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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 impairment in motor control, impulsive behavior, and other 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 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 clinical conditions. We provided an overview of the genetic bases of putamen volume in relation to these neuropsychiatric illnesses and explored potential mechanisms underlying these associations.

Keywords: Putamen; Gray matter volume; Dopamine; Neuropsychiatric disorder; Neurodegenerative disorder; Genotype

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Introduction

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) and probably many other neuropsychiatric and neurodegenerative disorders as well [3]. A primary function of the putamen is to regulate movement planning and execution and support the learning processes during various cognitive and affective challenges [4-10]. 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, motor imagery, and emotion, as well as clinical manifestations not directly related to motor control dysfunction, such as chronic pain [11-18]. 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), attention impairment in Attention Deficit Hyperactivity Disorder (ADHD), and reward seeking in frontotemporal dementia [19-21].

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 neurotransmitter and is supplied 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; conversely, gain of dopaminergic neurons and consequent

dopaminergic hyperactivity results in enlargement of both nuclei. Thus, altered putamen volume may occur in many dopamine-related neuropsychiatric and neurodegenerative disorders.

Genetics of Putamen Volume

The heritability of putamen volume is 71% to 79% [22]. Genome-Wide Association Studies (GWAS) identified at least 30 genes that might regulate the putamen volumes, including *KTN1, SLC39A8, DCC, DLG2* and others [22-29]. These genes were previously implicated in various phenotypes, including PD, Huntington's Disease (HD), ADHD, schizophrenia, OCD, and others [22,23,25,28,30-34]. Specifically, a common allele C of rs945270, a genetic marker at 3'-UTR of Kinectin 1 gene (*KTN1*), showed genome-wide strongest ($p=1.1 \times 10^{-33}$), replicable, and specific effects on the putamen Grey Matter Volume (GMV) [23,24]. Three other markers at *KTN1*, i.e., rs2181743 (5'-UTR), rs8017172 (3'-UTR) and rs17253792 (3'-UTR), were significantly associated with putamen GMVs too [$p=4.0 \times 10^{-8}$, (6.7×10^{-34} to 3.0×10^{-14}) and 3.2×10^{-7}, respectively] [22,25]. 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) [35,36]. Allele G of rs8017172 has been reported to be significantly associated with risk of PD ($p=1.9 \times 10^{-7}$) [30]. Allele C of rs945270 also 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, putamen activation during reward anticipation in a monetary incentive delay task increased with the number of C alleles, most significantly in the right putamen [23]. Another GWAS identified two SNPs at *DCC* (rs4632195) and *DLG2* (rs11233632) that affected putamen volume; and these two variants predisposed individuals to schizophrenia [28]. 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 [26]. 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

There was a significant trend in putamen volume decreasing with age and a significant volume difference between men and women [37,38]. The age-dependent reduction of GMV holds for bilateral putamen and both men and women, but appears to be more severe for right-hemispheric putamen [38,39]. However, the age-related reduction in putamen volume is frequently affected by neuropsychiatric and neurodegenerative disorders.

Putamen volume decreases in most neuropsychiatric and neurodegenerative disorders: Many neuropsychiatric and neurodegenerative disorders manifest with dopamine-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; and HD patients are known to demonstrate significant involuntary movements [40]. It has been reported that the putamen volume loss is associated with deficits in motor control [41]. Children with complex motor stereotypies demonstrated significant reductions in total putamen volume [42]. Additionally, many neuropsychiatric and neurodegenerative disorders, e.g., ADHD, are known to exhibit impulsive behavior. Impulsivity is related to smaller post-commissural putamen volumes [43]. Together, these findings suggest an association of reduced putamen volume with neuropsychiatric and neurodegenerative disorders that manifest with motor control problems 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 [44]. Importantly, reported consistently across all independent studies, putamen volumes were significantly decreased in PD patients regardless of medication status [45-49]. This reduction has also been observed in X-linked Dystonia-Parkinsonism (XDP) and REM sleep behavioral disorder that reflects a pattern of neurodegeneration predicting the development of PD [50,51]. Furthermore, putamen volume is reported to decrease by 50.1% in people with HD as compared with control subjects, showing the greatest atrophy of all brain regions [52]. The atrophy of putamen appears at the time when motor symptoms manifest during the course of HD [53].

