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Research report

Serotonin transporter gene status predicts caudate nucleus but not amygdala or hippocampal volumes in older persons with major depression

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Abstract

Background: Although the short allele of the serotonin transporter promoter polymorphism (5-HTT) has been linked to increased risk of major depression in early adult life, its relationships with late-life depression and to changes in subcortical nuclei remain unclear.
Methods: 5-HTT genotypes (SS, SL, LL) were determined for 45 older persons with major depression (mean age=52.0, sd=12.8) and 16 healthy controls (mean age=55.8, sd=10.3). MRI-derived volumes of the amygdala, hippocampus, caudate and putamen were determined by reliable tracing techniques.
Results: In those with depression, the short allele of 5-HTT was associated with smaller caudate nucleus volumes. Although hippocampal and amygdala volumes were smaller in those with depression as compared with control subjects, 5-HTT gene status did not predict this reduction in size.
Limitations: The findings are limited by the number of clinical and control participants.
Conclusions: Reduced caudate nucleus volume in older patients with major depression was associated with the short allele of the 5-HTT gene. This regional brain change may be a consequence of early developmental expression as well as later vascular or degenerative effects of this genotype.

Keywords: Depression; Serotonin transporter; Caudate nucleus; Putamen; Hippocampus; Amygdala

1. Introduction

There is increasing evidence that a range of genetic factors as well as cortical and subcortical brain changes are not only risk factors to major depression (MD) in late-

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life, but also affect age of onset, cognitive function, key psychopathological features, clinical outcomes, response to treatment and progression to dementia (Alexopoulos et al., 1997; Hickie et al., 2005a,b, 2001, 1997, 1999; Naismith et al., 2003; Steffens and Krishnan, 1998). Relationships between reduced volumes of the amygdala, hippocampus, caudate or putamen and risk to onset of MD in late-life have been described (Bell-McGinty et al., 2002; Krishnan et al., 1992; Sheline, 2003). Importantly, changes in subcortical structures in those with MD are related to cognitive functioning. For instance, we have previously reported that the volume of the right caudate nucleus is predictive of psychomotor speed, a key phenomenon in people with melancholia and/or late-onset depression (Naismith et al., 2002). We have also found that reduction in hippocampal volumes is associated with memory impairment in patients with both early- and late-onset depression (Hickie et al., 2005b; Naismith et al., 2002). Respecting the increasing recognition of cognitive disorders in later life (e.g., mild cognitive impairment), and their co-morbidity with affective symptoms, better characterization of underlying brain changes is warranted, particularly in terms of guiding preventative management.

Current structural models of late-life depression emphasize disruption of fronto–striatal–limbic pathways. Supporting research has shown reduced volumes of subcortical and temporal lobe structures and increases in the frequency or severity of white matter lesions (Alexopoulos, 2005; Hickie et al., 1995, 1997; Naismith et al., 2002). These structural changes are assumed to result from vascular pathologies, prolonged hypercortisolaemia or reductions in key neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) (Hickie et al., 2005a; Nestler et al., 2002; Sheline, 2003). Relevant genotypes may include those that are relevant to mid- or later-life vascular or neurodegenerative disorders (Gillespie et al., 2004; Hasler et al., 2004). Specifically, some evidence suggests a possible link to variations in the methylenetetrahydrofolate reductase (MTHFR) enzyme that regulates homocysteine metabolism (Hickie et al., 2001). Another important focus of research has been the potential role of apolipoprotein E, epsilon 4 (APOe4), with some but not all studies suggesting relationships to cognitive impairment (Geda et al., 2006; Hickie et al., 2005b).

Although a simple relationship between presence of the short allele of the serotonin transporter (5-HTT) promoter polymorphism and increased risk to major depression is unlikely, an increased risk does appear to occur in the presence of other environmental factors, notably interpersonal stressors in early adult life (Caspi et al., 2003; Wilhelm et al., 2006). Additionally, the short allele has been associated with affective temperaments (Gonda et al., 2006) and post-stroke depression (Ramasubbu et al., 2006), and appears to more broadly influence the reactivity of the amygdala to external threat (Hariri et al., 2005). Recently, Pezawas et al. (2005) demonstrated reduced volumes of the perigenual cingulate and amygdala in healthy short allele carriers. By contrast, two studies have suggested a relationship between the long allele and smaller hippocampal volumes in late-life depression (Frodl et al., 2004; Taylor et al., 2005). In this study, we examined relationships between one or two copies of the short allele of the 5-HTT promoter polymorphism and volumes of key subcortical and temporal lobe nuclei in older persons with MD. Specifically, we expected that any effect of the 5-HTT promoter polymorphism may be less apparent than associations with other aetiological factors salient to older persons with depression, such as age of onset and vascular risk factors.

