ADVANCES IN NEUROPSYCHIATRY

Neuropsychiatry of the basal ganglia

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This review aims to relate recent findings describing the role and neural connectivity of the basal ganglia to the clinical neuropsychiatry of basal ganglia movement disorders and to the role of basal ganglia disturbances in "psychiatric"' states. Articles relating to the relevant topics were initially collected through MEDLINE and papers relating to the clinical conditions discussed were also reviewed. The anatomy and connections of the basal ganglia indicate that these structures are important links between parts of the brain that have classically been considered to be related to emotional functioning and brain regions previously considered to have largely motor functions. The basal ganglia have a role in the development and integration of psychomotor behaviours, involving motor functions, memory and attentional mechanisms, and reward processes.

Basal ganglia disorders are characterised by the presence of abnormal movements, psychiatric signs and symptoms, and varying degrees of cognitive impairment. Traditionally, more attention has been paid to the motor abnormalities in these conditions than to the mental state and cognitive disturbances, despite the fact that these can be as disabling and distressing for both the patients and their carers as the abnormal movements. However, in recent years there has been increasing recognition of the non-motor consequences of disease of the basal ganglia. At the same time there have been major advances in our understanding of the functional anatomy and physiology of the basal ganglia and associated brain regions. This article will review recent developments in these fields, with particular reference to information helpful in understanding why basal ganglia diseases are so often associated with the development of psychiatric symptoms.

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WHAT ARE THE BASAL GANGLIA?

Anatomy of the basal ganglia

The basal ganglia are large subcortical nuclear masses. The naming of the basal ganglia has led to some confusion over the years as has the debate as to which structures should be included within this description. It is agreed that core components comprise the caudate nucleus, the nucleus accumbens, the putamen, and the globus pallidus. The caudate nucleus and putamen together are sometimes called the striatum, and the putamen and globus pallidus are together sometimes described as the lentiform nucleus.

More recently an additional term, "ventral striatum" has been introduced to describe those parts of the basal ganglia closest to limbic structures and that are involved in cognitive and behavioural functions. The term includes the nucleus accumbens.[1] This structure can be divided into a central core surrounded on its medial and ventral sides by a shell. The core is generally similar to the rest of the caudate/putamen and it is difficult to identify a distinct dorsal border between the core and the neighbouring striatum. The shell has a rich dopaminergic innervation arising from the ventral tegmental area and dense innervation from the basolateral complex of the amygdala.[2]

Some authorities also include the amygdala within a consideration of the basal ganglia as it occupies an important position between the basal ganglia and the limbic system and may play a part in integrating activity between these structures.[3] Embryological evidence supports inclusion of the amygdala. The basal ganglia develop as part of the telencephalon, from the basal region of the mantle layer of the primitive telencephalic vesicle and the amygdala complex develops from the same tissue mass as the caudate nucleus.[3]

These findings emphasise that there are important links between parts of the brain that have classically been considered to be related to emotional functioning and parts of the brain that have in the past been considered to play a part largely in motor functions.

Connections of the basal ganglia

The complex consequences of disturbances to the basal ganglia may be better understood when the connections of these structures are considered. The striatum is the major receptive component of the basal ganglia. It receives massive inputs from much of the cerebral cortex, from the substantia nigra, and the lateral amygdala, among other regions. Recent ideas regarding the connections of the basal ganglia have been shaped by descriptions of parallel circuits linking cortical association areas, through basal ganglia and thalamus, back to cortex.

Initially two loops were suggested, a motor loop passing through the putamen and an association or complex "loop" passing through the caudate. Subsequently Alexander *et al*,[4] using the "motor" circuit as a model, described evidence for other circuits. These circuits followed the general

Abbreviations: PD, Parkinson's disease; SSRIs, selective serotonin re-uptake inhibitors; ECT, electroconvulsive therapy; HD, Huntington's disease; PSP, progressive supranuclear palsy; WD, Wilson's disease; FD, Fahr's disease; GTS, Gilles de la Tourette's syndrome; OCD, obsessive-compulsive disorder; ADHD, attention deficit disorder with hyperactivity

principle that they were segregated from each other and that output from the circuits were transmitted to restricted portions of the frontal lobe. These circuits, which have subsequently become well known and have formed the basis of further investigation of basal ganglia function, were named as the "motor circuit", the "occulomotor circuit", the "dorsolateral prefrontal circuit", the "lateral orbitofrontal circuit" and the "anterior cingulate circuit". In their paper defining these circuits Alexander *et al*[4] note that this list is unlikely to be exhaustive and that there may well be additional parallel circuits whose identification is currently precluded by the lack of appropriate data.

Each circuit receives multiple corticostritate inputs that are progressively integrated in their passage through the basal ganglia, ultimately to a restricted area of the thalamus and from there back to a single cortical area. It has been concluded that in each of these circuits an important function is the integration or funnelling of multiple corticostritate inputs back to a single cortical area. It is also concluded that the multiple cortical areas that input into each circuit are functionally related to each other and also usually interconnected.[4] This pattern of organisation also seems to apply to the other output nucleus from the basal ganglia, the pars reticulata of the substantia nigra.[5]

Examining connections between the basal ganglia and prefrontal cortex has led to the following conclusions.[6 7] Firstly, several areas of the prefrontal cortex that are involved in higher order cognitive function, particularly some aspects of working memory, are targets of output from the basal ganglia. Secondly, the basal ganglia output channels related to cortical motor areas are topographically separate from those projecting to areas of prefrontal cortex associated with cognitive functions. Given this topographical organisation it would be easy to conclude that dysfunction of different regions in the output nuclei of the basal ganglia would lead to different patterns of symptomatology: lesions in one area may lead to problems with motor behaviour whereas lesions in others may result in cognitive dysfunction. However, although there are broad functional subdivisions within the basal ganglia, studies in primates looking at patterns of neural activity in various conditioning tasks, suggest that that it is probably the case that motor, cognitive, and motivational systems can interact within the caudate and putamen.[8] Whereas input derived from the limbic system has preferred distribution in the ventral striatum, some information also reaches the caudate and putamen.

