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Aberrant type 2 dopamine receptor availability in violent offenders with psychopathy

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ABSTRACT

Psychopathy is characterized by antisocial behavior, poor behavioral control and lacking empathy, and structural alterations in the corresponding neural circuits. Molecular brain basis of psychopathy remains poorly characterized. Here we studied type 2 dopamine receptor (D2R) and mu-opioid receptor (MOR) availability in convicted violent offenders with high psychopathic traits (n = 11) and healthy matched controls (n = 17) using positron emission tomography (PET). D2R were measured with radioligand [^{11}C]raclopride and MORs with radioligand [^{11}C]carfentanil. Psychopathic subjects had lowered D2R availability in caudate and putamen, and striatal D2R availability was also associated with degree of psychopathic traits in this prisoner sample. No group differences were found in MOR availability, although in the prisoner sample, psychopathic traits were negatively correlated with MOR availability in the amygdala and nucleus accumbens. We conclude that D2R signaling could be the putative neuromolecular pathway for psychopathy, whereas evidence for alterations in the MOR system is more limited.

1. Introduction

Psychopathy is characterized by persistent antisocial behavior, disinhibited and egotistical traits, and impaired empathy and remorse (Cooke and Michie, 2001). It is a clinically important predictor for criminality and violence (Salekin et al., 1997) and its prevalence is around 15–25 % in incarcerated offenders (Hare, 1991). The pervasive nature of both behavioral and emotional symptoms suggest that psychopathy has organic basis, and multiple studies have found that psychopathic offenders have lower grey matter density frontal cortex and in limbic regions including insula and amygdala (Ermer et al., 2012; Johanson et al., 2020; Muller et al., 2008; Tiihonen et al., 2008; Yang et al., 2009). These structural impairments are coupled with abnormal functioning of the affective division in the limbic system. Psychopathic subjects show less affect-related activity in amygdala and hippocampus, striatum and cingulate cortices while viewing emotional facial expressions, and stronger activation of frontal cortical regions (Dolan and Fullam, 2009; Kiehl et al., 2001; Poeppl et al., 2019; Sun et al., 2022b). Conversely, fronto-insular functional responses are typically increased in psychopathy (Poeppl et al., 2019), particularly when viewing violent scenes (Nummenmaa et al., 2021). Finally, psychopathic individuals show dampened autonomic nervous system (but typical self-evaluative) reactivity to a variety of emotional stimuli, suggesting affective disengagement (Marsh, 2013; Patrick et al., 1993). However, neuromolecular pathways underlying psychopathy are poorly understood.

There exist no *in vivo* imaging studies on neurotransmission in psychopathic violent offenders, yet studies on aggression and impulsivity – central aspects of the psychopathic phenotype – point towards the putative role of the endogenous dopamine (DA) and mu-opioid receptor (MOR) systems in psychopathy. DA is critical for in behavioral control,

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appetitive motivation, reward expectancy and prediction errors (Schultz, 1998), and the striatal dopamine system is involved in impulsive behavior in rodents (Dalley et al., 2007) and humans (Volkow et al., 2009). Aberrant DA functioning may predispose individuals to impulsive aggression (Seo et al., 2008), and in rats increased striatal dopamine is associated with aggressive behavior (van Erp and Miczek, 2000). However, in humans midbrain dopamine synthesis capacity is negatively associated with aggressive behavior in humans (Schluter et al., 2013) and subjects with high impulsivity have lowered baseline postsynaptic type 2 dopamine receptor (D2R) levels coupled with elevated dopamine release when receiving rewards (Buckholtz et al., 2010b). Finally, healthy volunteers with high psychopathic traits show amplified dopamine release during reward anticipation, indicating a link between impulsivity, psychopathy, and dopaminergic function (Buckholtz et al., 2010a).

Data from both nonhuman primates (Fabre-Nys et al., 1982; Keverne et al., 1989; Meller et al., 1980) and humans suggest that the endogenous opioid system and particularly the mu-opioid receptors (MORs) support multitude of prosocial functions including social bonding and attachment (Nummenmaa et al., 2015, 2016; Nummenmaa and Tuominen, 2024; Sun et al., 2022a) and empathy (Karjalainen et al., 2017; Rutgen et al., 2015). Because psychopathy is consistently associated with antisocial and callous behaviour, it can be hypothesized that the psychopathic phenotype would be associated with downregulated opioidergic functioning (Bandelow and Wedekind, 2015; Tiihonen et al., 2020). However, *in vivo* imaging data on ORs in psychopathy are lacking.

1.1. The current study

Here we tested the contribution of dopaminergic and opioidergic neuroreceptor systems to criminal psychopathy. We used *in vivo* positron emission tomography (PET) and measured availability of postsynaptic type 2 dopamine and mu-opioid receptors in the brains of psychopathic violent offenders and healthy control subjects. We show that psychopathy is associated with downregulated striatal D2R availability, whereas the evidence for downregulation in the MOR system is more limited.

2. Methods and materials

2.1. Subjects

All subjects gave an informed, written consent and were compensated for their participation. The ethics board of the Hospital District of Southwest Finland approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. We studied 11 convicted violent male offenders with high psychopathic traits and 19 age and sex-matched control subjects (Table 1). Offenders were inmates from the Turku Prison currently serving a sentence for murder (n = 5), manslaughter (n = 5), attempted manslaughter (n = 3) or grievous bodily harm (n = 6). Mean recidivism rate was 2.4 times after first conviction. Prisoner subjects were screened for illicit drug use both in the screening interview and on the day of the PET scans. Details on medication and psychiatric diagnoses of the forensic subjects are presented **in Table S1**. Forensic subjects were escorted to the hospital imaging site by two prison guards who monitored the whole study protocol.

