

RESEARCH ARTICLE

# Is dopamine D1 receptor availability related to social behavior? A positron emission tomography replication study

Pontus Plavén-Sigra<sup>1\*</sup>, Granville James Matheson<sup>1</sup>, Petter Gustavsson<sup>2</sup>, Per Stenkrona<sup>1</sup>, Christer Halldin<sup>1</sup>, Lars Farde<sup>1,3</sup>, Simon Cervenka<sup>1</sup>

**1** Department of Clinical Neuroscience, Center for Psychiatry Research, Karolinska Institutet and Stockholm County Council, SE, Stockholm, Sweden, **2** Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, **3** PET imaging Centre, Precision Medicine and Genomics, IMED Biotech unit, AstraZeneca, Karolinska Institutet, Stockholm, Sweden

\* [pontus.plaven-sigra@ki.se](mailto:pontus.plaven-sigra@ki.se)



**OPEN ACCESS**

**Citation:** Plavén-Sigra P, Matheson GJ, Gustavsson P, Stenkrona P, Halldin C, Farde L, et al. (2018) Is dopamine D1 receptor availability related to social behavior? A positron emission tomography replication study. PLoS ONE 13(3): e0193770. <https://doi.org/10.1371/journal.pone.0193770>

**Editor:** Véronique Sgambato-Faure, "INSERM", FRANCE

**Received:** December 11, 2017

**Accepted:** February 19, 2018

**Published:** March 15, 2018

**Copyright:** © 2018 Plavén-Sigra et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All data and code used for this study can be found at a public repository OSF (<https://osf.io/te5q7/>) and Github (<https://github.com/pontusps/D1R-personality-replication>).

**Funding:** This work was supported by the Söderström-Königska Stiftelsen (SLS-760561) and Swedish Research Council (523-2014-3467) and Stockholm County Council. The funders had no role in study design, data collection and analysis,

## Abstract

### Background

Associations between dopamine receptor levels and pro- and antisocial behavior have previously been demonstrated in human subjects using positron emission tomography (PET) and self-rated measures of personality traits. So far, only one study has focused on the dopamine D1-receptor (D1-R), finding a positive correlation with the trait social desirability, which is characterized by low dominant and high affiliative behavior, while physical aggression showed a negative correlation. The aim of the present study was to replicate these previous findings using a new independent sample of subjects.

### Materials and methods

Twenty-six healthy males were examined with the radioligand [<sup>11</sup>C]SCH-23390, and completed the Swedish universities Scales of Personality (SSP) which includes measures of social desirability and physical trait aggression. The simplified reference tissue model with cerebellum as reference region was used to calculate BP<sub>ND</sub> values in the whole striatum and limbic striatum. The two regions were selected since they showed strong association between D1-R availability and personality scores in the previous study. Pearson's correlation coefficients and replication Bayes factors were then employed to assess the replicability and robustness of previous results.

### Results

There were no significant correlations (all p values > 0.3) between regional BP<sub>ND</sub> values and personality scale scores. Replication Bayes factors showed strong to moderate evidence in favor no relationship between D1-receptor availability and social desirability (striatum BF01 = 12.4; limbic striatum BF01 = 7.2) or physical aggression scale scores (limbic striatum BF01 = 3.3), compared to the original correlations.

decision to publish, or preparation of the manuscript.

**Competing interests:** The authors declare no conflicts of interest related to this work. SC has received grant support from AstraZeneca as co-investigator, and has served as a one-off speaker for Roche and Otsuka Pharmaceuticals. LF is partially employed at the AstraZeneca PET imaging Centre at Karolinska Institutet. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

## Discussion

We could not replicate the previous findings of associations between D1-R availability and either pro- or antisocial behavior as measured using the SSP. Rather, there was evidence in favor of failed replications of associations between BP<sub>ND</sub> and scale scores. Potential reasons for these results are restrictive variance in both PET and personality outcomes due to high sample homogeneity, or that the previous findings were false positives.

