatment versus augmented IVIG therapy also found that those receiving standard treatment demonstrated poorer co-operation (p=0.009) and increased impulsivity (p=0.016).[91]

Several studies have specifically focused on symptoms of OCD and Obsessive-Compulsive Symptoms (OCS). A recent case series (n=73) found 38.4% to meet diagnostic criteria for OCD with contamination (p=0.006) and religious (p=0.019) obsessions, and cleaning (p=0.003) and repeating (p=0.012) compulsions being most common.[92] An earlier case-control study found that the majority of patients (21/30) had abrupt onset of OCS symptoms within the first two months of the streptococcal infection. These patients also demonstrated a significant increase in resistance (p=0.005) and interference (p=0.008) at two months post-symptom onset compared to those with rheumatic fever with these effects waning over time.[93]

Anti-NMDA Receptor Encephalitis (anti-NMDAR)

Although anti-NMDAR encephalitis is a diffuse encephalitis, movement disorders and psychiatric symptoms are highly recognised features. Several studies have reported frequencies of 65-69% (n=40-577) of psychiatric disorders at presentation

with a consistent pattern of symptomatology including hallucinations (auditory and visual), psychosis and agitation.[94-97] These findings are also supported by case-control studies where rates of psychosis ($p<0.001$), hallucinations ($p<0.05$) and personality change ($p<0.0001$) were significantly higher than cohorts of mixed infective encephalitidies and symptomatic, antibody-negative groups.[98] Similar results are also seen in pediatric cohorts where up to 87.5% (n=32) presented with psychiatric or behavioral changes, predominantly involving agitation, aggression and psychosis.[99] Long-term follow-up of twenty-three antibody-positive cases found eighteen had psychiatric symptoms during subsequent relapses, while 50% of cases at 12-60 months from symptom onset in another study had ongoing behavioural or cognitive difficulties. [100, 101]

Basal ganglia Encephalitis

Several cohort studies have reported psychiatric symptoms, noting a wide range in overall rates of psychiatric disturbance (49%-88%), but similar levels of depression and anxiety (38% and 40%).[102, 103] In contrast a more recent study of 12 patients with anti-DR2 basal ganglia antibodies found psychiatric symptoms in nine, with agitation (5/12) and psychosis or hallucinations (3/12) being most common. Approximately half of all cases recovered fully, while residual psychiatric symptoms were evident in the remainder.[104]

Opsoclonus-Myoclonus Ataxia Syndrome

A retrospective study using parent-completed questionnaires (n=105) identified rage attacks (79%), opposition defiant disorder (65%), OCS (58%) and hyperactivity

(47%) as the most common symptom subtypes.[105] Behavioural disturbance has also been highlighted in a number of other cohorts (n=51), with irritability reported during the acute phase, and rage (51%) and hyperactivity (55%) in the longer term.[106, 107] Retrospective analysis (n=101) found a potential link with disease course, behavioral disturbance being noted in 39% of those with a monophasic or intermediate illness compared to 74% of those with a chronic-relapsing form (p=0.006).[108] These findings have also been replicated in the single case-control study to date, demonstrating significantly higher scores relating to attention difficulties, social and thought problems compared to healthy controls.[109]

Discussion

The evidence summarised in Figure 3 suggests that patterns of psychiatric phenotypes or clusters of symptoms are associated with particular movement disorders. The most common disorders to emerge were anxiety disorders (GAD), mood disorders (depressive disorders) and schizophrenia and other psychotic disorders (psychosis). These symptoms were common across genetic and immunological disorders, as well as neurodegenerative and neurodevelopmental aetiologies. Frequent discussion focuses on whether these symptoms, especially mood disorders, represent primary or secondary-reactive features of the movement disorder phenotype. However, the consistent pre-motor onset of depressive symptoms in those with genetically determined parkinsonism and recurrent episodes of major depressive disorder in DYT1-positive patients suggests a more complex rather than causal relationship.

Interestingly, while some of the disorders discussed in this review have evidence of a

broad range of psychiatric symptoms (e.g. PANDAS: ADHD, ODD, depressive disorder, irritability, GAD, OCD), others have a much narrower spectrum of symptoms, e.g. DJ-1 (psychosis and GAD). Within individual psychiatric diagnoses, subsets of symptoms also differ between distinct movement disorder types. Case-control studies have demonstrated increased rates of OCD in both HD and Myoclonus Dystonia (DYT11). However, there was a greater tendency towards contamination-type obsessions in the former and a greater emphasis on compulsivity in the latter. Although clear pathophysiological mechanisms explaining both motor and psychiatric symptoms have yet to be fully elucidated, a comprehensive view of the distinct patterns of symptoms between disorders is important in contributing to robust mechanistic understanding.