Psychopathy in the convicted offenders was assessed with the Hare Psychopathy Checklist Revised (PCL-R; Hare, 1991), based on semi-structured interview by an experienced forensic psychologist / psychiatrist and review of collateral information. The PCL-R measures two dimensions of psychopathic traits: Factor 1 (Emotional/Interpersonal) psychopathy involving inclination to lie, lack of remorse, and callousness, and Factor 2 (Lifestyle/Behavioral elements) involving impulsivity, short temper and low tolerance for frustration. Mean PCL-R score was 26 (range 20–36). Because the PCL-R is an extensive assessment yielding extremely low scores in typical population, benign variation in psychopathic traits in the non-convicted population were measured with the Levenson Self-Report Psychopathy Scale (LSRP; Levenson et al., 1995). This self-report instrument is based on the two-factor (Factor1: Emotional/Interpersonal; Factor 2: Lifestyle/Behavioral elements.) conceptualization of the PCL. The psychopathic population also completed the LSRP scale for the sake of comparison. One subject had incomplete items in the Factor 2 psychopathy scale items and was left out from the corresponding analyses. Autism-like traits were measured with AQ (Baron-Cohen et al., 2001) and were found to be substantially lower than what has been reported in ASD population (Table 1).

Table 1
Subject characteristics.

	Controls Mean (Std.)	Offenders Mean (Std.)
Age	29 (8)	30 (6)
n (males)	17	11
Education		
No graduation	0	1
Primary School	0	8
Second degree	9	2
University	8	0
Psychopathy		
PCL-R	–	26 (5) n = 11
LSRP Factor 1	22 (3) n = 17	31 (4) n = 10
LSRP Factor 2	13 (3) n = 17	20 (5) n = 10
Autism		
AQ	11 (4) n = 17	18 (7) n = 11
Handedness		
Right	14	9
Smoking		
n(daily smokers)	0	11

***Note*:** AQ = Autism Quotient, PCL-*R* = Psychopathy Checklist -revised, LSRP = Levenson Self-Report Psychopathy Scale,.

2.2. Data acquisition

PET imaging was carried out with GE Discovery VCT PET/CT scanner (GE Healthcare) in Turku PET center. MOR availability was measured with high-affinity agonist radioligand [^{11}C]carfentanil (Eriksson and Antoni, 2015) and D2R availability with high-affinity antagonist radioligand [^{11}C]raclopride (Farde et al., 1986). Synthesis of [^{11}C]carfentanil and [^{11}C]raclopride have been described previously (Kantonen et al., 2021; Karlsson et al., 2015). Both radioligands were administered as a rapid bolus injection, after which the radioactivity in the brain was measured for 51 min. Injected radioactivities are shown in Table 2.

The [^{11}C]carfentanil and [^{11}C]raclopride PET imaging were

Table 2
Group-wise injected radioligand activities and masses.

	Injected activity	Molar activity	Injected mass	rcp %	Injected mass / kg
[11C] carfentanil					
Mean (controls)	249.0	273.5	0.5	98.4	0.006
SD (controls)	10.9	129.2	0.3	0.3	0.004
Mean (prisoners)	254.4	252.8	0.5	98.4	0.006
SD (prisoners)	14.5	109.1	0.3	0.4	0.004
[11C] raclopride					
Mean (controls)	257.2	294.7	0.5	98.9	0.006
SD (controls)	9.1	192.8	0.4	0.4	0.005
Mean (prisoners)	260.7	277.1	0.5	98.8	0.006
SD (prisoners)	8.3	132.3	0.4	0.5	0.005

performed on the same day > 2.5 h apart. All PET images were reconstructed using 13 time frames (3 × 1 min, 4 × 3 min, 6 × 6 min; total of 51 min). High-resolution anatomical T1-weighted images was obtained with 3T PET-MRI scanner (Philips Ingenuity TF PET-MR device, Philips Healthcare, Best the Netherlands) for reference and normalization purposes.

2.3. PET preprocessing and modelling

PET images were preprocessed in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) using Magia pipeline (Karjalainen et al., 2020) (https://github.com/tkkar jal/magia), which utilizes SPM12 (The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London) in the PET data motion correction, image registration and Freesurfer in automated ROI delineation. Six bilateral regions of interest (ROI) including amygdala, caudate, globus pallidus, nucleus accumbens, putamen, and thalamus were extracted from MRI by using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). Additionally, for investigating the MOR availability, we chose six other ROIs (dorsal and rostral anterior cingulate cortices, orbitofrontal cortex, posterior cingulate cortex, insular cortex and hippocampus) that have high MOR levels. Regions for reference tissue input required in kinetic modelling (cerebellum for [^{11}C]raclopride and occipital cortex for [^{11}C]carfentanil) were automatically corrected for specific radioligand binding, as described previously (Karjalainen et al., 2020).

Regional specific binding of [^{11}C]raclopride and [^{11}C]carfentanil was quantified as nondisplaceable binding potential (BP_{ND}) using simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996). Parametric BP_{ND} images were also calculated for voxel level analysis with basis function implementation of SRTM (bfSRTM) with 300 basis functions. Lower and upper bounds for theta parameter were set to 0.082 1/min and 0.6 1/min for [^{11}C]raclopride and 0.06 1/min and 0.6 1/min for [^{11}C]carfentanil. Before the parametric image calculation, the dynamic PET images were smoothed using Gaussian kernel with 4 mm full width at half maximum to reduce the effect of noise in voxel-level bfSRTM fit. The resulting parametric images were further normalized into MNI152 space and smoothed again using Gaussian 4 mm filter.