## Introduction

The dopamine system is involved in a wide range of behavior. A series of molecular imaging studies suggest that regional levels of the dopamine D2-receptor (D2-R) in the human brain are negatively related to pro-social behavior, such as the personality trait social desirability [1–4], although a null finding has also been reported [5]. Social desirability reflects how a person represents herself in a social setting in order to gain approval by others, and combines low dominance and high affiliation traits [6]. Compared to the D2-R, research on the relationship between personality traits and the dopamine D1-receptor (D1-R), which show different intracellular mechanisms and brain distribution [7,8], has been much more scarce.

In a previous publication [9] we reported a positive correlation between D1-R levels in striatum and social desirability in healthy subjects, while the opposite pattern was shown for measurements of aggressive personality traits. This finding mirrors that from animal literature [10] and when taken together with previous PET studies [1–4], suggests opposite regulatory mechanisms for the D1 and D2 dopamine systems in mediating pro- and antisocial behavior in humans. This in turn could have wide implications for diagnosing and treating psychiatric conditions associated with dysfunctional social behavior, such as antisocial personality disorder or social anxiety. However, common problems with studies using positron emission tomography (PET) to examine personality traits are that they often are based on small samples (with risks of selection bias and non-normal or restricted variability), employ many outcome measures, and allow for flexible modelling options, which can increase the risk for false positive findings. It is therefore important to replicate findings using independent samples in order to assess the robustness of published results.

The objective of the present study was to perform a replication of our previously reported associations [9] between D1-R in the striatum and social desirability and physical aggression, using a new and independent sample.

## Materials and methods

### Subjects and personality measures

Twenty-six male subjects (mean age = 26.2 ± 3.2) were recruited and participated in PET examinations with the D1-R radioligand [<sup>11</sup>C]SCH-23390 [11]. Exclusion criteria were historical or present episode of psychiatric illness, alcohol or drug abuse, major somatic illness or habitual use of nicotine as determined by a health screening carried out by a senior physician. The study and study design were approved by the Regional Ethics Committee in Stockholm and the Karolinska University Hospital Radiation Safety Committee. All subjects gave written informed consent prior to participating.

In addition to the PET examinations, subjects also completed the Swedish universities Scales of Personality (SSP) [12]. SSP is an established personality inventory that includes scales measuring social desirability (SocDes) and physical trait aggression (PhTA).

## MRI and PET examinations

Magnetic Resonance Imaging (MRI) and PET examination protocols were similar to those described in our previous study [9]. T1-weighted MRI images were acquired for all subjects using a 1.5T Siemens Magnetom Avanto system (Erlangen, Germany). All subjects were examined on a Siemens ECAT HR 47 (CTI/Siemens, Knoxville, TN), with [ $^{11}\text{C}$ ]SCH-23390 injected as a rapid bolus (mean injected activity =  $327 \pm 40$  MBq; mean specific activity =  $0.33 \pm 0.19$  GBq/ $\mu\text{mol}$ ; mean injected mass =  $388 \pm 237$   $\mu\text{g}$ ) in the antecubital vein. The whole of striatum (STR) and the sub-region limbic striatum (LST) were selected as regions of interest (ROIs), since they showed strong significant correlations to both SocDes (positive) and PhTA (negative) in our previous study [9]. All ROIs were grey-matter masked and automatically delineated on the T1 images using the FMRIB FSL software [13] and the Oxford-GSK-Imanova maximum probability 25% DTI-based atlas. In this atlas, the whole-striatum consist of both the putamen and caudate, and the limbic striatum consist of the ventral part of putamen and caudate (see Fig 1). D1-R  $\text{BP}_{\text{ND}}$  values (a measure of receptor availability) were derived using the simplified reference tissue model with cerebellum as reference region.