Tourette's Syndrome, although a widely recognised movement disorder with overlapping psychiatric phenotype, is not discussed in detail in this review as no definitive genetic or immunological aetiology has been consistently identified to date. Tourette's Syndrome typically involves motor and vocal tics, together with psychiatric symptoms including ADHD, OCD, anxiety and mood disorders. Many studies have sought to determine the underlying aetiology of Tourette's Syndrome with evidence suggesting both complex genetic and immunological contributions in the pathophysiological process.[110, 111] An added benefit of improved mechanistic understanding of the disorders discussed in this review is the opportunity to further explore disorders, such as Tourette's Syndrome, in which more complex aetiological processes are likely to be involved.

Overall this review has demonstrated a general paucity of case-controlled, systematic

assessments of psychiatric symptoms across many of the movement disorders discussed, with considerable inconsistency in the assessment techniques employed (Supplementary Figure 1). Of the 404 publications included only 64 involved comparison of the genetically/immunologically defined cohort to a control group (15.8%), and of these only 53 involved use of standardised questionnaires. Many of the control groups included unaffected family members, who although potentially controlled for environmental factors, their symptoms may also have been influenced by additional genetic variables, while others used groups unmatched for both gender and age. Finally, the focus of the questionnaires used varied frequently between studies, with some using broad diagnostic tools while others used questionnaires targeted at assessing specific disorders. Choice of questionnaires often appeared influenced by findings from previous case reports/case series, which combined with variations in assessment may have influenced findings in some disorders.

Conclusion

This review clearly illustrates that many movement disorders are associated with psychiatric co-morbidity. Although disease mechanisms causing psychiatric symptoms are largely undetermined, the underlying movement disorder aetiology, affected neural networks and environmental factors such as those governing reactive responses to a chronic neurological disorder are all likely to play a role (Figures 1 and 2). As the psychiatric phenotypes of movement disorders become increasingly refined, along with mechanistic insights from cellular- and systems-based approaches, it is hoped that future work will provide a model of pathogenesis that encompasses both motor and non-motor symptoms. Clinical recognition and awareness of the co-existence of movement disorders and psychiatric symptoms is therefore of relevance

to both neurologists and psychiatrists. Early recognition of these disorders is vital to allow prompt initiation of appropriate therapy and involvement of multidisciplinary allied specialities and support services.

With the rapid advancement of technologies, the rate at which novel genetic and immunological aetiologies for movement disorders are identified is ever increasing. Recognition of the significant prevalence of psychiatric co-morbidity should drive early systematic assessment for such symptoms in patients with movement disorders. The temporal pattern of onset of both motor and psychiatric symptoms is also an important diagnostic clue, and should form a core component of all clinical assessments. Collectively, this information, as well as improving understanding of the underlying aetiology or network disruption, will also form important outcome measures for future clinical trials.

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Table 1: Genetic Parkinsonism

PARK locus/ Disorder	Epidemiology	Causative gene	Inheritance	Motor phenotype	Psychiatric phenotype	Additional clinical characteristics
PARK1/4 (168601)	Rare. Disease causing in ~2.5% of unrelated affected carriers	*SNCA*	AD	L-dopa responsive parkinsonism, cortical myoclonus	Depression+ Hallucinations+ Delusions+	Dementia, speech disturbance, autonomic dysfunction
PARK8 (607060)	5% familial and 1-2% sporadic PD in European populations. G2019S most common mutation	*LRRK2*	AD	Tremor dominant Parkinsonism	Depression++ Apathy++ Hallucinations++ Anxiety+ Irritability+ Suicidal Ideation+	Amyotrophy, dystonia,
PARK2 (600116)	2.5% - 8.2% in <45 years	*Parkin*	AR	Onset <45 years, LL dystonia, L-dopa responsive, dyskinesias	Depression++ Psychosis+ Paranoia+ Panic Attacks+	Leg tremor, autonomic & peripheral neuropathy
PARK6 (605909)	Homozygous and compound heterozygous mutations accounting for 4-5% of AR disease & 1-2% of sporadic cases	*PINK1*	AR	Young-onset, slow disease progression, L-dopa responsive	Depression+ Anxiety+ Schizophrenia+ OCD+	-
PARK7 (606324)	Very rare <1% of EOPD cases	*DJ-1*	AR	Young-onset, slow disease progression, L-dopa responsive	Anxiety+ Psychosis+	Amyotrophic lateral sclerosis, scoliosis, blepharospasm
Gaucher's disease (168600)	1 in 20,000 live births	*GBA*	AR	Typical patterns of Lewy body disease.	Depression++ Anxiety++ Apathy++ Psychosis++	Hepatosplenomegaly, liver dysfunction, skeletal disorders
Niemann Pick Type C (257220: *NPC1*, 607625: *NPC2*)	1:100,000-150,000 live births	*NPC1 & NPC2*	AR	Cerebellar ataxia, saccadic disturbance, supranuclear gaze palsy	Psychosis+ Hallucinations+ Behavioural disturbance+	Dysphagia, Dysarthria, Epilepsy, Cataplexy, Cognitive impairment

Key: AD: Autosomal Dominant, ADHD: Attention Deficit Hyperactivity Disorder, AR: Autosomal Recessive, L-dopa: levodopa, LL: lower limb, OCD: Obsessive Compulsive Disorder, PD: Parkinson's disease. + Reported in large case series, ++ Reported in case-control studies, - no features reported to date., ≠ no psychiatric symptoms reported in large case series (n>5) or case-control studies.

