Dopamine D1 receptor availability is not associated with delusional ideation measures of psychosis proneness

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1. Introduction

The dopamine system has been centrally implicated in the pathophysiology of schizophrenia for over fifty years, due primarily to the fact that antipsychotic drugs exert their effect by blocking the D2 dopamine receptor (D2R) (Farde et al., 1988; Kapur and Mamo, 2003; Nordström et al., 1993). In vivo molecular imaging studies using positron emission tomography (PET) have provided a wealth of evidence for elevations in presynaptic dopamine synthesis capacity and amphetamine-induced dopamine release in schizophrenia (Howes and Kapur, 2009). Importantly, increases in presynaptic dopamine synthesis capacity have also been observed in individuals at high risk of developing schizophrenia (Howes et al., 2009), with greater levels observed specifically for those individuals who later developed a psychotic disorder compared to those who did not (Howes et al., 2011). These observations suggest that changes in dopamine function are evident prior to the onset of psychosis.

With regard to dopamine receptors, there have been a series of PET studies since the 1980s examining striatal D2 receptor availability in schizophrenia, finding evidence for a small increase in patients compared to controls (Howes et al., 2012). In contrast, there have only been a handful of PET studies examining the D1 receptor (D1R) in schizophrenia. Compared with the D2R, there is a high concentration of D1R in the cortex (Hall et al., 1994). The frontal cortex, and the dorsolateral prefrontal cortex (DLPFC) in particular, is thought to be a crucial brain region for understanding the biological underpinnings of schizophrenia symptoms (Callicott et al., 2000; Cannon et al., 2002; Selemon and Goldman-Rakic, 1999; Wagstyl et al., 2016), and further study of the D1R in this region therefore has the potential to provide important insights into the postsynaptic dopaminergic aberrations which may occur in the disorder.

In-vivo studies of the D1R performed in schizophrenia patients have yielded mixed results. Studies have reported higher D1R in schizophrenia patients compared to controls (Abi-Dargham et al., 2002, 2012; Peols et al., 2013), lower D1R in patients (Hirvonen et al., 2006; Kosaka et al., 2010; Okubo et al., 1997; Stenkrona et al., 2019), and no difference (Karlsson et al., 2002). At first, it was thought that different radioligands ([11C]NNC112 and [11C] SCH23390) might underlie these differences, but using both ligands in the same samples did not significantly alter the results (Kosaka et al., 2010; Peols et al., 2013). Another proposed explanatory factor is a potential reduction in D1R as a consequence of antipsychotic medication, which was shown in experimental studies in non-human primates (NHPs) (Lidow et al., 1997; Lidow and Goldman-Rakic, 1994) (although see Knable et al. (1996)). Notably, in studies...
where both drug naive and medicated (henceforth implied by chronic) patients were examined, the latter group has consistently exhibited numerically lower D1R binding (Abi-Dargham et al., 2002, 2012; Olubo et al., 1997; Poels et al., 2013). There have, however, even been inconsistencies between studies examining drug-naive patients exclusively, finding increases (Abi-Dargham et al., 2012) and decreases (Stenknora et al., 2019). Another potentially fruitful approach is to compare groups who share similarities with patients, of which two such studies have been conducted. Hirvonen et al. (2006) reported increases in D1R in monozygotic unaffected co-twins of patients. It has been shown that delusional psychosis—especially in the early stages of the illness or even prior to its onset in psychosis-prone individuals—