## Statistical analysis

Pearson correlation coefficients were calculated between the SocDes (one-sided test expecting a positive direction), PhTA (one-sided test expecting a negative direction) and ROI  $\text{BP}_{\text{ND}}$  values, using an alpha level of 0.05. Since a non-significant p-value in itself does not necessarily mean that a replication attempted failed, a statistical procedure known as *replication Bayes Factor (BF)* [14] was also employed. A replication BF quantifies the strength of evidence in favor of a successful replication ( $H_1$ ), over the null-hypothesis of no correlation (i.e. a failed replication:  $H_0$ ). This is done by using the previously published correlation as the prior for  $H_1$ , and then calculating the predictive adequacy of  $H_1$  over  $H_0$ . A BF above 3 for  $H_1$  ( $\text{BF}_{10} > 3$ ) is commonly interpreted as providing moderate evidence for a successful replication, and a BF above 3 for  $H_0$  ( $\text{BF}_{01} > 3$ ) as moderate evidence for a failed replication. A BF above 10 signifies strong evidence in favor of one hypothesis ( $H_1$  or  $H_0$ ), over the other. All statistical modelling was carried out using R (v.3.3.2).

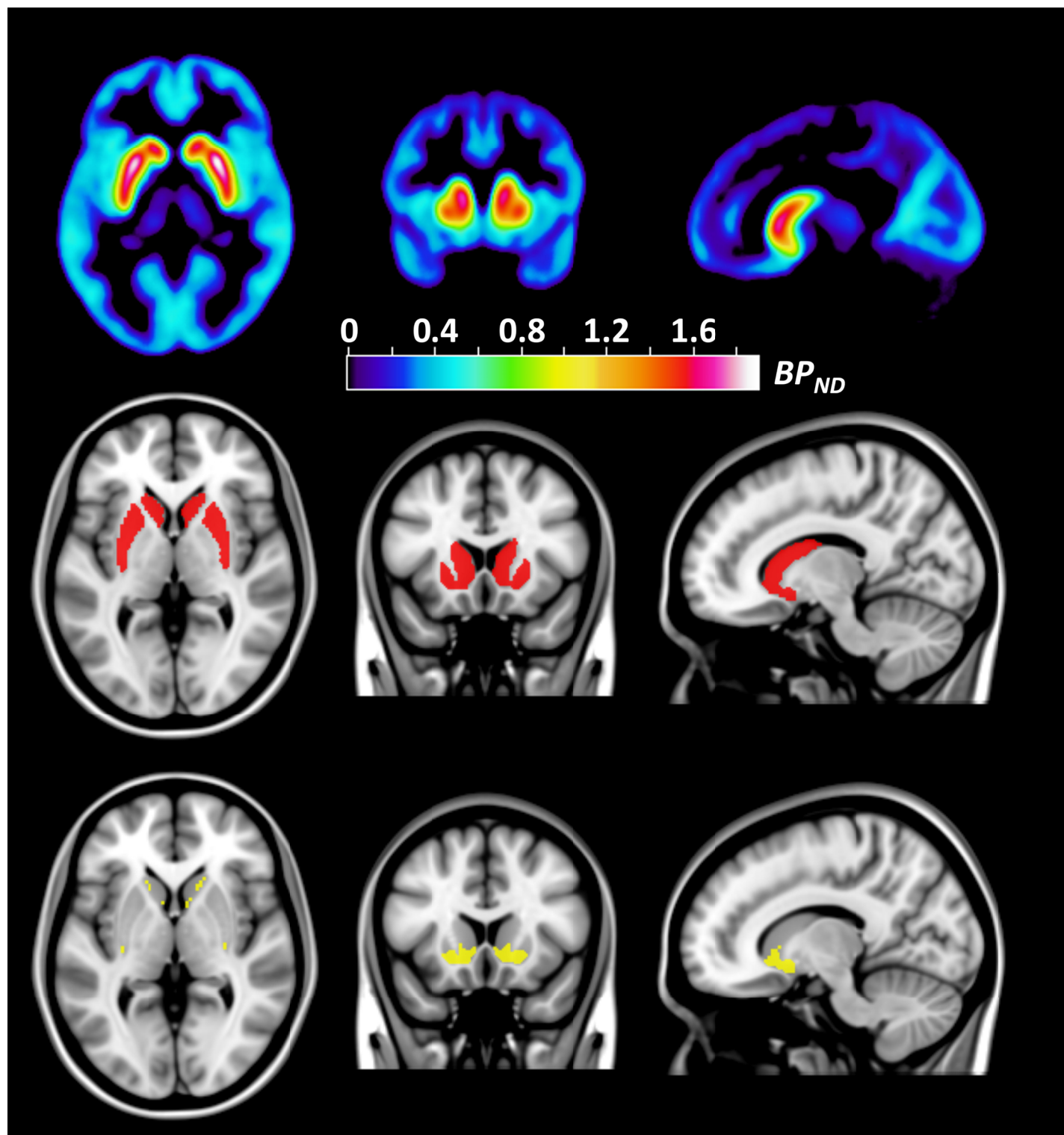
## Results

All subjects' personality scale scores fell within  $\pm 2\text{SD}$  of the population for both SocDes and PhTA (see T-scores on the y-axes of Fig 2). Neither of the scales showed a significant relationship to  $\text{BP}_{\text{ND}}$  in the STR or the LST (Fig 2 and Table 1). In fact, replication BF shows that there was strong to moderate evidence for no association between  $\text{BP}_{\text{ND}}$  and SocDes ( $\text{BF}_{01} = 12.4$  for STR,  $\text{BF}_{01} = 7.2$  for LST), compared to the original correlations, and hence signified a failed replication (Fig 3). For PhTA, there was moderate evidence in favor of a failed replication for the LST ( $\text{BF}_{01} = 3.3$ , see Fig 3), while the evidence in favor of the null was inconclusive for STR ( $\text{BF}_{01} = 1.9$ , see Fig 3).

## Discussion

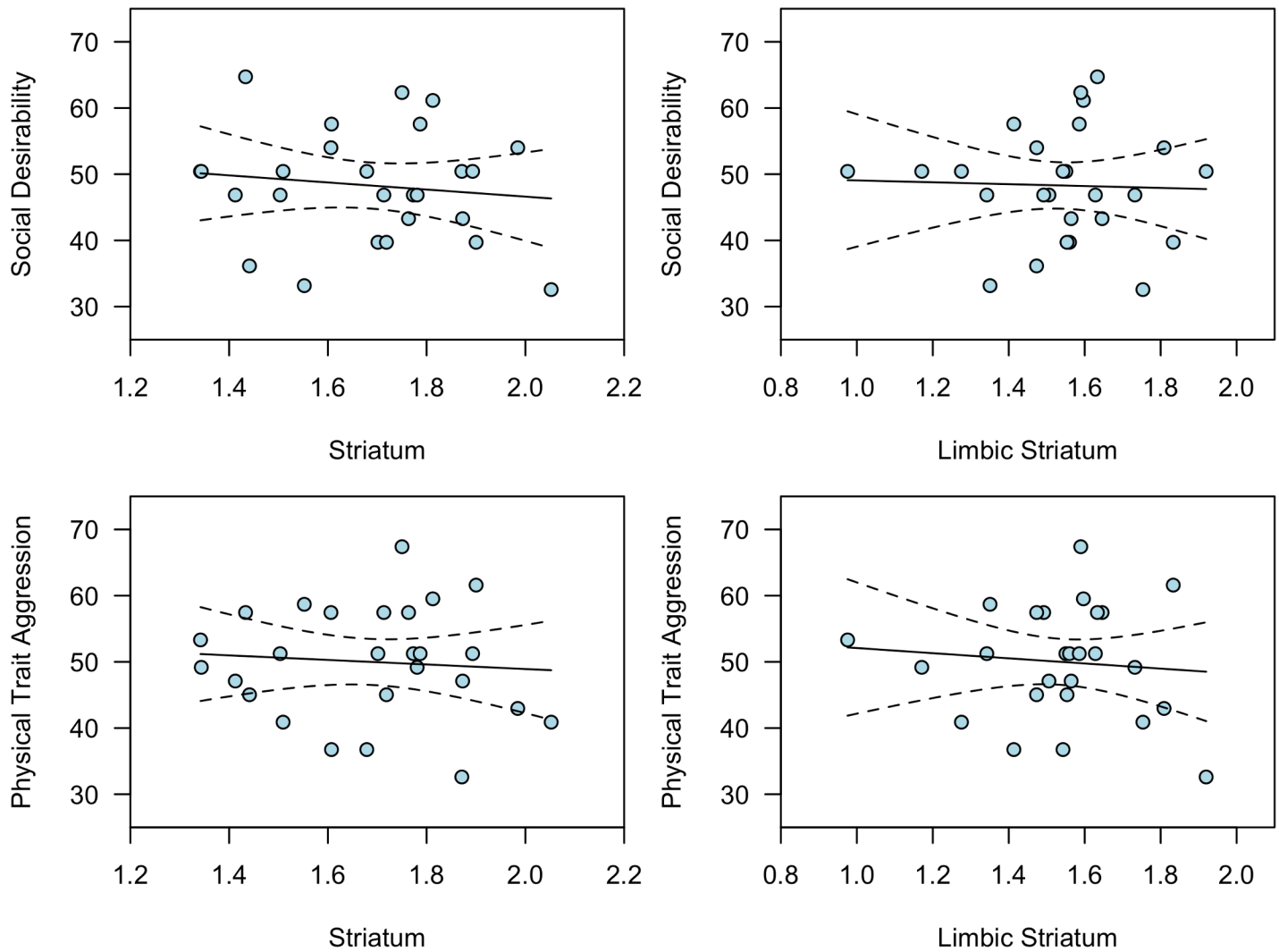
Using a new and slightly larger sample of healthy subjects, we were not able to replicate our previous findings of an association between D1-R availability in the striatum and social desirability or physical aggression [9]. Rather, data showed strong to moderate evidence in favor of failed replications of correlations between D1-R and SocDes or PhTA.