Table 2: Heredodegenerative disorders

Disorder	Epidemiology	Causative gene	Inheritance	Motor phenotype	Psychiatric phenotype	Additional characteristics
Huntington's disease (613004)	5-7/100,000 in Western populations	*HTT*	AD	Chorea, Dystonia, Bradykinesia, Rigidity	Depression++ OCD++ Psychosis++ apathy+ irritability+ aggressive behaviour+	Cognitive impairment, Dysarthria, Dysphagia, falls
Dentatorubral-pallidoluysian atrophy (DRPLA) (607462)	0.2-0.7/100,000 in Japan.	*ATN1 (CAG repeat)*	AD	Myoclonus, Ataxia, Chorea	Psychosis+ Depression+ Anxiety+ Irritability+	Seizures, dementia
Wilson's disease (606882)	30 per million population	*ATP7B*	AR	Chorea, tremor, dystonia, parkinsonism	Depression++ Mood disorder++ Psychosis+ Irritability+ Personality change+ Anxiety+	Hepatosplenomegaly Cognitive impairment Dysarthria
Pantothenate Kinase associated neurodegeneration (PKAN) (234200)	Rare	*PANK2*	AR	Typically childhood onset, extrapyramidal features, rapid immobility. Atypical: onset 2^{nd}-3^{rd} decade, slower progression, maintained mobility	Behavioural disturbance++ Depression++ Emotional lability++ OCD+	Dysarthria, psychomotor delay
PLA2G6-associated neurodegeneration (PLAN)/PARK14 (603604)	Rare	*PLA2G6*	AR	Sub-acute onset dystonia-parkinsonism	Behavioural disturbance+ Impulsivity+ Emotional lability+	Eye movement abnormalities, pyramidal tract signs, cognitive decline
Beta-propeller protein-associated neurodegeneration (BPAN) (234200)	Rare	*WDR45*	X-linked dominant	L-dopa responsive dystonia, parkinsonism, ataxia, spasticity	≠	Epilepsy, dementia, sleep disturbance, ocular defects, Rett-like hand stereotypies
Mitochondrial membrane protein-associated neurodegeneration (MPAN) (614298)	Rare	*C19ORF12*	AR	Gait disturbance, spastic paraparesis, dystonia	Emotional lability+ anxiety+ compulsions+ hallucination+ depression+	-
COASY Protein Associated Neurodegeneration (CoPAN)	Rare	*COASY*	AR	Spasticity, dystonia, paraparesis with later	≠	Cognitive impairment

(615643)				parkinsonism		
PARK9 Kufor-Rakeb disease (606693)	Rare	*ATP13A2*	AR	Rapidly progressive parkinsonism, facial-faucial-finger mini-myoclonus, vertical supra-nuclear gaze palsy	Psychosis+ Hallucinations+	Cognitive impairment, axonal peripheral neuropathy

Key: AD: Autosomal Dominant, ADHD: Attention Deficit Hyperactivity Disorder, AR: Autosomal Recessive, L-dopa: levodopa, OCD: Obsessive Compulsive Disorder.
+ Reported in large case series, ++ Reported in case-control studies, - no features reported to date, ≠ no psychiatric symptoms reported in large case series (n>5) or case-control studies.