2.4. Statistical analysis

Univariate statistical analyses for the ROI data were performed with R software (version 3.5.1). The normality distribution of the data was evaluated with the Shapiro-Wilk test and checked visually with density and Q-Q plots. The effect of subject group on regional BP_{ND} was investigated using independent samples t-test. The correlational analyses between psychopathy scores and regional radioligand availability were analyzed with Pearson's correlation test. Full-volume analysis of the smoothed [^{11}C]raclopride and [^{11}C]carfentanil images were performed with SPM12 software https://www.fil.ion.ucl.ac.uk/spm/software/spm12/. The difference between prisoners and control subjects were investigated also in voxel level with Student's *t*-test. Voxel-by-voxel associations between BP_{ND} and psychopathy scores (PCL and SRPS) were assessed with multiple regression in SPM12. The results were corrected for multiple comparisons by using false discovery rate (FDR) at $p < 0.05$.

3. Results

Mean MOR and D2R availability in the groups is shown in Fig. 1. The ROI analysis (Fig. 2 and **Table S-2**) revealed significantly lower D2R availability in the psychopath group in putamen and dorsal caudate. Exploratory hemisphere-specific analysis found significant effects for D2R bilaterally in putamen and in right caudate (**Table S-3**). These effects were also confirmed in the full-volume SPM analysis (Fig. 3). The ROI analysis (Fig. 3 and **Table S-4**) did not reveal group differences in MOR availability. No significant effects were found in the exploratory hemisphere-specific analysis (**Table S-5**). The SPM analysis revealed only increased MOR availability in the psychopath group in the dorsal part of the brainstem / ventral thalamus, but this effect was not significant after correcting for multiple comparisons.

Practically all the prisoners had history of substance abuse and there were also more smokers in the prisoners versus control group. Because both smoking and substance use may influence dopaminergic function (Ashok et al., 2019; Volkow et al., 2009), the different patterns of current smoking and past drug abuse might explain the between-groups differences. To rule this possibility out, we conducted supplementary regional analysis within the offender group, where we predicted regional D2R and MOR availabilities with the psychopathy scores. This analysis (Fig. 4) yielded consistently negative correlations between psychopathy and D2R availability. For the SRPS total score, the associations were significant in amygdala and nucleus accumbens; the effect for factor 2 psychopathy were also significant in the same areas. Similar analysis conducted with the PCL-R scores did not yield statistically significant effects. For healthy controls, no associations between SRPS scores and D2R availability were found.

Complementary voxel level correlation analysis also suggested that SRPS total scores were negatively associated with D2R availability in the striatum in the prisoner group (Fig. 5**A**). Interestingly, in the prisoner group, PCL-R was negatively associated with MOR availability in the frontal lobe, and SRPS secondary scores were positively associated with

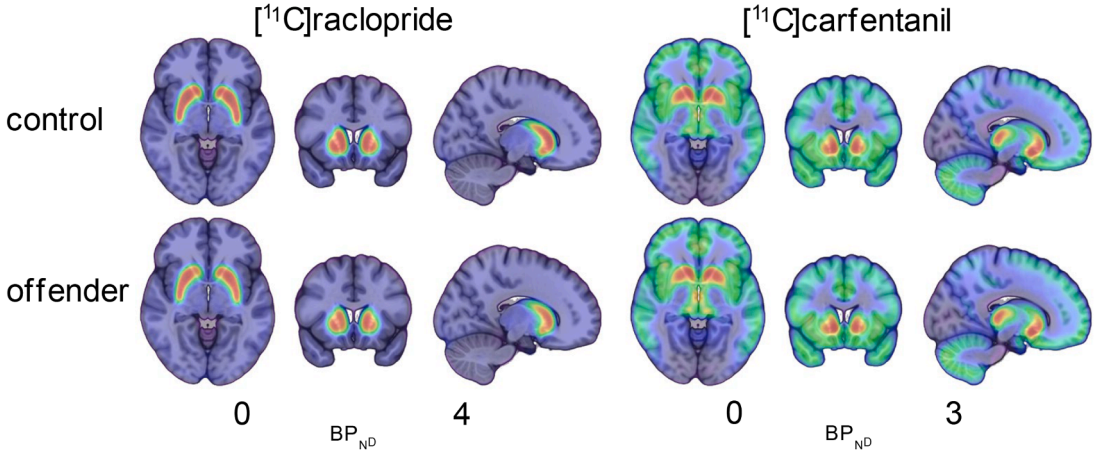

Fig. 1. Mean D2R and MOR availability in the control and prisoner groups.

