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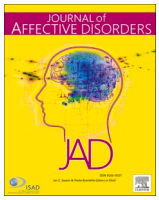

Research papers



Associations between polygenic risk for anhedonia and functional brain activity during reward processing

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ABSTRACT

Anhedonia is an important symptom in major mental disorders and is difficult to address due to a limited understanding of its neurobiological and genetic underpinnings. Here, we investigated the effect of a polygenic risk score (PRS) for anhedonia on brain activation during a well-established monetary incentive delay (MID) task, while performing functional magnetic resonance imaging. We derived an anhedonia PRS from a large genome wide analysis (n = 375,275) in our sample of 517 subjects. This sample consisted of four subgroups (healthy controls (n = 373), major depressive disorder (n = 57), schizophrenia (n = 39) and bipolar disorder (n = 48)). We tested for correlation between the individual PRS and brain activation during reward and during loss anticipation and feedback. Additionally, we analysed the correlation between PRS and structural volume size of three reward-related brain areas as well as between PRS and anhedonia scores. We showed that increased PRS was associated with decreased activation in bilateral putamen and left middle frontal gyrus during anticipation and decreased activation in the right caudate during feedback across all subgroups. Moreover, a higher PRS was also correlated with lower activation in left middle frontal gyrus during loss anticipation and salience processing. During loss feedback, higher PRS was correlated with hyperactivity of bilateral putamen and right caudate. No significant correlation was found between PRS and brain volume or anhedonia scores. Our results highlight the importance of the striatum and prefrontal cortex in the context of a genetic risk for anhedonia.

1. Introduction

Transdiagnostic studies of mental disorders have recently gained momentum since the introduction of approaches like the Research Domain Criteria (RDoC) (Morris and Cuthbert, 2012), which aims to develop neurobiologically informed constructs of mental disorders. In this context, anhedonia as a transdiagnostic symptom can be subsumed under the Positive Valence Domain and can be related to a dysfunctional reward network with abnormalities in structure and function of several key reward-related brain areas (Der-Avakian and Markou, 2012; Höflich et al., 2019).

Thus, anhedonia is not only a frequent symptom of severe mental disorders like major depressive disorder (Lambert et al., 2018; Whitton and Pizzagalli, 2022), schizophrenia (Lambert et al., 2018), bipolar disorder (Whitton and Pizzagalli, 2022) or substance abuse disorder (Destoop et al., 2019), but might also be the result of a shared neural dysfunction between these disorders (Der-Avakian and Markou, 2012). Therefore, it is important to study the neurobiological foundation of anhedonia across disorders. By this approach, it might be possible to improve stratification of mental disorders and finally be able to target subgroups or biological phenotypes beyond DSM-classification more precisely. For this purpose, it might also be helpful to understand how aberrant brain structure and function are influenced by genetic risk for anhedonia as a basic unit of analysis in the RDoC-framework.

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Most consistently, the mesolimbic reward network, including the ventral striatum as a central hub in this network, has been found to be attenuated in anhedonic populations. Anhedonia has been associated with (ventral) striatal hyporeactivity in response to reward cues (anticipatory anhedonia) and to reward feedback (consummatory anhedonia) (Corral-Frías et al., 2015; Zhang et al., 2016). More specifically, associations have been found within the ventral striatum (Carl et al., 2016; Corral-Frías et al., 2015; Keller et al., 2013; Wacker et al., 2009), caudate (Zhang et al., 2013) or putamen (Auerbach et al., 2017; Schaub et al., 2021).

To a lesser extent, there is also evidence for an association with other reward-related brain areas, e.g. the dorsal anterior cingulate cortex (dACC), and anticipatory anhedonia (Liu et al., 2021; Zhang et al., 2016). Prefrontal areas such as the orbitofrontal cortex (OFC) (Cressman et al., 2015; Liu et al., 2021) or middle frontal gyrus (MFG) (Zhang et al., 2016) have also been implicated to be modulated by anhedonia, although neuroimaging findings are not consistent (Der-Avakian and Markou, 2012).

However, while neuroimaging has underlined the key role of reward-related brain areas to anhedonia, the causal links to changes, that were outlined above, still remain unclear. Imaging Genetics approaches might contribute to disentangling the causal role of genetic variation in risk and severity of mental disorders as well as to stratifying subgroups. Recently, progress has been made by using polygenic risk scores (PRS) for correlation analyses between genetic risk and psychiatric diseases such as schizophrenia (SCZ) (Alnæs et al., 2019; Erk et al., 2017; Lancaster et al., 2016), and to a minor extent major depressive disorder (MDD) (Schmaal et al., 2017) and bipolar disorder (BPD) (Abé et al., 2021). However, transdiagnostic symptoms such as anhedonia have rarely been distinctly studied in Imaging Genetics studies. Investigating the role of genetic risk in anhedonia might however be an advancement, since there is good evidence that genetic risk (Anttila et al., 2018; Cattarinussi et al., 2022) as well as transdiagnostic symptoms such as anhedonia overlap in SCZ, MDD and BPD (Lambert et al., 2018; Whitton and Pizzagalli, 2022).