Indeed, although initial experiments suggested that the striatal output pathways were clearly segregated, more recently investigations in rats and monkeys have indicated that the circuits send colaterals to two or three of the possible striatal recipient structures implying that the simple pathways are not an accurate description.[9] In addition, the connections between the striatum and the dopaminergic system have been recognised as not obeying the parallel segregated principle.[10] However, the connections of the striatum with the dopaminergic system have not been incorporated into the existing schemes of basal ganglia thalamocortical circuits. Joel and Weiner[10] suggest that an additional means by which the limbic circuit can interact with the motor and associative circuits is provided by the connections of the limbic pallidum (the most ventral parts of the globus pallidus, innervated by the ventral striatum) with the dopaminergic system, as the limbic pallidum itself innervates regions of the dopaminergic system which provide dopamine input to the motor and associative striatum.

An increasingly complex picture of neurotransmitter distribution, interaction, and function in the basal ganglia has emerged involving dopamine, serotonin, acetylcholine, excitatory amino acids, GABA, nitric oxide, neuropeptides and adenosine and it is likely that much more remains to be clarified. (See for instance, Calabresi *et al* [11] for review.) In terms of clinical applications however, current employment of existing knowledge relates largely to interactions between dopamine and acetylcholine in Parkinson's disease, and between dopamine and serotonin in modulating the motor side effects of psychotropic medication.[12]

Functions of the basal ganglia

Although oversimplifications can clearly be misleading, a two word summary of the role of the basal ganglia that may be helpful in considering this region is that these structures are involved in "psychomotor behaviour".[13] More detailed considerations have proposed that the basal ganglia serve a computational role,[14 15] with each component being part of highly complex and widely distributed neural networks in which sequences "of activation and inhibition are coded in both time and space with exquisite precision". "This network endows the brain with a high level of neural plasticity necessary to modulate motor behaviour in a subtle manner and to overcome motor deficits through ingenious strategies".[9]

Functions in which the basal ganglia seem to be involved include motor learning, sequencing, and movements, attentional allocation and filtering, working memory, and implicit learning and memory. These operations may play a part in both the acquisition of behaviours that are performed automatically and in enhancing the efficiency of higher order processors such as those involved in working memory.[16]

There is also evidence that the basal ganglia may have an important role in reward processes.[17] Rewards elicit approach and consummatory behaviour. They increase the frequency and intensity of behaviour leading to such outcomes, serving as positive reinforcers. Dopaminergic pathways have been shown to play an important but rather non-specific part in reward, discriminating poorly between different rewards. However, neurons discriminating well between different rewards are found in the orbital frontal cortex. Hence, different aspects of rewards are processed by different neuronal systems. The relatively homogeneous dopaminergic response may be a reinforcement signal broadcast to many neurons in the striatum and the frontal cortex, generating a teaching signal for inducing synaptic changes underlying the reinforcement of reward directed behaviour. It has been proposed that this system may speed the learning of rewarding behaviours.[18]

NEUROPSYCHIATRIC MANIFESTATIONS OF BASAL GANGLIA DISORDERS

In this section we describe mental and cognitive manifestations in various basal ganglia disorders. Abnormalities in the basal ganglia are central to the pathophysiology of these conditions although pathology outside the basal ganglia—for example, in the thalamus, the frontal cortex, or aminergic nuclei—are also often present to various degrees. This distinction is relevant in attempting to understand the substrate of the various neuropsychiatric symptoms found in these disorders.

Parkinson's disease

The cardinal manifestations of Parkinson's disease (PD) are tremor, rigidity, bradykinesia, and postural instability. The prevalence of PD is 100–200/100 000 in western countries.[19] The age of onset is generally between 50 and 65 years but early and late onset cases are often reported. It is mostly sporadic but some genetic and environmental factors have been proposed. Pathologically, PD is characterised by depigmentation, loss of dopamine containing neurons, and the presence of Lewy bodies in the substantia nigra, locus coeruleus, nucleus basalis, raphe and ventral tegmental area.

Psychiatric manifestations

Up to 70% of patients with PD exhibit psychiatric symptoms[20 21]; hence they are a common occurrence.

Affective disturbances

Depression is the most frequent mental disorder in patients with PD, being found in up to 50% of cases.[22] The variation in prevalence is most likely due to the use of different diagnostic criteria and screening tools for depression, and also to the clinical overlap between signs and symptoms of depression and some of those of PD (for example, fatigue, slowness). Major depressive episodes may account for up to 20% of all cases of depression, whereas "minor" depression may account for the rest.[23]

There is considerable debate regarding the aetiology of depression in PD. The biological hypothesis postulates that the neurochemical deficits in PD (mainly deficits in noradrenaline (norepinephrine) and serotonin but also possibly deficits due to reduced dopaminergic stimulation of the orbitofrontal prefrontal cortex which is the origin of cortical input to serotonergic nuclei) are responsible for causing depression.[24] The psychosocial hypothesis postulates that it is having a chronic and disabling illness what causes depression.[25] An alternative mixed hypothesis proposes that the neurobiological abnormalities of PD make patients more vulnerable to react with depression to environmentally negative stimuli, through dysfunction of selective attention mechanisms leading to cognitive distortions predisposing to depression.[26]

The profile of depressive phenomena in PD is characterised by dysphoria, pessimism, irritability, sadness, and suicidal ideation; with guilt, self blame/reproach, and delusions—seen less often.[22] Possible risk factors for depression in PD are female sex, younger age at onset of PD, prominence of right sided signs, and prominence of bradykinesia and gait disturbance.[23 27] The presence of depression may correlate with faster progression of the disease and faster decline in cognitive status and activities of daily living.[28 29] No association has been clearly established, however, between severity of PD and presence or severity of depression.[30] Depression may also predate the motor features of PD,[31] adding weight to the neurobiological hypothesis of depressive aetiology.

