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ORIGINAL PAPER

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[^{123}I] ADAM brainstem binding correlates with the loudness dependence of auditory evoked potentials

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Abstract The in vivo assessment of brain serotonergic function might be of clinical relevance in neuropsychiatry. The loudness dependence of auditory evoked potentials (LD) has been proposed as an indirect indicator of cortical serotonergic activity, whereas single photon emission computed tomography (SPECT) and [^{123}I]ADAM allow the selective assessment of brain serotonin transporters (SERT). The aim of this study was to investigate LD and SERT availability as independent variables of the brain serotonergic system in healthy volunteers. Fifteen (six male, nine female) subjects received both neurophysiological and imaging investigations. Evoked potentials were recorded following the application of acoustic stimuli with increasing intensities; the LD was analyzed using dipole source analysis. SPECT was performed four hours after injection of 137 ± 11.4 MBq [^{123}I]ADAM. As a measure of SERT availability specific ADAM brainstem binding was used. LD correlated significantly with SERT availability (Pearson's correlations: rho = −0.57, $p < 0.05$). The correlations remained significant after controlling for the effects of age or gender (partial correlations: rho = −0.60, $p < 0.05$) but were pronounced in the female group (rho = −0.83, $p < 0.01$). Associations between LD and SERT availability contribute to the understanding of the central serotonergic system and further validate the use of neurophysiological approaches as indirect measures of neurochemical brain activity.

Key words serotonin transporter · SERT · single photon emission computed tomography · SPECT · [^{123}I] ADAM · auditory evoked potentials · loudness dependence

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Introduction

There is evidence from both human studies and animal experiments that central serotonergic neurotransmission plays a major role in the pathogenesis of various neuropsychiatric disorders and behavioral abnormalities [8, 14, 39, 55]. Brain serotonin activity is believed important for affect regulation, emotional stability, or impulse control and alterations of serotonin function have been associated with the development of a wide range of neuropsychiatric conditions [3, 4, 42, 53, 55, 57, 61]. The in vivo assessment of serotonergic neurotransmission is an important field of research, since valid indicators of brain neurochemical function could be useful for diagnostics and treatment decisions. Peripheral measures such as serum levels of monoamines or their metabolites only partially reflect central neurochemical activity [46] and have not been established in clinical practice.

The assessment of the loudness dependence of auditory evoked potentials (LD) might serve as an indirect neurophysiological approach to investigate central neurochemistry. The LD describes changes in amplitudes of the event related auditory N1/P2 component elicited by different stimulus intensities, which in animal experiments have been shown to be modulated by central serotonergic activity [27, 28]. Consequently, LD was proposed as a non-invasive indicator of cortical serotonergic function in humans [18]. High loudness dependence has been associated with a low function of serotonergic neurotransmission and vice versa. In clinical studies an increased LD has been shown in ecstasy (MDMA) users [9, 78] or patients with borderline personality disorder [53], indicative of a serotonergic dysfunction in these subjects. In depressed patients a high LD before drug treatment was associated with a favorable response to serotonergic medication [12, 18, 45]. Recently, Nathan et al. demonstrated that the LD is influenced by the enhancement of central serotonergic function with citalopram [49]. The observation that allelic variants of the serotonin transporter gene differ with respect to the magnitude of the LD further supports the hypothesis of an association with the serotonergic system [13, 72]. On the other hand there are also reports favoring dopaminergic aspects of the LD. Even though dopamine receptor modulation has not shown to modify LD in humans [54], some earlier studies revealed that a high intensity dependence of auditory and visual evoked potentials was related to low levels of dopamine metabolites in cerebrospinal fluid or urine [7, 81].

Nuclear medicine imaging techniques with specific radioligands expanded the investigation of central neurotransmitter systems. The monoamine transporter ligand β-CIT and single photon emission computed tomography (SPECT) have been used to visualize both central serotonin and dopamine transporters (SERT, DAT) of the human brain [5, 6, 25, 26, 34, 60]. Recently, the combination of SPECT with β-CIT and neurophysiological assessments in patients with obsessive-compulsive disorder (OCD) revealed a significant correlation of LD with both SERT and DAT availabilities [63]. This study provided preliminary evidence in vivo that LD is related to monoaminergic variables; however, due to the lack of specificity of β-CIT [25, 37, 50] definite conclusions in terms of serotonergic or dopaminergic associations could not be drawn. With [^{123}I] ADAM (2-([2-([dimethylamino] methyl) phenyl]thio)-5-I-123-iodophenylamine) a new and highly selective SERT ligand has been presented for use in SPECT imaging [35, 52, 56]. Previous clinical studies with this tracer have proven its ability to visualize, detect and quantify serotonergic dysfunction [21, 31, 51].

The aim of the present study was to investigate whether the LD of auditory evoked potentials is associated with serotonergic variables as assessed by SPECT and the serotonin specific radioligand [^{123}I] ADAM in a group of healthy subjects. According to previous studies it was hypothesized that there is a significant correlation between SERT availability within the brainstem region, the place of origin of most of the central serotonergic neurons, and the LD as an indirect functional measure of brain serotonergic activity of the primary auditory cortex.

Methods

The study was approved by the local ethics committee (University of Munich) and by federal regulatory authorities in terms of the use of radioactive agents. All subjects gave written informed consent for participation in this study, after the neurophysiological and imaging procedures had been fully explained by the research physicians of both the departments of psychiatry and nuclear medicine.

Subjects

The study population consists of 15 healthy volunteers (9 females) ranging in age from 22 to 39 years (mean ± standard deviation (SD): 27.1 ± 4.80 years).

