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The 5-HT$_{2A}$ receptor binding pattern in the human brain is strongly genetically determined

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With the appropriate radiolabeled tracers, positron emission tomography (PET) enables in vivo human brain imaging of markers for neurotransmission, including neurotransmitter synthesis, receptors, and transporters. Whereas structural imaging studies have provided compelling evidence that the human brain anatomy is largely genetically determined, it is currently unknown to what degree neuromodulatory markers are subjected to genetic and environmental influence. Changes in serotonin 2A (5-HT$_{2A}$) receptors have been reported to occur in various neuropsychiatric disorders and an association between 5-HT$_{2A}$ receptor gene variants and neuropsychiatric illness susceptibility also exists. In a classical twin design involving 24 healthy male subjects (6 monozygotic twin pairs and 6 dizygotic twin pairs), we examined the relative contribution of genetic and environmental factors to inter-individual variability in cortical 5-HT$_{2A}$ receptor binding as measured with [^{18}F]altanserin PET imaging. The intraclass correlation coefficients were 0.67 for dizygotic and 0.87 for monozygotic twin pairs. For comparison, the intraclass correlation coefficient was 0.93 in a group of six male healthy subjects examined twice within two weeks with an identical experimental setup. Multivariate analysis was used to separate the phenotypic variance of individuals into additive genetic (heritability) effect (A), shared (family) environment (C), and non-shared (individual-specific) environment (E). Irrespective of whether a full ACE model or a reduced AE model was used to fit the data, the variance due to non-shared environment was below 10% indicating that the contribution of individual specific environmental factors to 5-HT$_{2A}$ receptor binding is limited.

Keywords: Heritability; Serotonin 2A; Receptor; Positron emission tomography; Twins

Introduction

Through positron emission tomography, it is now possible to image a variety of different receptors and transporters in the living human brain. A striking feature is the large interindividual variability observed for most neurotransmitter systems; this difference is at least for the D2-receptors determined mainly by differences in D2- receptor density, and less by the affinity (Farde et al., 1995). By means of PET-studies, a number of specific alterations in pre- or postsynaptic receptors have been demonstrated in different neuropsychiatric disorders (Laruelle, 1998; Turjanski et al., 1995; Savic et al., 1988; Heiss and Hilker, 2004; Burn et al., 1994; Cagnin et al., 2001; Meyer et al., 2003; Adams et al., 2005) and more recently, specific neuroreceptor patterns have been associated with certain personality traits in healthy subjects (Farde et al., 1997; Borg et al., 2003). It is currently unknown firstly, to what extent these neuroreceptor patterns exist prior to occurrence of clinical signs of neuropsychiatric disorders and secondly, if these patterns can be modulated by environmental modulations.

Among several other phycho-physiological functions, the 5-HT$_{2A}$ receptor modulates mood and perception, and is involved

Abbreviations: PET, positron emission tomography; MRI, magnetic resonance imaging; MZ, monozygotic; DZ, dizygotic; ROI, region of interest; BP$_1$, binding potential; 5-HT$_{2A}$, serotonin 2A.

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in the actions of hallucinogens, atypical antipsychotic drugs, and antidepressants. Recently, PET studies have demonstrated changes in ligand binding to 5-HT_{2A} receptors in several neuropsychiatric disorders including affective disorders (Messa et al., 2003; Meyer et al., 2003; Sheline et al., 2004; Mintun et al., 2004), but an unchanged cortical binding in schizophrenia (Trichard et al., 1998; Verhoeff et al., 2000). In healthy control subjects, PET studies have consistently demonstrated a large intersubject variation in ligand binding to cortical 5-HT_{2A} receptors (Adams et al., 2004; Mintun et al., 2004), even when the well described age related decline in cortical 5-HT_{2A} receptor density is taken into account (Adams et al., 2004). Yet, since these observations all have been made in cross-sectional studies, a distinction between the relative contributions of genetic and environmental factors has not been possible.

It has proven difficult to demonstrate strong and reproducible associations between candidate genes and the complex behavioral phenotypes of neuropsychiatric disorders. The concept that allelic variants are more likely to have direct functional impact on cellular and molecular pathways has prompted the search for neuroanatomical and neurophysiological endophenotypes relating genes and behavior. Twin studies provide a method to evaluate the relative influence of genetic and environmental factors upon structural and functional outcome parameters of neuroimaging studies. We studied the 5-HT_{2A} receptor binding using [^{18}F]altanserin-PET in healthy monozygotic (MZ) and dizygotic (DZ) twin pairs. Since MZ twins share 100% of their segregating genes while DZ twin pairs share on average 50% of their genes, we hypothesized a larger similarity in 5-HT_{2A} receptor binding in MZ twin pairs as compared to DZ twin pairs. Furthermore, for assessment of intra-individual variability, additional six healthy subjects were scanned twice.

