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Brain neuroreceptor density and personality traits: towards dimensional biomarkers for psychiatric disorders

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Positron emission tomography has, for 30 years, been used in numerous case-control studies searching for hypothesized differences in the density of neuroreceptor or transporter proteins in psychiatric disorders such as schizophrenia and depression. In most cases, the results have not been conclusive. One reason could be the sizeable interindividual variability in biochemical markers, which in twin studies have shown to emanate from both environmental and genetic factors, leading to low statistical power for the detection of group effects. On the other hand, the same interindividual variability has served as an opportunity for correlative studies on the biological underpinning of behaviour. Using this approach, a series of studies has linked markers for the dopamine and serotonin system to personality traits associated with psychiatric conditions. Based on increasing evidence for the view that many psychopathological states represent extremes of a continuum rather than distinct categories, this research strategy may lead to new biological insights about the vulnerability to and pathophysiology of major psychiatric disorders.

This article is part of the theme issue 'Diverse perspectives on diversity: multi-disciplinary approaches to taxonomies of individual differences'.

1. Background

In early 1980s, methods were developed for quantification of brain neuroreceptors in humans *in vivo* using positron emission tomography (PET). The efforts were to a significant degree driven by the dopamine hypothesis of schizophrenia, postulating that the pathophysiology of this disorder is related to elevated dopaminergic transmission. The assumption in initial PET studies was that this overactivity was related to increased density of the D2-dopamine receptor (D2R) subtype. This somewhat simplistic model was justified by replicated findings of elevated D2R in brains of patients with schizophrenia *post mortem* [1], and experimental studies demonstrating that neuroleptic drugs are D2R antagonists. Beyond the primary aim of demonstrating significant differences between healthy subjects and young neuroleptic naive patients with schizophrenia, there was also a hope for a large separation between the groups. If a distinct separation was present, then D2R density could serve as a clinically useful and much sought for diagnostic marker for schizophrenia.

Over the years, numerous PET studies have been carried out in both neuroleptic naive and drug-treated patient samples. The overall view, supported by meta-analyses, is that the findings of elevated D2R *post mortem* cannot be replicated *in vivo* [2,3].

However, the concept of searching for a single biochemical abnormality in patients has been extended to other potential biomarkers of the dopamine system, as well as to other neurotransmission systems and disorders. For instance, following the development of radioligands for PET-imaging of the serotonin (5-HT) system, and supported by pharmacological evidence, many studies have been

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conducted in depression and anxiety. The results are not conclusive. Some reports suggest decreases in serotonin transporter levels [4], whereas studies on the 5-HT_{1A} receptor have shown mixed results [5,6] and only two small studies have reported changes in 5-HT_{1B} receptor binding [7,8].

In most such studies, the primary outcome used to compare patients and control subjects is the binding potential (BP_{nd}), which represents the ratio between receptor density (B_{max}) and affinity (K_d) [9,10]. BP_{nd} is commonly used as an index for density because K_d is assumed to be constant, albeit influenced by the endogenous neurotransmitter concentration. In the following text, we use the concept 'density' when we refer to BP_{nd}-values.

The aim of the present commentary is to review some of the studies on associations between imaging markers and personality traits, and to discuss if they can represent a valuable approach to understanding the underpinnings of mental illness.

2. Interindividual variability in neuroreceptor density

The initial discovery of neuroreceptors was a result of experimental pharmacological studies using inbred animal strains, where interindividual variability in receptor density is not a major concern. When translating this field of experimental research to humans, a different picture emerged. For instance, in a study of more than 200 human brains *post mortem*, a nearly fourfold range was reported for the striatal D2R density [11]. This finding of a large interindividual variability was later replicated *in vivo* using PET [12]. In this study, individual D2R density (B_{max}) and affinity (K_d) were calculated from a saturation analysis based on five PET-measurements in each of 10 males and 10 females. There was a 2.5-fold range in D2R density. Similar ranges of variability have been reported also for other neuroreceptors [13–19].