Patients with PD and depression show worse cognitive function than those without depression, particularly in tests of prefrontal/executive function.[32] Depression is also considered a risk factor for the development of dementia.[33]

Levodopa and dopamine agonists may occasionally be associated with mood changes ranging from a sense of wellbeing to euphoria and mania. The rate of hypomania is close to 2%,[34] and that of euphoria is about 10%.[35] Patients with pre-existing bipolar disorder may experience "high" mood swings when treatment with dopaminergic drugs is started. Antiparkinsonian medications affect depressive symptoms in a variable way; mild symptoms may improve but more severe depression tends to be unaffected by treatment with dopaminergic drugs. In patients with PD but without previous psychiatric illness who develop "on-off" phenomena, some may develop fluctuating mood states ranging from depression and anxiety while "off" to being euthymic when "on" and in a few patients, to the occasional manifestation of hypomanic symptoms during times of peak dose dyskinesias. Other mental and behavioural disorders related to drug treatment for PD are confusional states, altered sexual behaviour such as increased libido, hypersexuality, sexual deviation, and various paraphilias, and also sleep disturbances such as vivid dreams and nightmares, and multiple awakenings.

Anxiety

Anxiety disorders (such as generalised anxiety, panic and phobic disorders) are found in up to 40% of patients with PD,[36] especially in younger patients. These symptoms are often comorbid with depression. In some patients panic attacks occur with the onset of "freezing" or "off" episodes. This could lead to overuse of PRN medication such as subcutaneous apomorphine, to "prevent" freezing. Anxiety in PD has been related to noradrenergic and serotonergic deficits as well as psychosocial factors.

Apathy

This is another frequent symptom seen in PD, and although often related to depression it can be found in patients without mood disorder. Apathy is associated with cognitive dysfunction (mainly executive impairment),[21] and it has been suggested that its presence is related to dysfunction of forebrain dopaminergic systems.[37]

Psychosis

Psychotic symptoms occur in up to 40% of patients with PD,[38] and are mainly related to treatment with dopaminergic and/or anticholinergic medications. Psychoses unrelated to treatment are rare, and often associated with the onset of dementia.

Visual hallucinations are the most prevalent drug induced psychotic symptom in PD, occurring in 20% of cases.[39] Hallucinations in other sensory modalities are rarer. Visual hallucinations may appear with any of the drugs commonly used to treat PD. They are more commonly nocturnal and involve formed objects or animals. They are often associated with sleep disturbances. Some patients have benign visual hallucinations that are vivid and non-threatening, and in clear consciousness with preservation of insight and cognition. Those hallucinations associated with treatment with anticholinergic drugs tend to be threatening in nature and are often related to delirium.[39] Hallucinations may develop shortly after starting treatment for PD in some patients. More often, however, several years of treatment, increasing age, and multiple drug therapy are risk factors for the occurrence of hallucinations.

The prevalence of delusions ranges from 3% to 30%[40] and is greater when high doses of medication are used. Delusions tend to appear more than 2 years after initiating treatment with levodopa.[41] They are typically paranoid in nature but delusions of jealousy have also been described. Schizophrenic formal thought disorder is rare. Increasing age and presence of dementia are risk factors for the development of delusions.

Hedonistic homeostatic dysregulation

This is a behavioural disorder initially described in association with substance misuse and addiction.[42] In patients with PD it has been associated with stimulation, by dopamine substitution therapy, of the central dopaminergic pathways which are linked to the brain's reward system.[43] The patients affected by this syndrome (generally male and with young-onset PD) take increasing quantities of dopamine substitution therapy, either orally or subcutaneously, despite having severe dyskinetic side effects. This is accompanied by a behavioural and mood disorder which includes drug seeking behaviour, punding (a stereotyped motor behaviour in which there is repetitive handling and examining of inanimate objects), hypersexuality, urge to aimlessly walk, pathological gambling and shopping, appetite disturbance, hoarding of drugs, and hypomania or manic psychosis. This disorder is particularly problematic when subcutaneous apomorphine is used (see Giovannoni *et al*[43] for review).

Cognitive impairment and dementia

Patients with PD may have a range of cognitive deficits. The most common problems are in the domains of speed of mental processing (bradyphrenia), executive function, visuospatial function, and memory (retrieval related problems),[44] and are in keeping with a subcortical pattern of dysfunction caused by disruption of frontosubcortical circuits and a dopaminergic deficit in the mesocortical pathway. The presence of cognitive impairment increases with disease duration. Cognitive impairment has been estimated to be present in 19% of patients with PD without dementia.[45]

Dementia in patients with PD may affect around 15%-40% of cases,[46] occurring more often in older patients with late onset PD.[33] Other reported risk factors for the development of dementia in PD are low socioeconomic status and education,

greater severity of extrapyramidal signs, susceptibility to psychosis or confusion in response to levodopa, and depression.[33 47 48] Depression is, however, no more common in patients with dementia than in those without[49]; whereas psychotic symptoms are more frequent in demented patients.