Materials and methods

Twenty-four healthy male subjects (6 MZ twin pairs (mean age 35 years, range 27–47 years) and 6 DZ twin pairs (mean age 37 years, range 28–46 years)) were recruited from the Danish Twin Registry (Skytthe et al., 2002). In addition, to compare these data to the intraindividual variability with the [^{18}F]altanserin-PET method, six healthy male subjects (mean age 47 years, range 33–63 years) were PET-scanned twice within 2 weeks as described in a previous publication (Haugbol et al., 2006). None of the subjects had a history of major perinatal adversity, psychiatric or neurological disorders, nor were any of the subjects taking psychoactive drugs. Four MZ twins and 4 DZ twins were smokers. Subjects were not allowed to smoke for 4 h before tracer administration and until the end of the experiment. Except for one twin pair, occupational status was similar in all twin pairs. Physical examination, brain MRI, BMI and routine blood test results were normal in all subjects. The study was conducted according to the Helsinki declaration, the Scientific- Ethics Committee of Copenhagen and Frederiksberg approved the study (KF 02-058/99, KF 12-152/01, KF 12-142/03) and informed written consent was obtained from all subjects.

[^{18}F]altanserin was synthesized as previously reported (Lemaire et al., 1991). The specific activity at the end of synthesis was 190± 32 GBq/mmol and the radiochemical purity was greater than 99%. Twin pairs were studied on the same day with an interval of 75 min. Twin pairs received the same amount of radioactivity per kg body weight with a maximum of 3.7 MBq/kg of [^{18}F]altanserin. [^{18}F]altanserin was administrated as a combination of a bolus injection and a continuous infusion to produce tracer steady state in tissue and blood. The bolus component was worth 1.75 h of constant infusion (Pinborg et al., 2003). PET scans were performed with an 18-ring GE-Advance scanner (GE, Milwaukee, WI, USA) operating in 3D-acquisition mode (DeGrado et al., 1994; Lewellen et al., 1996). For correction of tissue attenuation, 10-min transmission scans were performed before each PET session using retractable ^{68}Ga/^{68}Ge-pin sources. The transmission scans were corrected for tracer activity by a 5 min emission scan performed in 2D mode. Dynamic 3D emission scans (five frames of 8 min) started 120 min after administration of [^{18}F]altanserin. Data were reconstructed into a sequence of 128*128*35 voxel matrices, each voxel measuring 2.0*2.0*4.25 mm, with software provided by the scanner manufacturer. A 3D reprojection algorithm with a transaxial Hann filter (6 mm) and an axial ramp filter (8.5 mm) was applied. Corrections for deadtime, attenuation and scatter were performed. During emission scanning, 5 venous blood samples were drawn for determination of total plasma radioactivity concentration and the plasma fraction of [^{18}F]altanserin. The plasma fraction of native [^{18}F]altanserin was determined through high-performance liquid chromatography analysis (Pinborg et al., 2003).

Magnetic resonance imaging (MRI) was performed on a 1.5 T Vision scanner (Siemens, Erlangen, Germany) using a 3D MPRAGE sequence (TI/TE/TR = 100/4.4/11.4 ms, flip angle 8°). PET and MR images were co-registered using a Matlab (Mathworks Inc., Natick, MA, USA) based made program where PET and MR images are co-registered through manual translation and rotation of the PET image with subsequent visual inspection in three planes (Willendrup et al., 2004). A total of 18 regions (35 ROIs) were automatically delineated on each subject's transaxial MRI slices in a strictly user-independent fashion (Svarer et al., 2005). Through a warping algorithm, 10 template MRIs with individually defined ROI sets were transferred to each subject's MRI. The identified transformation parameters were subsequently used to define a mean ROI set in the subject's MRI space and through the co-registering these ROIs were transferred onto the PET images. Cortical ROIs were lumped into frontal cortex, temporal cortex, parietal cortex and occipital cortex ROIs. In addition orbitofrontal cortex and anterior cingulate cortex, ROIs were included in the multivariate analysis of heritability. The large and receptor rich cortical ROIs were chosen due to the superior statistical quality of regional PET data compared to the small and receptor poor subcortical ROIs. To enable partial volume correction of the PET data, MR images were segmented into gray matter, white matter and cerebrospinal fluid tissue classes using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Partial volume correction was performed according to Muller-Gartner et al. (1992). The white matter value was extracted as the mean voxel value from a predominantly white matter ROI (midbrain) in the uncorrected PET image.

We used BP_1 as an outcome parameter (Pinborg et al., 2003):

$$BP_1 = f_1 \frac{B'_{max}}{K_d} = DV_{ROI} - DV_{REF} \quad \left(ml\ ml^{-1}\right) \tag{1}$$

The distribution volume (DV) is defined as the ratio of the steady state tissue ligand concentration to the steady state plasma ligand concentration. BP_1 is calculated as the difference between the total distribution volume of [^{18}F]altanserin in a region of interest (DV_{ROI}) and the distribution volume of [^{18}F]altanserin in cerebellum (DV_{REF}). The calculation of BP_1 presumes that DV_{REF}