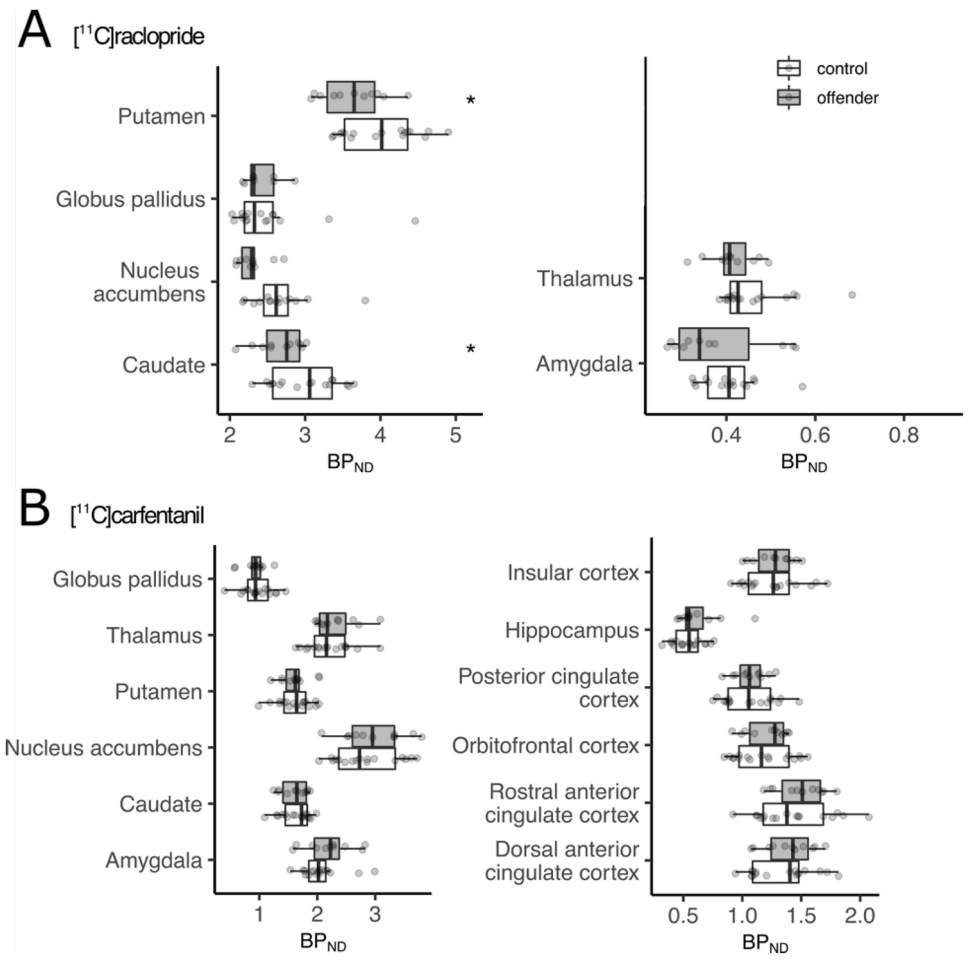

Fig. 2. Regional group differences in (A) D2R and (B) MOR availability between control subjects and prisoners. Significant group differences are denoted with asterisk.

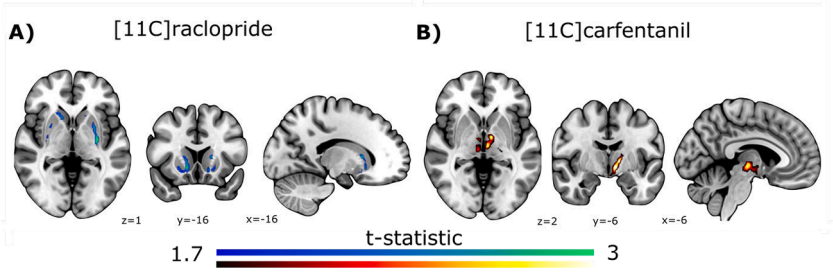

Fig. 3. Differences between control subjects and prisoners in A) D2R and B) MOR availability. D2R results are FDR corrected at $p < 0.05$ (small volume correction within striatum and pallidum was utilized), whereas MOR results are shown uncorrected. Cool colours indicate regions with higher BPND in healthy controls versus prisoners, whereas hot colours indicate regions with higher BPND in prisoners versus controls.

MOR availability in thalamus (Fig. 5B and C).

4. Discussion

Our main finding was that psychopathy among violent offenders is associated with lower striatal D2R availability. This effect was observed both in the direct comparison between healthy controls and subjects with psychopathy as well as correlational analysis between psychopathic traits and D2R availability in the prisoner population. There were no statistically significant differences in the MOR availability between the groups, but within-group analysis for the prisoner group revealed that MOR availability in ventral striatum and midbrain was positively correlated with psychopathic traits. These results show that aberrant D2R function is linked with criminal psychopathy, potentially explaining the aggressive and violent tendencies in this group.

4.1. Striatal dopaminergic downregulation in criminal psychopathy

Antisocial behaviour, lack of inhibition and low empathy are all distinctive traits of psychopathy, and the first two of these traits have consistently been linked with dopaminergic neurotransmission. The dopamine system is involved in motivated behavior (Ikemoto and Panksepp, 1999), behavioral control and particularly encoding reward prediction errors (Schultz, 2006). Previous PET studies have shown that