Psychiatric and cognitive complications of surgical treatment for PD

Unilateral pallidotomy has been reported to improve the motor state of patients (mainly contralaterally), and also dyskinesias bilaterally. After pallidotomy there have been reports of transient and mild cognitive problems mainly affecting frontosubcortical functions (for example, executive functions and memory).[50 51] For mental state changes, there have been reports of depressive and psychotic episodes, euphoria, and behavioural problems related to frontosubcortical circuit syndromes.[51 52] However, 1 year follow up studies have found no significant neuropsychological changes after unilateral pallidotomy.[53]

For unilateral thalamotomy (effective for severe tremor), no significant neurobehavioural morbidity has been found in a large series.[54]

Deep brain stimulation with implanted electrodes in the thalamus, pallidus, or subthalamic nucleus, seems to be safer than ablative procedures in respect of cognitive and mental morbidity; especially when it is unilateral.[55]

Treatment of psychiatric disorders in PD

Selective serotonin reuptake inhibitors (SSRIs) are perhaps the drugs of choice[56] for treating depression in PD. Tricyclic antidepressants may be effective in people with PD but their side effect profile often makes them more unsuitable in this often relatively elderly patient group. There have been anecdotal reports that SSRIs may exacerbate parkinsonism, but this seems uncommon.[56] The SSRIs may interact with selegiline causing a serotonin syndrome. Electroconvulsive therapy (ECT) is also a very effective and safe treatment for depression in PD, and it often transiently improves motor function.[57]

The reduction of the dose of levodopa or dopaminergic drugs has generally been the first step in the treatment of hallucinosis or delusions in PD when at all possible. Classic neuroleptic drugs are best avoided but there are reports that atypical antipsychotic drugs such as risperidone[58] or olanzapine,[59] are useful. Most literature, however, has been gathered regarding the use of clozapine which has been found to be effective (although it requires haematological monitoring for neutropaenia). Indeed, one recent randomised double blind placebo controlled trial[60] reported improvement of drug induced psychoses in patients who continued taking antiparkinsonian medications. In this trial antipsychotic efficacy was found with low doses of clozapine (up to a maximum of 50 mg/day, mean 25 mg/day), without worsening of parkinsonian symptoms. Other newer atypical antipsychotic drugs such as quetiapine may also have their place. As often occurs with neuropsychiatric conditions, there is a lack of randomised controlled studies of psychotropic drugs for the treatment of various mental conditions in PD.

Huntington's disease

Huntington's disease (HD) is an autosomal dominant disorder with a 100% penetrance caused by an unstable nucleotide repeat (CAG) in the IT15 gene on chromosome 4. Its prevalence has been estimated to be between 4.1 and 7.5/100 000,[61] and its onset to be typically between the ages of 35 and 50 although early and late onset forms have been described. The trinucleotide repeat expansions range from 36 to 121 repeats, and they are inversely correlated with age of onset. The repeats inherited from the paternal line are more likely to expand and the clinical features may appear at an earlier age in successive generations (genetic anticipation). There are diagnostic and predictive genetic tests available. The main clinical features are movement disorder (which includes chorea, athetosis, dystonia, motor restlessness, tremor, and myoclonus), personality change, psychiatric disorder, and cognitive impairment. No association between length of CAG expansion and psychiatric or motor disorder has been found. In HD there is degeneration of the striatum (mainly caudate nucleus) with selective loss of GABAergic neurons, and also degeneration of the deep layers of the cortex (mainly frontal).

A wide range of psychiatric disturbances are seen in HD and a recent study of 52 patients with HD found affective symptoms in 98% of the group[62] in the month before assessment. In many patients the psychiatric disturbances are the earliest manifestations of the disease and it has been suggested that this is because early pathological changes in HD occur in more ventral striatal regions receiving input from areas of the prefrontal cortex involved in behavioural processes.[63]

Depression

This is a very common mental disturbance in HD with a frequency of up to 40% of cases.[61] Of these, up to 20% meet criteria for major depressive episodes. Depression may predate the movement disorder by several years, but it may occur at any stage during the course of the disease. Phenomenologically, depression in HD is very similar to major depression and may be accompanied by mood congruent psychotic symptoms. Relatives of patients with HD and depression are significantly more likely to have mood disorder than relatives of patients without depression.[64]

The suicide rate for patients with HD is about five times higher than that of the general population,[65] and has been reported to be as high as 12.7%.[66] It can occur at any stage; even in patients not yet diagnosed.

The aetiology of depression in HD is unclear. In addition to psychosocial causes, depression may be caused by the brain disorder itself; having been related to dysfunction of limbic-caudate and frontocaudate circuitry.[67] PET data have demonstrated that depression in HD is associated with orbitofrontal and inferior prefrontal hypometabolism, implying selective dysfunction of the paralimbic regions of the frontal cortex.[68]

Mania

Up to 10% of patients may have manic/hypomanic episodes.[61]

Apathy and irritability

These behaviours are best regarded as part of the organic personality change that these patients develop as a result of frontosubcortical circuit dysfunction. Apathy can be found at any time during the course of the disease but worsens over time once present. Irritability and aggressiveness are also frequent. Severe irritability occurs in up to a third of patients.[61] Irritability and hostility can be also found in subjects at high risk of developing HD.[69]

Violent behaviours have at various times been reported to occur at higher than expected rates in patients with HD. In a national study, Jensen *et al* [70] investigated the relative importance of the psychosocial environment and of gene coding for HD on the development of criminal behaviour in patients and their relatives. They found a general increase in convictions and a specific increase in drunken driving in men with HD compared both with non-affected male first degree relatives and male controls from the general population. They conclude that the increased criminal behaviour in men with HD may be genetic, but mediated through the personality changes that are a recognised feature of the disease. It should be noted, however, that it has also been reported that cognitive decline may significantly precede apparent disease onset and that this decline is correlated with number of trinucleotide repeats,[71]

suggesting that cognitive state may also account for some of the apparently genetic basis to behavioural disturbance. Nevertheless and not surprisingly, the observations that no significant differences in convictions were found between female patients with HD, female first degree relatives, and female controls, and that even within the male patients, most did not have any convictions, emphasises that simply carrying the HD gene is at most only a partial determinant underlying criminal behaviour in this group. The study also serves to place in context the more anecdotal reports of increased criminality in HD, demonstrating that this is only an issue in a small proportion of patients.