2. Method

2.1. Participants

Sixteen healthy control participants were recruited from the community via local newspaper advertisement. Forty-five persons meeting DSM-IV criteria (American Psychiatric Association, 1994) for major depression were recruited from tertiary referral services in South Eastern Sydney. Participants formed part of a larger sample from which clinical, neuropsychological and genetic features, as well as hippocampal and caudate nucleus volumes, have been previously reported (Hickie et al., 2005a,b, 2001; Naismith et al., 2002, 2003). Those with MD secondary to a major medical illness were excluded. Patients were not excluded on the basis of concurrent Axis II disorders. Exclusion criteria also included electroconvulsive therapy within the last 3 months, a history of substance abuse, head injury resulting in loss of consciousness, neurological illness (e.g., Parkinson's Disease), prior stroke, or suspected dementia verified by neuropsychological assessment, Mini-mental state examination score <24 (Folstein et al., 1975) and clinical consensus.

2.2. Clinical assessment

Those with MD were assessed by a psychiatrist who recorded depression severity using the 21-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), duration of current illness (max = 450 weeks)

and age of illness onset. As reported previously (Hickie et al., 2005b), we also calculated a 'years of illness' variable (current age − age of illness onset) and a summed vascular risk factor score (maximum = 6) where the following vascular risk factors were weighted equally (0 = absent, 1 = present) and summed: heart disease, hypertension, hypercholesterolemia, smoking history, diabetes and family history of vascular disease.

2.3. Magnetic resonance imaging (MRI) volumetrics

As previously described (Hickie et al., 2005b; Naismith et al., 2002), subjects underwent high-resolution MRI scanning on a 1.5 Tesla GE machine (124 × 1.5 mm coronal slices, TR = 24 ms, TE = 5 ms, field of view = 26 cm, matrix = 256 × 256). The hippocampus, amygdala, caudate nucleus and putamen were manually traced by two raters on contiguous coronal slices using the BRAINS software package (Andreasen et al., 1993). Neuroanatomical boundaries and tracing protocols were derived through consultation with a neuroanatomist and use of an atlas (Duvernoy et al., 1999). Inter-rater reliability statistics yielded an intra-class correlation of 0.9, 0.8, 0.9 and 0.9 for the hippocampus, amygdala, caudate and putamen respectively.

2.4. Serotonin transporter genotyping

Deoxyribonucleic acid (DNA) for participants was stored and only recently analyzed for 5-HTT genotype. The 5-HTT gene promoter region was amplified from genomic DNA with the primers 5′-TGCC GCTCTGAATGCCAGCAC-3′ and 5′-GCGGGA TTCTGGTGCCACCTA-3′ to generate a 464 bp product for the 16 repeat (L) allele, and 420 bp for the 14 repeat (S) allele. PCR was carried out as described previously (Wilhelm et al., 2006).

Table 1
Clinical characteristics of participants with major depression

	Mean	Standard deviation
Hamilton Depression Rating Scale	26.8	6.2
Duration of current illness, weeks[a]	50.1	79.0
Age of depression onset, years	36.1	17.2
Years of illness[b]	15.6	16.1
Number of lifetime episodes[c]	6.9	9.8
Late-onset (onset ≥ age 50) depression	11/45	–
Antidepressant medication use[d]	29/45	–

[a]Duration of current illness to maximum of 450 weeks [b]Illness duration = age − age of depression onset [c]Maximum of 35 lifetime episodes [d]Newer generation antidepressants with the exception of $n = 3$ taking tricyclic antidepressants.

Table 2
Demographics and regional cerebral volumes for control paricipants and those with major depression

	Control $n = 16$	Major depression $n = 45$	F	P
Age, mean (sd)	55.8 (10.3)	52.0 (12.8)	1.1	ns
Sex, % female[a]	56 (9/16)	67 (30/45)	0.5	ns
MMSE, mean (sd)	28.4 (1.6)	28.1 (1.6)	0.5	ns
Vascrisk, mean (sd)	1.1 (1.0)	1.8 (1.2)	4.0	.051
Volumetrics, mean cm^3 (sd)				
Cranial volume	1325.4 (118.5)	1272.3 (111.6)	2.6	ns
Caudate nucleus	6.2 (.9)	5.9 (.9)	1.2	ns
Putamen	7.6 (.8)	7.2 (1.1)	1.2	ns
Amygdala	3.4 (.5)	3.1 (.6)	4.5	.038
Hippocampus	6.4 (.7)	5.9 (.7)	5.4	.023

[a]Chi-square test; ns = not significant at $p < .05$; MMSE = Mini-mental state examination; Vascrisk = summed vascular risk factors (range 0–6).

