

The Serotonin System and Spiritual Experiences

Jacqueline Borg, Psychol., M.Sc.

Bengt Andréé, M.D., Ph.D.

Henrik Soderstrom, M.D., Ph.D.

Lars Farde, M.D., Ph.D.

Objective: The serotonin system has long been of interest in biological models of human personality. The purpose of this positron emission tomography (PET) study was to search for relationships between serotonin 5-HT_{1A} receptor density and personality traits.

Method: Fifteen normal male subjects, ages 20–45 years, were examined with PET and the radioligand [¹¹C]WAY100635. Personality traits were assessed with the Swedish version of the Temperament and Character Inventory self-report questionnaire. Binding potential, an index for the density of available 5-HT_{1A} receptors, was calculated for the dorsal raphe nuclei, the hippocampal formation, and the neocortex. For each region, correlation coefficients between 5-HT_{1A} receptor binding potential and Temperament and Character Inventory personality dimensions were calcu-

lated and analyzed in two-tailed tests for significance.

Results: The authors found that the binding potential correlated inversely with scores for self-transcendence, a personality trait covering religious behavior and attitudes. No correlations were found for any of the other six Temperament and Character Inventory dimensions. The self-transcendence dimension consists of three distinct subscales, and further analysis showed that the subscale for spiritual acceptance correlated significantly with binding potential but not with the other two subscales.

Conclusions: This finding in normal male subjects indicated that the serotonin system may serve as a biological basis for spiritual experiences. The authors speculated that the several-fold variability in 5-HT_{1A} receptor density may explain why people vary greatly in spiritual zeal.

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Religious behavior, like other human behavior, varies widely among individuals. There is increasing support for the view that such interindividual differences can be explained by biological and genetic factors. A role for the serotonin system was suggested early on from subjective experiences induced by mind-altering drugs, such as LSD and psilocybin.

Central serotonergic neurons originate from the raphe nuclei in the brainstem and innervate major brain regions, such as the hypothalamus, the limbic system, the striatum, and the neocortex. Fourteen serotonin receptor subtypes have thus far been identified in the human brain (1). The most extensively investigated is the serotonin 5-HT_{1A} receptor. Presynaptic 5-HT_{1A} autoreceptors are highly concentrated on cell bodies in the raphe and mediate the inhibition of cell firing and serotonin release in all projection areas. Thus, the 5-HT_{1A} receptor may have a role as general regulator of serotonergic activity. In human subjects, the 5-HT_{1A} receptor can be examined in vivo by using position emission tomography (PET) and the radioligand [¹¹C]WAY100635 (2).

Previous studies have demonstrated considerable variability in the expression of some G-protein-coupled receptors in the human brain (3). This interindividual variability has been taken advantage of in studies of the

dopamine system in demonstrations of associations between receptor density and higher brain functions (4, 5).

Initial PET studies with [¹¹C]WAY100635 have shown that 5-HT_{1A} receptor density varies more than twofold in normal subjects (6). Given this interindividual variability, we here used an open explorative design to search for associations between 5-HT_{1A} receptor density and personality traits. The Temperament and Character Inventory (7) was used to assess personality dimensions.

Method

Subjects

The study was approved by the ethics and radiation safety committees of Karolinska Hospital and was conducted in full compliance with the Declaration of Madrid. Only male subjects were included since most participants were recruited from studies regarding radioligand development (8) or from experimental drug trials (9). Only baseline data obtained during drug-naïve conditions were used for this study. Fifteen men, ages 20–45 years (mean=27, SD=8), participated after giving written informed consent. They were healthy, according to their histories and results of physical examinations, psychiatric screening interviews, routine blood and urine analyses, and magnetic resonance imaging (MRI) of their brains. The names of all subjects were searched in a register of patients who were seen for psychiatric care in Stockholm County. Exclusion criteria were somatic disorder, heredity for or history of psychiatric disorder according to DSM-IV, previous intake of psychotropic drugs, or history of substance addiction.

