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Putamen gray matter volumes in neuropsychiatric and neurodegenerative disorders

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Abstract

Putamen is enriched with dopamine and associated with dopamine-related phenotypes including many neuropsychiatric and neurodegenerative disorders that manifest with motor impairment, impulsive behavior, and cognitive deficits. The gray matter volume of the putamen is age-dependent and genetically controlled. In most neuropsychiatric and neurodegenerative disorders, including Parkinson's spectrum disorders, Huntington's disease, dementia with Lewy bodies, Alzheimer's disease, multiple sclerosis, attention deficit hyperactivity disorder, developmental dyslexia, and major depression, the putamen volume is significantly reduced. On the other hand, in individuals with bipolar disorder, schizophrenia spectrum disorders, especially neuroleptics-medicated patients with schizophrenia, autism spectrum disorders, obsessive-compulsive spectrum disorders, and cocaine/amphetamine dependence, the putamen volume is significantly enlarged. Therefore, the putamen volume may serve as a structural neural marker for many neuropsychiatric and neurodegenerative disorders and a predictor of treatment outcomes in individuals afflicted with these conditions. We provided an overview of the genetic bases of putamen volume and explored potential mechanisms whereby altered putamen volume manifests in these neuropsychiatric and neurodegenerative conditions, with a specific focus on dopaminergic processes.

Keywords

Putamen; GMV; dopamine; neuropsychiatric disorder; neurodegenerative disorder; genotype

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Together with the caudate nucleus and globus pallidus, the putamen forms the dorsal striatum, a main component of the basal ganglia to support a variety of motor and cognitive functions. The putamen is connected with the substantia nigra, globus pallidus, claustrum, thalamus, and many regions of the cerebral cortex [1, 2]. The nigrostriatal pathway, one of the major dopaminergic pathways in the brain and connecting the substantia nigra pars compacta (SNc) with the dorsal striatum, is best known for its association with the development of Parkinson's disease (PD) [3]. A primary function of the putamen is to regulate movement planning and execution [4–8] and support the learning processes during various cognitive and affective challenges [9, 10]. Although the literature has focused on the role of the putamen in cognitive motor control, this subcortical structure may be involved in other functions, such as language [11], motor imagery [12, 13], and emotional processing [14–16], as well as in clinical conditions not directly related to motor control dysfunction, such as chronic pain [17, 18]. Imaging and lesion studies have implicated the putamen in a wide variety of neuropsychiatric conditions, including, for example, altered emotional processing in obsessive-compulsive disorder (OCD) [19], attention impairment in attention deficit hyperactivity disorder (ADHD) [20], and reward seeking in frontotemporal dementia [21].

Putamen functions are supported by a variety of neurotransmitters, including dopamine, gamma-aminobutyric acid, acetylcholine, and encephalin, among which dopamine is the most widely studied. The putamen receives extensive dopaminergic projections from the SNc. Loss of dopaminergic neurons in the SNc and consequent depletion of dopaminergic inputs in the striatum results in shrinkage of both the SNc and striatum, as in PD [22–25]. Conversely, increases in neuronal numbers are usually related to the increased size in nuclear gray matter volume (GMV) [26]. In addition to dopaminergic innervation, the putamen also receives extensive glutamatergic projections from frontal cortical regions [1]. Via output nuclei the basal ganglia project to the thalamus, which in turn innervates the cortical regions, forming a topographically organized cortical-striatal-thalamic-cortical loop [1]. Thus, altered putamen volume would likely influence a wide variety of motor and cognitive functions, as occurs in many neuropsychiatric and neurodegenerative disorders.