Pychosis

Psychotic symptoms are considerably less common than non-psychotic psychiatric symptoms in people with HD. The prevalence of psychosis in HD has been reported to be 4% to 12%.[61 65] Patients with a younger age at onset seem to be at a higher risk for psychosis.[65] Typical presentations are of poorly defined delusions, specific delusional states, or schizophrenia-like psychoses. Symptoms of psychosis may gradually fade away as the cognitive impairment progresses.[65] The pathophysiology of psychosis in HD is unknown.

Obsessive-compulsive phenomena

True obsessive-compulsive disorder in people with HD is rare[72] but patients may become obsessively preoccupied about cleanliness or about the manner in which particular activities are performed. It has been suggested that the development of these symptoms, although possibly explained by local caudate damage associated directly with the pathophysiology of HD, may alternatively arise out of disturbances to frontostriatal pathways. In view of the anatomical connections reviewed above, it may turn out to be a more general principle that behavioural associations of basal ganglia disease arise variably from intrinsic basal ganglia mechanisms or from disruption to circuits incorporating these structures.

Cognitive impairment

Cognitive impairment is present early in the course of the disease. Slowing of cognitive speed and difficulties with mental flexibility appear soon after the onset of the chorea. Impairment of verbal fluency is one of the earliest cognitive deficits that can be measured. Memory disturbance is also common and is more related to retrieval problems than to actual encoding. Later on, frank executive dysfunction occurs, and the cognitive impairment gradually worsens to dementia. This pattern of deficits is suggestive of frontosubcortical dementia. In a detailed clinical study of 52 patients with HD it was found that the behavioural and psychiatric consequences of the condition occurred independently of motor and cognitive symptoms, at least early in the course of the disease.[62]

Treatment

There is no particular treatment for apathy. Stimulant drugs worsen the chorea and can induce psychosis. The use of high potency neuroleptic drugs should be avoided in patients with apathy as this becomes worse.

Irritability and aggression should be treated first by identifying and altering the triggers. There is evidence that SSRIs can be of help.[65] Carbamazepine and sodium valproate are also useful.

Guidelines for treating depression in people with HD are similar to those described for PD.

Progressive supranuclear palsy (Steele-Richardson-Olszweski's disease)

Progressive supranuclear palsy (PSP) is a degenerative disorder characterised by supranuclear opthalmoplegia (mainly of vertical gaze downwards) with normal vestibulo-ocular reflexes, pseudobulbar palsy with prominent dysarthria, axial extrapyramidal rigidity (neck and upper trunk), and cognitive impairment. Pathologically, PSP is considered a "tauopathy" and the main neurochemical deficits found relate to dopamine (in the nigrostriatal pathway) and acetylcholine.

The disease has a prevalence of 1.4/100 000[73] and it affects between 4% and 6% of those with an akinetic-rigid syndrome attending a movement disorders clinic. Its age of onset is between 45 and 75 years (mostly after the age of 60). The most frequent initial symptoms are gait abnormalities and falls (62%) and mental disturbance (22%).

Cognitive impairment is very common in PSP, affecting 80% of patients to some degree.[74] The pattern of deficits is characteristic of the so called "subcortical dementia": with bradyphrenia, executive deficits, forgetfulness (related to retrieval difficulties), visuospatial problems, and frontal lobe-type behavioural abnormalities (inertia, stereotyped behaviour, apathy, disinterest, environmental dependency, etc) which are most likely related to denervation of the prefrontal cortex. Mood symptoms of depression and lability have also been described. Much less often, these patients may present with a psychotic illness.

Wilson's disease

Wilson's disease (WD) is also known as hepatolenticular degeneration. It is an autosomal recessive disorder of copper metabolism. The abnormal gene (ATP7B) is located in chromosome 13.[75] In WD caeruloplasmin fails to bind copper, and its excretion by the liver is impaired. The excess of copper accumulates first in the liver and then in the brain and other tissues.

The prevalence of WD is 1/40 000 and the incidence is 3/100 000.[76] Typical age of onset is during the 2nd and 3rd decades, but may be delayed as late as the 5th decade.

The cerebral pathology of WD mainly affects the lenticular nuclei (pallidus and putamen), but abnormalities can also be found in the caudate, thalamus, cerebellar nuclei, and white matter. The main neurological abnormalities are rigidity, dystonia, chorea, athetosis, dysarthria, and tremor. It is considered that psychiatric presentation of WD occurs in up to a third of cases, and that a pure psychiatric presentation occurs in 20% of cases,[77 78] with personality disturbances, mood abnormalities, and cognitive dysfunction being the most common psychiatric symptoms. Around 50% of patients will have mental disturbances at some point during the course of the disease.[78] Psychiatric manifestations tend to occur with neurological forms of WD rather than with hepatic ones. Cognitive impairment occurs in up to 25% of patients[79] and it adopts a frontosubcortical pattern as described in other conditions above.

Depression occurs in 30% of cases of WD and suicidal behaviour may occur in between 4% and 16%.[79] Mania can occur but is less frequent than depression.

