Psychiatry Research: Neuroimaging 221 (2014) 162–168

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Dorsal prefrontal cortical serotonin 2A receptor binding indices are differentially related to individual scores on harm avoidance

Chris Baeken [a,b,c,*], Axel Bossuyt [d], Rudi De Raedt [e]

[a] Department of Psychiatry and Medical Psychology, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium
[b] Department of Psychiatry, University Hospital UZBrussel, Brussels, Belgium
[c] Ghent Experimental Psychiatry (GHEP) Lab, Ghent, Belgium
[d] Department of Nuclear Medicine, University Hospital UZBrussel, Brussels, Belgium
[e] Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

ARTICLE INFO

Article history:
Received 14 November 2012
Received in revised form
20 November 2013
Accepted 19 December 2013
Available online 27 December 2013

Keywords:
5-HT_{2A} receptor
SPECT
Harm avoidance
Dorsal prefrontal cortex

ABSTRACT

Although the serotonergic system has been implicated in healthy as well as in pathological emotional states, knowledge about its involvement in personality is limited. Earlier research on this topic suggests that post-synaptic 5-HT_{2A} receptors could be involved in particular in frontal cortical areas. In drug-naïve healthy individuals, we examined the relationship between these 5-HT_{2A} receptors and the temperament dimension harm avoidance (HA) using ^{123}I-5-I-R91150 single photon emission computed tomography (SPECT). HA is a personality feature closely related to stress, anxiety and depression proneness, and it is thought to be mediated by the serotonergic system. We focused on the prefrontal cortices as these regions are frequently implicated in cognitive processes related to a variety of affective disorders. We found a positive relationship between dorsal prefrontal cortical (DPFC) 5-HT_{2A} receptor binding indices (BI) and individual HA scores. Further, our results suggest that those individuals with a tendency to worry or to ruminate are particularly prone to display significantly higher 5-HT_{2A} receptor BI in the left DPFC. Although we only examined psychologically healthy individuals, this relationship suggests a possible vulnerability for affective disorders.

1. Introduction

The serotonergic system, one of the major neurotransmitter (NT) systems in the human brain, influences frontocortico-limbic neural circuits that mediate emotion and cognition, personality, learning and memory (Carver and Miller, 2006; Leonard, 2006). Ascending serotonergic projections arise from the raphe nuclei and arborize widely throughout the brain, innervating prefrontal cortical and limbic areas (Hensler, 2006; Puig and Gulledge, 2011). Homeostatic disturbances have been linked to higher risks of developing affective disorders (Andrade, 2011). In particular, serotonergic dysfunctions have been observed in prefrontal and anterior cingulate cortical (ACC) areas. As stated by Meyer (2012), these regions are frequently activated in paradigms involving the induction of sad mood states, and these anatomical structures are implicated in cognitive processes leading to pessimism.

Interestingly, Cloninger's influential psychobiologically oriented theory on personality and genetic inheritance states that the serotonergic system is predominantly related to behavioral differences in the temperament dimension harm avoidance (HA) (Cloninger, 1987; Peirson et al., 1999; Hansenne and Ansseau, 1999; Wu et al., 2010; Montag et al., 2013). Also according to this theory, HA is related to behavioral inhibition and implies a genetically determined bias towards being cautious, apprehensive and overly pessimistic (Youn et al., 2002). Individuals who score high on HA describe themselves as fearful, pessimistic, shy and fatigued, and they have the tendency to respond intensely to signals of aversive stimuli, whereas those scoring low on HA see themselves as optimistic and outgoing risk-takers (Cloninger et al., 1994). Furthermore, individuals scoring higher on this personality dimension seem to be more vulnerable to develop mood and anxiety disorders over the lifetime (Cloninger et al., 2006; Kampman and Poutanen, 2011). Although in healthy individuals some evidence has been found to link HA with the serotonergic system, not all studies have yielded unequivocal results. Serotonergic aberrations, as found in both brain-imaging and genetic studies (Ebstein, 2006; Carver and Miller, 2006; Tuominen et al., 2013), seem to be more clearly present in psychopathological states, such as mood and anxiety disorders as well as alcohol dependency (Marchesi et al., 2008; Koller et al., 2008; Mandelli et al., 2009; Kampman et al., 2012).

The post-synaptic 5-HT_{2A} receptor, one of the seven serotonin receptor subtypes, has widespread distributions throughout the

* Corresponding author at: Department of Psychiatry and Medical Psychology, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium. Tel.: +32 9 332 4330; fax: +32 9 332 4989.
E-mail addresses: cbaeken@hotmail.com, chris.baeken@UGent.be (C. Baeken).