The subjects were recruited at the Department of Psychiatry, University of Munich, mainly from medical students and hospital personnel. They were free of any previous or current neuropsychiatric disorders, exposure to psychotropic medication or other substances known to affect the brain serotonin system, or a family history of neurological or psychiatric diseases, as assessed by medical history, structured interviews and checklists, adopted from the structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID for DSM IV, German version) [2, 83]. Exclusion criteria were an age below 20 or above 60 years, any psychiatric disorders (DSM IV axis I or II), or any other medical or neurological illnesses. After study enrolment, the subjects underwent both the SPECT and neurophysiological investigations subsequently within two days. Female subjects were required to have a negative urine pregnancy test, performed immediately before the application of the radiotracer.

SPECT Imaging

Subjects received a bolus injection of a mean 137 ± 11.4 (range: 121 to 162) MBq [^{123}I] ADAM (Map Medical, Tikkakoski, Finland). Data were acquired with a triple-headed gamma camera (Philips Prism 3000, Philips Medical Systems, Bothell, Washington, USA) using low-energy, high-resolution fan beam collimators. Stringent quality control of the camera system was assured.

Scans of the healthy volunteers were acquired at a standardized time point four hours after intravenous injection of the radiopharmaceutical. A 128 × 128 matrix was used for all acquisitions. The rotational radius was minimized and less than 13 cm in all cases. A total of 120 projections were acquired at 60 sec/view with the camera heads following a circular orbit, resulting in a total scan time of 43 min. The projection data was checked visually for patient motion using the cine display and sinograms provided by the software of the camera manufacturer (Odyssey-FX software, Philips Medical Systems). SPECT data was reconstructed by filtered backprojection (ramp filter), filtered with a Butterworth 3-D postfilter (0.6 cycles/cm, 5th order) and corrected for attenuation according to Chang's method (μ = 0.11/cm, value confirmed from previous phantom measurements, elliptic fitting with separate contours for each slice) as outlined in the EANM neuroimaging guidelines [75].

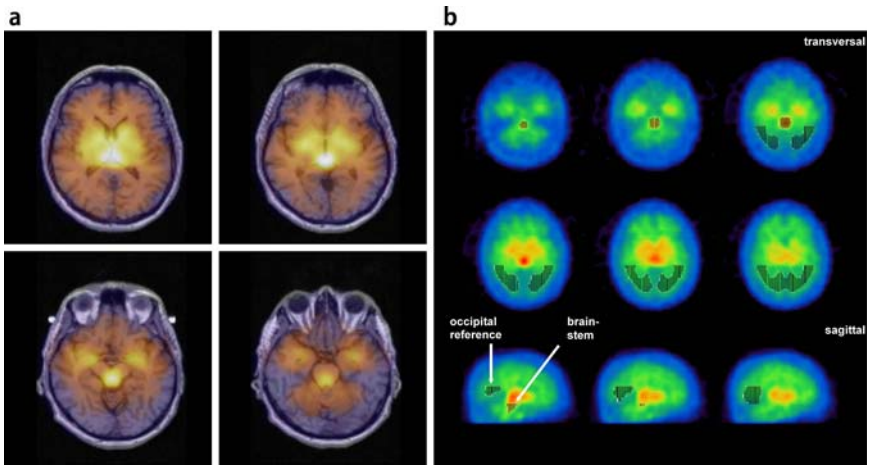

Fig. 1 [^{123}I] ADAM SPECT template used for the automated semi-quantification. Image fusion (**A**) with the MRI and the 3-D region map (**B**) derived from the MRI scan. Delineation of the region of interest (brainstem) and the nonspecific occipital reference region

Quantitative Evaluation

Images were evaluated using a semi-automated quantification software based on a modified version of the Brain Analysis Software (BRASS, version 3.4.4) running on a Hermes workstation (Nuclear Diagnostics, Stockholm, Sweden). It is based on a multi-step registration of individual patient studies to a template of healthy controls. For this software approach, a template and a 3-D volume of interest map was specifically created for [^{123}I] ADAM scans as follows.

Creation of the Template of Healthy Controls and the Corresponding Volume of Interest Map

The SPECT template was created using the images of the 15 healthy controls. In 4 subjects, additional MRI images (sagittal MPRAGE sequence, $1 \times 1 \times 1$ mm voxel size) were obtained with fiducial MRI/SPECT markers (nitro-glycerine pills injected with approximately 10 kBq I-123) attached, which served as basis for the co registration and were used to align images according to the Talairach space. Based on these MRI scans, a standardized 3-dimensional volume of interest map was created including regions for the brainstem (456 voxels), and an occipital reference region (9008 voxels). The method follows the previously developed quantification approach for dopamine transporter SPECT images [30].

Registration Process

Individual scans of subjects were then registered to the [^{123}I] ADAM-template by applying an automated fitting algorithm. The software registers individual studies to the mean template adjusting 9 parameters (3 each for rotation, translation and anisotropic scaling) of an alignment transformation matrix, using principal axes technique and an iterative, simplex algorithm to maximize normalized mutual information, a measure of similarity between the transformed individual study and the template [24, 64, 73]. After successful registration, the standardized 3-D VOI map is applied to the study, consisting of an occipital reference region and a specific region for the brainstem. Due to variation in anatomy, the specific region was adjusted manually to match the corresponding structures where necessary. Based on the mean counts per voxel within each volume of interest in the region map, the specific radiotracer binding for the brainstem was calculated by applying the formula: specific binding = [brainstem – occipital]/occipital (Figure 1).