Psychosis has been described in WD and can indeed be the initial presentation but its frequency is very low at about 2% with WD.[78]

Specific treatment of WD is with copper chelating or copper depleting agents. It must start as soon as possible and should be continued for life. Most neurological and psychiatric manifestations of WD can improve with this treatment; however, the early diagnosis and initiation of the treatment is essential as it has been suggested that improvement of symptoms is limited to the first 5 years of symptomatic illness and the first 2 years of treatment.[80] The improvement may not be noticed until the first 6 months of treatment have elapsed.[80] Some degree of cognitive deficit and personality change may persist despite treatment.

Fahr's disease (idiopathic clacification of the basal ganglia)

In Fahr's disease (FD) there is a progressive calcium deposition in the basal ganglia. Onset between the ages of 20

and 40 has been associated with schizophreniform psychoses and catatonic symptoms, and onset between the ages of 40 and 60 has been associated with dementia and choreoathetosis.[81] Depression is also very common, but mania much less so.[76] In a series of patients with Fahr's syndrome, 50% had psychiatric problems,[82] and these were associated with more extensive calcification. The pattern of cognitive impairment found in FD is of the frontosubcortical type. The commonest neurological features of FD are parkinsonism, chorea, dystonia, tremor, gait disturbance, dysarthria, seizures, and myoclonus.[79]

Fahr's disease must be distinguished from Fahr's syndrome where there are specific causes of calcium deposition in the basal ganglia such as hypoparathyroidism. It should also be differentiated from "radiological" basal ganglia calcification without clinical features and across the general population the frequency of basal ganglia calcification on CT is about 0.9%.[79] The true prevalence of FD is not known; that of Fahr's syndrome may be around 0.5%.[76] Although FD has generally been considered to be idiopathic, recently a linkage to chromosome 14q in a family with multiple affected members has been described,[83] in which genetic anticipation was also found.

It has been suggested that tissue damage by free radicals or by abnormal iron transport may trigger calcification.[76] The pallidus is most affected, but depositions can also be found in the putamen, caudate, thalamus, dentate nucleus, corona radiata, and cerebellar white matter.[81]

There is no specific treatment for FD. In Fahr's syndrome, the primary causes should be treated. Patients with FD are more susceptible to neuroleptic malignant syndrome when treated with antipsychotic drugs.

Gilles de la Tourette's syndrome

Gilles de la Tourette's syndrome (GTS) (also known as Tourette's disorder) is characterised by a combination of both multiple motor and one or more vocal (phonic) tics which wax and wane and occur many times a day in bouts with varying intensity and complexity.[84–86] Its onset occurs before the age of 18 years. The syndrome is also associated with a range of abnormal mental states and behaviours including coprophenomena, echophenomena, palilalia, obsessive-compulsive behaviour, depression, anxiety, self-injurious behaviour, attention deficit hyperactivity disorder, and personality disorder. However, attention deficit hyperactivity disorder and obsessive-compulsive behaviours may differ phenomenologically from their "primary" counterparts.[86]

The prevalence of GTS has been estimated to be of the order of 5 per 10 000 with a male to female ratio of 4:1. Its cause is without doubt genetic, although the precise inheritance pattern is still unclear.[85] There is some evidence of genomic imprinting with earlier age at onset in maternally transmitted cases.[87] It has also been suggested that perinatal insults and streptococcal or viral infections may affect the expression of GTS.[86]

Although the neurochemical basis of GTS is unclear, there is evidence of involvement of the dopaminergic system, based on the findings of the beneficial effects of dopamine blocking agents on the motor signs of GTS, and of their exacerbation with dopamine enhancing drugs. In addition, several aspects of dopaminergic system activity using imaging techniques have been investigated in GTS, yielding contradictory results. Studies of striatal postsynaptic D2 receptors have failed to demonstrate any abnormality[88–90] except in one study in which higher striatal binding of IBZM to D2 receptors was found in the clinically more affected sibling of twin pairs.[91] Studies of striatal presynaptic dopaminergic function have shown increased[92 93] or unchanged[94] binding to dopamine reuptake sites in patients with GTS. A study of striatal vesicular monoamine transporter type 2 did not find any abnormalities.[95] In a postmortem study, however, increased binding of a tracer to striatal dopamine reuptake sites was found.[96] Obsessive-compulsive behaviours are also recognised in a proportion of patients with GTS. It has been suggested that for obsessive-compulsive behaviours to also be present, the pathology of GTS, whatever its nature, must extend from putamen to ventral striatal regions.[97]

Treatment of GTS

Increased understanding of basal ganglia pathophysiology has not yet led to the development of novel treatment strategies. Dopamine antagonists, such as haloperidol, sulpiride, and pimozide, have successfully been used to treat motor and vocal tics. Atypical neuroleptic drugs such as risperidone and olanzapine have also been used, although the literature is limited to case reports and small series of patients.

For the treatment of attention deficit hyperactivity disorder in GTS the most widely used drug is clonidine. Obsessive-compulsive phenomena may respond to treatment with selective serotonin re-uptake inhibitors or clomipramine. Behavioural or cognitive-behavioural therapy may also be useful. Drugs of choice for depression are the selective serotonin reuptake inhibitors. Psychosocial management is also paramount.

THE ROLE OF THE BASAL GANGLIA IN GENERATING NEUROPSYCHIATRIC SYMPTOMS

Obsessive-compulsive disorder (ODC) and related conditions

There is evidence of basal ganglia dysfunction from imaging studies of OCD, with both reduced and increased volumes of caudate nuclei reported.[98 99] Increased caudate metabolism has been found to reduce after effective treatment of the OCD[100] and in provoked or activated conditions, patients with OCD have shown increased caudate blood flow.[101]

Such imagining studies point to the importance of limbic and orbitofrontal basal ganglia thalamocortical circuits in the pathogenesis of OCD. However, Sheppard *et al*[102] have pointed out that symptom provocation studies in simple phobic patients have produced increased regional cerebral blood flow in regions such as the orbitofrontal cortex, anterolateral prefrontal cortex and left thalamus, suggesting that these areas, which also exhibited increased blood flow during provocation of OCD symptoms, may actually mediate non-specific anxiety.