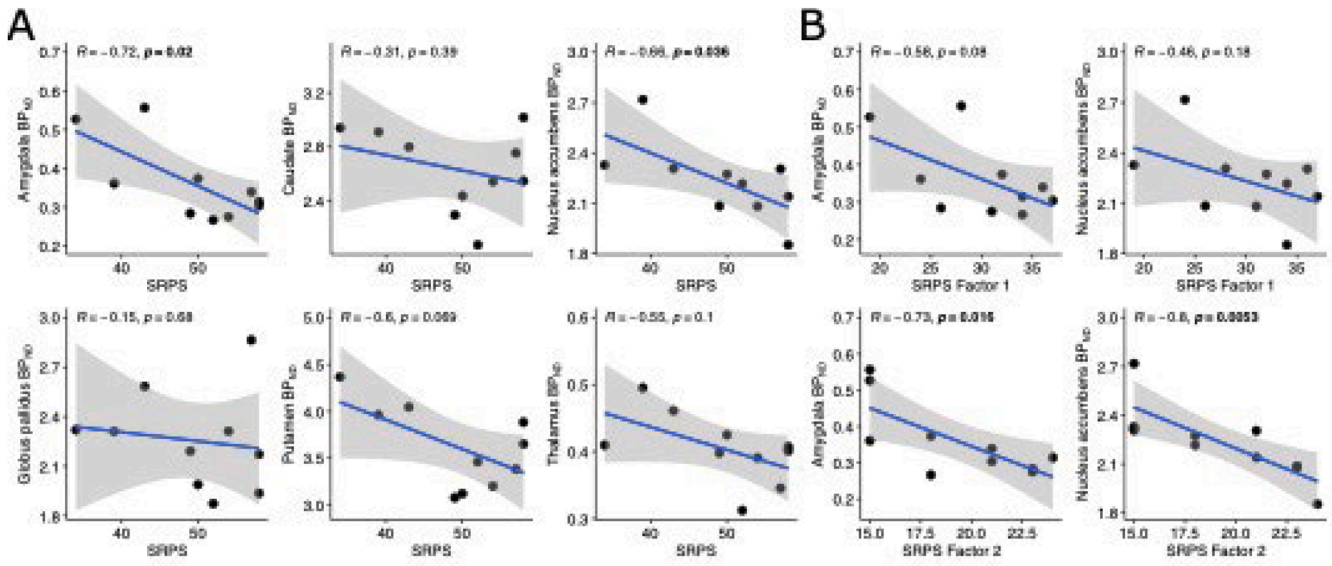

Fig. 4. Scatterplots with LS-regression lines and 95 % confidence intervals illustrating (A) the association between SRPS total scores and regional D2R availability, and (B) the association between D2R availability and Factor 1 and 2 psychopathy dimensions measured with SRPS within in the prisoner group.

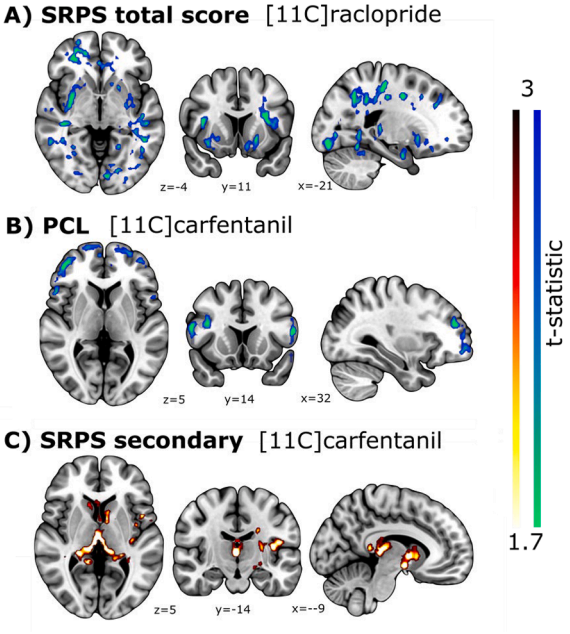

Fig. 5. (A) Voxel level correlation between D2R availability and SRPS total scores in the prisoner group. (B) Voxel level correlation between MOR availability and PCL-R in the prisoner group. (C) Voxel level correlation between MOR availability secondary SPRS in the prisoner group. The results were corrected for multiple comparisons by using FDR at $p < 0.05$. Cool colors indicate a negative association and hot colors a positive association.

in noninstitutionalized subjects, low dopamine synthesis capacity as measured with FDOPA-PET is associated with impulsive/reactive aggression in laboratory tasks (Schlüter et al., 2013). Additionally, impulsive subjects have lowered D2R baseline availability, but exhibit increased dopamine release during reward reception (Buckholtz et al., 2010b). In line with these data, second-generation antipsychotics such as clozapine, which occupy D2R transiently are also effective in reducing aggression in addition to their antipsychotic effects (Frogley et al., 2012; Krakowski et al., 2006). Accordingly, the presently observed D2R dysregulation in criminal psychopathy might also reflect aggression-related traits.

Subjects with psychopathy had most consistently lowered D2R availability in striatum, a high-binding site for [^{11}C]raclopride (Malén et al., 2022). This effect was observed both in the FDR-corrected full-volume analyses and also in the region-of-interest analyses although the regional effects did not survive multiple comparison correction. Structural and functional imaging studies have however not consistently found altered structure or function of striatum in psychopathy (De Brito et al., 2021; Deming and Koenigs, 2020; Poeppl et al., 2019). This likely reflects the lacking molecular specificity of these approaches, as well as the fact that the fMRI studies do not necessarily directly tap striatally mediated aspects of psychopathy. The striatal effects for lowered D2R availability however accord with the putative role of striatum in antisociality (Glenn and Yang, 2012). In antisocial individuals, striatum may not be flexibly encoding to altered reward value and particularly lack of reward in the environment. This may explain why healthy subjects with psychopathic traits show increased dopamine release during reward (Buckholtz et al., 2010a). Accordingly, the lowered baseline D2R availability might predispose psychopathic individuals to impulsive sensation-seeking and antisocial behavior for triggering sufficient reward signaling in the striatum.

Correlation analyses within the psychopathy group revealed associations between striatal D2R availability and LPRS scores, suggesting that the severity of psychopathic traits is associated with larger down-regulation in D2R availability. Surprisingly, similar association was not observed with the PCL-R scores, although this instrument is considered as the gold standard in assessing psychopathy. We have no clear explanation for this pattern – the sample size ($n = 11$) is small for correlational analysis to begin with, and the correlations are thus sensitive to small variations in the analyzed variables. We however stress that the group comparisons constituted our primary analysis, and that the correlational analyses within the psychopathy group should be interpreted cautiously as they were primarily conducted as secondary tests to account for the differences in smoking, medication, and psychiatric diagnoses between the groups. Yet, even this test should be interpreted with caution, as our study did not involve non-psychopathic offender group. It is thus possible that the observed alterations in D2R may pertain some general tendency for extreme antisocial / impulsive / violent behaviour independently of psychopathy, as studies have established that dopaminergic neurotransmission is involved in modulating impulsive behaviour in humans (Volkow et al., 2009). This issue thus needs to be addressed in future studies. The present study was the

first multi-ligand PET study on D2R / MOR alterations in psychopathy, and we wanted to minimize the radiation load caused to the subjects, thus only one group of psychopathic offenders was recruited.