PET is costly and the recruitment of subjects is demanding, in particular if drug-free or drug-naive patients are required. By consequence, patient samples have been small in a majority of clinical studies, typically fewer than 20. When combined with the sizeable interindividual variability, this has led to low statistical power for the detection of group effects. This is especially the case for psychiatric disorders devoid of known histopathology, where group differences are expected to be small. For instance, arguably the most robust observation of a neurotransmission marker in psychiatric patients is an elevation of the presynaptic marker [^{18}F]FDOPA in schizophrenia patients, showing an effect size of 0.79 (Cohen's *D*) [2]. In comparison, radioligand binding to the dopamine transporter (DAT) in Parkinson's Disease, which is characterized by a major loss of cells, is reduced by about 50% already at clinical onset, with effect sizes up to Cohen's $D = 3.8$ for striatal regions later in the disease stage [20]. Hence, whereas DAT-imaging using PET or SPECT (single photon emission computed tomography) is a long-established diagnostic tool in Parkinson's Disease [21], thus far there are no such PET markers suitable for such clinical use in psychiatric populations.

3. Sources of variability

Despite the high interest in the serotonin and dopamine neurotransmission systems in psychiatry research, little is known about the regulation of receptor and transporter density levels. Considering the high heritability of major psychiatric disorders, it is of fundamental interest to understand if their densities in adult life are genetically determined or influenced by the environment. This lack of knowledge limits the interpretation of changes in protein availability reported in psychiatric patients. In a recent attempt to elucidate this issue, we used PET in a twin design to estimate the relative contribution of genetic and environmental factors, respectively, on dopaminergic and serotonergic markers in the living human brain [14]. Heritability, shared environmental effects and individual-specific non-shared effects were estimated for 5-HT_{1A} receptor availability in serotonergic projection areas and for D2R in striatum. We found a major contribution of genetic factors (heritability 0.67; shared environment effect 0.00; non-shared environment effect 0.33) on individual variability in striatal D2R binding and a major contribution of environmental factors (heritability 0.17–0.22; pair-wise shared environment effect 0.70–0.75; unique individual effect 0.08) on neocortical 5-HT_{1A} receptor binding. Interestingly, the heritability for D2R was in a similar range, as was previously reported for the presynaptic marker [^{18}F]FDOPA [22]. These results confirm that both genetic and environmental factors should be taken into account in disease models of psychiatric disorders that are based on aberrations in the brain neurotransmission systems.

4. Correlative studies: personality traits

Though interindividual variability is a problem for comparisons aiming for large separations of groups, it has shown to serve as an opportunity for correlative studies on the biological underpinning of behavioural markers in healthy control subjects. An area of specific interest has been stable patterns of behaviour, cognition and emotion conceptualized as personality traits, typically measured by self-assessment questionnaires. These traits are generally characterized by a substantial heritability, both for scales traditionally referred to as measuring 'temperament' and for 'personality' scales [23,24] and have shown to be important predictors for psychiatric disorders [25,26]. Consequently, markers of brain neurotransmission may serve as useful means of tracking down gene–protein-behavioural pathways towards psychiatric disease. This approach is in line with the view that psychiatric disorders may represent extremes on a continuum rather than being qualitatively different from normal behaviour—even for psychotic disorders [27,28]. Indeed, moving towards a dimensional approach of diagnosis rather than the existing prototypic classification was an early ambition for the revised edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5 [29]). However, this development has been hampered by a lack of biological validation of the proposed models.

In an early study on personality traits and neuroreceptor density, The Karolinska Scales of Personality (KSP) was administered to 18 of the 20 healthy subjects in the D2R study mentioned earlier [12]. KSP is a self-rating instrument, and measures 15 different personality traits that were developed to be sensitive for vulnerability of mental illness [30]. There was a significant correlation between striatal D2R density and detachment, a measure of social avoidance and withdrawal [31]. This finding was shortly thereafter replicated by an independent centre [32] and initiated a series of similar molecular imaging studies summarized in tables 1 and 2.

Table 1. Molecular imaging studies of associations between dopamine receptors and transporter and personality traits in healthy control subjects. The following denotes correlations between dopaminergic markers and the specific behavioural traits: *r*, correlation coefficient; +, positive correlation; −, negative correlation; nl, nonlinear. (In case-control studies including patient groups, only results for the control groups have been included.) KSP, Karolinska Scales of Personality; TCI, Temperament and Character inventory; MPI, Maudsley Personality Inventory; EPQ-R, Eysenck Personality Questionnaire Revised; TPQ, Tridimensional Personality Questionnaire; BSMSS, Barratt Simplified Measure of Social Status; ZS, Zuckerman Scale; I7, Impulsiveness-Venturesomeness-Empathy questionnaire; BIS, Barratt's Impulsivity Scale; HS, Hollingshead Scale; D2/D3, Dopamine D2/D3 receptors; DAT, Dopamine transporter; DOPA, L-Dopa uptake; FDOPA, [^{18}F]FDOPA; SSP, Swedish University Scales of Personality; RAC, [^{11}C]Raclopride; CFT, [^{18}F]CFT; FLB, [^{11}C]FLB 457; FP, [^{18}F]Fallypride; NEO-PI-R, NEO Personality Inventory-Revised; IB, [^{123}I]iodo-benzamide (SPECT); PHNO, [^{11}C](+)PHNO; SCH, [^{11}C]SCH23390; TC, temporal cortex; VST, ventral striatum; MTL, medial temporal lobe; amyg, amygdala; FC, frontal cortex; SN, substantia nigra; VTA, ventral tegmental area.