Atrophy of the putamen, as a neurodegenerative trait, is also a feature of Dementia with Lewy Bodies (DLB) and Alzheimer's disease and multiple sclerosis [22,54-56]. The decrease in putamen volume is linearly correlated with impairment in global cognitive performance [22,55].

Putamen may also be involved in impulsivity trait or impulsive behavior that has long been linked to dopamine [57]. A critical dimension of personality, impulsivity also represents a major symptom of many neuropsychiatric disorders, including ADHD, bipolar disorder, antisocial personality disorder, borderline personality disorder, and some neurodegenerative diseases. In particular, impulsivity or hyperactivity is perhaps best known in ADHD. In healthy people, right putamen is smaller than left putamen; however, children with ADHD (mostly unmedicated) more frequently have a smaller left than right putamen and the reversal of symmetry may relate to ADHD symptomology [58]. The primary pharmacological treatments for ADHD are methylphenidate (Ritalin) and amphetamine 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 [59]. Furthermore, as described above, the putamen volume declines with age; however, this shrinkage was independent of age in patients with ADHD and their unaffected siblings, suggesting a critical link to familial risk for ADHD [37,60]. 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 [61]. Decreased myelination of the ventral putamen has been associated with premature responding in performing a serial reaction time task in youth [62].

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 and age-dependent putamen shrinkage is accelerated in patients with major depressive disorder at younger ages (60 years to 65 years) but not older [63-66]. 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 some 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 schizophrenia spectrum disorders, including schizophrenia and schizotypal personality disorder, autism spectrum disorders, including autism and Tourette syndrome, and obsessive-compulsive spectrum disorders, including obsession and compulsion traits and OCD.

Larger putamen sizes have been reported in antipsychotic-naïve individuals with schizotypal personality disorder or schizophrenia, which suggests the possibility that excessive dopamine may cause schizophrenia spectrum disorders and enlarged putamen may be a predictor of these disorders [67,68]. These patients with enlarged putamen are usually sensitive to and benefit from antipsychotics that block dopamine neurotransmission in treatment. In contrast, if dopaminergic hyperfunction is not the predominant cause for these disorders, patients might neither have larger putamen sizes nor responds to typical antipsychotics. However, perhaps as a compensatory response to the blockage by typical antipsychotics, the putamen might further expand to maintain dopaminergic neurotransmission, consistent with the finding that the neuroleptic-medicated schizophrenia patients have larger putamen sizes [69-71]. Patients with good treatment outcomes have larger putamen than those with poor outcomes or normal controls, which support the proposition that enlarged putamen, may represent a physiological correlate of neuroleptic responsiveness or a predictor of treatment outcome [68,70,72].

Presynaptic transporters remove dopamine from the synapses of neurons to be recycled for further use [73]. Cocaine acts by binding to the dopamine transporters, blocking the removal of dopamine from the synapses and thus reducing the recycling dopamine [69,74]. As a result, chronic cocaine use may result in putaminal hypertrophy as a compensatory response to produce more dopamine. Additionally, larger putamen sizes have been reported for autism spectrum disorders too. Increased putamen volume was found in adults with autism spectrum disorder and boys with Tourette syndrome [75,76]. The enlargement of bilateral putamen may also reflect dopaminergic dysfunction in autism spectrum disorders [76].

Finally, dysfunctional cortico-anterior striatal pathway may underlie subclinical obsessions and compulsions [77]. Volumetric analysis revealed a positive relationship between the Maudsley Obsessive Compulsive Inventory (MOCI) total score and bilateral putamen volumes in healthy populations [77]. Further, a GWAS identified a set of markers of increased putamen volumes and the risk for OCD [34]. 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, Alzheimer's disease, multiple sclerosis, ADHD, developmental dyslexia, and major depression, the putamen volume is significantly reduced. However, in schizophrenia spectrum disorders, especially the neuroleptics-medicated schizophrenia, autism spectrum disorders, OC spectrum disorders, and cocaine dependence, the putamen volume is significantly enlarged. Interestingly, these volumetric features of the putamen were observed independent of the caudate, other nuclei of the basal ganglia, or cortical structures, suggesting a specific role of putamen in the pathophysiological processes underlying these disorders [42,52,68,69,71,72]. 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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