Psychiatry Research: Neuroimaging 231 (2015) 320–324

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Which demographic variables are necessary to correct in neuroimaging studies of serotonin transporter availability? A SPECT study with [^{123}I]ADAM

Wei Hung Chang [a,b], Lan-Ting Lee [b], I Hui Lee [b,c], Mei Hung Chi [b], Kao Chin Chen [a,b,c], Nan Tsing Chiu [d], Wei Jen Yao [d], Po See Chen [b,c], Yen Kuang Yang [b,c,*]

[a] Department of Psychiatry, National Cheng Kung University Hospital, Dou-Liou Branch, Yunlin, Taiwan
[b] Department of Psychiatry, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[c] Addiction Research Center, National Cheng Kung University, Tainan, Taiwan
[d] Department of Nuclear Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

ARTICLE INFO

Article history:
Received 5 December 2013
Received in revised form
7 April 2014
Accepted 14 January 2015
Available online 24 January 2015

Keywords:
Age
Educational level
Obesity
Seasonal change
Serotonin transporter
Substance use

ABSTRACT

Previous studies have shown that many demographic variables influence serotonin transporter (SERT) availability as assessed by single photon emission computed tomography (SPECT). The aim of this study was to explore which demographic variables influenced the SERT availability most in a SPECT study with [^{123}I]ADAM. Ninety-five healthy volunteers were recruited. Age, sex, smoking, alcohol intake, educational level, body mass index, seasonal change, and SERT availability were recorded and then analyzed by multivariate linear regression. Age was the only variable that was significantly associated with SERT availability (calculate: (midbrain – cerebellum)/cerebellum). Furthermore, the inverse correlation of age and SERT availability may be present only before the age of 47. Age should be a covariate in SERT-related neuroimaging analyses, particularly in participants under the age of 47 years.

1. Introduction

Central serotonin (5-HT) plays an important role in many aspects of cognitive, behavioral and emotional regulation (Yang et al., 2007; Crockett et al., 2010; Meneses and Liy-Salmeron, 2012). Dysregulation of serotonin may be implicated in various psychiatric illnesses, including depression, sleep problems and even psychosis (Salomon et al., 1994; Meltzer et al., 2011). In the serotonergic system, the serotonin transporter (SERT) plays a crucial role in modulating serotonin-signaling processes and subsequent serotonin-mediated activities (Hesse et al., 2004). Therefore, increasingly neuroimaging studies have focused on detection of SERT availability using various radioligands, including *N*,*N*-dimethyl-2- (2′-amino-4′-iodophenylthio) benzylamine (Jarkas et al., 2005), [^{11}C]DASB (3-amino-4- (2-dimethylamino-methyl-phenylsulfanyl)-benzonitrile), methyl 3 beta- (4-[^{125}I]iodophenyl) tropane-2 beta-carboxylate ([^{123}I]beta-CIT), [^{11}C]McN5652 and [^{11}C]MADAM (Suehiro et al., 1993; Laruelle et al., 1994; Paterson et al., 2013). A ligand that has been widely used in single photon emission computed tomography (SPECT) studies is [^{123}I]-labeled 2-((2-((dimethylamino)methyl) phenyl)thio)-5-iodophenylamine ([^{123}I]ADAM), a highly selective and strongly affinitive SERT ligand synthesized by Oya et al. (2000). The ligand has been used to assess SERT in relation to, for example, substance dependence, personality characteristics, and even mood disorder subtype variations in biological regulation (Chou et al., 2010, 2012; van de Giessen and Booij, 2010; Yeh et al., 2012).

Previous research has demonstrated that SERT availability is influenced by certain demographic characteristics. For example, age is an important covariate, and a decline of SERT availability with age has been demonstrated (van Dyck et al., 2000; Hesse et al., 2003). Conflicting results have also been reported by Buchert et al. (2006), who found no significant effects of age in young healthy adults. Also, seasonal changes (especially in winter) (Neumeister et al., 2000; Ruhe et al., 2009), sex differences (male subjects) (Ruhe et al., 2009) and even educational level (Madsen et al., 2011) have been associated with SERT availability in either inverse or positive correlations. No seasonal variation in SERT availability was found in our previous study (Cheng et al., 2011), and no significant effects of sex on SERT availability were observed by other investigators (Praschak-Rieder et al., 2008). Lifestyle