 Core symptoms of psychosis are hallucinations (false perceptions) and delusions (irrational or strange inflexible beliefs), referred to as positive symptoms. It has been shown that delusional beliefs (Peters et al., 2004, 1999), hallucinations and other anomalous perceptions (Bell et al., 2005), are not uncommon in normal populations of whom the vast majority never go on to develop a psychotic disorder. Moreover, delusional beliefs and anomalous perceptions appear to co-vary to a large extent (Bell et al., 2005), are more commonly experienced by relatives of schizophrenia patients than by the general population (Schirhoff et al., 2003), and constitute an important risk factor for later psychosis (Freeman, 2006; Os et al., 2008). They are thus conceptualized as psychosis proneness traits, whose underlying cognitive, thought- and perceptual mechanisms are considered to be similar to those associated with clinical psychotic symptoms (Powers et al., 2017; Schmack et al., 2013, 2015; Teufel et al., 2015). While these traits do not represent a “psychosis-spectrum”, they can be considered as a personality trait whose study may allow for the examination of the biological correlates of individual psychotic-like symptoms, without the confounding effect of medication or other limitations common in clinical samples such as comorbidity, disease heterogeneity or differences in physical health between groups. For instance, such a view has been growing in popularity with the predictive coding account of psychosis (Fletcher and Frith, 2009; Sterzer et al., 2018).

Here, we aimed to investigate the association between D1R availability and delusional ideation assessed using these psychotic symptoms (Powers et al., 2017; Schmack et al., 2013, 2015; Teufel et al., 2015). While these traits do not represent a “psychosis-spectrum”, they can be considered as a personality trait whose study may allow for the examination of the biological correlates of individual psychotic-like symptoms, without the confounding effect of medication or other limitations common in clinical samples such as comorbidity, disease heterogeneity or differences in physical health between groups. For instance, such a view has been growing in popularity with the predictive coding account of psychosis (Fletcher and Frith, 2009; Sterzer et al., 2018).

We made use of both the Peters Delusion Inventory (PDI) (Peters et al., 2004), an established scale for delusional ideation, as well as a novel scale of delusional ideation in samples when this was not available. We performed both initial exploratory work, and subsequent confirmatory studies, to evaluate the relationship between D1R availability and delusional ideation assessed using these psychometric instruments.

2. Methods

2.1. Study design

This investigation consists of four substudies from four separate data collections. A summary of the substudies is presented in Fig. 1. Substudies 0A–B were for validation purposes, substudy 1 was exploratory (i.e. hypothesis-generating), while substudies 2–4 were confirmatory (i.e. hypothesis-testing) studies. Our investigation was divided in this way in order to ensure that we could explore the data fully and transparently, and subsequently commit to a principled test of our hypotheses based on previous results from our own exploratory findings as well as the scientific literature. This avoids the potential for presenting the conclusions of our experimental studies as if they were confirmatory based on hindsight bias, and ensures that the statistics from our confirmatory studies are valid, and hence possess greater evidentiary weight (Nosek et al., 2018; Wagenmakers et al., 2012).

2.2. Participants

The participants in this study were from three independent cohorts from four separate data collections, consisting of 76 individuals measured with PET using 11C-[CH23390 and 217 individuals who completed delusional ideation questionnaires. More details about these cohorts can be seen in Fig. 1 as well as in the Supplementary Methods (Supplementary Material S1).

Nine individuals were overlapping between the samples from exploratory substudy 1 and confirmatory substudy 3, who both completed the TCI-DI questionnaire at the time of PET, as well as completed the PDI questionnaire online. All individuals belonging to confirmatory substudies 2 and 4 were overlapping, and they also all belonged to the sample in validation substudy 0B. The additional four individuals in validation substudy 0B were those lacking valid PET measurements (see Supplementary Material S1).

2.2.1. Ethics

All studies were approved by the Regional Ethics Committee in Stockholm and all subjects provided informed consent prior to their participation in the studies. All studies making use of PET imaging were approved by the Radiation Safety Committee of the Karolinska Hospital.

2.3. MRI and PET procedures and image analysis

This information is provided in the Supplementary Methods (Supplementary Material S1).

2.4. Psychometric assessment

A Swedish translation of the 21-item Peters Delusion Inventory (PDI) (Peters et al., 2004) and the Swedish language version of the 238-item Temperament and Character Inventory (TCI) (Brandström et al., 1998; Cloninger, 1993) were used in this study. The Self-Transcendence (ST) scale of the TCI was originally intended to measure creativity and spirituality (Cloninger, 1993), but has later been shown to be associated with proneness to psychosis, as well as clinical psychotic phenotypes (Cortés et al., 2009; Daneluzzo et al., 2005; Guilleum et al., 2002; Padilla et al., 2006; Smith et al., 2008). In order to specifically examine delusional ideation, we created the new scale used in this study by selecting TCI items from the ST scale which exhibit face validity for this construct. For both inventories, missing items were corrected for by calculating the average score on each item of the scale, and multiplying this by the number of questions.