personality trait	marker	tracer	*n*	region	*r*	publication
detachment (KSP)	D2	RAC	24; 18	striatum	−	Farde *et al.* [31]; Breier *et al.* [32]
	DAT	CFT	18	striatum	−	Laakso *et al.* [53]
attachment (TCI)	D2/D3	PHNO	32	VST	−	Caravaggio *et al.* [38]
novelty seeking (TCI)	D2	FLB	24	right insula	−	Suhara *et al.* [54]
novelty seeking (TPQ)	D2	FP	34	midbrain	−	Zald *et al.* [55]
sensation seeking (ZS)	D2	RAC	18	striatum	nl	Gjedde *et al.* [56]
venturesomeness (I7)	D2	FP	18	TC, thalamus	+	Bernow *et al.* [57]
impulsivity (NEO-PI-R)	DA release	RAC	40	right VST	−	Oswald *et al.* [58]
impulsivity (BIS)	D2	FP	32	midbrain	−	Buckholtz *et al.* [59]
impulsivity (BIS)	DA release			striatum	+	
depression (NEO-PI-R)	D2	RAC	18	striatum	+	Kestler *et al.* [60]
harm avoidance (TCI)	D2	RAC	21	dorsal striatum	−	Kim *et al.* [61]
anxiety, irritability (KSP)	DOPA	FDOPA	33	striatum	−	Laakso *et al.* [62]
lie scale (MPI)	D2	IB	42	striatum	−	Huang *et al.* [18]
lie scale (MPI, EPQ-R)	D2	RAC	28; 13; 23	striatum	−	Reeves *et al.* [34], Egerton *et al.* [35]
lie scale (EPQ-R)	DOPA	FDOPA	46	striatum	n.s.	Stokes *et al.* [63]
social desirability (SSP)	D2	RAC; FLB	16	striatum, MTL	−	Cervenka *et al.* [33]
social desirability (SSP)	D1	SCH	23	striatum/amyg, FC	+	Plavén-Sigray *et al.* [64]
+ physical trait aggression (SSP)				−		
socialization (KSP)	D2	RAC	30	VST	+	Caravaggio *et al.* [65]
socioeconomic status (HS)	D2	RAC	42	striatum	+	Wiers *et al.* [36]
social status (BSMSS)	D2	RAC	14	striatum	+	Martinez *et al.* [37]
social status (BSMSS)	D2/D3	PHNO	16	SN/VTA	−	Matuskey *et al.* [38]

From this literature, it is clear that several brain proteins may serve as correlates to personality traits. Importantly, a reported and replicated correlation between a single receptor or transport protein and a certain personality trait does not imply that the protein *per se* has a causal role in neuronal mechanisms related to the trait or that the density may serve as a biochemical marker for the trait. However, by indicating that a certain neurotransmission system is part of the biological underpinning of a trait, these findings may lead to biological insights and hypotheses about the vulnerability, genesis and progress of psychiatric disorders. One advantage of this research strategy is to circumvent the influence of unspecific factors, such as stress and insomnia, that often characterize the transition from a high risk or vulnerable state into a full-blown psychiatric condition.

As can be seen from table 1, initial findings of a relationship between D2R and traits related to social behaviour have been corroborated in multiple studies when using antagonist radioligands. Specifically, a negative correlation has been reported between D2R and the social desirability scale of the Swedish University Scales of Personality (SSP) [33] and Lie scale of the Maudsley Personality Inventory (MPI) [18,34,35], a line of research that has also been extended to include measures of social status [36,37]. Interestingly, recent studies using the agonist radioligand [^{11}C]PHNO have shown patterns of the opposite direction [38,39]. It may be speculated that this is an effect of the increased sensitivity for endogenous dopamine (DA) levels, suggesting that previous studies in part may be influenced by synaptic DA. Alternatively, it may be a consequence of the relatively higher D3 dopamine receptor affinity for [^{11}C]PHNO [40]. Taken together, these findings suggest an intricate relationship between DA function and social behaviour, and may serve as a starting point for investigations in relevant patient groups [41,42].