In autism stereotyped, ritualistic and repetitive behaviours including compulsive rituals and difficulties in tolerating changes in routine or environment, are characteristic. It has been suggested that these behaviours may share related pathophysiological mechanisms with those implicated in obsessive-compulsive behaviours seen in OCD and GTS.[103] These authors therefore used high resolution MRI to perform volumetric analyses from the bilateral caudate, putamen, and globus pallidus regions in a group with autism and a control group. The nucleus accumbens was not included in any of the regions. No differences were detected in volumes of the globus pallidus or the putamen. Significant enlargement of the total caudate volume, in the order of 8%, was found in the subjects with autism. This greater caudate volume was proportional to the increased total brain volume and enlargement of other brain structures previously reported in the patients with autism.[104] Interestingly, they also showed a significant negative correlation between ritualistic and repetitive behaviours and caudate volumes although not between social or communication aspects of the autism and caudate volumes. The authors suggested that this might be because the former behaviours in autism are associated with abnormal control relations between the caudate and other brain areas. The nature of these behavioural correlations suggests that the generation of

the observed phenomenology of autism may in part arise out of a disturbed relation between basal ganglia and other brain regions.

Another condition linked clinically and genetically to GTS and OCD is attention deficit disorder with hyperactivity (ADHD). There is evidence from neuroimaging studies of striatal dysfunction in patients with ADHD.[105 106] Disturbed caudate function may, across these disorders, result in abnormal activation of the frontal lobes and thalamus, via dorsal lateral prefrontal and orbitofrontal circuits, leading to their overlapping clinical characteristics.

Schizophrenia

Evidence from various research methodologies supports the suggestion that basal ganglia disturbance has a role in schizophrenia.[107] Given the evidence that OCD is associated with disturbances of basal ganglia function, it is of interest to note that patients with schizophrenia who also have obsessive-compulsive symptoms seem to manifest more motor abnormalities.[108] In a study of 76 patients with schizophrenia, 16% were found to also have OCD.[109] Controlling for medication exposure, this subgroup had more severe akathisia and more abnormal involuntary movements, possibly arising out of the increased basal ganglia pathophysiology in this group, suggested by the presence of additional OCD symptoms. In support of this, an abnormal asymmetry in regional glucose metabolism in the basal ganglia during a catatonic episode[110] has previously been reported.

Limbic structures,[111] the mesolimbic dopamine system, and the D3 receptor have been implicated in schizophrenia. It has been demonstrated that D3 mRNA positive neurons are highly concentrated in the ventral striatum and in regions projecting to the ventral striatum including the extended amygdala.[112] D3 receptors are also present in large numbers in the limbic striatal-pallidal thalamic loop, exhibiting segregation from the D2 receptor enriched motor loop (although D2 and D3 receptors and their mRNAs are colocalised in many sensory regions and in areas of the thalamus and amygdala). Joyce and Gurevich[112] have shown that there are 45% increases in D3 receptor numbers in ventral striatal neurons and their striatopallidal targets in patients with schizophrenia and that this increase is reduced by antipsychotic treatment. They suggest that the increased number of D3 receptors in the ventral striatum and its efferents found in unmedicated schizophrenic patients results in altered neural processing through the striatal pallidal thalamic cortical "limbic" loop. Antipsychotic down regulation of the D3 receptor mediated limbic loop may provide a means of resolving the imbalance in this loop.

The cause of this increase in D3 neurons has been suggested by experiments in rats.[113] Early damage in the ventral striatum of neonatal rats leads to an initial reduction in the number of D3 mRNA positive neurons in the ventral striatum. However, by 1 month after birth there is an up regulation of D3 binding sites and by 3 months there is an increase in D3 mRNA. Hence, the early loss of dopamine seems to modify the normal developmental regulation of expression of D3 mRNA. If the dopamine system of schizophrenic patients had been damaged subtotally in early development similar charges to those found in the animal studies may develop.

Investigation of critical sites of action of antipsychotic drugs also implicates areas of the ventral striatum in schizophrenia. It has been demonstrated that in animals neurons can be identified which show increased expression of immediate early genes such as C-FOS in response to contact with antipsychotic drugs.[114] Increased C-FOS expression has been found in the dorsal striatum after the use of haloperidol and other typical antipsychotic agents that cause extrapyramidal symptoms, but not with clozapine and other atypical drugs. By contrast, C-FOS expression in the medial prefrontal cortex has been elicited only by atypical drugs. It is interesting to note that all typical and atypical antipsychotic agents tested so far have been found to consistently increase the expression of C-FOS in the nucleus accumbens. This suggests that the accumbens may be a common locus for antipsychotic action and an important site of neurochemical control in schizophrenia.[115 116]

The finding that "atypical antipsychotic drugs", particularly clozapine with its $5HT_2$ antagonist action, are effective in control of both positive and negative symptoms of schizophrenia, while causing fewer extra-pyramidal side effects, has focused attention on the interactions within the striatum between dopamine and serotonin systems. There is evidence, reviewed by Kapur and Remington,[16] that blockade of nigral $5HT_2$ receptors can lead to disinhibition of striatal dopamine release. These mechanisms are likely to be the focus of future therapeutic drug development programmes in schizophrenia.

Depression

Two interrelated basal ganglia thalamocortical circuits may be of particular relevance to the pathophysiology of depression.[117] These are the limbic circuit, connecting the amygdala and anterior cingulate with the ventral striatum and the medial and ventral lateral prefrontal cortex and the prefrontal circuit connecting the basal ganglia, particularly the head of the caudate, and the lateral prefrontal cortex.