0925-4927/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pscychresns.2013.12.005

brain with high densities in frontal cortical areas (Barnes and Sharp, 1999). This receptor is implicated in emotion and cognition processing, and it has been related to self-harm behavior, suicide and affective disorders (Audenaert et al., 2001; van Heeringen et al., 2003; Stein et al., 2007). Recently, we demonstrated in a group of severely treatment-resistant melancholic depressed patients that these receptors were affected in the dorsal prefrontal cortical and ACC areas (Baeken et al., 2011, 2012). Further, depressed patients with a higher degree of dysfunctional attitudes have been found to display higher 5-HT_{2A} binding potential, in particular in Brodmann area (BA) 9, part of the dorsal prefrontal cortex (DPFC) (Meyer et al., 2003).

Only recently researchers have shown interest in the relationship of these 5-HT_{2A} receptors to personality features (Frokjaer et al., 2008, 2010; Soloff et al., 2007, 2010; Rosell et al., 2010; Gerretsen et al., 2010). Genetically determined personality traits associated with stress-related behavioral responses, such as HA, were reported to be related to prefrontal cortical 5-HT_{2A} receptor binding indices (BI) (Moresco et al., 2002; Soloff et al., 2010). However, the relationship between 5-HT_{2A} receptor BI in these anatomical regions and HA is inconsistent across studies. Lower (Moresco et al., 2002) or no 5-HT_{2A} receptor BI (Soloff et al., 2010) in association with higher HA scores have been reported. Methodological differences such as sample size, scanning procedures and the exploratory nature of that data-analytic approach could to some extent explain the discrepancies. Furthermore, not all studies examining the relationship between personality traits and the 5-HT_{2A} receptor focused on possible laterality differences.

Consequently, in this study, based on earlier findings of possible serotonergic dysfunctions, we tested the hypothesis that individual scores on HA would be related to 5-HT_{2A} receptor BI, using single photon emission computed tomography (SPECT) and the radioligand 4-amino-N-[1-[3-(4-fluorophenoxy)propyl]-4-methyl-4-piperidinyl]-5-iodo-2-methoxybenzamide (^{123}I-5-I-R91150) (Terriere et al., 1995; Catafau et al., 2006a, 2006b). We explicitly focused on the DPFC and the ACC based on earlier studies in depressed patients that found 5-HT_{2A} receptor alterations related to dysfunctional attitudes (more pessimistic) (Meyer et al., 2003), and treatment resistance (Baeken et al., 2012). We used the Temperament and Character Inventory (TCI) because this questionnaire is based on a model that explicitly proposes hypotheses on the relationship between HA and the serotonergic system. As age and gender could confound 5-HT_{2A} receptor imaging results (Biver et al., 1996; Baeken et al., 1998; Soloff et al., 2010), we corrected for these variables. Further, we also investigated possible laterality differences.

2. Methods

2.1. Subjects

The study was approved by the ethics committee of our University Hospital, and all subjects gave written informed consent. This study was part of a larger project investigating different neuro-cognitive markers in affective disorders. Data of all participants were also used for another study examining the influence of age and gender on 5-HT_{2A} receptor distribution in the entire neocortex (Baeken et al., 1998).

Twenty-six healthy participants (female:male = 13:13) in the age range of 18–65 years were studied. To exclude psychiatric or neurological diseases, participants were clinically interviewed for past or current major psychiatric illnesses such as mood, anxiety and psychotic disorders according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-IV, American Psychiatric Association, 1994). Further, they were asked if they had ever encountered major neurological problems, suffered brain damage or undergone brain neurosurgery. Subjects with a personal current or former history of psychiatric or neurological disorders, including substance abuse or dependency, were not included in the study. None had ever used major psychotropic medications such as antidepressants, mood stabilizers or antipsychotics, and all were free of any medication, except contraceptives. There was no family history of depression or other major psychiatric and neurological disorders. The absence of major medical conditions was determined by standard medical interview by a physician. Subjects were instructed to avoid the use of alcohol for at least 48 h before the SPECT study.