2.5. Statistical analysis

All statistical analyses were performed using R version 3.4.2 (R Core Team, 2017).

2.5.1. Validation substudies: psychometric analysis (substudies 0A and 0B)

For substudy 0A, in which TCI-ST items were selected to create a new measure of delusional ideation, we used Cronbach’s α to assess lower-bound estimates of split-half reliability. We considered a reliability of about 0.7 to be acceptable, according to the heuristic recommendation for basic research by Nunnally and Bernstein (1978). For substudy 0B, we assessed the convergent validity of the TCI-DI scales by comparing TCI-DI scores with the more well-established PDI questionnaire within the same individuals, using Pearson’s correlation coefficient.
2.5.2. Exploratory correlational analysis (substudy 1)

To compare TCI-DI scores with BP, we made use of multiple regression taking the effects of the nuisance variables of age and gender into account. Due to the bimodal age distribution and the highly unequal gender ratio in this data set, there was little reason to prefer exclusion of older individuals and/or women, or inclusion of these variables in the regression model. Furthermore, this analysis was undertaken prior to the collection of the data from validation substudy 0B, and therefore made use of both the longer and shorter variants of the TCI-DI scale. Due to the multiplicity of potential analysis decisions which could potentially have been undertaken for this analysis, we made use of a multiverse analysis (Steegen et al., 2016). This means that we present the results following each potential analysis decision, i.e. each path within the “garden of forking paths” (Gelman and Loken, 2014), with regard to subject inclusion and/or correction for nuisance variables, and draw conclusions based on the general distribution of outcomes. This helps to guard against the influence of hindsight bias in selecting only the most optimistic outcomes, thereby increasing the risk of type I errors.

2.5.3. Confirmatory analyses

For the confirmatory analyses, Bayesian statistical analytical procedures were used. A brief description of these procedures is provided in the Supplementary Methods (Supplementary Material S1).

2.5.3.1. Replication analysis (substudy 2). For performing a replication analysis of the results of exploratory substudy 1, we made use of the correlation replication BF (Wagenmakers et al., 2016), with the posterior calculated analytically. The correlation replication BF uses the posterior distribution of the original analysis as the prior for the replication attempt, which is compared to a null hypothesis. In this way, the replication BF compares the skeptic’s null hypothesis with the proponent’s posterior of the original findings, and evaluates the

| Sample Age  | PDI-21 | TCI-DI | [11C]SCH23390 PET | Variables of Interest |
|-------------|--------|--------|-------------------|-----------------------|
| 132 (72F) 22-76 |        | <2000  |                   | 0A. Psychometric Validation |
|             |        |        |                   | TCI-DI                 |
| 24 (OF) 22-35 | 2014   | 2014   |                   | 0B. Convergent validity |
|             | 2015   | 2015   |                   | PDI ~ TCI-DI           |
| 27 (BF) 23-76 |        |        |                   | 1. Association         |
|             | 2002   | 2002   |                   | D1R ~ TCI-DI           |
|             | 2010   | 2010   |                   |                       |
| 20 (OF) 22-35 | 2014   | 2014   |                   | 2. Replication         |
|             | 2015   | 2015   |                   | D1R ~ TCI-DI           |
| 41 (OF) 21-35 | 2014   | 2002   |                   | 3. Hypothesis Testing & Estimation |
|             | 2015   | 2010   |                   | D1R ~ PDI              |
| 20 (OF) 22-35 | 2014   | 2014   |                   | 4. Parameter Updating  |
|             | 2015   | 2015   |                   | D1R ~ PDI              |

Key

- TCI Personality Cohort: previous studies of healthy controls
- D1R PET Cohort 1: previous [11C]SCH23390 PET studies
- D1R PET Cohort 1: online PDI completion
- D1R PET Cohort 2: current [11C]SCH23390 PET study

Fig. 1. Summary of the included substudies.
relative probability of these two hypotheses given a new set of data (Wagenmakers et al., 2016).