Unlike for impulsivity and aggression, the evidence for the role of D2R in empathy and related socioemotional functions is less consistent. PET-MRI fusion imaging work has shown that specifically MOR but not D2R system is involved in empathy for pain (Karjalainen et al., 2017). However, in monkeys, access to social contact increases D2R levels and in humans social bonding may be mediated via D2R (Atzil et al., 2017; Morgan et al., 2002). Accordingly, the presently observed D2R downregulation might pertain atypical socioemotional functioning in psychopathy. In sum, the most parsimonious explaining for the present findings may be that they reflect the joint contribution of D2R to the core manifestations of psychopathy including impulsivity, aggression, and aberrant socioemotional function.

4.2. Endogenous mu-opioid receptor system and psychopathy

Because imaging studies have consistently implicated elevated MOR availability in trait prosociality and empathy (Karjalainen et al., 2017; Manninen et al., 2017; Nummenmaa et al., 2015; Turtonen et al., 2021) and as genetic studies also implicate the contribution of MORs in psychopathy (Tiihonen et al., 2020) we expected that the low trait empathy in psychopathy would link with lowered MOR availability. Against our predictions we observed no differences in MOR availability between the groups with the a priori statistical threshold. Weak evidence for MOR upregulation (rather than expected downregulation) in psychopathy was only found when lenient, uncorrected statistical thresholding was used. This result was however corroborated in the correlational analyses within the incarcerated sample, which confirmed that secondary psychopathic traits (pertaining to impulsivity and hostility) were positively associated with MOR availability in striatum, midbrain, and thalamus.

Because prior PET work has shown that impulsivity-related traits are associated with elevated MOR availability (Karjalainen et al., 2016; Love et al., 2009), the present results may imply that MOR downregulation in psychopathy reflects psychopathy-related impulsiveness, rather than aberrant social cognition and affect. The present data thus show that associations between MOR function and extreme antisocial behaviour are nuanced. This may also reflect the complex patterns of aberrant socioemotional functioning in psychopathy. For example, psychopathic individuals show reduced frontocortical empathy responses in comparison with healthy controls (Decety et al., 2013), but this may only relate to spontaneous empathy. When deliberately asked to empathize with others, psychopathic individuals show nearly normal responses in the brain's social perception and empathy networks (Meffert et al., 2013). In future it would thus be important to assess specifically the molecular alterations behind the different (primary and secondary) subtypes of psychopathy.

4.3. Limitations

We did not have the information about genetic profile of the subjects and could not directly assess whether the alterations of D2R availability are genetic; this kind of genotyped imaging study would however require substantially larger sample for sufficient statistical power. Similarly, we cannot address the exact role of experience-dependent plasticity in the observed alteration in the D2R system. Because the study was cross-sectional it cannot show whether there is a causal link between psychopathy and D2R availability. Future studies could address this by, for example, evaluating the effects of dopaminergic drugs on aggression, violence and callous behaviour in psychopathic individuals-Alternatively, longitudinal studies could use non-invasive measurements (such as neuromelanin-sensitive MRI; see Cassidy et al., 2019) of dopamine levels in children with callous-unemotional traits and subsequently assess whether childhood dopamine levels are indicative of psychopathy in adulthood.

Although we aimed at recruiting prisoner volunteers not using antipsychotics, antidepressants, or anxiolytics, it was not possible to recruit a completely drug-naive sample. Despite terminating all possible drugs during the study, this may confound the results either directly or indirectly. All prisoners were regular cigarette smokers, whereas none of the controls were (11/11 vs 0/17), and the sample size was finally limited due to the complicated recruitment and measurement protocols in the prison environment. Our results thus need to be replicated using larger samples with wider range pf PCL-scores while matching for nicotine use across groups. Education levels should also be matched more carefully across groups, and ideally a non-psychopathic offender group should be included to make strictly psychopathy-related conclusions regarding the results. Although there is evidence on the acute effects of smoking on dopaminergic activity, meta-analytic data shows that the long-term effects of smoking pertain only to dopamine transporters and not D2/3R availability (Ashok et al., 2019), which was measured in the present studies so this is unlikely to confound with the results. Moreover, correlational analysis within the forensic sample only also corroborated the association between psychopathy and D2R function.

4.4. Conclusions

We conclude that criminal psychopathy is linked with downregulated D2R, whereas the contribution of MOR system is more subtle, highlighting the role of D2R in aggression and antisocial behavior in general. Together with the abnormal frontotemporal metabolism is consistently linked with violence (George et al., 2004; Raine et al., 1997, 1994, 1998; Volkow et al., 1995), the lowered D2R availability may contribute to impulsive, atypical sensation seeking and violence in psychopathy. Altogether these data show that dysfunctional dopamine system contributes to the psychopathic phenotype and support the idea that dopamine antagonists might be an effective treatment for violent psychopathy.

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Data and code availability

Per national legislation, sensitive medical data cannot be distributed even anonymously. Other data and code are available from the first author upon request.

Ethics approval

The ethics board of the Hospital District of Southwest Finland approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki.

Consent to participate

All subjects gave an informed, written consent and were compensated for their participation.

CRediT authorship contribution statement

Lasse Lukkarinen: Investigation, Writing – original draft, Writing – review & editing. **Jouni Tuisku:** Investigation, Methodology, Writing – original draft, Writing – review & editing, Formal analysis. **Lihua Sun:** Investigation, Writing – original draft, Writing – review & editing. **Semi Helin:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **Henry K. Karlsson:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **Niina Venetjoki:**

Investigation. **Marja Salomaa:** Investigation. **Päivi Rautio:** Investigation. **Jussi Hirvonen:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Hannu Lauerma:** Conceptualization, Writing – original draft, Writing – review & editing. **Jari Tiihonen:** Conceptualization, Writing – original draft, Writing – review & editing. **Lauri Nummenmaa:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors disclose no conflict of interest

Data availability

The authors do not have permission to share data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120724.