TABLE 1. Correlations of Serotonin 5-HT_{1A} Receptor Binding Potentials and Personality Dimensions in 15 Normal Male Subjects Examined With PET

Personality Dimension ^a	Pearson's Correlation With Binding Potential					
	Neocortex		Hippocampus		Raphe	
	r	p	r	p	r	p
Novelty seeking	0.07	0.80	-0.02	0.94	-0.26	0.24
Harm avoidance	-0.19	0.51	-0.10	0.71	-0.33	0.23
Reward dependence	0.26	0.34	0.01	0.97	-0.26	0.34
Persistence	-0.21	0.44	-0.36	0.18	-0.16	0.57
Self-direction	0.07	0.81	0.00	0.99	0.30	0.27
Cooperativeness	0.28	0.32	0.06	0.82	0.11	0.69
Self-transcendence	-0.59*	0.02	-0.61*	0.02	-0.62**	0.01
Self-forgetful versus self-conscious experiences	-0.33	0.23	-0.11	0.69	-0.07	0.80
Transpersonal identification versus self-isolation	0.16	0.56	0.21	0.46	0.15	0.59
Spiritual acceptance versus material rationalism	-0.62**	0.01	-0.78***	0.0007	-0.79***	0.0004

^a Measured with the Swedish version of the Temperament and Character Inventory, a self-report questionnaire (13).

*p<0.05. **p<0.01. ***p<0.001.

MRI and PET Protocols

The subjects were examined with the Signa Advantage 1.5-T MRI system (General Electric, Milwaukee). A standard spin-echo sequence with a 256×256 matrix was used, with a TR of 4 seconds. Proton density weighted images (17 msec) and T₂-weighted images (85 msec) were obtained to achieve one set of images with high spatial resolution and another with high sensitivity for pathology. Both MRI and PET measurements and an individual head fixation system were used to allow for the same head positioning in the two imaging systems (10).

[Carbonyl-¹¹C]-WAY-100635 was prepared from ¹¹C-acylation of WAY100634 with carbonyl-¹¹C-cyclohexanecarbonyl chloride, as described previously (11). A sterile phosphate buffer solution (pH=7.4) of 205-303.5 MBq of [¹¹C]WAY100635 was injected intravenously at the start of the PET measurement. The specific radioactivity at the time of injection was >1000 Ci/mmol. The PET system used was Siemens ECAT Exact HR 47 (Siemens/CTI, Knoxville, Tenn.), run in three-dimensional mode with dual energy windows scatter correction. The system covers an axial distance of 15 cm. Radioactivity in the brain was measured in a series of 16 consecutive frames for 69 minutes. The frame sequence consisted of three 1-minute frames followed by four 3-minute frames and nine 6-minute frames. The in-plane resolution of the reconstructed images was 3.8 mm full width at half maximum, and the axial resolution was 4.0 mm full width at half maximum (12). The reconstructed volume was displayed as 47 horizontal brain sections with a center-to-center distance of 3.125 mm.

Personality Assessment

The Swedish translation of the Temperament and Character Inventory self-report questionnaire was used (13). The Temperament and Character Inventory consists of 238 items covering the four temperament dimensions of novelty seeking, harm avoidance, reward dependence, and persistence and the three character dimensions of self-directedness, cooperativeness, and self-transcendence. The Temperament and Character Inventory has been developed according to a suggestion that the four temperament dimensions reflect inherited behavior, whereas the three character dimensions are thought to be influenced by environment. For the first five subjects, the Temperament and Character Inventory was administered retrospectively less than 8 months after the PET examination. For the remaining 10 subjects, the Temperament and Character Inventory was administered on the same day as the PET.