* Corresponding author at: Department of Psychiatry, National Cheng Kung University Hospital, 138 Sheng Li Road, North Dist., Tainan 70403, Taiwan. Tel.: +886 6 2353535x5213; fax: +886 6 2084767.
E-mail address: ykyang@mail.ncku.edu.tw (Y.K. Yang).

http://dx.doi.org/10.1016/j.pscychresns.2015.01.015
0925-4927/

habits/stressors that have been found to alter SERT availability include alcohol consumption or life events (Heinz et al., 1998; Yeh et al., 2009) and smoking behavior in male subjects (Staley et al., 2001). Obesity is also correlated with SERT functioning (Chen et al., 2012), and a functional imaging study showed that body-mass index (BMI) was inversely correlated with SERT in the subcortical regions of normal healthy subjects (Erritzoe et al., 2010). Although treatment for binge-eating behavior may enhance SERT binding affinity, no correlation has been found between SERT binding and BMI (Tammela et al., 2003).

To conclude, many demographic covariates might influence SERT availability; however, the small number of participants in most studies could be an issue, leading to inconsistent results. Therefore, it is critical to establish which demographic variables need to be controlled in neuroimaging studies of central SERT in studies with larger sample sizes. The aim of the current study was to explore which covariates influence SERT availability as measured using [^{123}I]ADAM with SPECT in healthy participants. In this study, age, sex, educational level, seasonal changes, smoking behavior, drinking behavior, and BMI were chosen as dependent covariates. The reasons for choosing these factors were not only previous evidence as mentioned above, but also ease of assessing and evaluating these factors without further complicated measurements.

2. Methods

2.1. Ethics statement

The research protocol was approved by the Ethical Committee for Human Research at the National Cheng Kung University, and written informed consent was obtained from each subject before any procedures were performed.

2.2. Subjects

The participants were enrolled from the community through advertisement. They were recruited as healthy controls in our previous studies (Yeh et al., 2009, 2012; Hsieh et al., 2010; Tsai et al., 2013). All of the subjects recruited in our study were Han Chinese. The subjects were excluded if they were found to have a mental illness after evaluation with the Chinese version of the Mini International Neuropsychiatry Interview (MINI) (Sheehan et al., 1998). Meanwhile, participants with (i) any acute or unstable medical condition, (ii) history of head trauma or neurological disease, (iii) use of current medication with an effect on the central dopamine and serotonin systems, and (iv) alcohol abuse or other substance abuse were omitted from our study, except for subjects with nicotine/tobacco dependence. Finally, 95 healthy participants (43 males and 52 females, mean age=34.10 years, S.D.=12.20; age range=18.9–60.8 years) were recruited. Fig. 1 shows the histogram of age in the sample. The mean educational level was 13.88 (S.D.=3.64) years. The mean score on the 17-item Hamilton Depression Rating Scale (Hamilton, 1960) was 3.6 (S.D.=1.8).

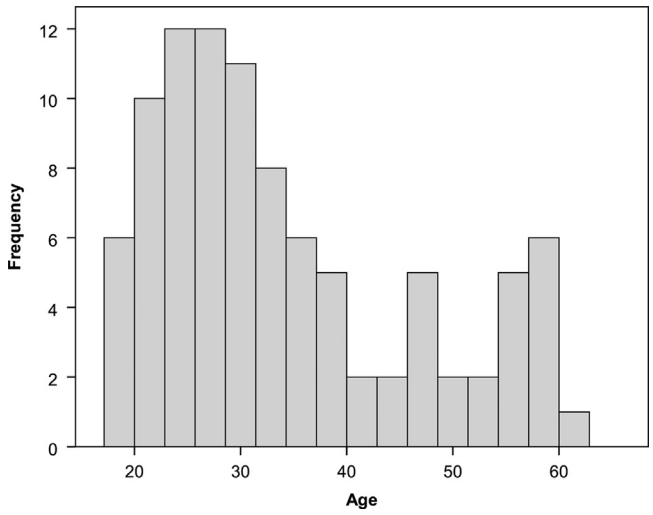

Fig. 1. The histogram of age.