Table 3: Genetic Dystonia

Disorder (MIM number)	Epidemiology	Causative Gene	Inheritance	Motor Phenotype	Psychiatric Phenotype	Additional Clinical Characteristics
DYT1 (605204)	Mutation frequency: 0.17/100,000	GAG deletion of *TorsinA*	AD with reduced penetrance(~30%)	Range from mild focal dystonia to generalised form	Early onset recurrent major depression++	-
DYT2 (224500)	Unknown	No gene as yet identified	Suggested AR	Predominantly LL dystonia with possible subsequent generalisation	Nil reported to date	Identified in Sephardic Jewish and Spanish gypsy families.
DYT3 XDP/Lubag's disease (313650)	Worldwide: <1/1,000,000 Philippines: overall 1/322000, men 1/4000	*TAF1*	X-Linked	Focal/segmental dystonia with later generalisation. Parkinsonian features in later stages	Depression++ Anxiety++ Social phobia++ Agoraphobia++	-
DYT4 Whispering dysphonia (602662)	Unknown	*TUBB4*	AD	Craniocervical dystonia with prominent laryngeal dystonia. Frequent generalisation	Nil reported to date	Thin face and body habitus. Partial response to alcohol and propranolol.
DYT5a Segawa's disease (600225)	0.5/1,000,000 (Nygaard 1993)	*GCH1*	AD with reduced penetrance	LL dystonia with subsequent generalisation. Diurnal fluctuation. Parkinsonism, dystonic tremor	Depression+ anxiety+ OCD+	Spastic paraparesis.
DYT5b (605407)	Rare	*TH*	AR	Hypokinesia, rigidity and encephalopathy	≠	-
DYT5b (612716)	Rare	*SPR*	AR	Onset 1st year of life, diurnal fluctuation, ataxia, myoclonus	Inattention+ Irritability+ Anxiety+ Hyperactivity+ Aggression+ OCD+	Delayed motor development, cognitive impairment
Vesicular Monoamine Transporter 2 (193001)	Rare	*SLC18A2*	AR	Hypotonia, parkinsonism, dystonia	Depression+	Developmental delay, improved motor symptoms with dopamine agonists, worsening with L-dopa
Aromatic L-amino acid decarboxylase deficiency (608643)	Rare	*DDC*	AR	Hypotonia, oculgyric crises	Irritability+ Emotional lability+	Developmental delay
Dopamine Transporter Deficiency Syndrome (613135)	Rare	*SLC6A3*	AR	Early infantile and juvenile parkinsonism dystpnia	Irritability+	
DYT6 (609520)	Unknown,	*THAP1*	AD (~60% penetrance)	Adult onset torsion dystonia. Prominent cranio-cervical and laryngeal involvement	Nil reported to date	Women more commonly affected than men

DYT7 (602124)	Unknown	No gene as yet identified	Unknown	Focal dystonia typically involving neck, eyes or hands	Nil reported to date	-
DYT8 Paroxysmal Non-Kinesigenic Dyskinesia (609023)	Rare	*MR-1*	AD	Intermittent attacks lasting 10 minutes-1 hour. Dystonia, chorea, ballism, blepharospasm	Nil reported to date	Attacks precipitated by alcohol, coffee, stress, exercise.
DYT10 Paroxysmal Kinesigenic Dyskinesia (614386)	1/150,000	*PRRT2*	AD (incomplete penetrance)	Attacks of isolated/mixed dystonia, chorea, athetosis, ballism.	Depression+ ADHD+ Behavioural disturbance+	Associated with other clinical phenotypes: ICCA, episodic ataxia, hemiplegic migraine
DYT11 Myoclonus Dystonia (604149)	Rare	*SGCE*	AD (reduced penetrance due to maternal imprinting)	Truncal & UL myoclonus +/- cervical/hand dystonia.	OCD++ GAD++ alcohol dependence++ Depression++ Personality disorder+	Motor symptoms typically alcohol responsive. Additional clinical characteristics observed with WGD cases
DYT12 Rapid-onset Dystonia Parkinsonism (182350)	Rare	*ATP1A3*	AD with reduced penetrance	Sudden onset raustro-caudal pattern of dystonia and gait instabiliity	Psychosis++ Anxiety++ Depression++ Suicidal ideation+	Symptoms typically develop in response to a physical or psychological stressor
DYT13 (607671)	Unknown	No gene as yet identified	AD	Idiopathic torsion dystonia (predominant upper body and cranio-cervical involvement)	Nil reported to date	-
DYT15 (607488)	Reported in a single 4-generation family	No gene as yet identified	Possible AD	Myoclonic dystonia involving trunk, hands and upper limbs	Nil reported to date	Alcohol responsive
DYT16 (603424)	Reported in two consanguineous Brazilian families and a single German case	*PRKRA*	AR	2 forms: 1) pure generalised dystonia 2) dystonia-parkinsonism	Aggression+	Cognitive impairment reported in two cases
DYT17 (612406)	Reported in single consanguineous Lebanese family	No gene as yet identified	AR	Primary focal torsion dystonia with segmental or generalised spread	Nil reported to date	-
DYT18 GLUT1 Deficiency Syndrome 2 (138140)	1 in 90,000	*SLC2A1*	AD	Dyskinetic episodes, typically distal lower limb dystonia. May be triggered by exercise or hunger	≠	Associated with ataxia, spasticity, seizures, encephalopathy and haemolytic anaemia.
DYT20 Paroxysmal Non-Kinesigenic Dyskinesia 2 (138140)	Reported in single 4-generation Canadian family	No gene as yet identified	AD	Intermittent dystonia with symmetrical involvement of the hands and feet	Nil reported to date	-
DYT21 (614588)	Reported in single large Swedish family	No gene as yet identified	AD (incomplete penetrance)	Focal dystonia, predominantly blepharospasm and torticollis.	Nil reported to date	-