Regions of Interest

The [¹¹C]WAY100635 binding potential was calculated for three regions of interest. The neocortex has a high density of postsyn-

aptic 5-HT_{1A} receptors, the hippocampus is a part of the limbic system and has a high density of postsynaptic 5-HT_{1A} receptors, and the dorsal raphe nuclei (raphe) is a region of the brainstem with a high density of presynaptic 5-HT_{1A} receptors. In addition, the cerebellum serves as a reference region since it is devoid of 5-HT_{1A} receptors.

Regions of interest were manually delineated on the MRI images and transferred to corresponding PET images. The neocortex was drawn in four adjacent horizontal sections at the level of basal ganglia, whereas the hippocampal formation and the cerebellum were drawn in three adjacent sections. The raphe is not visible on MRI images and was therefore delineated on PET images in four to six consecutive sections at the level of the hippocampal formation and below. Data were pooled so that the average radioactivity concentration for the whole volume of interest was obtained.

Data Analysis

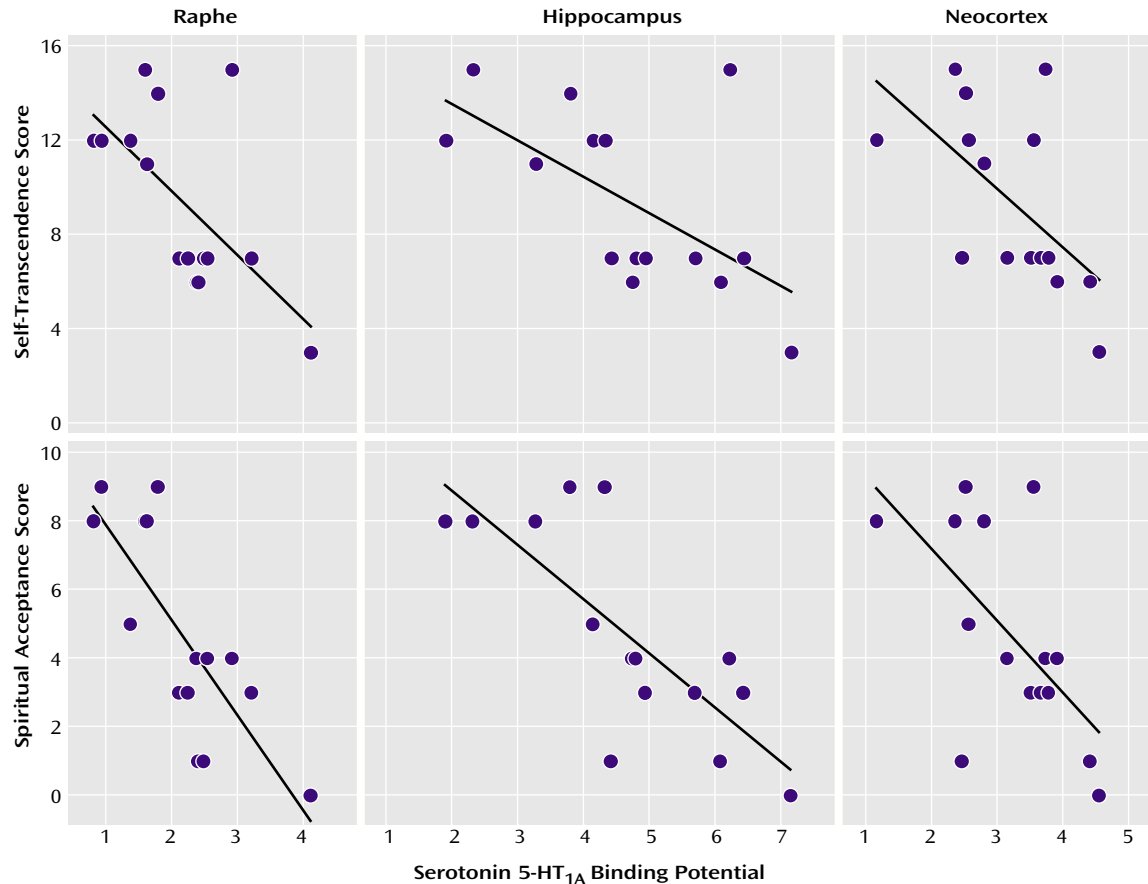
To obtain time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted against time. The binding potential (14) for [¹¹C]WAY100635 to 5-HT_{1A} receptors was calculated according to the simplified reference tissue model, as previously described in the literature (2). Region-of-interest analysis and calculations of binding potential were made by one of the authors (B.A.), who was blind to personality data.