2.5.3.2. Multiple regression analysis (substudies 3–4). For confirmatory substudies 3 and 4, we made use of Bayesian multiple regression to examine the association between PDI scores and $[^{11}C]$CNS23390 BP$_{ND}$. The regression model was specified using unstandardised units, thereby restricting the potential for limited variation in delusional ideation scores to influence the parameter of interest.

We defined informative priors derived from the literature to account for the effects of age on BP$_{ND}$ and PDI scores, a uniform prior for the intercept, and we defined zero-centred regularising priors for the parameter of interest. The definition of the priors is described in Supplementary Material S2. The model was specified such that Beta1 represents the intercept, Beta2 represents the association between BP$_{ND}$ values and Age, Beta3 represents the primary association of interest, i.e. the relationship between PDI scores and BP$_{ND}$ and Beta4 represents the relationship between PDI scores and age. The model was specified as follows:

$$BP_{ND} = \beta_1 + \beta_2 \text{PETAge} + \beta_3 \text{PDI} - \beta_4 \text{PETAge} \times \text{PDI}$$

(1)

The derivation of this model is shown in the Supplementary Methods (Supplementary Material S1).

2.5.3.3. Bayesian hypothesis testing. In confirmatory substudy 3, we made use of Bayesian hypothesis testing. Based on the mixed results of clinical PET studies comparing D1R availability in schizophrenia patients and controls (Abi-Dargham et al., 2002, 2012; Hirvonen et al., 2006; Karlsson et al., 2002; Kosaka et al., 2010; Okubo et al., 1997; Stenkrona et al., 2019), we defined and compared three hypotheses: an increase, a decrease, and no change in D1R BP$_{ND}$ with increasing proclivity to psychosis.

In order to generate statistical definitions of these hypotheses, we assumed that the differences between the mean $[^{11}C]$CNS23390 BP$_{ND}$ and mean PDI scores between patient and control groups would correspond with one another between studies. For PDI scores, Peters et al. (2004) observed a difference of five points between delusional patients and controls. For DLPCF $[^{11}C]$CNS23390 BP$_{ND}$, the effect magnitude was defined using the mean absolute proportional difference between groups, weighted by the sample size, in each study reporting differences between groups. For the definition of the priors over the association between age and BP$_{ND}$ and PDI scores, we defined informative normal priors whose mean and standard deviation were derived from estimates from previous studies reporting these associations. More details are provided in Supplementary Material S2.

2.5.3.4. Bayesian parameter estimation. In confirmatory substudies 3 and 4, we performed Bayesian parameter estimation to investigate the association between D1R BP$_{ND}$ and PDI scores. This method makes weaker assumptions about the magnitude of the relationship than the Bayesian hypothesis testing method above, but yields conclusions relating to the magnitude and direction of the effect rather than the relative likelihood of the different hypotheses. For confirmatory substudy 3, we used a bidirectional variant of the prior used above for hypothesis testing as a regularising prior to estimate the strength of association. For confirmatory substudy 4, we used mean-scaled normal approximations of the posterior estimates from confirmatory substudy 3 as priors for all parameters except for the intercept in order to update posterior estimates in an independent sample.

2.6. Data and code availability

The full analysis notebook and all analysis code is available at https://github.com/matheson/D1R_PsychProneess. Due to institutional restrictions, the data cannot be shared openly within this repository. These data are pseudonymised according to national (Swedish) and EU legislation, and cannot be anonymised and published in an open repository. Metadata can be openly published, and the underlying data can instead be made available upon request on a case by case basis as allowed by the legislation and ethical permits. Requests for access can be made to the Karolinska Institute’s Research Data Office at rdoo@ki.se.

