



## Dopamine D2/D3 receptor availability and venturesomeness

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### ARTICLE INFO

#### Article history:

Received 30 July 2009

Received in revised form 1 December 2010

Accepted 13 January 2011

#### Keywords:

Impulsivity

Fallypride

Positron emission tomography

I7

Personality

D2-like receptors

### ABSTRACT

The construct of impulsivity is considered as a major trait of personality. There is growing evidence that the mesolimbic dopamine system plays an important role in the modulation of impulsivity and venturesomeness, the two key components within the impulsivity-construct. The aim of the present study was to explore an association between trait impulsivity measured with self-assessment and the dopaminergic neurotransmission as measured by positron emission tomography (PET) in a cohort of healthy male subjects. In vivo D2/D3 receptor availability was determined with [<sup>18</sup>F]fallypride PET in 18 non-smoking healthy subjects. The character trait impulsivity was measured using the Impulsiveness-Venturesomeness-Empathy questionnaire (I7). Image processing and statistical analysis was performed on a voxel-by-voxel basis using statistical parametric mapping (SPM) software. The I7 subscale venturesomeness correlated positively with the D2/D3 receptor availability within the left temporal cortex and the thalamus. Measures on the I7 subscale impulsiveness and empathy did not correlate with the D2/D3 receptor availability in any brain region investigated. Our results suggest the involvement of extrastriatal dopaminergic neurotransmission in venturesomeness, a component of impulsivity.

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### 1. Introduction

The construct of impulsivity is considered as a major trait of personality (Moeller et al., 2001). Pathological impulsivity is associated with a number of psychiatric disorders such as attention deficit hyperactivity disorder (ADHD) (Winstanley et al., 2006), alcohol and drug dependence (Coffey et al., 2003; Soloff et al., 2003), and borderline and antisocial personality disorder (Petry, 2002; Fossati et al., 2004). Based on findings from animal and human behavioral studies, different concepts of impulsivity have been developed (overview in Evenden, 1999).

Eysenck and Eysenck (1978) postulated two distinct components within the impulsivity-construct: impulsiveness as doing and saying things without thinking and without realizing the risk involved in actions and venturesomeness as conscious taking risks and seeking thrill and adventure. The construct of impulsivity has been included in the psychoticism–extraversion–neuroticism (P–E–N) system of personality and conceptualized as one of the personality traits (Eysenck

and Eysenck, 1978; Caci et al., 2003). To measure the components of impulsivity, Eysenck and Eysenck (1978) developed the Impulsiveness–Venturesomeness–Empathy questionnaire (I7). Within the above concept, impulsiveness is related to neuroticism and psychoticism, while venturesomeness is closely associated with extraversion (Eysenck and Eysenck, 1978).

Beside I7, there are some other popular constructs of impulsivity and risk taking such as Barratt's impulsiveness, Zuckerman's sensation seeking and Cloninger's novelty seeking (see e.g. Arce and Santisteban, 2006 for review). Thus, the Barratt Impulsiveness Scale (BIS) was developed by Barratt (1965, 1987), who conceptualized three subtraits of impulsiveness: motor impulsiveness, cognitive impulsiveness and non-planning. The Sensation Seeking Scale (SSS) was constructed by Zuckerman et al. (1964), who defined sensation seeking as “the seeking of novel, varied, complex, and intense sensations and experiences, and the willingness to take physical, social, legal, and financial risks for the sake of such experience” (Zuckerman, 1994, page 27). Finally, the Temperament and Character Inventory (TCI) (Cloninger et al., 1993) was suggested by Cloninger (1986), who conceptualized novelty seeking as a tendency toward frequent exploratory activity and intense excitement in response to novel stimuli. A number of studies have explored differences and overlaps between the self-reported impulsivity, risk-taking concepts

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and the I7. For instance, the total BIS score is highly correlated with the I7 subscale impulsiveness (Campbell, 1987; Luengo et al., 1991), but only moderately with I7 venturesomeness (Reynolds et al., 2006; Aluja and Blanch, 2007). The I7 venturesomeness subscale is, however, highly correlated with Zuckerman's sensation seeking, especially with the thrill and adventure subscale (Campbell, 1987; Corulla, 1988), whereas there is no association between I7 impulsiveness and sensation seeking (Corulla, 1988). Cloninger's novelty seeking, correlates with both I7 impulsiveness and venturesomeness (Weyers et al., 1995). Thus, venturesomeness, sensation seeking and novelty seeking seem to be related but not identical concepts of personality traits, while I7 impulsiveness represents an instrument measuring especially motor impulsiveness (Luengo et al., 1991) and the tendency to behave without thinking and without realizing the risk.