Neurophysiological assessments

Subjects were seated in a comfortable armchair in an electrically shielded and sound-attenuated room. They were instructed to avoid movements and blinking during the recording. Sinus tones 1000-Hz, 40-ms duration with 10-ms rise and fall time, and an interstimulus interval randomized between 1800 and 2200 ms of five intensities 60, 70, 80, 90 and 100 dB sound pressure level (SPL) were presented in a pseudo randomized order through earphones. Electroencephalographic (EEG) activity was recorded with 32 tin electrodes placed via electro caps according to the international 10/20 system, with Cz as reference and Fpz as ground electrode. Additional electrodes (above the left eye and at the left ocular canthis) were used to monitor ocular artifacts. Impedances were kept at 5 kΩ or below. EEG was filtered using a band-pass of 0.16 to 70 Hz and digitized at a sample rate of 250 Hz with an epoch length of 800 ms (200 ms pre-stimulus baseline). A total of 500 sweeps (100 per intensity) were evaluated. Epochs with excessive eye or body movements (± 50 mV) in any of the 32 channels were automatically rejected, as well as the first five responses to each intensity to reduce short-term habituation effects. At least 30 artifact-free sweeps in any of the intensities were required. For each subject, the remaining sweeps were averaged separately for the five intensity levels.

Dipole source analysis (DSA)

Since the auditory evoked N1/P2 potential is generated by overlapping subcomponents, dipole source analysis (DSA) has been used to differentiate a dipole, mainly representing the activity of the primary auditory cortex, which shows a high rate of serotonergic innervation [16, 38, 48, 65–67]. DSA was performed with Brain Electrical Source Analysis (BESA; Scherg and Picton, 1991), assuming that the cortical activity in the time range of the N1/P2 component would be adequately represented by the activity of two dipoles per hemisphere: a tangential and a radial dipole. The tangential dipole explains most of the variance of cortical activity at this latency range, shows the strongest loudness dependence and mainly represents the activity of the primary auditory cortex, whereas the radial dipole represents the secondary auditory cortex activity [16]. For analysis the averaged curves of each subject were entered into BESA. A grand mean of the five averaged curves was calculated and used to individually adjust the dipole model. The individual curves were entered separately for the five intensities. The N1/P2 epoch amplitude or dipole moment, i.e. the root-mean-squared effective amplitude over the epoch of the N1/P2 component (μVeff), was determined for the 66.7–233 ms epoch and obtained for each dipole (mean of right and left sides) and intensity. The loudness dependence (LD) was operationalized as an amplitude/intensity function slope on the basis of N1/P2 epoch amplitudes and calculated for the

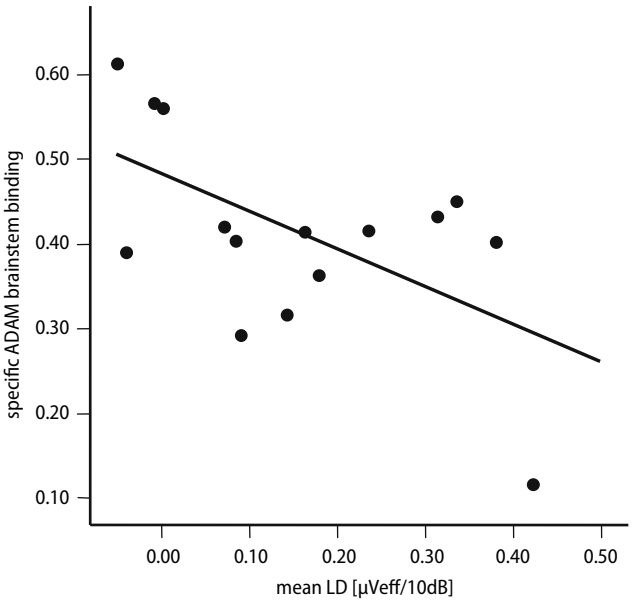

Fig. 2 Mean loudness dependence of auditory evoked potentials (LD) as assessed by dipole source analysis (tangential dipole of N1/P2 component) and specific brainstem ADAM binding (specific brainstem to nonspecific occipital cortex binding ratio: [brainstem-occipital] occipital) in 15 healthy subjects. Pearson's correlation: rho = −0.57, $p < 0.05$, partial correlation (controlled for age, gender): rho = −0.60, $p < 0.05$

tangential and radial dipoles. A median slope in μVeff/10 dB was calculated from the slopes of all possible connections (n = 10) between the five amplitude values to the five intensities (for details of the procedure see [16]).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 13.0 for Microsoft Windows). Descriptive analyses of clinical, neurophysiological, and SPECT variables are given as means and standard deviations. To explore the possible relationships between LD and the specific to nonspecific [^{123}I] ADAM binding ratios (brainstem SERT availability), Pearson's correlation coefficients (rho) between ADAM ratios and the LD of the dipoles of right and left hemispheres were calculated. To control the data for the effects of age and gender, two sided partial correlations were calculated with age and gender as control variables. Male and female subgroups were analysed separately using nonparametric (Spearman's) correlations. The $p < 0.05$ level was considered statistically significant. Due to the exploratory character of the study and the small sample size no alpha correction was performed.

Results

The mean (± SD) specific to nonspecific ADAM binding ratio for the brainstem was 0.41 ± 0.12. The mean LD of the tangential dipole was 0.15 ± 0.15 μVeff/10dB (0.17 ± 0.18 μVeff/10dB for the left and 0.14 ± 0.14 μVeff/10dB for the right hemisphere).