There are several possible explanations for this lack of replication. The present study was based on a sample of healthy young males, while the original study included both males and



**Fig 1. D1-R  $BP_{ND}$  map and regions of interest.** The top row displays an average D1-R  $BP_{ND}$  brain map of all subjects. The middle row shows the whole-striatum ROI (red). The bottom row shows the limbic striatum ROI (yellow) used in this replication study.

<https://doi.org/10.1371/journal.pone.0193770.g001>



**Fig 2. Relationships between D1-R BP<sub>ND</sub> in striatum and social desirability and physical trait aggression.** The dotted lines indicate the 95% confidence intervals. Raw scale scores have been transformed to T-scores for illustrative purposes in this figure.

<https://doi.org/10.1371/journal.pone.0193770.g002>

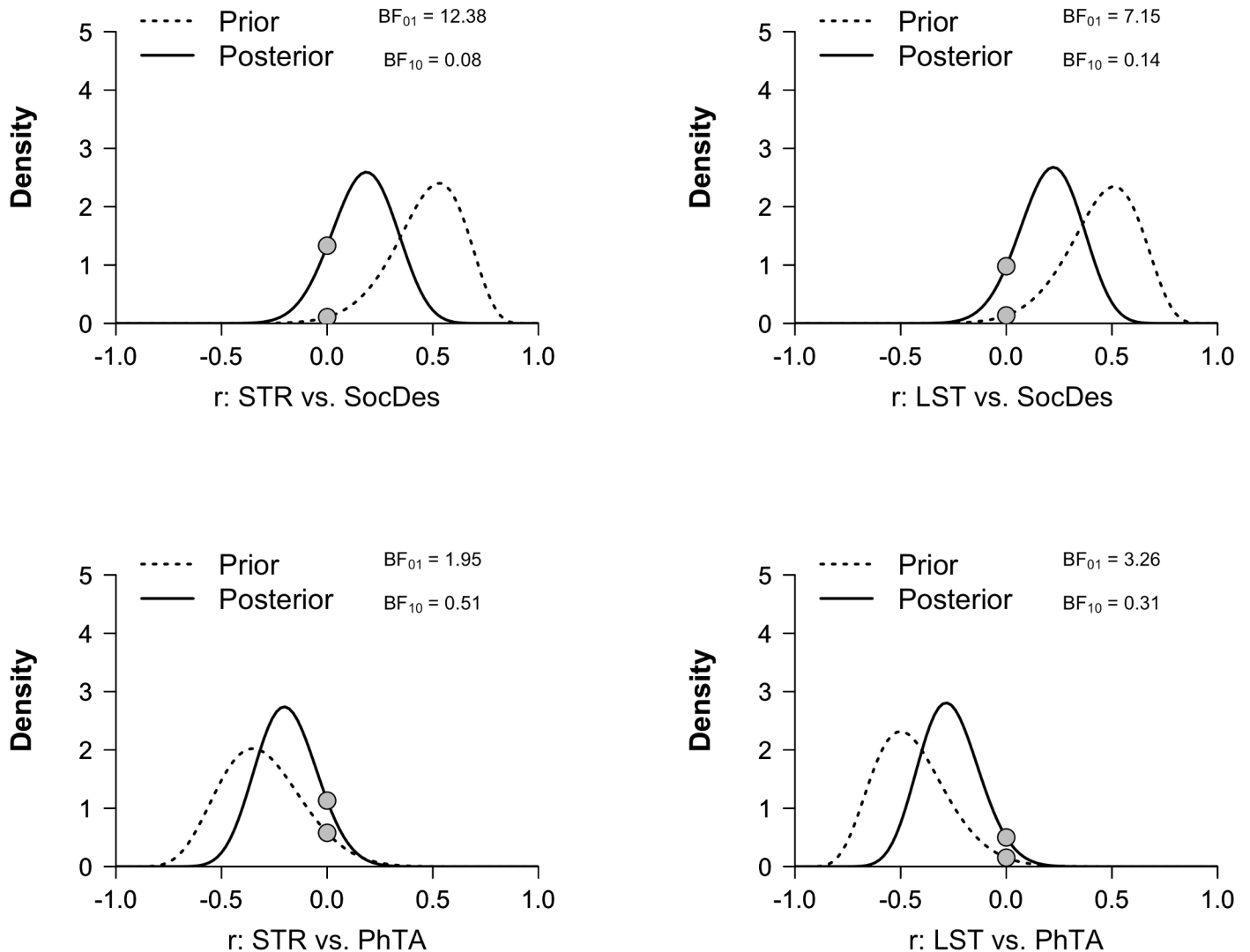
**Table 1. Correlations between SocDes and PhTA scores and ROI BPND from the previous [9] and present study.** The table also displays the replication BFs which denotes how much support there is for a successful replication, by quantifying how much evidence there is in favor of the original correlation compared to no correlation. Note that the correlation between PhTA and STR was not significant in the original study but have still been included here for completeness.

	Original study <sup>a</sup>			Present study <sup>b</sup>			Replication BF	
	r	df	p	r	df	p	BF01	BF10
<b>SocDes</b>								
STR	0.54	19	0.012	-0.12	24	0.73	12.4	0.08
LST	0.52	19	0.015	-0.03	24	0.57	7.2	0.14
<b>PhTA</b>								
STR	-0.36	19	0.106	-0.08	24	0.35	2	0.51
LST	-0.51	19	0.019	-0.09	24	0.32	3.3	0.31

a. two-sided test

b. one-sided test in direction of the original study

<https://doi.org/10.1371/journal.pone.0193770.t001>



**Fig 3. Prior and posterior distributions underlying the replication Bayes factors.** In each graph the dotted line denotes the prior which is determined by the correlation from the original study. The posterior (solid line) is obtained by updating the prior using the correlation from the present study. The Savage-Dickey Ratio (the ratio between the heights of the two dots) is then used to calculate the Bayes factor in favor of the original correlation over the null-hypothesis of no correlation. See Verhagen & Wagenmakers [14] for a full explanation of this procedure. In this study, data support the null hypothesis over the original correlations and the Bayes factors hence signifies failed replications.