Genetics of putamen volume:

The heritability of putamen volume is approximately 71–79% [27]. Genome-wide association studies (GWAS) identified at least 30 genes that might regulate the putamen volumes, including *KTN1* [27–30], *SLC39A8* [31, 32], *DCC* [29, 30, 33], *DLG2* [27, 29, 30, 33] and others [27, 29–32, 34]. These genes were previously implicated in various phenotypes, including PD [35, 36], Huntington's disease (HD) [37], ADHD [28], schizophrenia [33, 38], OCD [39], and others [27, 30]. Specifically, a common allele C of rs945270, a genetic marker at 3'-UTR of kinectin 1 gene (*KTN1*), showed genome-wide strongest ($p=1.1\times10^{-33}$), replicable, and specific effects on the putamen GMV [28, 29]. Three other markers at *KTN1*, i.e., rs2181743 (5'-UTR), rs8017172 (3'-UTR) and rs17253792 (3'-UTR), were also significantly associated with putamen GMVs [$p=4.0\times10^{-8}$, (6.7×10^{-34} to 3.0×10^{-14}) and 3.2×10^{-7}, respectively] [27, 30]. All of the common alleles G of rs8017172, T of rs17253792 and C of rs945270 significantly increased the *KTN1* mRNA expression in the putamen (p=0.049, 0.010 and 0.049, respectively) [40, 41].

Allele C of rs945270 showed a significant, positive effect on the severity of hyperactivity symptoms of ADHD patients. In boys, the C allele was associated with lower putamen activity during successful response inhibition in a cognitive control task; in girls, activation, most significantly in the right putamen, during reward anticipation in a monetary incentive delay task increased with the number of C alleles [28]. Another GWAS identified two SNPs at *DCC* (rs4632195) and *DLG2* (rs11233632) that affected putamen volume; and these two variants predisposed individuals to schizophrenia [33]. Most recently, a minor T allele of rs13107325 in *SLC39A8*, a gene implicated in the pathogenesis of schizophrenia, was associated both with greater putamen GMV and with lower mRNA expression of *SLC39A8* specifically in the putamen [31]. These genetic studies broadly support an association and shared genetic factors between putamen volume and neuropsychiatric and neurodegenerative disorders. Altered putamen volume may represent a risk or etiological factor of the neuropsychiatric conditions.

Putamen volume and neuropsychiatric and neurodegenerative disorders:

Putamen volume decreases with age [42] and shows a significant difference between men and women [43, 44]. The age-dependent reduction of GMV holds for bilateral putamen and both men and women [45], but appears to be more severe for right-hemispheric putamen [43].

Putamen volume decreases in most neuropsychiatric and neurodegenerative disorders:

Many neuropsychiatric and neurodegenerative disorders manifest with putamen-related motor control dysfunction. For example, individuals with Tourette Syndrome suffer difficulties in movement control; patients with PD exhibit “automatic” performance of previously learned movements [46]; and HD patients demonstrate significant involuntary movements or chorea. It has been reported that the putamen volume loss is associated with deficits in motor control [47]. Children with complex motor stereotypies demonstrated significant reductions in total putamen volume [48]. Further, many neuropsychiatric and neurodegenerative disorders, e.g., ADHD, are known to exhibit impulsive behavior, in relation to smaller post-commissural putamen volumes [49]. Together, these findings suggest an association of reduced putamen volume with neuropsychiatric and neurodegenerative disorders that manifest with motor control deficits and/or impulsivity behaviors.

The central pathological features of PD include the selective loss of dopaminergic neurons in the SNc and consequent dopamine depletion in the striatum. Individuals with PD demonstrate significant motor symptoms including tremors, rigidity, hypokinesia and postural imbalance [50]. Importantly, reported consistently across all independent studies, putamen volumes were significantly decreased in PD patients regardless of medication status [24, 51–54]. This reduction has also been observed in X-linked dystonia-parkinsonism (XDP) [55] and REM sleep behavioral disorder that reflects a pattern of neurodegeneration predicting the development of PD [56]. Furthermore, putamen is reported to decrease by 50.1% in volume, showing the greatest atrophy of all brain regions, in people with HD as compared with control subjects [57]. The atrophy of putamen appears at the time when motor symptoms manifest during the course of HD [58]. Atrophy of the putamen, as a

neurodegenerative trait, is also a feature of dementia with Lewy bodies (DLB) [59] and Alzheimer's disease (AD) [27, 60] and multiple sclerosis [61]. The decrease in putamen volume is linearly correlated with impairment in global cognitive performance [27, 60].