There was a significant correlation of mean LD (tangential dipole) with brainstem ADAM binding (Pearson's correlation, rho = −0.57, p = 0.03). Separate analyses regarding the LD (tangential dipole) of each hemisphere revealed that the significant associations with ADAM binding were pronounced for the right hemisphere (right hemisphere: rho = −0.57; p = 0.03; left hemisphere, rho = −0.50, p = 0.06). To control for the effects of age and gender, which are known to influence either variable, partial correlations were calculated. The correlations between mean LD and brainstem binding remained significant after controlling the data for these variables (rho = −0.60, p = 0.03). Again the significant correlation was attributed primarily to the LD of the right hemisphere (right hemisphere: rho = −0.58; p = 0.04; left hemisphere, rho = −0.52, p = 0.07).

However, when male (n = 6) and female (n = 9) subjects were analysed separately, it turned out that the correlations were especially pronounced in the female group (Spearman's rho = −0.83, p = 0.005) but not in the male group alone (n = 6), suggestive of a marked effect of gender.

Regarding the radial dipoles of the dipole source model, the mean LD was 0.05 ± 0.07 μVeff/10dB (0.09 ± 0.09, and 0.03 ± 0.08 μVeff/10dB for left and right hemispheres, respectively).

There were no significant correlations of radial dipoles with brainstem ADAM binding (mean radial dipole LD: Pearson's rho = −0.07, p = 0.8; left radial dipole LD: rho = 0.08, p = 0.8; right radial dipole LD: rho = −0.22, p = 0.42) (Fig. 2).

Discussion

A significant correlation was found between measures of two different tools for the assessment of brain serotonergic function. SPECT imaging with the radioligand ADAM allows the selective assessment of SERT availabilities in brain regions with dense serotonergic innervation [35, 56]. Here we focused on ADAM binding to the brainstem region as the place of origin of central serotonergic innervation [77]. The loudness dependence of the auditory evoked N1/P2 component has been suggested to mainly reflect the serotonergic activity of the auditory cortex. The implementation of dipole source analysis with a separation of two dipoles per hemisphere allows in part to focus on the brain activity of the primary auditory cortex, a region with a dense serotonergic innervation [16, 17, 38, 65]. However, up to date there is only limited direct validation from human studies with independent measures that LD is modulated by brain serotonergic activity [13, 63].

In a recent study with SPECT and β-CIT it has been shown in a small cohort of subjects with obsessive-compulsive disorder (OCD) that LD is correlated with monoamine transporter availabilities [63]. β-CIT is a monoamine transporter ligand that allows investigating both SERT and DAT status by using a region of interest technique. However, due to the lack of specificity of β-CIT definite conclusions regarding differential monoaminergic properties of LD cannot be drawn. Furthermore the subjects en-

rolled suffered from OCD, a clinical condition with increasing evidence of both serotonergic and dopaminergic pathophysiology [1, 11, 29, 61, 74, 79], which might have confounded the results. Also central interconnections of monoamine systems have to be taken into account [22, 44, 58]; functional interactions between SERT and DAT have recently been reported in healthy subjects, patients with depression, or OCD [33, 62].

Thus, the further validation of LD as a clinical serotonergic parameter [9, 15] in imaging studies requires highly selective markers. To counteract the above limitations we used the recently established serotonin selective radioligand ADAM in a group of drug naïve healthy volunteers. There was a statistically significant negative correlation of ADAM brainstem binding as a measure of SERT availability and the LD of the tangential dipole, which is suggested to reflect the serotonergic activity of the primary auditory cortex. Conversely, the LD of the radial dipoles, which are associated with the activity of secondary auditory cortices without substantial serotonergic activity, did not show similar associations. This is in line with the concept of different generators contributing differentially to the loudness dependence of auditory evoked potentials, supports the monoaminergic hypothesis of LD and favors the serotonergic aspects of LD modulation.

Both SERT availability and LD are reported to be influenced by age and gender [16, 19, 23, 36, 60, 68, 70, 80] but the correlations remained stable upon control for both these variables using partial correlations. However, separate analyses of male and female subjects revealed that the correlation between LD and SERT availability was pronounced in the female group but not significant within the limited number (n = 6) of male subjects alone. This finding is suggestive of a marked influence of gender on serotonergic parameters as reported in earlier investigations [69, 70].

The associations were more pronounced for the LD of the right hemispheres, which is in line with earlier reports in OCD, where only the right LD, representing the right primary auditory cortex revealed significant correlations with the imaging data [63].

The correlations between neurophysiological and nuclear medicine measures suggest that LD is related to brainstem SERT availability as assessed by SPECT imaging.

Nevertheless the associations between these parameters might be rather complex and several aspects have to be taken into account.

Serotonin brainstem availability and loudness dependence (cortical brain electrical activity) reflect two different limbs of the serotonergic system: the origin or the neuronal part within the brainstem and the terminal serotonergic activity within the primary auditory cortices.

Regarding clinical aspects Meyer et al. (2004) showed a strong positive correlation of SERT availability and negativistic dysfunctional attitudes in patients with major depression in various cortical and subcortical brain regions, except for the midbrain using PET and [^{11}C] DASB [43]. In a study with [^{123}I] ADAM and SPECT in patients with borderline personality disorder Koch et al. (2007) could recently demonstrate a positive correlation of brainstem SERT binding and impulsiveness [31]. These data provide evidence for a significant role of the serotonergic system for the pathophysiology of these symptoms, since an elevated SERT availability could reflect an increased capacity of presynaptic serotonin reuptake or be the consequence of an elevated number of available binding sites due to decreased competition by lower endogenous serotonin levels [20, 37, 43]. Both possible mechanisms would be associated with a serotonergic deficit and explain the efficacy of serotonin reuptake inhibiting drugs in these disorders, which have been shown to lower SERT availability in neuroimaging studies [10, 32, 33, 71].