DYT23 (614860)	Reported in single German family	No gene as yet identified	AD	Adult onset cervical dystonia with head and limb tremor	Nil reported to date	-
DYT24 (615034)		*ANO3*	AD	Adult-onset cervical dystonia with laryngeal involvement and upper limb tremor	Nil reported to date	-
DYT28 (617284)	Reported in 31 unrelated individuals worldwide	*KMT2B*	AD	Childhood-onset progressive dystonia, initially involving the lower limbs and progressing to the orofacial region	Anxiety+ ADHD+ Obsessive-Compulsive traits+ self-harm behaviours+	Dysmorphic facial features, microcephaly, mild/moderate cognitive impairment, eye movement abnormalities, seizures

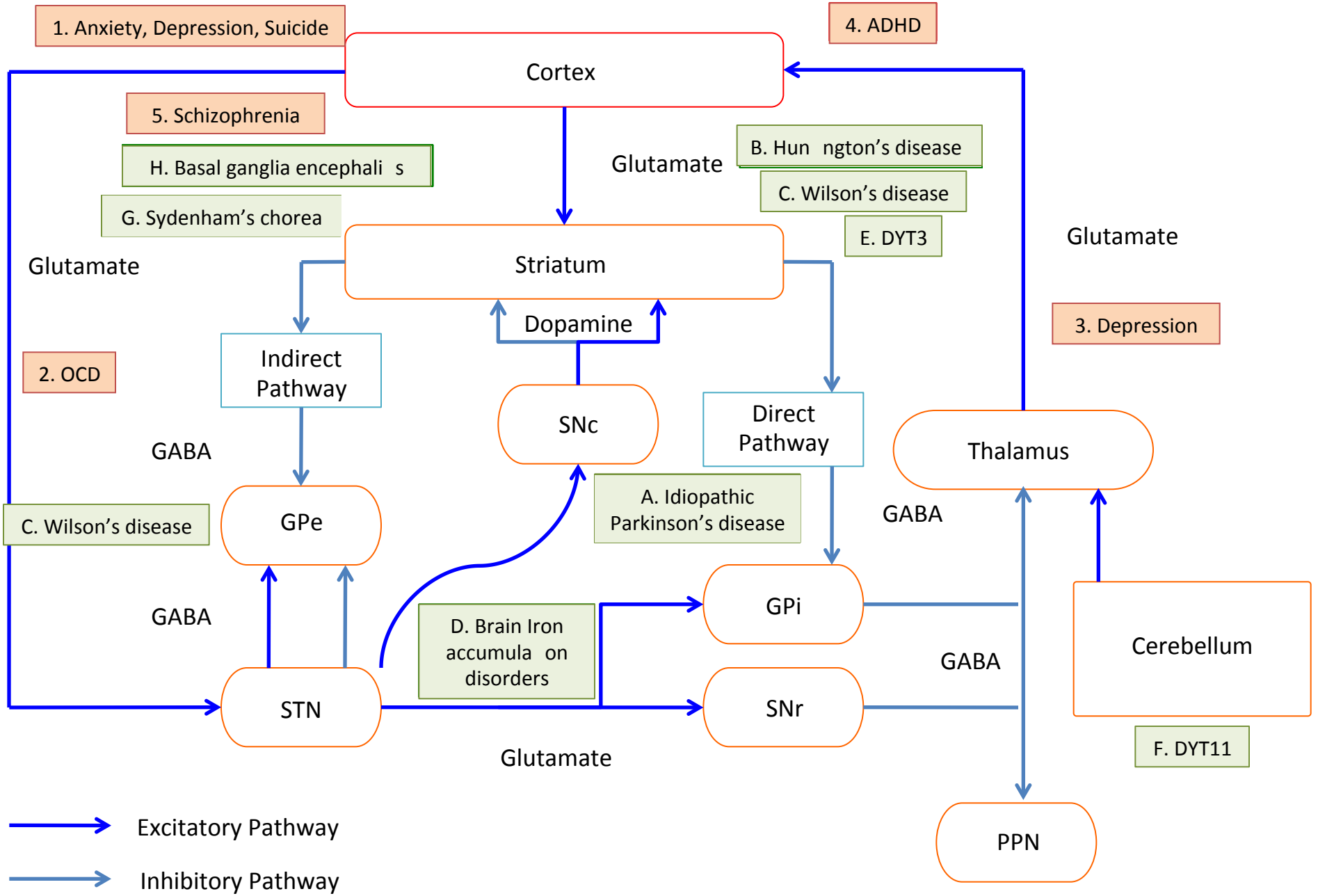
Key: AD: Autosomal Dominant, ADHD: Attention Deficit Hyperactivity Disorder AR: Autosomal Recessive, DBS: Deep Brain Stimulation, GAD: Generalised Anxiety Disorder, GP: Globus Pallidus Internus,$_i$ ICCA: infantile convulsions with choreoathetosis, OCD: Obsessive-Compulsive Disorder. +Reported in large case series, ++Reported in case-control studies, - no features reported to date, ≠ no psychiatric symptoms reported in large case series (n>5) or case-control studies, nil reported to date: indicates no psychiatric symptoms reported in case reports, small case series (n<5), large case series (n>5) nor case-control studies.