2.3. Imaging

Before SPECT examination with [^{123}I]ADAM, the thyroid gland was protected with 9 ml of Lugol's solution. For brain SPECT imaging, each participant was intravenously administered 185 MBq (5 mCi) of [^{123}I]ADAM in a quiet environment about 10 min after insertion of the intravenous lines. We used a triple-headed rotating gamma camera (Multispect 3; Siemens Medical Systems, Hoffman Estates, IL, USA) with fan-beam collimators, which yielded an image resolution of approximately 8.5 mm full width at half-maximum (FWHM). A 20% energy window was symmetrically placed at 159 keV. The SPECT images were acquired over a circular 360° rotation of 120 steps, at 50 s/step, in a $128 \times \times 128 \times 16$ matrix. The images were reconstructed using Butterworth and Ramp filters (cut-off frequency=0.3 Nyquist; power factor=7) with attenuation by Chang's method (Chang, 1978). The reconstructed transverse images were then realigned parallel to the canthomeatal line, and the slice thickness was 2.89 mm. All the participants underwent magnetic resonance imaging (MRI) (Signa CV-I, 1.5 T, GE Medical Systems, Milwaukee, WI, USA). With the commercial software PMOD (PMOD Technologies, Zurich, Switzerland), each subject's SPECT image was co-registered with the corresponding T2-weighted MR image automatically and was then finely adjusted manually by an experienced nuclear medicine physician without knowledge of the participants's clinical data. The MR image was loaded as a reference, so the slice thickness of the co-registered images was the thickness of the T2-weighted MR images (3.3 mm). For co-registration, rigid transformations were defined by six parameters, the rotation angles and the translation distances in the three spatial directions. The interpolation method was tri-linear. To ensure fine co-registration, especially in the midbrain, on the co-registered images, the two contiguous transverse slices that contained the most intense midbrain radioactivity were further examined in order to ascertain whether the SPECT and MRI images were co-registered accurately by checking the transverse slices showing the midbrain and the interpeduncular cistern on MR images. If necessary, further adjustment of co-registration was performed manually until a satisfactory outcome was achieved. Regions of interest (ROIs), including the midbrain and cerebellum, were then drawn on the two contiguous MRI transverse slices, and these ROIs were projected onto the co-registered SPECT images. We focused on the SERT level in the midbrain due to high availability, sufficient level and specificity of SERT in the midbrain (Erlandsson et al., 2005). Also, SPECT with [^{123}I]ADAM has been shown to be an ideal tracer for the imaging of SERT in the midbrain, but not in the striatum or thalamus due to the low signal-to-noise ratios (Chou et al., 2009). SERT availability was calculated as the average count in the midbrain ROI minus the average count in the cerebellum ROI divided by the average count in the cerebellum ROI, (midbrain − cerebellum)/cerebellum.

2.4. Influential factors

In addition to age, sex, and years of education, BMI was recorded and calculated as weight in kilograms divided by the square of height in meters. Smoking and alcohol drinking behaviors were reported by the subjects themselves and measured by senior psychiatrists at recruitment. For example, the subjects were asked "Have you had the habit of drinking alcohol or smoking in the past 12 months?" The answer "Yes" or "No" was recorded. In the "Yes" groups, breath carbon monoxide was tested by a carbon monoxide monitor (Vitalograph, Inc., Lenexa, KS, USA), and subjects further interviewed to exclude the possibilities of nicotine or alcohol abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV TR).

Seasonal changes were recorded and analyzed. Taiwan is in a subtropical area (120°12′17″E, 22°59′36″N) with little seasonal change, and the duration of sun exposure does not vary considerably between seasons (Cheng et al., 2011). Therefore, the sun exposure data in this study were not calculated on the basis of traditional seasonal changes but were instead obtained from the Central Weather Bureau database in Taiwan for 2005–2010.

2.5. Statistical analysis

The data were analyzed using SPSS software (v17, SPSS Inc., Chicago, IL, USA). Means and standard deviations (S.D.) were calculated for descriptive analysis of SERT availability and possible influential factors. A stepwise multivariate linear regression model was applied to assess the influence of age, sex, smoking, alcohol drinking behavior, educational level, BMI, sleep quality, and seasonal change on SERT availability. The standardized coefficients (β) are presented. The threshold for statistical significance was set at $p < 0.05$.

As the findings of previous studies concerning the association between age and SERT availability were inconsistent (van Dyck et al., 2000; Hesse et al., 2003; Buchert et al., 2006), we speculated that there might be a cut-off point of the differential association between age and SERT. To probe this, segmented regression analysis was further used to test whether there were any cut-off points of