2.5. Statistical analysis

All analyses were conducted using SPSS, version 13.0. Pearson correlation coefficients and chi-square statistics were used to examine relationships between continuous and categorical data respectively. Analysis of variance was used to examine continuous data between groups. All analyses employed two-tailed tests and a .05 significance level.

3. Results

3.1. Demographic, clinical and MRI variables in those with major depression and control subjects

Tables 1 and 2 present clinical data on depressed and control subjects. Table 2 shows that there were no group differences in age, sex or cognitive status. While there was no difference between groups in caudate nucleus or putamen volumes, those with MD had significantly smaller hippocampus and amygdala volumes. They also had a significantly greater number of vascular risk factors than control participants. There was no relationship between antidepressant medication use and volumes of the hippocampus ($F = 0.2$, ns), amygdala ($F = 0.7$, ns), putamen ($F = 0.2$, ns) or caudate nucleus ($F = 0.4$, ns).

3.2. Frequency of the allele

Table 3 shows the frequency distribution of the polymorphisms (SS, SL, LL) and demonstrates that there were no significant group differences. Those who were homozygous or heterozygous for the short allele

Table 3
Serotonin transporter genotype distribution for control participants and those with major depression

Genotype	Control	Major depression	Chi-square
SS	19% (3/16)	27% (12/45)	1.4, ns
SL	31% (5/16)	40% (18/45)	
LL	50% (8/16)	33% (15/45)	

ns = not significant at $p<.05$; $df=2$.

were pooled (i.e. short allele carriers, $n=38$), as were those who were homozygous for the long allele ($n=23$). Sixty-seven percent of the MD group and 50% of the control group were short allele carriers ($\chi^2=1.4$, ns).

3.3. Relationship to clinical predictors in persons with MD only

In those with MD, there was no relationship between vascular risk factors and volume of the caudate nucleus ($r=0.3$, ns), putamen ($r=-0.04$, ns), amygdala ($r=-0.1$, ns) or hippocampus ($r=-0.1$, ns). There was no association between the short allele and depression severity (HAM-D: $t=0.5$, ns), age of onset ($t=0.1$, ns), duration of current episode ($t=1.4$, ns) or 'years of illness' ($t=1.2$, ns).

3.4. Short versus long alleles of 5-HTT

For control participants and those with MD, Table 4 data show that there was no association between those with the short and long allele variants with respect to age, sex, MMSE scores or summed vascular risk factors. There was also no difference between short and long allele carriers in cranial, putamen (left: $F=0.0$, ns; right: $F=0.4$, ns), hippocampal (left: $F=0.8$, ns; right: $F=0.0$, ns) or amygdala (left: $F=1.4$, ns; right: $F=0.3$, ns) volumes. However, for those with MD, the caudate nucleus was significantly smaller for short allele carriers (left: $F=4.3$, $p<.05$; right: $F=4.2$, $p<.05$).

3.5. Multivariate analyses

In order to determine the relative contribution of depression diagnosis and 5-HTT genotype to regional cerebral volumes, stepwise regressions were conducted in the whole sample. For the amygdala and hippocampus, MD diagnosis remained the only significant predictor of volume, explaining 7.2% ($t=-2.1$, $df=58$, $p<.05$) and 8.6% ($t=-2.3$, $df=58$, $p<.05$) of the variance respectively. Presence of the short form of the 5-HTT promoter polymorphism did not make a further significant contribution ($t=1.7$, ns; $t=1.2$, ns respectively).

For the caudate nucleus, however, MD diagnosis was not a significant predictor ($t=-0.8$, ns). Rather, presence of at least one short allele of the 5-HTT promoter polymorphism was associated with significantly smaller caudate volumes and predicted 8.5% ($t=2.3$, $df=59$, $p<.05$) of the variance. For the putamen, neither depression diagnosis nor serotonin transporter allele status were significant predictors of volume.