On the other hand, low serotonin transporter availability could reflect a low serotonergic tone which could lead to a down regulation of the presynaptic reuptake sites of endogenous serotonin, i.e. serotonin transporters. This mechanism has first been discussed by Malison et al (1998), who demonstrated reduced serotonin transporter availability within the brainstem in patients with major depression [41]. Serotonin transporters are located presynaptically, mediate the removal of synaptic serotonin, and are involved in the regulation of the serotonergic tone [47, 59]. Consequently a lower expression of serotonin transporters (i.e. low SERT availability), could reflect a lower activity of the serotonergic system in general.

In our study low SERT availability was associated with high LD and vice versa. Given the above considerations and reports in psychiatric disorders with a suggested serotonergic deficit using SPECT and β-CIT [40, 76, 82] or ADAM [51], a reduction in SERT availability is indicative of a serotonergic dysfunction. Conversely, an increase in LD has been associated with a low serotonergic activity of the primary auditory cortex according to theoretical considerations, animal experiments and human clinical data [9, 18, 27, 28, 49, 53, 78]. Therefore negative correlations as reported here are in line with the clinical significance of either measure.

In a previous study in subjects with OCD, however, there was a positive correlation of LD and SERT availability as assessed by β-CIT and SPECT, which seems to be contradictory at the first glance. However, OCD is a clinical condition associated with a complex central monoaminergic dysfunction, and compared to healthy subjects there was evidence of an increase in SERT availability in these subjects [61]. Consequently, a positive correlation between LD and SERT availability seems plausible in this particular condition [63], and therefore does not necessarily contradict the associations found in healthy subjects without any

evidence of serotonergic dysfunction. In summary the different studies suggest that loudness dependence and nuclear medicine techniques can be used to assess the serotonin system in groups of patients or healthy control subjects and that there is a correlation between these variables reflecting different aspects of the serotonergic system.

Conclusion

We have combined neurophysiological and specific SPECT imaging measures of brain serotonergic function and could demonstrate an association between these variables in a group of healthy subjects. The data provide evidence that central neurotransmission can complementarily be assessed by combining different techniques and contribute to the understanding of the complex relationships between SERT and functional aspects of the serotonergic system. Furthermore the study suggests that neurophysiological parameters such as LD might be valid screening tools and clinically useful indicators of brain neurochemical function, and in particular of central serotonin activity.

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References

1. Adams KH, Hansen ES, Pinborg LH, Hasselbalch SG, Svarer C, Holm S, Bolwig TG, Knudsen GM (2005) Patients with obsessive-compulsive disorder have increased 5-HT2A receptor binding in the caudate nuclei. Int J Neuropsychopharmacol 8:391–401
2. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. American Psychiatric Press, Washington, DC
3. Arora RC, Meltzer HY (1989) Serotonergic measures in the brains of suicide victims: 5-HT2 binding sites in the frontal cortex of suicide victims and control subjects. Am J Psychiatry 146:730–736
4. Benkelfat C (1993) Serotonergic mechanisms in psychiatric disorders: new research tools, new ideas. Int Clin Psychopharmacol 8 Suppl 2:53–56
5. Boja JW, Mitchell WM, Patel A, Kopajtic TA, Carroll FI, Lewin AH, Abraham P, Kuhar MJ (1992) High-affinity binding of [125I]RTI-55 to dopamine and serotonin transporters in rat brain. Synapse 12:27–36
6. Brucke T, Kornhuber J, Angelberger P, Asenbaum S, Frassine H, Podreka I (1993) SPECT imaging of dopamine and serotonin transporters with [123I]beta-CIT. Binding kinetics in the human brain. J Neural Transm Gen Sect 94:137–146
7. Bruneau N, Barthelemy C, Jouve J, Lelord G (1986) Frontal auditory-evoked potential augmenting-reducing and urinary homovanillic acid. Neuropsychobiology 16:78–84
8. Charney DS (1998) Monoamine dysfunction and the pathophysiology and treatment of depression. J Clin Psychiatry 59 Suppl 14:11–14
9. Croft RJ, Klugman A, Baldeweg T, Gruzelier JH (2001) Electrophysiological evidence of serotonergic impairment in long-term MDMA (ecstasy) users. Am J Psychiatry 158:1687–1692
10. de Win MM, Habraken JB, Reneman L, van den Brink W, den Heeten GJ, Booij J (2005) Validation of [(123)I]beta-CIT SPECT to assess serotonin transporters in vivo in humans: a double-blind, placebo-controlled, crossover study with the selective serotonin reuptake inhibitor citalopram. Neuropsychopharmacology 30:996–1005
11. Denys D, Zohar J, Westenberg HG (2004) The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. J Clin Psychiatry 65 Suppl 14:11–17
12. Gallinat J, Bottlender R, Juckel G, Munke-Puchner A, Stotz G, Kuss HJ, Mavrogiorgou P, Hegerl U (2000) The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. Psychopharmacology (Berl) 148:404–411
13. Gallinat J, Senkowski D, Wernicke C, Juckel G, Becker I, Sander T, Smolka M, Hegerl U, Rommelspacher H, Winterer G, Herrmann WM (2003) Allelic variants of the functional promoter polymorphism of the human serotonin transporter gene is associated with auditory cortical stimulus processing. Neuropsychopharmacology 28:530–532
14. Gingrich JA, Hen R (2001) Dissecting the role of the serotonin system in neuropsychiatric disorders using knockout mice. Psychopharmacology (Berl) 155:1–10
15. Hegerl U, Gallinat J, Juckel G (2001) Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? J Affect Disord 62:93–100
16. Hegerl U, Gallinat J, Mrowinski D (1994) Intensity dependence of auditory evoked dipole source activity. Int J Psychophysiol 17:1–13
17. Hegerl U, Juckel G (1994) Auditory evoked dipole source activity: indicator of central serotonergic dysfunction in psychiatric patients? Pharmacopsychiatry 27:75–78
18. Hegerl U, Juckel G (1993) Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biol Psychiatry 33:173–187
19. Hegerl U, Prochno I, Ulrich G, Muller-Oerlinghausen B (1988) Are auditory evoked potentials suitable for predicting the response to lithium prophylaxis? A study on the effects of repeated measurement, age, gender, and personality on the amplitude/stimulus intensity function in healthy volunteers. Pharmacopsychiatry 21:336–337
20. Heinz A, Higley JD, Gorey JG, Saunders RC, Jones DW, Hommer D, Zajicek K, Suomi SJ, Lesch KP, Weinberger DR, Linnoila M (1998) In vivo association between alcohol intoxication, aggression, and serotonin transporter availability in nonhuman primates. Am J Psychiatry 155:1023–1028
21. Herold N, Uebelhack K, Franke L, Amthauer H, Luedemann L, Bruhn H, Felix R, Uebelhack R, Plotkin M (2006) Imaging of serotonin transporters and its blockade by citalopram in patients with major depression using a novel SPECT ligand [123I]-ADAM. J Neural Transm 113:659–670
22. Herve D, Pickel VM, Joh TH, Beaudet A (1987) Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. Brain Res 435:71–83
23. Hesse S, Barthel H, Murai T, Muller U, Muller D, Seese A, Kluge R, Sabri O (2003) Is correction for age necessary in neuroimaging studies of the central serotonin transporter? Eur J Nucl Med Mol Imaging 30:427–430
24. Hill DL, Maurer CR Jr, Studholme C, Fitzpatrick JM, Hawkes DJ (1998) Correcting scaling errors in tomographic images using a nine degree of freedom registration algorithm. J Comput Assist Tomogr 22:317–323
25. Innis R, Baldwin R, Sybirska E, Zea Y, Laruelle M, al-Tikriti M, Charney D, Zoghbi S, Smith E, Wisniewski G, et al. (1991) Single photon emission computed tomography imaging of monoamine reuptake sites in primate brain with [123I]CIT. Eur J Pharmacol 200:369–370