Putamen may also be involved in impulsivity trait or impulsive behavior that has long been linked to dopamine [62]. A critical dimension of personality, impulsivity represents a major symptom dimension of many neuropsychiatric disorders, including ADHD, bipolar disorder, antisocial personality disorder, borderline personality disorder, and some neurodegenerative diseases. Impulsivity or hyperactivity is perhaps best known in ADHD. In healthy people, the right putamen is smaller in volume than the left putamen [63]; however, children with ADHD (mostly unmedicated) more frequently have a smaller left than right putamen, and the reversal of this structural symmetry may relate to ADHD symptomology [63]. The primary pharmacological treatments for ADHD are methylphenidate (Ritalin) and amphetamine (Adderal) that block re-uptake of dopamine and norepinephrine into the pre-synaptic neurons and, as a result, increase the synaptic levels of the catecholamines. Of these two monoamines, increased availability of dopamine is generally considered the primary mechanism of the therapeutic effects of ADHD medications. In support, lesions within the dopamine-rich ventral putamen have been reported to increase the risk of ADHD in humans [64]. Furthermore, as described above, the putamen volume declines with age [42]; however, this shrinkage was independent of age in patients with ADHD and their unaffected siblings, suggesting a critical link to familial risk for ADHD [65]. In addition to ADHD, putamen volume may be related to other disorders that manifest with developmental delays in cognition. For example, individuals with developmental dyslexia show reduced left putamen volume, which is suggested to contribute to phonological deficits [66]. Decreased myelination of the ventral putamen has been associated with premature responding, a sign of impulsivity, in a serial reaction time task in youth [67].

More broadly, the basal ganglia are recognized as putative mediators of certain cognitive and behavioral symptoms of major depression. Patients with basal ganglia lesions exhibit significant affective symptomatology, including apathy, depressive mood, and psychosis. Depression patients demonstrate significantly smaller putamen [68, 69] and age-dependent putamen shrinkage is accelerated in young [70] (60–65 years) but not older [71] patients with major depressive disorder. Thus, the putamen may contribute to depressive psychopathology and represent a useful target for the treatment of MDD at younger ages.

Putamen volume increases in other neuropsychiatric disorders:

When the dopaminergic neurons are overly expressed in the nigrostriatal pathway, the dopamine-rich putamen may be enlarged, causing dopamine-excessive phenotypes such as bipolar disorder, schizophrenia spectrum disorders, including schizophrenia and schizotypal personality disorder, autism spectrum disorders, including autism and Tourette syndrome (TS), obsessive-compulsive spectrum disorders, including obsession and compulsion traits and OCD, and restless leg syndrome (RLS). Although other neurotransmitters are likely involved in the pathophysiology, abundant evidence suggests that schizophrenia and other psychoses are hyperdopaminergic disorders [72, 73]. Likewise, although studies have focused on histamine and other molecular systems, extensive evidence supports a

hyperdopaminegic state in TS and antidopaminergic medications represent the most effective treatment of TS [74]. PET imaging studies showed decreased striatal dopamine D2/3 receptor availability in both TS and OCD, reflecting higher endogenous dopamine levels in these disorders [75]. Finally, although the etiologies of RLS are far from clear, increased levels of the dopamine metabolite 3-ortho-methyldopa in the cerebrospinal fluid and significant decrease in dopamine D2 receptors in the putamen as shown in postmortem studies are consistent with a hyperdopaminergic state in RLS [76]. The neuropsychiatric conditions that involve hyperdopaminergic states all appear to be associated with increases in putamen volume.

A meta-analysis showed increases in right-hemispheric putamen volume in bipolar disorder [77]. Larger putamen sizes have also been reported in antipsychotic-naïve individuals with schizotypal personality disorder [78] or schizophrenia [79], suggesting that excessive dopamine may underlie schizophrenia spectrum disorders and that enlarged putamen may be an important neural marker of these disorders. The patients with enlarged putamen are usually sensitive to and benefit from treatment with antipsychotics that block dopamine neurotransmission [79–81]. In contrast, if dopaminergic hyperfunction is not a predominant cause, patients may not respond to typical antipsychotics that target primarily dopaminergic neurotransmission [82]. Perhaps as a compensatory response to the blockage by typical antipsychotics, the putamen may further expand to maintain dopaminergic neurotransmission [81, 83], consistent with the finding that the neuroleptic-medicated schizophrenia patients have larger putamen sizes [84]. Further, patients with good treatment outcomes have larger putamen than those with poor outcomes or healthy controls, in support of enlarged putamen as a physiological correlate of neuroleptic responsiveness and a predictor of treatment outcome [79–81].