4. Discussion

This study demonstrates a relationship between the short allele of the 5-HTT promoter polymorphism and

Table 4
Relationship between the short (SS, SL) and long (LL) variants of the serotonin transporter promoter polymorphism and demographic and brain volumetric data for control participants and those with major depression

	Control				Major depression			
	SS, SL	LL	F	P	SS, SL	LL	F	P
Allele frequency, %[a]	50 (8/16)	50 (8/16)	–	–	67 (30/45)	33 (15/45)	–	–
Age, mean (sd)	58.4 (11.7)	53.3 (8.6)	1.0	ns	53.9 (10.9)	48.3 (15.7)	2.0	ns
Female sex, %[b]	50 (4/8)	63 (5/8)	0.3	ns	60 (18/30)	80 (12/15)	1.8	ns
MMSE, mean (sd)	28.5 (1.1)	28.4 (2.1)	0.02	ns	27.9 (1.5)	28.5 (1.7)	0.9	ns
Vascrisk, mean (sd)	1.1 (1.1)	1.0 (1.1)	0.1	ns	1.8 (1.2)	1.8 (1.4)	0.1	ns
Volumetrics, cm^3 (sd)								
Cranial volume	1333.1 (127.1)	1317.7 (117.4)	0.6	ns	1279.7 (112.8)	1256.3 (111.4)	0.4	ns
Caudate nucleus	6.1 (.8)	6.4 (1.0)	2.4	ns	5.7 (.9)	6.3 (.8)	4.6	.038
Putamen	7.3 (.8)	7.8 (.9)	1.2	ns	7.3 (1.1)	7.1 (1.1)	0.1	ns
Amygdala	3.2 (.4)	3.6 (.6)	2.7	ns	3.0 (.5)	3.2 (.7)	1.0	ns
Hippocampus	6.2 (.6)	6.7 (.7)	0.5	ns	5.9 (.6)	6.0 (.8)	0.2	ns

[a]No significant difference in frequency of short allele carriers between groups ($\chi^2=1.4$, $df=1$, ns); [b]Chi-square statistic, ns = not significant at $p<.05$; MMSE = Mini-mental state examination; Vascrisk = Sum of vascular risk factors (range 0–6).

reduced volumes of the caudate nucleus. Reduction in caudate volume is assumed to be of functional and clinical significance in persons with MD. For instance, we have previously demonstrated correlations between slowed psychomotor speed and caudate nucleus volumes (Naismith et al., 2002) and reduced caudate blood flow (Hickie et al., 1999). It is possible that reductions in subcortical nuclei volumes are markers of a particular depressive subtype characterised by psychomotor change and associated cognitive impairment (Hickie, 1996). Importantly, our data suggest that the volume of the caudate nucleus is linked to the short allele and is not simply a correlate of a depression diagnosis. For the amygdala and hippocampus, however, a diagnosis of MD rather than 5-HTT status was the key predictor of reduced volumes.

The short allele of the 5-HTT gene has been linked to volumes of limbic regions in healthy persons (Pezawas et al., 2005) and is increasingly recognized as a potential risk factor to MD, particularly in early rather than later-life (Caspi et al., 2003; Wilhelm et al., 2006). However, current models of late-life depression tend to emphasise vascular, neurodegenerative or other medical risk factors. While any relationships between the short 5-HTT allele and cortical and subcortical volumes may be less evident in older persons with MD, this study suggests that direct or illness-dependent effects related to serotonin gene status may still be relevant. Probable illness-dependent factors could include reduced BDNF, other neurotrophins or hypercortisolemia. The effects of these possible pathophysiological paths would be expected to increase with the duration of untreated illness (Sheline, 2003).

Previous studies of older individuals with MD have suggested a relationship between the long allele of 5-HTT and late-onset depression (Taylor et al., 2005). While our results do not directly contradict such findings (as our analyses were not limited to those with late-onset disorders), our study does suggest that relationships between 5-HTT genotype and various clinical and neuroimaging correlates of MD may well vary according to the age or other demographic or treatment characteristics of different clinical samples. The findings do not appear to have any clear relationship with patterns of current medication use. Further analysis of the detailed genetic structure of the 5-HTT promoter may add greater precision to the current analyses as Wendland et al. (2006) have reported that the Lg allele also results in low expression levels of the transporter gene.

The generalisability of this study is limited by the clinical nature of the sample and that it included subjects with a wide range of age, age of onset and duration of illness. As our major objective was the elucidation of the relationship between genotype and regional brain volumes in those with major depression, we included only a small number of normal control subjects. Hence the broader relationships between 5-HTT genotype, age and regional brain changes in the population now require appropriate non-clinical and longitudinal study designs.

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