3. Results

3.1. Validation and exploratory analysis

3.1.1. Validation substudies OA and OB: validating the reliability and validity of a novel measurement instrument for assessing delusional ideation

We aimed to assess the relationship between delusional ideation and D1R availability using previously collected data, however the validated delusional ideation scale, the PDI (Peters et al., 2004), was not collected in this dataset. Instead, as a proxy for the PDI scale, we selected items from the TCI-ST scale which were considered to be representative of delusional ideation. Using these items, we compiled two candidates TCI Delusional ideation (TCI-DI) scales, and validated their psychometric properties using a sample of 132 individuals who completed the TCI questionnaire. These scales showed good to acceptable reliability (Cronbach's $\alpha = 0.82$ and 0.76 respectively) (Supplementary Material S3). Both scales were positively associated with the PDI in a sample of 24 individuals in which both questionnaires were collected ($r = 0.46$ and $r = 0.64$) (Supplementary Material S4). We therefore concluded that the TCI-DI scales, and in particular the shorter variant, were capable of measuring delusional ideation with an acceptable psychometric properties.

3.1.2. Exploratory substudy 1: analysis of the association between delusional ideation and D1 receptor BP$_{ND}$ measured using $[^{11}C]$CNS23390

Using this scale, we assessed the relationship of these scales with $[^{11}C]$CNS23390 BP$_{ND}$ in the DLPCF and striatum using a multivariate analysis, using a previously-collected sample of 27 individuals. We tested 8 different model specifications for each of the two regions (Supplementary Material S5). We observed a negative relationship between TCI-DI scores and $[^{11}C]$CNS23390 BP$_{ND}$ of generally large effect size (Fig. 2). This association did not appear to be greatly influenced by the different analytical alternatives, although effect sizes tended to be larger when examining only young male participants ($n = 13$) rather than including the whole sample with gender and age as covariates in the model.

In summary, we found preliminary evidence of a negative association between delusional ideation and D1R availability in both the DLPCF and striatum. We therefore considered the association between delusional ideation and D1R availability a promising hypothesis to be tested in a confirmatory study.

3.2. Confirmatory analyses

3.2.1. Substudy 2: confirmatory replication of results from exploratory substudy 1

We examined the relationship between $[^{11}C]$CNS23390 BP$_{ND}$ and TCI-DI scores in a sample of 20 young males to assess whether the results of exploratory substudy 1 could be replicated in an independent sample. The Cronbach's $\alpha$ of the TCI-DI scale in this sample was 0.61. In contrast to the results of exploratory substudy 1, there was no apparent association between TCI-DI scores and BP$_{ND}$ (Fig. 3). Replication BFs, using the most appropriate multivariate beta (described further in Supplementary Material S5) showed moderate to strong support in favour of the null hypothesis relative to the posterior distribution of the correlation coefficient from the original study (DLPCF BF$_{OB} = 5.5$, Striatum BF$_{OB} = 10.5$). As an additional robustness check, we performed the replication analysis using the median beta for the relevant variant of the scale, yielding reduced replication BFs (DLPCF BF$_{OB} = 3.3$, Striatum BF$_{OB} = 5.5$).
B_{\text{FDR}} = 5.5), but which still provided moderate evidence for the null hypothesis.

In summary, this means that the data were more likely under the null hypothesis of no association compared to the original hypothesis of the negative association observed in exploratory substudy 1.

3.2.2. Substudy 3: confirmatory analysis of the association between PDI scores and D1 receptor BP_{ND} measured using [11C]SCH23390