2.2. Temperament and character inventory

The TCI is 240-item questionnaire developed by Cloninger (1987) and Cloninger et al. (1994). It is considered to be the psychobiological model that aims to explain individual differences in personality traits (Cloninger et al., 1993). The TCI consists of four temperament scales (harm avoidance (HA), novelty seeking (NS), reward dependence (RD), persistence (P)), and three character scales (cooperativeness (CO), self-directedness (SD) and self-transcendence (ST)) (Cloninger et al., 1994). The TCI has been used in a variety of studies examining psychobiological substrates for personality, including neurobiological, neuroimaging and genetic methods (Munafò et al., 2005; Baeken et al., 2009; Soloff et al., 2010; Van Schuerbeek et al., 2011). As it is hypothesized that the serotonergic system is mainly related to HA, we only extracted this temperament dimension for further analysis (minimum score = 0, maximum score is 35). HA is further divided into four subscales: anticipatory worry (HA1), fear of uncertainty (HA2), shyness (HA3), and fatigability (HA4) (Cloninger, 1987; Peirson et al., 1999). All volunteers were assessed using a Dutch version of the TCI (de la Rie et al., 1998).

2.3. Scanning procedure

All participants received a static baseline SPECT scan. SPECT imaging was performed with a Siemens MultiSPECT triple-headed gamma camera, equipped with parallel-hole medium-energy collimators. All subjects received oral Lugol's solution containing 400 mg of potassium iodide 15 min before injection of the tracer, for thyroid blockage. An average of 155.84 (S.D. = 34.45) MBq ^{123}I-5-I-R91150, with a specific activity of 370 TBq/mmol (10,000 mCi/mmol), was injected as a single bolus over a 30-s period followed by 10 ml saline. SPECT acquisition was performed at a minimum of 120 min after administration of the tracer. Data were collected from 96 angular positions over 360° in a 128 × 128 matrix, with a total acquisition time of 32 min. Reconstruction of all projection images was performed using an iterative reconstruction algorithm (Ordered Subset Expectation Maximization, OSEM, 8 iterations, 8 subsets) and filtered with a 3D Gaussian filter using 15-mm full-width at half-maximum.

SPECT scans were automatically co-registered to a template image that was placed in a predefined stereotactic (image) space (BRASS; Nuclear Diagnostics Ltd., Sweden). Predefined volumes-of-interest (VOI), which allowed a user-independent sampling of the whole-brain volume, were used. In short, the BRASS program fits and compares (S)PE(C)T images to 3D reference templates created from images of healthy subjects. Sixty-three VOI regions in total are defined on this template for automated VOI quantification (Montandon and Zaidi, 2007). In our study, all images were visually double-checked to ensure correct anatomical positioning of the VOIs (Audenaert et al., 2001; Goethals et al., 2004).

Radioactivity estimates in the cortex were assumed to represent total ligand binding (specific plus nonspecific binding plus free ligand) (Busatto et al., 1997). Because very few 5-HT_{2A} receptors are present in the cerebellum (Terriere et al., 1995), this region was chosen to represent nonspecific activity. Calculation of relative indices of specific BI was performed by VOI normalization to the activity per volume element in the cerebellum. Under these pseudo-equilibrium circumstances, BI is directly related to the in vivo receptor density (B_{max}) and affinity ($1/K_d$). BI was defined as (target activity-background activity in the brain)/(background activity), which was operationally estimated as (counts/pixel in VOI-counts/pixel in the cerebellum)/(counts/pixel in the cerebellum) (Audenaert et al., 2001).

In a first step, the following VOIs were defined: the entire DPFC and ACC consisting of a left and right hemispheric parts. According to the BRASS program, the DPFC consists of the superior frontal gyrus (BA 6, 8, 9, and 10) and the ACC VOI consists of the ventral (BA 25 and 32) and dorsal (BA 24) ACC. See also Fig. 1. In the second step of VOI analyses, only when the result of the entire DPFC-ACC analysis was significant, we defined left and right DPFC-ACC VOIs separately. Both DPFC and ACC VOIs were explicitly chosen based on the findings of earlier studies in depressed patients that found 5-HT_{2A} receptor alterations related to dysfunctional attitudes (more pessimistic) (Meyer et al., 2003) and treatment resistance (Baeken et al., 2012).

2.4. Statistical methods

All statistical analyses were performed with SPSS 19 (Statistical Package for the Social Sciences, IBM, Chicago). To evaluate whether individual scores on HA are differentially related to DPFC or ACC 5-HT_{2A} receptor BI, we performed multiple regression analyses. 5-HT_{2A} receptor binding indices in each VOI were the dependent variables. In a first step of multiple regression analyses, we entered gender and age to control the possible confounding effects of these variables. In the second step of multiple regression analyses, we added to the gender and age variables the individual scores on HA as predictors to the model. Only significant