Functional imaging studies have suggested pathological interactions between the amygdala and related parts of the ventral striatum and prefrontal cortex in the genesis of major depression.[118] Studies in patients with depression have demonstrated that in the amygdala there are positive correlations between regional cerebral blood flow and glucose metabolism and depression severity ratings. During antidepressant treatment that induces and maintains symptom remission, amygdala metabolism decreases towards normal.[119]

Suggestions that basal ganglia disturbances may play a part in depression also come from clinical observations. Depression is associated with several neuropsychological deficits including some suggestive of prefrontal dysfunction.[120] It has been shown that depressed patients performing a complex planning task fail to demonstrate the normal control finding of increased caudate activation with increasing task difficulty.[121]

The depression that is seen in Parkinson's disease and Huntington's disease, as discussed above, provides further evidence of a role for basal ganglia in the development of depression and animal studies have shown an association with the nucleus accumbens and locomotion and motivation.[122] A more recent study in humans has also suggested that the nucleus accumbens may be an important focus of pathological change in patients with affective disorders. In postmortem brain examinations of 16 patients with mood disorders compared with controls, the patients had a 32% smaller left nucleus accumbens, 20% smaller left and right external pallidum, and 15% smaller right putamen.[123]

Areas of periventricular and white matter hyperintensity have been demonstrated in a relatively large number of reports of patients with bipolar affective disorder and in elderly patients with unipolar depression.[124] Several MRI studies have also reported increased incidence of caudate hyperintensities in elderly depressed patients.[125–127] The presence of subcortical hyperintensities may be associated with poor prognosis in patients with late onset depression in the absence of a family history of early age onset of depression. These findings have been taken to suggest that cerebrovascular insufficiency in subcortical and basal ganglia structures may precipitate some cases of late onset affective disturbance.[126] As such lesions generally do not occur often in younger patients it is difficult to establish whether the same mechanisms could operate in the aetiology of depression in younger patients.

Given the similarities between psychomotor retardation in depression and the bradykinesia of PD, as well as the increased

incidence of depression in PD, dopamine systems have also been explored in people with depression. Laasonen-Balk *et al*[128] considered the hypothesis that depression is associated with a net decrease in dopamine transmission, thereby leading to secondary or compensatory up regulation of D2 receptor density as well as to compensatory down regulation of DAT density, (assessed by measuring ^{123}I-βCIT uptake), leading to increased synaptic transmission. What they found was significantly higher βCIT uptake ganglia in patients with major depression. On the basis of these unexpected results they subsequently suggested that up regulation of DAT may be the primary alteration, leading in turn to lower intrasynaptic dopamine concentration and to lower dopaminergic neural activity. It is known that antidepressant treatment leads to an increase in striatal dopamine release. These findings all suggest that dopaminergic neurotransmission is lower during periods of depression.

Addiction

The nucleus accumbens has been described as a "limbic-motor interface"[129] and receives a dense innervation from the basolateral complex of the amygdala.[130] It has been hypothesised that the extended amygdala is a critical structure in which neuroadaptations underlie both the positive effects of many drugs of misuse and the opposite processes that are set in train after abstinence or withdrawal of these drugs. However, the precise mechanisms by which the amygdala influences drug reinforcement, whether directly or out of a relation with the nucleus accumbens, remain unclear.[131] It has also been suggested that connections of the orbitofrontal cortex with the ventral tegmental area, the nucleus accumbens, and the thalamus are important for drug reinforcement and addiction.[132] This circuit may be particularly important in the compulsive aspect of drug taking behaviour. In early cocaine withdrawal, metabolism is increased in the orbitofrontal cortex and striatum and the magnitude of this increase is significantly correlated with the intensity of craving.[132] By contrast, cocaine misusers after prolonged withdrawal had significantly reduced metabolism in regions including orbitofrontal cortex compared with non-abusing controls.

For dopamine activity, cocaine misusers after several drug free weeks showed significantly lower dopamine D2 receptor activities in the striatum, with this reduction persisting for 3 to 4 months after detoxification. It has been suggested that this reduction in dopamine transmission is associated with the anhedonia of acute drug withdrawal.[42] According to this model, relapse to drug taking is largely driven by the desire to avoid the anhedonic (hypodopaminergic) state associated with withdrawal. However, as Jentsch and Taylor[133] point out, the situation is also more complicated in that several stimuli such as restraint and stress can increase dopamine release from the nucleus accumbens. It has been suggested that dopamine in the nucleus accumbens is not related to pure distinctions between reward and anhedonia but rather that the system is important for gating behaviour in the face of varying motivations and demands. Hence, increased dopamine release in the nucleus accumbens may affect the ability of stimuli with incentive motivational qualities to generate behavioural responses regardless of whether the stimuli are associated with rewarding or aversive events. This model of addiction has therapeutic implications as it implies that drugs that could modify this activity could change reward experiences and the drives leading to drug seeking behaviour.

SUMMARY

Although the basic anatomy of the core structures of the basal ganglia has been known for many years, it is only more recently that the role of these structures in circuits linking a wide range of cortical and subcortical regions has become clear. This in turn has led to an understanding of the clinical observations that movement disorders with demonstrable basal ganglia pathology are often accompanied by cognitive and psychopathological disturbances. Similarly, consideration of the extrinsic connections of the basal ganglia, and in particular the strong links to limbic and prefrontal cortical structures, demonstrates that psychiatric conditions previously only considered in behavioural terms in fact have a detectable underlying biology involving the ventral striatum or its connections. In the future this knowledge may be expected to open new therapeutic avenues.

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