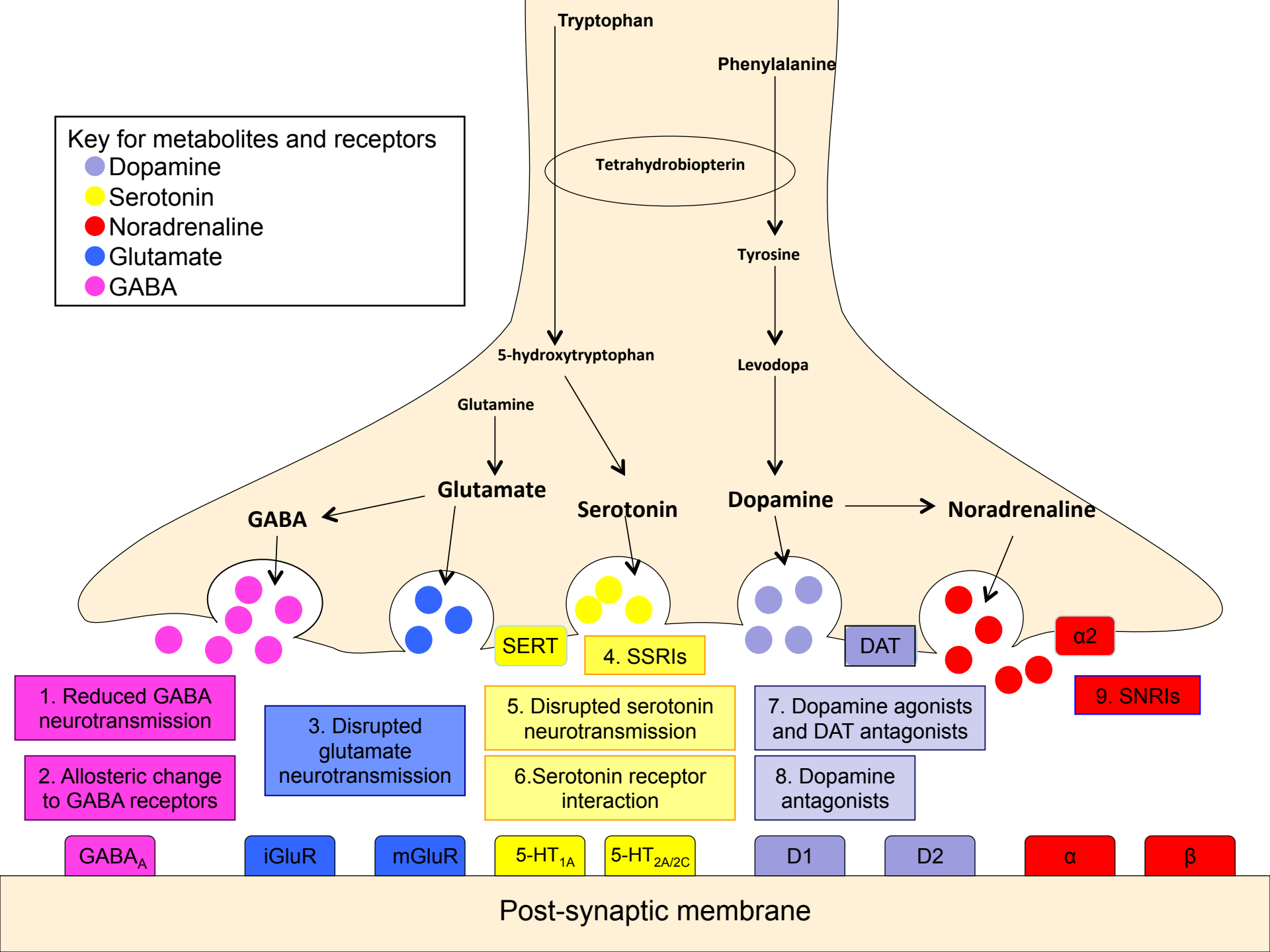
Table 4: Immunological disorders

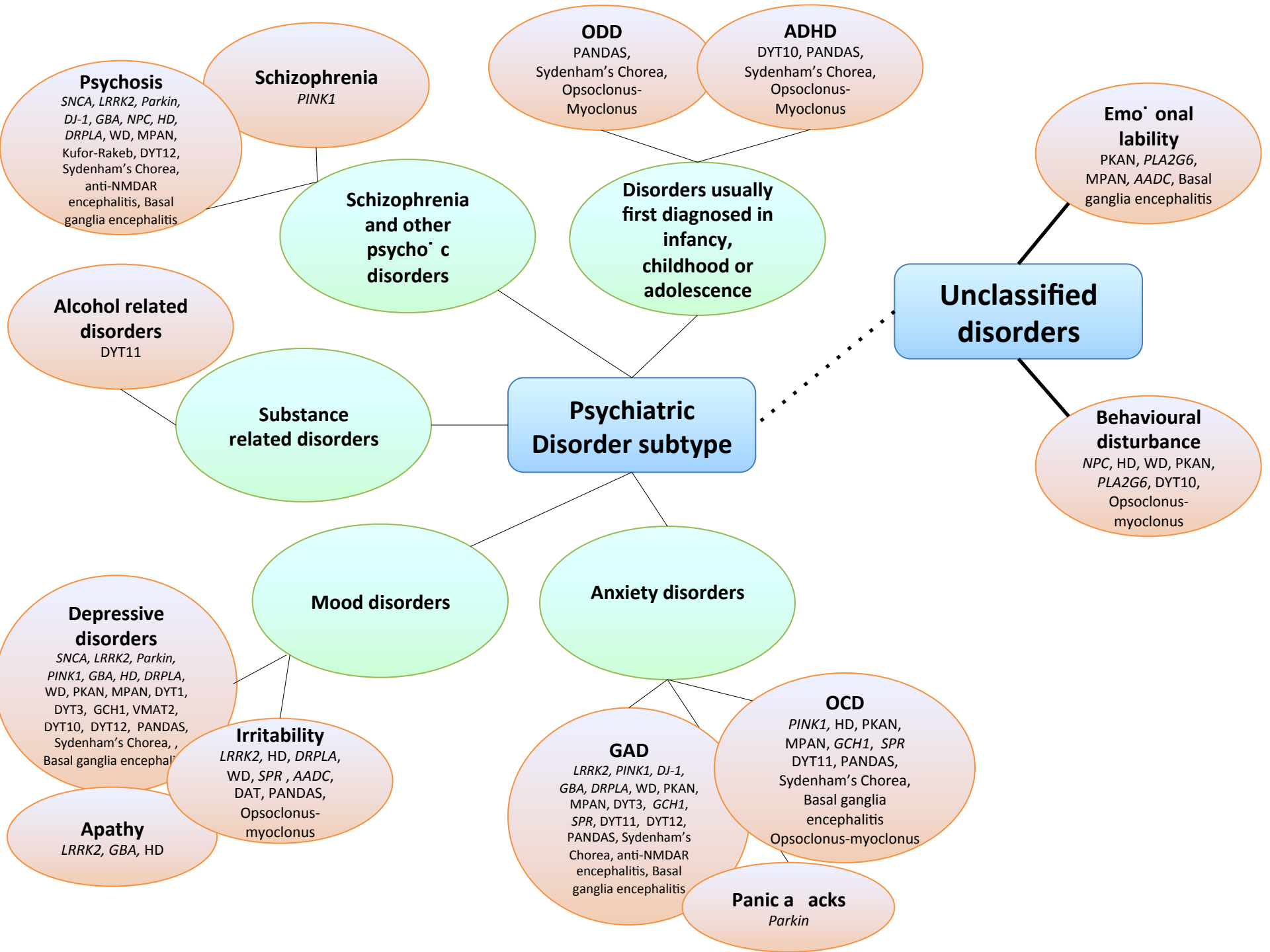
Disorder	Epidemiology	Pathophysiology	Inheritance	Motor Phenotype	Psychiatric phenotype	Additional clinical characteristics
Paediatric Autoimmune Neuropsychiatric Disorders associated with streptococcus (PANDAS), Paediatric Acute neuropsychiatric syndrome (PANS)	Uncertain, probably rare.	Unknown. Infection associated immune dysregulation of unclear aetiology.	Uncertain, increased rates of autoimmunity and tics, OCD in first degree relatives	Relapsing-remitting hyper-motor activity including: tics (e.g. eye blinking, tongue protrusion)	Anxiety++ Irritability++ Oppositional disorder++ OCD+ ADHD+ Depression+ Emotional lability+	Deterioration in handwriting Higher rates of tonsillectomies and adenoidectomies.
Sydenham's chorea	0.5/100,000 annual incidence of ARF in school age children. 10-30% of children with ARF affected by Sydenham's chorea	Associated with Group A Streptococcal infection.	Increased rate of ARF in families of those diagnosed with Sydenham's chorea	Chorea, hypotonia, dysarthria and saccadic slowing	OCD++ ADHD++ Depression++ Psychosis++ Anxiety+ Oppositional disorder+ Behavioural disturbance+	Most cases have symptomatic improvement at 2 years.
NMDA Receptor Encephalitis	Approximately 4-10% of all patients hospitalised for encephalitis	Hypofunction of the NMDA receptor secondary to autoantibodies targeting the NR1a subunit.	Not known	Orofacial dyskinesias, choreoathetosis, dystonia, myoclonus, tremor and ballismus	Psychosis++Hallucinations++ Personality change++ Anxiety+ Agitation+ Paranoia+ Aggression+ Hyperactivity+	Progression to encephalopathy, movement disorder,, mutism, catatonia and autonomic instability.
Basal ganglia Encephalitis	Rare, <2% of all encephalitis in children	Autoantibodies targeting D2 receptor in the basal ganglia	Not known	Dystonia, parkinsonism, chorea, oculogyric crisis	Depression+ Anxiety+ Apathy+ Agitation+ Psychosis+ OC symptoms+ Emotional lability+	Encephalopathy, radiological basal ganglia involvement
Opsoclous-myoclonus ataxia	Rare, 2-3% of children with neuroblastoma	Unknown, possible autoantibodies or other acquired immune	Not known	Myoclonus, ataxia, opsoclonus	Irritability++ Aggression+ Behavioural disturbance+ Opposition defiant disorder+	Cognitive impairment, language difficulties,