In recent years, positron emission tomography (PET) has been increasingly applied to characterize the relationship between impulsivity and the function of the dopamine system in general, and the status of dopamine D2-mediated dopaminergic transmission in particular. For instance, in their [<sup>11</sup>C]raclopride PET study, Oswald et al. (2007) found that high trait impulsivity measured with the NEO Personality Inventory was associated with blunted ventral striatal dopamine release after amphetamine injection. In a study with the same tracer, Gjedde et al. (2010) reported an inverse u-shaped correlation between striatal D2-receptor availability and sensation seeking as measured with the Zuckerman scale. Furthermore, Sahara et al. (2001) observed a significant negative correlation between novelty seeking and right insular dopamine D2 receptor availability as measured with [<sup>11</sup>C]FLB 457 PET. More recently, Zald et al. (2008) examined the correlation between novelty seeking and dopamine D2 receptor availability ([<sup>18</sup>F]fallypride PET) in the substantia nigra/ventral tegmental area and detected an inverse correlation in the ventral midbrain. Overall, data on the role of postsynaptic dopaminergic function in impulsivity and risk taking are still rather sparse and inconsistent. Besides, no study has examined an association between I7 measures and in vivo dopamine receptor availability. Indeed, the I7 is meanwhile one of the most widely applied personality measures developed for the assessment of impulsivity. Due to its high internal consistency (Eysenck et al., 1990) and reliability (Eysenck et al., 1985, 1990; Caci et al., 2003; Lijffijt et al., 2005), the I7 has been repeatedly used in the field of genetics (e.g. Benko et al., 2010), clinical psychiatry (e.g. Clark et al., 2009; Johnson et al., 2010), psychopharmacology (Boileau et al., 2006; Cools et al., 2007), and electrophysiology (Fallgatter and Herrmann, 2001; Horn et al., 2003).

Thus, the aim of the present study was to explore an association between trait impulsivity and venturesomeness as assessed by the I7 and the dopaminergic neurotransmission as measured by [<sup>18</sup>F]fallypride PET in a cohort of healthy male subjects. The potential link would help to understand the neurobiological correlates of self-reported impulsivity and, prospectively, to evaluate the contribution of altered dopaminergic transmission to the pathogenesis of impulsivity and venturesomeness in disorders such as substance abuse and ADHD.

## 2. Methods

### 2.1. Ethical approval

This study was carried out in accordance with the Helsinki Declaration and was approved by the local ethics committee, the Federal Health Administration (BfArM) and the radiation protection authorities (BFS).

### 2.2. Study inclusion and exclusion criteria

Study participants were recruited by public advertisement. Before entering the study, subjects were screened with a standard psychiatric interview (CIDI: Composite International Diagnostic Interview)

(Wittchen et al., 1998), a medical history, an electrocardiographic examination, a blood test and a clinical examination including a screening test for illicit drugs. The study participants had no current or previous history of relevant physical illness, no current or past psychiatric and substance abuse disorders, and no family history of major psychiatric disorder in first-degree relatives, and they were not regularly taking medication. After the complete description of the study to the subjects, written informed consent was obtained.

### 2.3. Study schedule

All participants underwent a detailed neuropsychological examination, a personality questionnaire, and a single [<sup>18</sup>F]fallypride (FP) PET scan. PET scanning and psychological assessments were performed on a single day in all subjects included; furthermore, the tie-schedule of the protocol remained unchanged over all subjects to exclude any possible artifacts that may be caused by circadian changes of the dopamine transmission. The results from the neuropsychological studies will be the subject of additional reports.

### 2.4. Psychological assessment

To measure impulsiveness and venturesomeness, we used a German version of the Impulsiveness–Venturesomeness–Empathy questionnaire (I7) developed by Eysenck et al. (1985). The I7 is a 54-item questionnaire in a yes/no format that includes three scales: Impulsiveness (Imp) (19 items), Venturesomeness (Vent) (16 items), and Empathy (Emp) (19 items). The last scale was originally included to provide meaningful buffer items to relieve the monotony, and was derived from the work of Mehrabian and Epstein (1972).

### 2.5. Data acquisition, image analysis and statistical analysis

PET scans were acquired using a Siemens ECAT EXACT scanner (CTI, Knoxville, Tennessee). The camera has a field-of-view of 16.2 cm in 47 planes with a plane spacing of 3.375 mm, an axial resolution of 6.0 mm full width at half-maximum (FWHM) in 3D mode (Wienhard et al., 1992) and an in-plane resolution of 6.0 mm (resolution in center with the scanner in 3D mode). Parametric maps of [<sup>18</sup>F]FP binding potential (BP<sub>ND</sub>) were calculated on a voxel-wise basis using the simplified reference tissue model (Gunn et al., 1997). By analogy with previous studies (Werhahn et al., 2006; Yakushev et al., 2010) the cerebellum was chosen as a reference region since it is generally considered to contain a minute density of D2 receptors (Hall et al., 1996). In particular, only 3% of the cerebellar uptake specifically binds to DA D2 receptors, and the reference region method estimates of binding potentials are highly correlated ( $r > 0.99$ ) with modeled estimates with a metabolite-corrected plasma input function (Kessler et al., 2005). Throughout the other brain regions dopamine D2-like receptors are widely expressed with the highest levels in the striatum and moderate levels in the thalamus, hypothalamus, amygdala, hippocampus and midbrain (e.g. Mukherjee et al., 2002). Cortical areas possess substantially lower receptor density with the highest levels in temporal cortices (e.g. Olsson et al., 1999). Prior to statistical analysis, BP<sub>ND</sub> images were spatially normalized into the MNI space (Montreal Neurological Institute, McGill University, Montreal, Canada) to remove inter-subject anatomical variability. For this purpose, integral images (sum of frames between 4 min to 8 min p. i.) were calculated and spatially normalized using SPM99 routines (Wellcome Department of Cognitive Neurology, London, UK) and a ligand-specific D2 template. Subsequently, transformation parameters of normalization were applied to respective individual BP<sub>ND</sub> images. An isotropic Gaussian filter was used for smoothing of the spatially normalized images with an FWHM 12-mm kernel.

In order to detect a relationship between impulsivity and dopamine receptor availability, a voxel-wise statistical analysis of the data was

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