26. Innis RB, Seibyl JP, Scanley BE, Laruelle M, Abi-Dargham A, Wallace E, Baldwin RM, Zea-Ponce Y, Zoghbi S, Wang S, et al. (1993) Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in Parkinson disease. Proc Natl Acad Sci USA 90:11965–11969
27. Juckel G, Hegerl U, Molnar M, Csepe V, Karmos G (1999) Auditory evoked potentials reflect serotonergic neuronal activity—a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. Neuropsychopharmacology 21:710–716
28. Juckel G, Molnar M, Hegerl U, Csepe V, Karmos G (1997) Auditory-evoked potentials as indicator of brain serotonergic activity—first evidence in behaving cats. Biol Psychiatry 41:1181–1195
29. Kim CH, Koo MS, Cheon KA, Ryu YH, Lee JD, Lee HS (2003) Dopamine transporter density of basal ganglia assessed with [123I]IPT SPET in obsessive-compulsive disorder. Eur J Nucl Med Mol Imaging 30:1637–1643
30. Koch W, Radau PE, Hamann C, Tatsch K (2005) Clinical testing of an optimized software solution for an automated, observer-independent evaluation of dopamine transporter SPECT studies. J Nucl Med 46:1109–1118
31. Koch W, Schaaff N, Pöpperl G, Mulert C, Juckel G, Reicherzer M, Ehmer von-Geiso C, Möller HJ, Hegerl U, Tatsch K, Pogarell O (2007) [I-123] ADAM and SPECT in patients with borderline personality disorder and healthy control subjects. J Psychiatry Neurosci 32:234–240
32. Kugaya A, Sanacora G, Staley JK, Malison RT, Bozkurt A, Khan S, Anand A, Van Dyck CH, Baldwin RM, Seibyl JP, Charney D, Innis RB (2004) Brain serotonin transporter availability predicts treatment response to selective serotonin reuptake inhibitors. Biol Psychiatry 56:497–502
33. Kugaya A, Seneca NM, Snyder PJ, Williams SA, Malison RT, Baldwin RM, Seibyl JP, Innis RB (2003) Changes in human in vivo serotonin and dopamine transporter availabilities during chronic antidepressant administration. Neuropsychopharmacology 28:413–420
34. Kuikka JT, Bergstrom KA, Vanninen E, Laulumaa V, Hartikainen P, Lansimies E (1993) Initial experience with single-photon emission tomography using iodine-123-labelled 2 beta-carbomethoxy-3 beta-(4-iodophenyl) tropane in human brain. Eur J Nucl Med 20:783–786
35. Kung HF, Newman S, Choi SR, Oya S, Hou C, Zhuang ZP, Acton PD, Plossl K, Winkler J, Kung MP (2004) 2-(2-(dimethylaminomethyl)phenoxy)-5-iodophenylamine: an improved serotonin transporter imaging agent. J Med Chem 47:5258–5264
36. Laffont F, Bruneau N, Roux S, Agar N, Minz M, Cathala HP (1989) Effect of age on auditory evoked responses (AER) and augmenting-reducing. Neurophysiol Clin 19:15–23
37. Laruelle M, Baldwin RM, Malison RT, Zea-Ponce Y, Zoghbi SS, al-Tikriti MS, Sybirska EH, Zimmermann RC, Wisniewski G, Neumeyer JL, et al. (1993) SPECT imaging of dopamine and serotonin transporters with [123I]beta-CIT: pharmacological characterization of brain uptake in nonhuman primates. Synapse 13:295–309
38. Lewis DA, Campbell MJ, Foote SL, Morrison JH (1986) The monoaminergic innervation of primate neocortex. Hum Neurobiol 5:181–188
39. Lucki I (1998) The spectrum of behaviors influenced by serotonin. Biol Psychiatry 44:151–162
40. Malison RT, Best SE, van Dyck CH, McCance EF, Wallace EA, Laruelle M, Baldwin RM, Seibyl JP, Price LH, Kosten TR, Innis RB (1998) Elevated striatal dopamine transporters during acute cocaine abstinence as measured by [123I] beta-CIT SPECT. Am J Psychiatry 155:832–834
41. Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N, Baldwin RM, Seibyl JP, Innis RB, Charney DS (1998) Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. Biol Psychiatry 44:1090–1098
42. Mann JJ, Stanley M, McBride PA, McEwen BS (1986) Increased serotonin2 and beta-adrenergic receptor binding in the frontal cortices of suicide victims. Arch Gen Psychiatry 43:954–959