	mechanisms	OCD+ ADHD+

Key: ADHD: Attention Deficit Hyperactivity Disorder, ARF: Acute Rheumatic Fever, GAD: Generalised Anxiety Disorder, OCD: Obsessive-Compulsive Disorder.
+Reported in large case series, ++Reported in case-control studies.


1. Anxiety, Depression, Suicide
4. ADHD
Cortex
5. Schizophrenia
H. Basal ganglia encephali s
Glutamate
B. Hun ngton's disease
C. Wilson's disease
G. Sydenham's chorea
E. DYT3
Glutamate
Striatum
Glutamate
3. Depression
Dopamine
2. OCD
Indirect Pathway
SNc
Direct Pathway
Thalamus
GABA
A. Idiopathic Parkinson's disease
GABA
C. Wilson's disease
GPe
GPi
Cerebellum
GABA
D. Brain Iron accumula on disorders
GABA
STN
SNr
F. DYT11
Glutamate
PPN
Excitatory Pathway
Inhibitory Pathway


Key for metabolites and receptors
Dopamine
Serotonin
Noradrenaline
Glutamate
GABA
Tryptophan
Phenylalanine
Tetrahydrobiopterin
Tyrosine
5-hydroxytryptophan
Levodopa
Glutamine
Glutamate
GABA
Serotonin
Dopamine
Noradrenaline
SERT
4. SSRIs
DAT
α2
9. SNRIs
1. Reduced GABA neurotransmission
2. Allosteric change to GABA receptors
3. Disrupted glutamate neurotransmission
5. Disrupted serotonin neurotransmission
6.Serotonin receptor interaction
7. Dopamine agonists and DAT antagonists
8. Dopamine antagonists
GABA$_A$
iGluR
mGluR
5-HT$_{1A}$
5-HT$_{2A/2C}$
D1
D2
α
β
Post-synaptic membrane


Psychosis
SNCA, LRRK2, Parkin, DJ-1, GBA, NPC, HD, DRPLA, WD, MPAN, Kufor-Rakeb, DYT12, Sydenham's Chorea, anti-NMDAR encephalitis, Basal ganglia encephalitis
Schizophrenia
PINK1
ODD
PANDAS, Sydenham's Chorea, Opsoclonus-Myoclonus
ADHD
DYT10, PANDAS, Sydenham's Chorea, Opsoclonus-Myoclonus
Schizophrenia and other psychotic disorders
Disorders usually first diagnosed in infancy, childhood or adolescence
Emotional lability
PKAN, PLA2G6, MPAN, AADC, Basal ganglia encephalitis
Unclassified disorders
Alcohol related disorders
DYT11
Substance related disorders
Psychiatric Disorder subtype
Behavioural disturbance
NPC, HD, WD, PKAN, PLA2G6, DYT10, Opsoclonus-myoclonus
Mood disorders
Anxiety disorders
Depressive disorders
SNCA, LRRK2, Parkin, PINK1, GBA, HD, DRPLA, WD, PKAN, MPAN, DYT1, DYT3, GCH1, VMAT2, DYT10, DYT12, PANDAS, Sydenham's Chorea, , Basal ganglia encephali
Irritability
LRRK2, HD, DRPLA, WD, SPR , AADC, DAT, PANDAS, Opsoclonus-myoclonus
Apathy
LRRK2, GBA, HD
GAD
LRRK2, PINK1, DJ-1, GBA, DRPLA, WD, PKAN, MPAN, DYT3, GCH1, SPR, DYT11, DYT12, PANDAS, Sydenham's Chorea, anti-NMDAR encephalitis, Basal ganglia encephalitis
OCD
PINK1, HD, PKAN, MPAN, GCH1, SPR DYT11, PANDAS, Sydenham's Chorea, Basal ganglia encephalitis Opsoclonus-myoclonus
Panic attacks
Parkin