With regard to psychosis-related traits, there are to date no reports on associations with D2R, mirroring findings in patients. By contrast, striatal amphetamine-induced DA release has shown to be associated with schizotypal

Table 2. Molecular imaging studies of associations between serotonin receptors and transporter and personality traits in healthy control subjects. The following denotes correlations between serotonergic markers and the specific behavioural traits: *r*, correlation coefficient; +, positive correlation; −, negative correlation. (In case-control studies including patient groups, only results for the control groups have been included.) NEO-PI-R, Revised NEO Personality Inventory; TCI, Temperament and Character inventory; KSP, Karolinska Scales of Personality; TPQ, Tridimensional Personality Questionnaire; EPQ, Eysenck Personality Questionnaire; STAI, State-Trait Anxiety Inventory; BGLHA, Brown-Goodwin Assessment for Lifetime History of Aggression; BPAQ, Buss-Perry Aggression Questionnaire; BIS-11, Barratt's Impulsivity Scale 11; UG, Ultimatum Game; 5-HTT, serotonin transporter; 5-HT1A, serotonin 1A receptors; 5-HT2A, serotonin 2A receptor; 5-HT4, serotonin 4 receptor; DASB, [^{11}C]DASB, MADAM, [^{11}C]MADAM; WAY, [^{11}C]WAY100635; FESP, [^{18}F]FESP; ALT, [^{18}F]altanserin; SB, [^{11}C]SB207145; SET, [^{18}F]setoperone; DLPFC, dorsolateral prefrontal cortex; PC, parietal cortex; OC, occipital cortex; ACC, accumbens; FC, frontal cortex; STG, superior temporal gyrus. HC, hippocampus; OFC, orbitofrontal cortex; rPRG, right pregenual cingulate.

personality trait	marker	tracer	*n*	region	*r*	publication
neuroticism (NEO-PI-R)	5-HTT	DASB	31	thalamus	+	Takano *et al*. [66]
harm avoidance (TCI)	5-HTT	DASB	19		n.s.	Reimold *et al*. [67]
harm avoidance (TCI)	5-HTT	MADAM	22		n.s.	Tuominen *et al*. [48]
neuroticism (NEO-PI-R)	5-HT1A	WAY	19	DLPFC, PC, OC, ACC	−	Tauscher *et al*. [19]
harm avoidance (TPQ); neuroticism (EPQ); state anxiety (STAI)	5-HT1A	WAY	49; 44; 22		n.s.	Rabiner *et al*. [13]
harm avoidance (TCI)	5-HT1A	WAY	15		n.s.	Borg *et al*. [68]
neuroticism (KSP)	5-HT1A	WAY	34	DLPFC; STG, HC	−	Hirvonen *et al*. [47]
harm avoidance (TPQ)	5-HT2A	FESP	11	FC, PC	−	Moresco *et al*. [69]
neuroticism (NEO-PI-R)	5-HT2A	ALT	83	frontolimbic	+	Frokjaer *et al*. [70]
harm avoidance (TCI)	5-HT2A	ALT	21		n.s.	Soloff *et al*. [71]
harm avoidance (TCI)	5-HT2A	ALT	27	HC	+	Soloff *et al*. [72]
dysfunctional attitudes	5-HTT	DASB	20		n.s.	Meyer *et al*. [73]
life-time aggression (BGLHA)	5-HT1A	WAY	25	FC, raphe	−	Parsey *et al*. [74]
questionnaire for measuring factors of aggression	5-HT1A	WAY	36	ACC	+	Witte *et al*. [17]
life-time aggression (BGLHA)	5-HT2A	ALT	21		n.s.	Soloff *et al*. [71]
trait aggression (BPAQ); trait impulsivity (BIS-11); angry hostility (NEO-PI-R)	5-HT2A	ALT	94		n.s.	da Cunha-Bang *et al*. [75]
trait aggression (BPAQ); trait impulsivity (BIS-11)	5-HT4	SB	47 males (n.s. in females)	whole brain	+	da Cunha-Bang *et al*. [76]
openness (NEO-PI-R)	5-HTT	DASB	50	midbrain, putamen, thalamus	−	Kalbitzer *et al*. [77]
self-transcendence/spiritual acceptance (TCI)	5-HTT	DASB	16	raphe	−	Kim *et al*. [78]
self-transcendence/spiritual acceptance (TCI)	5-HT1A	WAY	15	neocortex, HC, raphe	−	Borg *et al*. [68]
self-transcendence/spiritual acceptance (TCI)	5-HT1A	WAY	20		n.s.	Karlsson *et al*. [79]
reward dependence (TCI)	5-HT2A	SET	24	ACC, OFC	−	Gerretsen *et al*. [80]
reward dependence (TCI)	5-HT2A	ALT	21		n.s.	Soloff *et al*. [71]
reward dependence (TCI)	5-HT2A	ALT	27	rPRG	+	Soloff *et al*. [72]
straightforwardness, trust; low tolerance of unfairness (NEO-PI-R; UG)	5-HTT	DASB	20	midbrain	−	Takahashi *et al*. [81]