For each region, the association between binding potential and individual scores for the seven personality dimensions was explored by calculations of Pearson's correlation coefficients. Two-tailed tests for significance were performed, and p values were corrected for the seven comparisons. The statistical analyses were performed with SPSS 9.0 for Windows.

Results

Among the 15 subjects, the binding potential of [¹¹C]WAY100635 to 5-HT_{1A} receptors varied markedly and was between 0.81 and 4.11 (mean=2.17, SD=0.87) for the raphe, 1.91 and 7.15 (mean=4.68, SD=1.49) for the hippocampus, and 1.60 and 4.55 (mean=3.21, SD=0.90) for the neocortex. The between-subject variability in levels of 5-HT_{1A} receptor binding potential was maintained across the three regions examined; Spearman's correlation for the neocortex versus the hippocampus was r_s=0.86, p=0.00004, for the neocortex versus the raphe, r_s=0.65, p=0.009, and for hippocampus versus the raphe, r_s=0.86, p=0.00004.

FIGURE 1. Ratings of Self-Transcendence and Spiritual Acceptance^a in Relation to Serotonin 5-HT_{1A} Receptor Binding Potentials in 15 Normal Male Subjects Examined With PET



^a Ratings were made with the Swedish version of the Temperament and Character Inventory, a self-report questionnaire (13).

The values for binding potential correlated significantly with the self-transcendence dimension but not with any of the other six Temperament and Character Inventory dimensions (Table 1). The self-transcendence dimension is a composite of three distinct subscales that describe aspects of spirituality. After the demonstration of statistical significance for the self-transcendence dimension, correlations for each of the dimension's three subscales were examined. Scores for spiritual acceptance versus material rationalism correlated significantly with 5-HT_{1A} binding potential for all three regions (Figure 1). No significant correlations were found for any of the remaining two subscales (Table 1).

Discussion

In the present study, we found an association between interindividual variability in 5-HT_{1A} receptor binding potential and the self-transcendence score on the Temperament and Character Inventory. We found no correlation for any of the other dimensions. The lack of correlation for the other dimensions is consistent with a previous study that used Tridimensional Personality Questionnaire, and an earlier questionnaire covering the four tem-

perament dimensions of the Temperament and Character Inventory (6).

The self-transcendence dimension is the most stable Temperament and Character Inventory dimension over time and is also one of the two Temperament and Character Inventory dimensions showing the largest variability (13). The self-transcendence dimension consists of three subscales representing several aspects of religious behavior, subjective experience, and individual worldview. Of interest, in the extended analysis, we found that the correlation of self-transcendence was shown to be fully dependent on the spiritual acceptance scale, whereas no correlation was found to the other two subscales.

The spiritual acceptance scale measures a person's apprehension of phenomena that cannot be explained by objective demonstration. Subjects with high scores tend to endorse extrasensory perception and ideation, whether named deities or a commonly unifying force. Low scorers, by contrast, tend to favor a reductionistic and empirical worldview (15).

A role for the serotonin system in relation to spiritual experiences is supported by observations of drugs such as LSD, psilocybin, *N,N*-dimethyltryptamine, mescaline, and

3,4-methylenedioxymethamphetamine that are known to cause perturbations of the serotonin system in several brain regions (16–18).