<https://doi.org/10.1371/journal.pone.0193770.g003>

females from a wider age range. Although both gender and age were controlled for in the original study, the homogeneous sample used in the present study restricts the variance of both D1-R BP<sub>ND</sub> and the social desirability measures, possibly leading to lower sensitivity to detect an association. Another explanation is that the original findings were false positives, and that there is no direct correlation between D1-R in striatum and pro- and antisocial behavior as measured with SSP. Replication failures are common in science [15,16]. In neuroimaging specifically, small sample sizes and multiple comparisons without adequate correction can lead to incorrect inference. It is also worth noting that a p-value of 0.05, a commonly set threshold for significance, provides only modest evidence in favor of the research hypothesis being true, compared to the null-hypothesis [17].

One way forward is to use a larger and demographically more diverse sample of subjects, in order to maximize both the power and the interindividual variability of PET and personality outcomes. To facilitate this approach, we provide the BP<sub>ND</sub> and personality data from this study on an online public repository (<https://osf.io/te5q7/>), so that other PET researchers can pool our data with their samples. Another future line of research could be to correlate D1-R availability with different tests of specific types of pro- and antisocial behavior that could yield more precise outcomes than self-report questionnaires, with larger interindividual variation. Examples of such endophenotypes of social behavior include experimental measures of trustful, altruistic and vindictive decision-making commonly used within the field of behavioral economics [18].

## Acknowledgments

We thank the staff of the PET group at Karolinska Institutet for their assistance during this study. Code and data can be found at <https://osf.io/te5q7/> or <https://github.com/pontusps/D1R-personality-replication>.

## Author Contributions

**Conceptualization:** Pontus Plavén-Sigray, Granville James Matheson, Petter Gustavsson, Per Stenkrona, Lars Farde, Simon Cervenka.

**Data curation:** Pontus Plavén-Sigray, Granville James Matheson.

**Formal analysis:** Pontus Plavén-Sigray, Granville James Matheson.

**Funding acquisition:** Lars Farde, Simon Cervenka.

**Investigation:** Pontus Plavén-Sigray.

**Methodology:** Pontus Plavén-Sigray, Granville James Matheson.

**Project administration:** Pontus Plavén-Sigray, Per Stenkrona.

**Resources:** Per Stenkrona, Christer Halldin, Lars Farde, Simon Cervenka.

**Software:** Pontus Plavén-Sigray.

**Supervision:** Petter Gustavsson, Christer Halldin, Lars Farde, Simon Cervenka.

**Visualization:** Pontus Plavén-Sigray.

**Writing – original draft:** Pontus Plavén-Sigray, Simon Cervenka.

**Writing – review & editing:** Pontus Plavén-Sigray, Granville James Matheson, Petter Gustavsson, Per Stenkrona, Christer Halldin, Lars Farde, Simon Cervenka.

## References

1. Huang CL, Yang YK, Chu CL, Lee IH, Yeh TL, Chen PS, et al. The association between the Lie scale of the Maudsley personality inventory and striatal dopamine D2/D3 receptor availability of healthy Chinese community subjects. *European Psychiatry: The Journal of the Association of European Psychiatrists*. 2006; 21: 62–65. <https://doi.org/10.1016/j.eurpsy.2005.05.004> PMID: 16137865
2. Reeves SJ, Mehta MA, Montgomery AJ, Amiras D, Egerton A, Howard RJ, et al. Striatal dopamine (D2) receptor availability predicts socially desirable responding. *NeuroImage*. 2007; 34: 1782–1789. <https://doi.org/10.1016/j.neuroimage.2006.10.042> PMID: 17188897
3. Egerton A, Rees E, Bose SK, Lappin JM, Stokes PRA, Turkheimer FE, et al. Truth, lies or self-deception? Striatal D(2/3) receptor availability predicts individual differences in social conformity. *NeuroImage*. 2010; 53: 777–781. <https://doi.org/10.1016/j.neuroimage.2010.06.031> PMID: 20558302