personality traits [43], which is in line with reports of increases in DA release and the presynaptic marker [18F]DOPA in schizophrenia patients and individuals at high risk for the disorder [2,44–46].

For the serotonin system, focus has been mainly on traits related to anxiety and mood disorders, but, the results have been less clear. A strong negative correlation has been shown between 5-HT$_{1A}$ receptor and neuroticism, a trait

associated with vulnerability for anxiety and depression [47], whereas no associations were found for the serotonin transporter (5HTT) [48]. Following our observations of a strong contribution of environmental factors for the 5-HT_{1A} receptor, we recently studied the effect of seasonal and diurnal variation on the serotonin system by combining healthy control subjects from several small individual studies [49]. In this sample including 96 PET-measurements, we observed decreases in midbrain 5HTT during the day, and higher 5-HT_{1A} receptor availability on days with longer daylight. The observations suggest a link between the serotonin system and observations of disruptions in chronobiology in both seasonal and non-seasonal affective disorders [50–52].

Importantly, while many associations between behavioural traits and neurotransmitter receptor density have been replicated by independent centres, this is not the case for all findings depicted in tables 1 and 2. Low reliability of measurements, small sample sizes and the failure to publish inconclusive replication attempts could potentially lead to a number of false positives being left uncontested in the literature. Possible remedies for this are open sharing of data and code [82], as well as pre-registration of new trials [83]. Another caveat that needs to be considered when interpreting association between biochemical outcomes and personality traits is that the samples might not always be perfect representations of the general population, such that the personality of individuals volunteering to research might differ on certain traits [84].

The examples listed in tables 1 and 2, involving the two major neurotransmitter systems implicated in treatment of psychiatric patients, show that research into biological correlates of stable behavioural phenotypes may be a way forward to gain insights regarding disease mechanisms of psychiatric disorders. This approach is also in line with the shift from categorical to a more dimensional conceptualization of psychiatric diagnoses. However, small effect sizes are likely to be continually expected in the field of PET and psychiatry, and with more studies moving from being exploratory to being confirmatory, increased statistical power will be required. For this reason, we believe an increased focus on multicentre collaboration is necessary.

Another way forward is to go beyond mere association between neuroreceptor density and self-reported personality dimensions, and to examine the neurobiology of underlying behavioural phenotypes. This can be done by measuring behaviour in an experimental setting, and as such, pinpointing the constituents that are driving the relationships reported in tables 1 and 2. Current attempts in this direction include studies showing associations between [18F]FDOPA uptake and paradigms of prediction error coding [85] and salience attribution [86], which are both of interest in relation to cognitive models of schizophrenia [87]. With regard to traits tapping social behaviour, we suggest that future studies should examine the relationship between dopamine receptor availability and social trust and status, as measured using paradigms from behavioural economics and social psychology [88]. Observation of such less complex, observable traits both within a patient group and across different diagnostic groups, can aid discovery of behavioural and biological diagnostic markers as well as markers of vulnerability. It may also enhance translational science between species, and therefore facilitate more precise studies of molecular mechanisms in drug development.

In summary, we think that investigations of the biological underpinnings of personality traits and their constituents using molecular imaging techniques hold several advantages, and may lead to biological insights regarding the genesis, progress and, ultimately, treatment of psychiatric disorder.

Data accessibility. This article has no additional data.

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