References

Ashok, A.H., Mizuno, Y., Howes, O.D., 2019. Tobacco smoking and dopaminergic function in humans: a meta-analysis of molecular imaging studies. Psychopharmacol. (Berl.) 236, 1119–1129.

Atzil, S., et al., 2017. Dopamine in the Medial amygdala network mediates human bonding. Proc. Natl. Acad. Sci., 201612233

Bandelow, B., Wedekind, D., 2015. Possible role of a dysregulation of the endogenous opioid system in antisocial personality disorder. Hum. Psychopharmacol.: Clin. Exp. 30, 393–415.

Baron-Cohen, S., et al., 2001. The Autism-Spectrum Quotient (Aq): evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J. Autism. Dev. Disord. 31, 5–17.

Buckholtz, J.W., et al., 2010a. Mesolimbic Dopamine reward system hypersensitivity in individuals with psychopathic traits. Nat. Neurosci. 13, 419–421.

Buckholtz, J.W., et al., 2010b. Dopaminergic network differences in human impulsivity. Science 329, 532.

Cassidy, C.M., et al., 2019. Neuromelanin-Sensitive Mri as a noninvasive proxy measure of dopamine function in the human brain. Proc. Natl. Acad.Sci. 116, 5108.

Cooke, D.J., Michie, C., 2001. Refining the construct of psychopathy: towards a hierarchical model. Psychol. Assess. 13, 171–188.

Dalley, J.W., et al., 2007. Nucleus Accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315, 1267–1270.

De Brito, S.A., Mcdonald, D., Camilleri, J.A., Rogers, J.C., 2021. Cortical and subcortical gray matter volume in psychopathy: a voxel-wise meta-analysis. J. Abnorm. Psychol. 130, 627–640.

Decety, J., Skelly, L.R., Kiehl, K.A., 2013. Brain Response to empathy-eliciting scenarios involving pain in incarcerated individuals with psychopathy. JAMa Psychiatry 70, 638–645.

Deming, P., Koenigs, M., 2020. Functional neural correlates of psychopathy: a meta-analysis of Mri Data. Transl. Psychiatry 10, 133.

Dolan, M.C., Fullam, R.S., 2009. Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. Biol. Psychiatry 66, 570–577.

Eriksson, O., Antoni, G., 2015. [11c]Carfentanil Binds Preferentially to Mu-Opioid Receptor Subtype 1 Compared to Subtype 2. Mol. ImAging 14, 476–483.

Ermer, E., et al., 2012. Aberrant paralimbic gray matter in criminal psychopathy. J. Abnorm. Psychol. 121, 649–658.

Fabre-Nys, C., Meller, R.E., Keverne, E.B., 1982. Opiate antagonists stimulate affiliative behaviour in monkeys. Pharmacol. Biochem. Behav. 16, 653–659.

Farde, L., Hall, H., Ehrin, E., Sedvall, G., 1986. Quantitative Analysis of D2 dopamine receptor binding in the living human brain by pet. Science 231, 258–261.

Frogley, C., Taylor, D., Dickens, G., Picchioni, M., 2012. A systematic review of the evidence of clozapine's anti-aggressive effects. Int. J. Neuropsychopharmacol. 15, 1351–1371.

George, D.T., et al., 2004. A Select Group of perpetrators of domestic violence: evidence of decreased metabolism in the right hypothalamus and reduced relationships between cortical/subcortical brain structures in position emission tomography. Psychiatry Res. NeuroimAging 130, 11–25.

Glenn, A.L., Yang, Y., 2012. The potential role of the striatum in antisocial behavior and psychopathy. Biol. Psychiatry 72, 817–822.

Hare, R.D., 1991. Manual For the Hare Psychopathy Checklist-Revised. Multi-Health Systems, Toronto.

Ikemoto, S., Panksepp, J., 1999. The Role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res. Brain Res. Rev. 31, 6–41.

Johanson, M., Vaurio, O., Tiihonen, J., Lähteenvuo, M., 2020. A systematic literature review of neuroimaging of psychopathic traits. Front. Psychiatry 10, 1027.

Kantonen, T., et al., 2021. Obesity risk is associated with altered cerebral glucose metabolism and decreased mu-opioid and cb1-receptor availability. Int. J. Obes. 46, 400–407.

Karjalainen, T., et al., 2017. Dissociable roles of cerebral mu-opioid and type 2 dopamine receptors in vicarious pain: a combined pet-fmri study. Cereb. Cortex (New York, NY: 1991) 1–10.

Karjalainen, T., et al., 2020. Magia: robust automated modeling and image processing toolbox for pet neuroinformatics. Front. Neuroinform., 604835

Karjalainen, T., et al., 2016. Behavioural activation system sensitivity is associated with cerebral μ-opioid receptor availability. Soc. Cogn. Affect. Neurosci. 11, 1310–1316.

Karlsson, H.K., et al., 2015. Obesity is associated with decreased mu-opioid but unaltered dopamine D-2 receptor availability in the brain. J. Neurosci. 35, 3959–3965.

Keverne, E.B., Martensz, N.D., Tuite, B., 1989. Beta-endorphin concentrations in cerebrospinal-fluid of monkeys are influenced by grooming relationships. Psychoneuroendocrinology. 14, 155–161.

Kiehl, K.A., et al., 2001. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol. Psychiatry 50, 677–684.

Krakowski, M.I., et al., 2006. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch. Gen. Psychiatry 63, 622–629.