Presynaptic transporters play a central role in maintaining physiological levels of synaptic dopamine by removing dopamine molecules from the synaptic terminals [85]. Cocaine acts by binding to the presynaptic dopamine transporters, blocking the removal of dopamine from the synapses and thus reducing the number of recyclable dopamine molecules [83, 86]. On the other hand, chronic cocaine use leads to down-regulation of post-synaptic dopamine receptors [86]. As a result, chronic cocaine use may result in putaminal hypertrophy as a compensatory process to produce more dopamine to maintain dopaminergic transmission. Individuals who engage in chronic use of psychostimulants, including cocaine and amphetamine, showed increases in putamen volume [83, 87–89]. These findings are intriguing because cocaine induced oxidative stress and vasoconstriction and would typically lead to GMV loss, as observed in all brain regions other than the putamen. It is possible that chronic exposure to stimulants may have led to down-regulation of dopamine receptors, and, as a result, compensatory increase in putamen volume. Alternatively, higher putamen volume may be a premorbid risk factor that disposes individuals to stimulant misuse. Indeed, Ersche and colleagues showed in another study that putamen is enlarged both in stimulant-dependent individuals and their non-dependent siblings, suggesting that this structural change in the striatum may be a neural marker of genetic predisposition to drug use rather than a consequence of chronic consumption of stimulants [90].

Additionally, larger putamen volumes have also been reported for autism spectrum disorders. Increased putamen volume was found in adults with autism spectrum disorder [91] and boys with Tourette syndrome [92]. The enlargement of bilateral putamen may also reflect dopaminergic dysfunction underlying these disorders [91]. Total putamen volumes were correlated positively with repetitive behaviors, particularly OCD-like repetitive behaviors, in individuals with of autism [93]. Individuals with restless leg syndrome showed increases in bilateral putamen volume as well as altered resting-state putamen connectivity, as compared to healthy controls [94]. Dysfunctional cortico-anterior striatal pathway may underlie subclinical obsessions and compulsions [95]. Volumetric analysis revealed a positive relationship between the Maudsley Obsessive Compulsive Inventory (MOCI) total score and bilateral putamen volumes in healthy populations [95]. Patients with OCD demonstrated increases in the GMV of the basal ganglia, including the putamen, independent of antidepressant treatment [96, 97]. Further, a GWAS identified a set of markers of increased putamen volumes and the risk for OCD [39]. These studies suggest an association between OCD spectrum disorders and hypertrophy of putamen.

Summary:

Putamen is dopamine-rich, and its volume is age-dependent and genetically controlled. Putamen volume is associated with many dopamine-related phenotypes that usually involve motor control dysfunction (e.g., PD, HD, Tourette syndrome, and catatonic schizophrenia) and/or impulsive behavior (e.g., ADHD, schizophrenia, substance use disorders, bipolar disorder, antisocial personality disorder, some neurodegenerative disorders and OCD). In most neuropsychiatric and neurodegenerative disorders, including PD spectrum disorders, HD, DLB, AD, multiple sclerosis, ADHD, developmental dyslexia, and major depression, the putamen volume is significantly reduced. However, in bipolar disorder, schizophrenia spectrum disorders, especially the neuroleptics-medicated schizophrenia, autism spectrum disorders, OC spectrum disorders, and stimulant dependence, the putamen volume is significantly enlarged. Interestingly, the volumetric features of the putamen were observed independent of other nuclei of the basal ganglia or cortical structures [48, 57, 79, 80, 83, 84], suggesting a specific role of putamen in the pathophysiological processes underlying these disorders. The putamen volume may represent a neural marker that predicts vulnerability to many neuropsychiatric conditions and/or treatment responsiveness in patients afflicted with these conditions.

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