4. Cervenka S, Gustavsson P, Halldin C, Farde L. Association between striatal and extrastriatal dopamine D2-receptor binding and social desirability. *Neuroimage*. 2010; 50: 323–8. doi:S1053-8119(09)01293-2 [pii] <https://doi.org/10.1016/j.neuroimage.2009.12.006> PMID: 20004254
5. Caravaggio F, Fervaha G, Chung JK, Gerretsen P, Nakajima S, Plitman E, et al. Exploring personality traits related to dopamine D2/3 receptor availability in striatal subregions of humans. *European Neuropsychopharmacology*. Elsevier; 2016; 26: 644–652. <https://doi.org/10.1016/j.euroneuro.2016.02.010> PMID: 26944295
6. Paulhus DL. Two-component models of socially desirable responding. *Journal of personality and social psychology*. American Psychological Association; 1984; 46: 598.
7. Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L. Distribution of D1-and D2-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 1994; 11: 245.
8. Vallone D, Picetti R, Borrelli E. Structure and function of dopamine receptors. *Neuroscience & Biobehavioral Reviews*. 2000; 24: 125–132. [https://doi.org/10.1016/s0149-7634\(99\)00063-9](https://doi.org/10.1016/s0149-7634(99)00063-9)
9. Plavén-Sigra P, Gustavsson P, Farde L, Borg J, Stenkrona P, Nyberg L, et al. Dopamine D1 receptor availability is related to social behavior: A positron emission tomography study. *Neuroimage*. 2014; 102: 590–595. <https://doi.org/10.1016/j.neuroimage.2014.08.018> PMID: 25134976
10. Couppis MH, Kennedy CH, Stanwood GD. Differences in aggressive behavior and in the mesocortico-limbic DA system between A/J and BALB/cJ mice. *Synapse*. 2008; 62: 715–724. <https://doi.org/10.1002/syn.20545> PMID: 18651644
11. Halldin C, Stone-Elander S, Farde L, Ehrin E, Fasth KJ, Langstrom B, et al. Preparation of <sup>11</sup>C-labelled SCH 23390 for the in vivo study of dopamine D-1 receptors using positron emission tomography. *Int J Rad Appl Instrum [A]*. 1986; 37: 1039–1043.
12. Gustavsson JP, Bergman H, Edman G, Ekselius L, Knorrning L von, Linder J. Swedish universities Scales of Personality (SSP): construction, internal consistency and normative data. *Acta psychiatrica Scandinavica*. 2000; 102: 217–225. PMID: 11008858
13. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. *Fsl*. *Neuroimage*. Elsevier; 2012; 62: 782–790. <https://doi.org/10.1016/j.neuroimage.2011.09.015> PMID: 21979382
14. Verhagen J, Wagenmakers E-J. Bayesian tests to quantify the result of a replication attempt. *Journal of Experimental Psychology: General*. American Psychological Association; 2014; 143: 1457.
15. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. *Nature*. *Nature Research*; 2012; 483: 531–533. <https://doi.org/10.1038/483531a> PMID: 22460880
16. Open-Science-Collaboration. Estimating the reproducibility of psychological science. *Science*. American Association for the Advancement of Science; 2015; 349: aac4716. <https://doi.org/10.1126/science.aac4716> PMID: 26315443
17. Benjamin DJ, Berger JO, Johannesson M, Nosek BA, Wagenmakers E-J, Berk R, et al. Redefine statistical significance. *Nature Human Behaviour*. 2017;
18. Berg J, Dickhaut J, McCabe K. Trust, reciprocity, and social history. *Games and economic behavior*. 1995; 10: 122–142.