Lammertsma, A.A., Hume, S.P., 1996. Simplified reference tissue model for pet receptor studies. Neuroimage 4, 153–158.

Levenson, M.R., Kiehl, K.A., Fitzpatrick, C.M., 1995. Assessing psychopathic attributes in a noninstitutionalized population. J. Pers. Soc. Psychol. 68, 151–158.

Love, T.M., Stohler, C.S., Zubieta, J.K., 2009. Positron emission tomography measures of endogenous opioid neurotransmission and impulsiveness traits in humans. Arch. Gen. Psychiatry 66, 1124–1134.

Malén, T., et al., 2022. Age and Sex dependent variability of type 2 dopamine receptors in the human brain: a large-scale pet cohort. Neuroimage.

Manninen, S., et al., 2017. Social laughter triggers endogenous opioid release in humans. J. Neurosci. 37, 6125–6131.

Marsh, A.A., 2013. What can we learn about emotion by studying psychopathy? Front. Hum. Neurosci. 7, 181.

Meffert, H., et al., 2013. Reduced spontaneous but relatively normal deliberate vicarious representations in psychopathy. Brain 136, 2550–2562.

Meller, R.E., Keverne, E.B., Herbert, J., 1980. Behavioral and endocrine effects of naltrexone in male talapoin monkeys. Pharmacol. Biochem. Behav. 13, 663–672.

Morgan, D., et al., 2002. Social dominance in monkeys: dopamine d2 receptors and cocaine self-administration. Nat. Neurosci. 5, 169–174.

Muller, J.L., et al., 2008. Gray matter changes in right superior temporal gyrus in criminal psychopaths. evidence from voxel-based morphometry. Psychiatry Res. NeuroimAging 163, 213–222.

Nummenmaa, L., et al., 2021. Brain basis of psychopathy in criminal offenders and general population. Cereb. Cortex.

Nummenmaa, L., et al., 2015. Adult Attachment style is associated with cerebral μ-opioid receptor availability in humans. Hum. Brain Mapp. 36, 3621–3628.

Nummenmaa, L., et al., 2016. Social Touch Modulates Endogenous M-Opioid System Activity in Humans. Neuroimage 138, 242–247.

Nummenmaa, L., & Tuominen, L.J. (in press). Opioid System and Human Emotions.

Patrick, C.J., Bradley, M.M., Lang, P.J., 1993. Emotion in the criminal psychopath - startle reflex modulation. J. Abnorm. Psychol. 102, 82–92.

Poeppl, T.B., et al., 2019. A View Behind the Mask of Sanity: meta-analysis of aberrant brain activity in psychopaths. Mol. Psychiatry 24, 463–470.

Raine, A., Buchsbaum, M., Lacasse, L., 1997. Brain abnormalities in murderers indicated by positron emission tomography. Biol. Psychiatry 42, 495–508.

Raine, A., et al., 1994. Selective reductions in prefrontal glucose-metabolism in murderers. Biol. Psychiatry 36, 365–373.

Raine, A., et al., 1998. Reduced Prefrontal and Increased Subcortical Brain Functioning Assessed Using Positron Emission Tomography in Predatory and Affective Murderers. Behav. Sci. Law 16, 319–332.

Rutgen, M., et al., 2015. Placebo Analgesia and its opioidergic regulation suggest that empathy for pain is grounded in self pain. Proc. Natl. Acad. Sci. U S. A 112, 5638–5646.

Salekin, R.T., Rogers, R., Sewell, K.W., 1997. Construct validity of psychopathy in a female offender sample: a multitrait-multimethod evaluation. J. Abnorm. Psychol. 106, 576–585.

Schluter, T., et al., 2013. The Impact of Dopamine on Aggression: an F-18 -Fdopa Pet Study in Healthy Males. J. Neurosci. 33, 16889–16896.

Schlüter, T., et al., 2013. The Impact of Dopamine on Aggression: an [18f]-Fdopa Pet Study in Healthy Males. J. Neurosci. 33, 16889.

Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27.

Schultz, W., 2006. Behavioral theories and the neurophysiology of reward. Annu. Rev. Psychol. 57, 87–115.

Seo, D.J., Patrick, C.J., Kennealy, P.J., 2008. Role of serotonin and dopamine system interactions in the neurobioloy of impulsive aggression and its comorbidity with other clinical disorders. Aggress. Violent. Behav. 13, 383–395.

Sun, L., et al., 2022a. Mu-opioid receptor system modulates responses to vocal bonding and distress signals in humans. Phil Trans B B 377, 20210181.

Sun, L., et al., 2022b. Aberrant motor contagion of emotions in psychopathy and high-functioning Autism. Cereb. Cortex 33, 374–384.

Tiihonen, J., et al., 2020. Neurobiological Roots of Psychopathy. Mol. Psychiatry 25, 3432–3441.

Tiihonen, J., et al., 2008. Brain anatomy of persistent violent offenders: more rather than less. Psychiatry Res. Neuroimaging 163, 201–212.
Turtonen, O., et al., 2021. Adult attachment system links with brain μ-opioid receptor availability in vivo. Biol. Psychiatry.
Van Erp, A.M.M., Miczek, K.A., 2000. Aggressive behavior, increased accumbal dopamine, and decreased cortical serotonin in rats. J. Neurosci. 20, 9320–9325.
Volkow, N.D., et al., 2009. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. 56, 3–8.
Volkow, N.D., et al., 1995. Brain glucose metabolism in violent psychiatric patients: a preliminary study. Psychiatry Res.: Neuroimaging 61, 243–253.
Yang, Y.L., et al., 2009. Localization of Deformations within the Amygdala in Individuals with Psychopathy. Arch. Gen. Psychiatry 66, 986–994.