43. Meyer JH, Houle S, Sagrati S, Carella A, Hussey DF, Ginovart N, Goulding V, Kennedy J, Wilson AA (2004) Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: effects of major depressive episodes and severity of dysfunctional attitudes. Arch Gen Psychiatry 61:1271–1279
44. Moukhles H, Bosler O, Bolam JP, Vallee A, Umbriaco D, Geffard M, Doucet G (1997) Quantitative and morphometric data indicate precise cellular interactions between serotonin terminals and postsynaptic targets in rat substantia nigra. Neuroscience 76:1159–1171
45. Mulert C, Juckel G, Augustin H, Hegerl U (2002) Comparison between the analysis of the loudness dependency of the auditory N1/P2 component with LORETA and dipole source analysis in the prediction of treatment response to the selective serotonin reuptake inhibitor citalopram in major depression. Clin Neurophysiol 113:1566–1572
46. Murphy DL (1990) Peripheral indices of central serotonin function in humans. Ann NY Acad Sci 600:282–295; discussion 295–286
47. Murphy DL, Lerner A, Rudnick G, Lesch KP (2004) Serotonin transporter: gene, genetic disorders, and pharmacogenetics. Mol Interv 4:109–123
48. Naatanen R, Picton T (1987) The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 24:375–425
49. Nathan PJ, Segrave R, Phan KL, O'Neill B, Croft RJ (2006) Direct evidence that acutely enhancing serotonin with the selective serotonin reuptake inhibitor citalopram modulates the loudness dependence of the auditory evoked potential (LDAEP) marker of central serotonin function. Hum Psychopharmacol 21:47–52
50. Neumeyer JL, Tamagnan G, Wang S, Gao Y, Milius RA, Kula NS, Baldessarini RJ (1996) N-substituted analogs of 2 beta-carbomethoxy-3 beta-(4′-iodophenyl)tropane (beta-CIT) with selective affinity to dopamine or serotonin transporters in rat forebrain. J Med Chem 39:543–548
51. Newberg AB, Amsterdam JD, Wintering N, Ploessl K, Swanson RL, Shults J, Alavi A (2005) 123I-ADAM binding to serotonin transporters in patients with major depression and healthy controls: a preliminary study. J Nucl Med 46:973–977
52. Newberg AB, Plossl K, Mozley PD, Stubbs JB, Wintering N, Udeshi M, Alavi A, Kauppinen T, Kung HF (2004) Biodistribution and imaging with (123)I-ADAM: a serotonin transporter imaging agent. J Nucl Med 45:834–841
53. Norra C, Mrazek M, Tuchtenhagen F, Gobbele R, Buchner H, Sass H, Herpertz SC (2003) Enhanced intensity dependence as a marker of low serotonergic neurotransmission in borderline personality disorder. J Psychiatr Res 37:23–33
54. O'Neill BV, Croft RJ, Leung S, Guille V, Galloway M, Phan KL, Nathan PJ (2006) Dopamine receptor stimulation does not modulate the loudness dependence of the auditory evoked potential in humans. Psychopharmacology (Berl) 188:92–99
55. Owens MJ, Nemeroff CB (1998) The serotonin transporter and depression. Depress Anxiety 8 Suppl 1:5–12
56. Oya S, Choi SR, Hou C, Mu M, Kung MP, Acton PD, Siciliano M, Kung HF (2000) 2-((2-((dimethylamino)methyl)phenyl) thio)-5-iodophenylamine (ADAM): an improved serotonin transporter ligand. Nucl Med Biol 27:249–254
57. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Pandey SC, Pesold C, Roberts RC, Conley RR, Tamminga CA (2002) Higher expression of serotonin 5-HT(2A) receptors in the postmortem brains of teenage suicide victims. Am J Psychiatry 159:419–429
58. Parsons LH, Justice JB Jr (1993) Perfusate serotonin increases extracellular dopamine in the nucleus accumbens as measured by in vivo microdialysis. Brain Res 606:195–199
59. Pineyro G, Blier P (1999) Autoregulation of serotonin neurons: role in antidepressant drug action. Pharmacol Rev 51:533–591