This sample consisted of 41 participants who had previously undergone PET measurements with [11C]SCH23390, who later completed the PDI through an online questionnaire. In this sample, the Cronbach’s α for the PDI was 0.78, and the median PDI score was 4 (range: 0–14). For comparison, Peters et al. (2004) observed medians of 6 and 11 in controls and patients respectively. The mean BP_{ND} was 0.29 (0.08–0.47) for the DLPFC, and 1.53 (0.82–2.02) for the striatum. The number of years elapsed between participants’ PET measurements and their completion of the scale ranged between 4.8 and 12.7 years (mean 7.9, sd 1.6). Despite the limited variation in age in the data set, we still observed negative correlations with age for both DLPFC BP_{ND} (r = −0.18) as well as PDI scores (r = −0.23) as expected from previous literature. Informative priors derived from the literature were defined to account for the effects of age on both D1R BP_{ND} (Bäckman et al., 2011; De Boer et al., 2017; Fonseca-Pedrero et al., 2012; Jucaite et al., 2010; Peters et al., 2004; Wang et al., 1998) and PDI scores in the model (Fonseca-Pedrero et al., 2012; Peters et al., 2004) (Supplementary Material S2).

Fig. 2. Distribution of the effect sizes from the multiverse analysis for the association between TCI-DI scores and D1R availability following different analytical paths.
Bayes Factors (BFs) comparing the relative likelihood of the data under each of the three hypotheses describing the association between D1R BP\textsubscript{ND} and delusional ideation are shown in Table 1. We found medium to strong evidence in favour of the null hypothesis compared to the other two hypotheses. This means that the data is over 3 times more likely to have occurred under the null hypothesis model than it is under the increase model, and over 6 times more likely than under the decrease model. Parameter estimates using a bidirection prior are provided in Supplementary Material S6.

We also performed a similar analysis for the striatum, assessing the hypothesis of a negative association between striatal BP\textsubscript{ND} and PDI scores based on the results of exploratory substudy 1. In this analysis, we found strong support for the null hypothesis (BF\textsubscript{01} = 16.1), supporting the results of confirmatory substudy 2. For this reason, and since the DLPFC was our primary region of interest, the striatum was not further examined in confirmatory substudy 4. Parameter estimates using a bidirection prior are provided in Supplementary Material S6.

### Table 1
Bayes factors comparing each hypothesis (rows) against each other hypothesis (columns). A value greater than 1 means that the data is more consistent under the row hypothesis than the column hypothesis, and vice versa.

| Model  | Decrease | Increase | Null  |
|--------|----------|----------|-------|
| Decrease | 1.000    | 0.495    | 0.146 |
| Increase | 2.022    | 1.000    | 0.296 |
| Null    | 6.832    | 3.379    | 1.000 |

### 3.2.3. Substudy 4: parameter estimation for the association between PDI scores and D1 receptor BP\textsubscript{ND} measured using \textsuperscript{11}C SCH23390

We aimed to estimate the potential magnitude, and associated uncertainty, of the association between PDI scores and \textsuperscript{11}C SCH23390 BP\textsubscript{ND}. Using parameter estimates from confirmatory substudy 3, we derived updated parameter estimates using an independent sample of 20 individuals who had completed PDI scales within two weeks of the PET measurements. The Cronbach’s \(\alpha\) of the PDI scale in this sample was 0.68, and the median PDI score was 3 (range: 0–9). The mean BP\textsubscript{ND} was 0.33 (0.22–0.43) for the DLPFC. Estimates for the association between DLPFC \textsuperscript{11}C SCH23390 BP\textsubscript{ND} and PDI scores were calculated using the same regression model as in Substudy 3, using posterior estimates from Substudy 3 scaled to the mean BP\textsubscript{ND} in this sample as priors for all parameters except for the intercept (see Supplementary Material S6).

The posterior distribution for the regression coefficient representing the association between PDI scores and DLPFC BP\textsubscript{ND} (\(\beta_3\)) was updated (Table 2) such that it became both narrower (i.e. more precise), but also closer to zero (Fig. 4, and Supplementary Material S7). According to this final estimate, a change of 5 points on the PDI, the margin of difference previously observed between populations of healthy controls and delusional patients (Peters et al., 2004), is associated with a change in BP\textsubscript{ND} of 0.0% of the mean (95% CredInt: −5.5 to 7.5%).