On a behavioral level, these drugs elicit perceptual distortions, illusions, a sense of insight, spiritual awareness, mystical experiences, and religious ecstasy. Of interest, such pharmacological effects induced by hallucinogens resemble the extrasensory perception and ideation endorsed by subjects scoring high on the spiritual acceptance scale.

However, another drug causing spiritual experiences is salvinorin A. This drug may act primarily on the kappa opioid receptor system (19), indicating that the serotonin system is not the only brain neurotransmitter system that may be related to spiritual experiences.

The between-subject variability in levels of 5-HT_{1A} receptor binding potential were maintained across all regions examined. In subjects with high spiritual acceptance scores, a key question is whether the observation of low 5-HT_{1A} receptor levels corresponds to low or high activity in serotonergic cortical projection areas. Currently, the literature provides support for both interpretations.

If receptor density serves as a marker for neuron number, low 5-HT_{1A} receptor density may represent sparse serotonergic innervation. On a functional level, the effect of globally low serotonin has been examined using the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (20), a drug that impairs serotonin synthesis and release in all brain regions. Animal studies have shown that *p*-chlorophenylalanine induces greater sensitivity to sensory stimuli and facilitates greater arousal and unspecific aggressive behavior (21). These observations support the hypothesis that the physiological role of the serotonin system includes inhibition of sensory stimuli and arousal. Low serotonin activity may thus pave the way for sensory stimuli otherwise not experienced. One interpretation of the present finding is that subjects with low 5-HT_{1A} receptor density have sparse serotonergic innervation and thereby a weaker filtering function, allowing for increased perception and decreased inhibition.

Another interpretation is that globally low density of 5-HT_{1A} receptors is associated with greater postsynaptic activity. The 5-HT_{1A} autoreceptors in the raphe modulate cell firing and serotonin release. Low expression of 5-HT_{1A} autoreceptor in the raphe may thus accordingly correspond to high release of serotonin in projection areas.

These findings may have implications for the pathophysiology of several psychiatric conditions. Clinical studies have demonstrated that extreme scores in any direction on the self-transcendence scale can reflect individuals with impairment in social interaction and adaptation to society (22, 23). Furthermore, delusions and hallucinations with religious content have been reported in neuropsychiatric disorders such as bipolar mania, schizophrenia, and com-

plex seizure disorder (24). The findings of the present study may provide additional support for current hypotheses on a role for the serotonin system in the pathophysiology of these disorders.

A limitation of the study is that the study group included male subjects only. Gender differences in religious behavior have been reported in several studies and documented by use of the Temperament and Character Inventory (25, 26). Previous PET studies have not supported a statistically significant difference between men and women in 5-HT_{1A} receptor density. However, a difference in the age effect on 5-HT_{1A} receptor density has been reported in two studies (27, 28) that supported age-related gender differences in binding potential. Therefore, caution must be exercised when generalizing the present finding in male subjects to the female population.

Another limitation of this study is the small group size. However, with the exception of the harm avoidance scale, a scale that consistently has shown large variation, the means and standard deviations of the present scores on the Temperament and Character Inventory were close to results from Swedish normative data, thereby suggesting that the study group was representative. The Swedish version of the Temperament and Character Inventory has been demonstrated to replicate the American version for means, distribution of scores, and relationships between scales and subscales, except for the self-transcendence scale (13). Here, the Swedish normative sample showed lower values than the U.S. normative sample. This is believed to reflect cultural differences between the Swedish and U.S. populations.

A common view is that variability in religious behavior among people is determined by environmental and cultural differences. However, a twin and adoption study has reported that genetic variation contributes to about 50% of individual variation in religiosity (29), thereby suggesting a biological underpinning. The findings of the present study may provide support for a biological underpinning specifically related to the central serotonergic system. Whereas experimental studies support a relationship between serotonin related gene polymorphisms and expression of 5-HT_{1A} receptors (30), a genetic basis for interindividual variability in 5-HT_{1A} receptor density remains to be confirmed in humans.

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