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LETTER TO THE EDITOR

Decreased regional gray matter volume in S' allele carriers of the 5-HTTLPR triallelic polymorphism

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The short (S) allele of an insertion/deletion variant in the promoter region of the human serotonin transporter (5-HTT) gene (SLC6A4), has been associated with increased risk of depression in stressful life circumstances.[1] The way in which this genetic variation influences brain function is the subject of intensive research. Despite suggestive *in vitro* evidence, current positron emission tomography studies do not show a consistent effect of the promoter variant on the availability of the 5-HTT in the brain *in vivo*, and attention has shifted to differential effects of the S allele on brain morphology.[2,3] In the present study, we used voxel-based morphometry in a large sample of healthy control subjects to assess the effect of the triallelic 5-HTTLPR polymorphism. This includes an embedded A/G substitution, rs25531 (S/La/Lg), where the Lg allele is considered functionally similar to and grouped together with the S allele (L' = La; S' = S and Lg).[2]

We studied 113 volunteers (females 43, males 70), mean age 37.6 years (range 18–60 years, s.d. 11.3). There were 22 S'-non-carriers (L'L' genotype) (mean age 32.7 years, s.d. 11.2) and 91 S' carriers (mean age 37.6 years, s.d. 11.2). All volunteers were free from any lifetime psychiatric or neurological disorder. Structural magnetic resonance imaging data were acquired at 3T (TR = 9.6 ms, TE = 4.6 ms, flip angle = 8, voxel dimensions $0.94 \times 0.94 \times 1.2\,mm^3$). Image preprocessing utilized an optimized voxel-based morphometry protocol (FSL v4.1.4). Effects of the 5-HTTLPR on gray matter volume were examined using an analysis of covariance model with age and gender as covariates of no interest. Gray matter volume changes were assessed statistically with one-tailed *t*-tests using a threshold-free cluster-based approach with correction for multiple comparisons at the whole-brain level. In addition, regions of interest for bilateral amygdala and subgenual cingulate were used. The genetic variants of 5-HTTLPR rs25531polymorphism were determined by the PCR reaction, followed by digestion with *Msp*I restriction enzyme.[4]

Whole-brain analysis revealed significantly reduced gray matter volume in S' allele carriers vs L'L' homozygotes in three regions; (1) right inferior frontal gyrus ($x = 54$, $y = 18$, $z = 22$); (2) left anterior cingulate ($x = -8$, $y = -16$, $z = 36$) and (3) superior temporal gyrus ($x = 62$, $y = -14$, $z = -4$) (Figure 1). There were no significant between-group differences in any of the *a priori* regions. Also, there were no regions that displayed greater volume in S' allele carriers vs L'L' homozygotes. Comparison of L'L' and S'S' homozygotes ($n = 31$) showed reduced gray matter volume in S'S' participants in right inferior frontal gyrus ($x = 56$, $y = 18$, $z = 22$) and right superior temporal gyrus ($x = 62$, $y = -14$, $z = -4$).

Our findings, in a large sample, support earlier observations showing decreased regional gray matter volume in S' carriers. However, our data indicate that the regional localization of this effect shows significant variation between studies. Pezawas *et al.*[5] found decreased volume in perigenual anterior cingulate and amygdala in 114 controls (L'L' = 35, S' = 79) classified according to the bialleleic promoter polymorphism. In contrast, Canli and Lesch[6] studying 41 healthy controls (L'L = 13, S' = 28) found widespread reductions in gray matter in S' carriers (insula, left

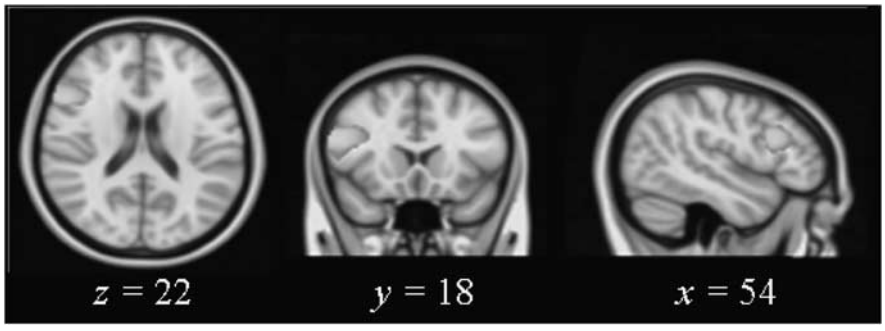

Figure 1 Axial, coronal and sagittal images depicting significantly reduced gray matter volume in S' allele carriers vs L'L' homozygotes in right inferior frontal gyrus. Numerals refer to coordinates in Montreal Neurological Institute space. Images are in radiological format.

middle frontal gyrus and gyrus rectus, right inferior temporal gyrus, anterior cingulate and cerebellum). Frodl *et al.*,[7] using the trialleleic polymorphism in 77 healthy controls, also found rather more widespread reductions in gray matter in S' carriers (left amygdala, right hippocampus, left anterior cingulate cortex and bilateral dorsolateral prefrontal cortex). However, in the latter study, the morphometric comparisons appear to have been restricted to L'L' ($n=10$) and S'S' ($n=23$) homozygotes. Finally, a recent study in non-human primates[3] (4 L'L' vs 4 L'S') reported widespread reductions in gray matter volume in S' carriers including anterior cingulate, medial prefrontal and orbitofrontal cortex as well as the amygdala.

Taken together, the studies suggest that carriage of the S' allele may influence brain function through an effect on brain morphology, perhaps exerted during neurodevelopment. Larger samples appear to have more restricted morphological changes; however, an effect of S' carriage on anterior cingulate volume appears a reliable finding between different studies. This is of interest in view of the role of the anterior cingulate in integrating cognitive and emotional information as well as its frequent implication in functional imaging studies in depressed patients.

Conflict of interest

The authors declare no conflict of interest.

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