### 3.3. Exploratory post hoc analyses

#### 3.3.1. Monotonic relationships in the combined sample

To explore the possibility of a nonlinear monotonic relationship between delusional ideation scores and D1R BP\textsubscript{ND}, we also examined

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Fig. 3. Scatterplots demonstrating the association and their effect sizes between TCI-DI scores and \textsuperscript{11}C SCH23390 BP\textsubscript{ND} in the DLPFC and striatum from the cohorts examined in exploratory substudy 1 and confirmatory substudy 2.
associations of rank between TCI-DI and PDI scores and BP\textsubscript{ND} values. We regressed all both D1R BP\textsubscript{ND} values and psychometric scale scores with age and study cohort, and corrected each outcome for the coefficients to an age of 25 years old (the mean age). This correction was restricted to individuals under 50 years old on account of the otherwise bi-modal age distribution. For this exploratory analysis, we also included PDI total scores, in addition to PDI Yes/No outcomes, despite their high association with one another (Supplementary Material S8). All absolute Spearman rho were less than 0.1, and none were significant. More details are provided in Supplementary Material S9.

4. Discussion

In this study, we aimed to investigate the relationship between D1R availability and delusional ideation in healthy control subjects using a combination of exploratory and confirmatory analyses, in order to generate and test hypotheses respectively. First, we created a new scale for measurement of delusional ideation from items of the TCI questionnaire and validated its psychometric properties (validation substudies 0A and 0B). In an exploratory study, this scale exhibited a negative association with dopamine D1R availability in both the DLPFC and striatum (exploratory substudy 1). In the confirmatory part of this investigation, we first found moderate to strong evidence that the results of exploratory substudy 1 could not be successfully replicated, suggesting that they were likely to be attributable to a false positive (confirmatory substudy 2). We went on to demonstrate evidence in favour of no association between PDI scores and D1R availability (confirmatory substudy 3). Further estimation also revealed that the expected changes in D1R availability for increasing scores on the PDI scale were too small to be of relevance (confirmatory substudies 3–4). In summary, our results show, with a high degree of precision, that there is little to no linear, and perhaps even monotonic, relationship between DLPFC D1R availability and delusional ideation in healthy controls.

Studies showing differences in DLPFC \([11\text{C}]\text{SCH23390} \text{BP}_{\text{ND}}\) between schizophrenia patients and controls have found fairly large differences: 18.5% on average (Supplementary Material S2) - however these studies differ in both magnitude and direction of observed effects, and have been conducted using medicated and drug-naive patients. Such large effects should be easily detectable given the repeatability (test-retest variability) of DLPFC \([11\text{C}]\text{SCH23390} \text{BP}_{\text{ND}}\) of 9.5% and reliability (ICC) of 0.79 (Stenkrona et al., 2018). Delusional patients and controls also show differences in PDI scores (Peters et al., 2004). If changes in D1R availability were to underlie these differences in delusional ideation, then we might expect such differences in PDI scores to be associated with similar changes in healthy controls. Instead, we found that such a difference in delusional ideation was only associated with a 0.9% change in BP\textsubscript{ND} (up to 7.5% within the 95% Credible Interval): this is not consistent with the results of any of the previous studies reporting significant differences between groups. To contextualise this result further, the resulting model from confirmatory substudy 4 estimates that a change across the entire extent of the PDI scale, 21 points (which is impossibly large as it would require all controls to obtain a score of 0), would still only amount to a 3.6% change in BP\textsubscript{ND}. We can therefore conclude that our results, and their associated uncertainty, are not consistent with

### Table 2

Posterior summaries of unstandardised coefficients from updated parameters.

| Parameter | Mean   | SD    | 2.5%   | 97.5%   |
|-----------|--------|-------|--------|---------|
| Beta1     | 0.323  | 0.015 | 0.294  | 0.352   |
| Beta2     | −0.005 | 0.002 | −0.008 | −0.002  |
| Beta3     | 0.001  | 0.002 | −0.004 | 0.000   |
| Beta4     | −0.119 | 0.041 | −0.200 | −0.040  |