60. Pirker W, Asenbaum S, Hauk M, Kandlhofer S, Tauscher J, Willeit M, Neumeister A, Praschak-Rieder N, Angelberger P, Brucke T (2000) Imaging serotonin and dopamine transporters with 123I-beta-CIT SPECT: binding kinetics and effects of normal aging. J Nucl Med 41:36–44
61. Pogarell O, Hamann C, Popperl G, Juckel G, Chouker M, Zaudig M, Riedel M, Moller HJ, Hegerl U, Tatsch K (2003) Elevated brain serotonin transporter availability in patients with obsessive-compulsive disorder. Biol Psychiatry 54:1406–1413
62. Pogarell O, Poepperl G, Mulert C, Hamann C, Sadowsky N, Riedel M, Moeller HJ, Hegerl U, Tatsch K (2005) SERT and DAT availabilities under citalopram treatment in obsessive-compulsive disorder (OCD). Eur Neuropsychopharmacol 15:521–524
63. Pogarell O, Tatsch K, Juckel G, Hamann C, Mulert C, Popperl G, Folkerts M, Chouker M, Riedel M, Zaudig M, Moller HJ, Hegerl U (2004) Serotonin and dopamine transporter availabilities correlate with the loudness dependence of auditory evoked potentials in patients with obsessive-compulsive disorder. Neuropsychopharmacology 29:1910–1917
64. Radau PE, Slomka PJ, Julin P, Svensson L, Wahlund LO (2001) Evaluation of linear registration algorithms for brain SPECT and the errors due to hypoperfusion lesions. Med Phys 28:1660–1668
65. Scherg M, Berg P (1996) New concepts of brain source imaging and localization. Electroencephalogr Clin Neurophysiol Suppl 46:127–137
66. Scherg M, Picton TW (1991) Separation and identification of event-related potential components by brain electric source analysis. Electroencephalogr Clin Neurophysiol Suppl 42:24–37
67. Scherg M, Vajsar J, Picton TW (1989) Source analysis of the late human auditory evoked potentials. J Cogn Neurosci 4:336–355
68. Staley JK, Basile M, Flynn DD, Mash DC (1994) Visualizing dopamine and serotonin transporters in the human brain with the potent cocaine analogue [125I]RTI-55: in vitro binding and autoradiographic characterization. J Neurochem 62:549–556
69. Staley JK, Krishnan-Sarin S, Zoghbi S, Tamagnan G, Fujita M, Seibyl JP, Maciejewski PK, O'Malley S, Innis RB (2001) Sex differences in [123I]beta-CIT SPECT measures of dopamine and serotonin transporter availability in healthy smokers and nonsmokers. Synapse 41:275–284
70. Staley JK, Sanacora G, Tamagnan G, Maciejewski PK, Malison RT, Berman RM, Vythilingam M, Kugaya A, Baldwin RM, Seibyl JP, Charney D, Innis RB (2006) Sex differences in diencephalon serotonin transporter availability in major depression. Biol Psychiatry 59:40–47
71. Stengler-Wenzke K, Muller U, Barthel H, Angermeyer MC, Sabri O, Hesse S (2006) Serotonin transporter imaging with [123I]beta-CIT SPECT before and after one year of citalopram treatment of obsessive-compulsive disorder. Neuropsychobiology 53:40–45
72. Strobel A, Debener S, Schmidt D, Hunnerkopf R, Lesch KP, Brocke B (2003) Allelic variation in serotonin transporter function associated with the intensity dependence of the auditory evoked potential. Am J Med Genet 118B:41–47
73. Studholme C, Hawkes DJ, Hill DL (1998) A normalized entropy measure for multimodality image alignment. In: Hansen KM (ed) Proceedings of SPIE: Medical Imaging 1998: Image Processing. SPIE, Bellingham, p 132–143
74. Szymanski S, Kane JM, Lieberman JA (1991) A selective review of biological markers in schizophrenia. Schizophr Bull 17:99–111
75. Tatsch K, Asenbaum S, Bartenstein P, Catafau A, Halldin C, Pilowsky LS, Pupi A (2002) European Association of Nuclear Medicine procedure guidelines for brain neurotransmission SPET using (123)I-labelled dopamine D(2) transporter ligands. Eur J Nucl Med Mol Imaging 29:BP30–BP35
76. Tauscher J, Pirker W, Willeit M, de Zwaan M, Bailer U, Neumeister A, Asenbaum S, Lennkh C, Praschak-Rieder N, Brucke T, Kasper S (2001) [123I] beta-CIT and single photon emission computed tomography reveal reduced brain serotonin transporter availability in bulimia nervosa. Biol Psychiatry 49:326–332
77. Tork I (1990) Anatomy of the serotonergic system. Ann NY Acad Sci 600:9–34
78. Tuchtenhagen F, Daumann J, Norra C, Gobbele R, Becker S, Pelz S, Sass H, Buchner H, Gouzoulis-Mayfrank E (2000) High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology 22:608–617
79. van der Wee NJ, Stevens H, Hardeman JA, Mandl RC, Denys DA, van Megen HJ, Kahn RS, Westenberg HM (2004) Enhanced dopamine transporter density in psychotropic-naive patients with obsessive-compulsive disorder shown by [123I]{beta}-CIT SPECT. Am J Psychiatry 161:2201–2206
80. van Dyck CH, Malison RT, Seibyl JP, Laruelle M, Klumpp H, Zoghbi SS, Baldwin RM, Innis RB (2000) Age-related decline in central serotonin transporter availability with [(123)I]beta-CIT SPECT. Neurobiol Aging 21:497–501
81. von Knorring L, Perris C (1981) Biochemistry of the augmenting-reducing response in visual evoked potentials. Neuropsychobiology 7:1–8
82. Willeit M, Praschak-Rieder N, Neumeister A, Pirker W, Asenbaum S, Vitouch O, Tauscher J, Hilger E, Stastny J, Brucke T, Kasper S (2000) [123I]-beta-CIT SPECT imaging shows reduced brain serotonin transporter availability in drug-free depressed patients with seasonal affective disorder. Biol Psychiatry 47:482–489
83. Wittchen HU, Zaudig M, Fydrich T (1997) SKID - Strukturiertes klinisches Interview für DSM IV. Achse I und II: Handanweisungen. Hogrefe Verlag, Goettingen, Germany