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**Confirmatory Substudy 3**

**Confirmatory Substudy 4**

![Scatterplots and parameter plots demonstrating the association between \([11\text{C}]\text{SCH23390} \text{BP}_{\text{ND}}\) in the DLPFC and PDI scores (left), and the associated parameter estimates for beta3 (right), corresponding to the expected change in \([11\text{C}]\text{SCH23390} \text{BP}_{\text{ND}}\) corresponding to a change of 5 units on the PDI scale. In confirmatory substudy 3, the prior over this parameter was defined as a wide regularising prior based on the literature, while confirmatory substudy 4 made use of the posterior from the former study as its prior.**
the magnitude of change which would have been expected in healthy controls based on studies examining patients and controls. The D1 receptor has historically been studied primarily in relation to the cognitive deficits present in schizophrenia. The hypothesis has been that dopaminergic neurotransmission at subcortical D2 receptors is primarily responsible for positive symptoms, while neurotransmission at cortical D1 receptors is primarily responsible for negative and cognitive symptoms, a model based on the differential distributions of the two receptors in these anatomical regions (Howes et al., 2009). Indeed, there has been much evidence suggesting that deficits in working memory and cognition could be elicited by modifying neurotransmission to dopamine D1 receptors in the prefrontal cortex (Goldman-Rakic et al., 2004; Tamminga, 2006). However, this anatomical and biochemical separation of function has never been empirically verified. Rather, recent findings from cognitive neuroscience have attributed an important role of the prefrontal cortex in the manifestation of positive symptoms specifically in schizophrenia - and the predictive coding account of the disorder suggests that there is a delay in the onset of these symptoms compared to healthy controls (Fletcher and Frith, 2009; Sterzer et al., 2018). It is important to understand the current results in this context, and not as an absolute indication regarding the role of D1R for delusional ideation in schizophrenia. The present results did not however lend support to a role of frontal D1R in the development of these symptoms in healthy controls. Other neurotransmission systems may underlie delusional ideation, as was the case in our sample. Further research into the D1R in schizophrenia and in proneness for psychosis is warranted to ascertain which of these alternatives is most likely.

Contributors

| Contributor role | Authors | Detailed contributions |
|------------------|---------|------------------------|
| Conceptualization | GJM, PP, SC | Study and research goals were formulated by GJM, PP and SC |
| Methodology | GJM, PPS, AL | TCI-DI items were selected by AL and PPS. Psychometric analysis of the TCI-DI scale was performed by PPS and GJM |
| Software | GJM | GJM wrote the software for extraction of the DLFPIC and for kinetic modelling. |
| Formal analysis | NA | NA |
| Investigation | GJM, PPS, LF, JB | GJM and PPS performed the psychometric analysis. GJM performed the image analysis, kinetic modelling and statistical modelling. JB administered the TCI questionnaires in Study 3. PPS performed data entry for the TCI questionnaire in Study 3. LF supervised the PET data collection in both PET studies. GJM recruited, administered, collected and entered personality data for D1R PET Cohort 2 and for the online PDI questionnaires. |
| Resources | SC, LF | LF and SC funded the data acquisition in cohort 2. SC purchased the analysis computer. |
| Data curation | GJM | GJM compiled and anonymised the data. |
| Writing - original draft preparation | GJM, SC, PPS | These authors contributed to drafting of the original manuscript. |
| Writing - review & editing | GJM, PPS, AL, PP, LF, JB, SC | All authors reviewed and edited the manuscript |
| Visualization | GJM | GJM prepared all figures as part of the analysis |
| Supervision | SC, PP, LF | SC and PP supervised the planning of this study. SC and LF supervised the data collection in D1R PET Cohort 2. LF supervised data collection in D1R PET Cohort 1. |
| Project administration | GJM, SC, PPS | GJM performed recruitment, and administered payments for D1R PET Cohort 1. SC provided oversight and leadership over the research activity planning for this investigation. |
| Funding acquisition | SC, PP, LF | Funding was provided by SC, PP and LF |
Role of funding sources
The funding sources had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Declaration of competing interest
The authors declare no conflicts of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.06.011.

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