Studying genetic associations can include either candidate genes or a PRS, which aggregates the effects of several thousands of uncorrelated single nucleotide polymorphisms (SNPs) across the whole genome to estimate an individual's genetic predisposition to a specific phenotype. For anhedonia, associations between candidate genes and neuronal processes have been elusive, with few underpowered exceptions (Bondy and Bogdan, 2022).

In contrast, two recent reports have linked a PRS for anhedonia to variability in parameters of brain structure, including total gray matter volume, cortical thickness and volumes of reward-related brain areas (Ward et al., 2019; Zhu et al., 2021). Ward et al. (Ward et al., 2019) were the first to perform a genome-wide association study (GWAS) for anhedonia in a sample of 375,275 UK Biobank participants. Both reports used a PRS derived from this GWAS and showed that a higher PRS was associated with reduced volumes in reward-related brain areas. These comprised the insula, OFC, the MFG, the anterior temporal fusiform cortex, and as well at a lower significance level the Ncl. accumbens, medial frontal cortex and caudate (Ward et al., 2019). Zhu et al., who investigated the effects of the same anhedonia-PRS on global brain structure metrics, found correlations between a PRS for anhedonia and reduced total gray matter volume, increased white matter volume and reduced cortical thickness within the parahippocampal cortex, superior temporal gyrus and insula (Zhu et al., 2021).

In the present study, we investigated the role of a PRS for anhedonia in functional brain activity during a well-established functional magnetic resonance imaging (fMRI)-based reward task, the MID task (Kirsch et al., 2003; Knutson et al., 2000). To our knowledge, this is the first attempt to investigate the effect of a PRS for the transdiagnostic symptom anhedonia on fMRI activity. Using imaging genetics methods, we sought to contribute to the analysis of functional brain abnormalities in anhedonia by focusing on genetic influences. We focused on anhedonia because numerous studies have demonstrated its strong association with dysfunctions in reward processing and particularly by employing the MID task. In contrast, other negative symptoms such as avolition or asociality are more difficult to quantify and analyse, and they have been studied predominantly in schizophrenic patients only (Der-Avakian and Markou, 2012; Strauss and Cohen, 2017). We employed a similar approach to Ward et al. by calculating a PRS based on their original anhedonia GWAS. We hypothesized that attenuation of functional activity in reward-related brain areas, particularly in the striatum, would be associated with an increased PRS for anhedonia.

2. Methods

2.1. Sample/subjects

All subjects were part of the IntegraMent and MooDs sample, a multisite, cross-diagnostic neuroimaging study recruiting a total of 974 subjects (Erk et al., 2017). Subjects underwent an fMRI reward task and were genotyped (see below). Questionnaires that were used in this study were the Symptom-Checklist-90 (SCL-90), a widely used tool for the evaluation of self-reported psychopathological symptoms (Derogatis et al., 1976). Imaging data, genotyped data and questionnaires were available for 517 subjects in total. The 517 subjects included in this study comprised healthy controls ($n = 243$), healthy first-degree relatives of patients with MDD ($n = 61$), SCZ ($n = 31$) and BPD ($n = 38$) and patients with SCZ ($n = 39$), MDD ($n = 57$) and BPD ($n = 48$). Patients were included to investigate the effect of PRS in the three subgroups post hoc in case of a positive finding for the whole group, since all patient subgroups have significantly higher levels of anhedonia compared to the general population (Lambert et al., 2018; Whitton and Pizzagalli, 2022). It is important to note that healthy relatives of patient groups were not related to patients in this sample and were included in the control group.

All subjects provided written informed consent, and the study was approved by the local ethics committee. All patients were diagnosed according to Structured Clinical Interview for DSM Disorders I (SCID-I) by trained clinical professionals.

2.2. Anhedonia scores

As the sample was not assessed with a specific anhedonia questionnaire, we calculated an anhedonia score from three anhedonia symptoms as assessed by the SCL-90 via a principal component analysis. The three items were loss of sexual interest (item 5), loss of energy or feeling of slow thinking/movements (item 14) and feeling of (a general) loss in interest (item 32) during the last 14 days. First, we tested the data for suitability for a principal component analysis (PCA) by Bartlett's test and Kaiser-Mayer-Olkin criteria. Bartlett's test of sphericity showed that variables were significantly divergent ($p < 0.001$). Kaiser-Mayer-Olkin Measure of Sampling Adequacy showed the overall value of 0.67 and each single item was above the recommended value of 0.5. The subsequent PCA yielded one factor explaining 69 % of the total variance. The factor scores for each subject were then used as anhedonia proxies in the downward analysis. This procedure has been adapted from Yang et al. (Yang et al., 2020) and was performed in R Statistical Software v4.2.0 (R Core Team, 2021).

2.3. Genotypes QC and imputation

All subjects were genotyped by using the same genotyping platform, PsychArray-24 BeadChips (Illumina, San Diego, CA, USA), and underwent the same quality control procedures. The genotype quality control of 974 genotyped subjects (MooDs $n = 621$, IntegraMent $n = 353$) was performed using the Ricopili Pipeline (Lam et al., 2020) using following standard parameters for retaining subjects and SNPs: SNP missingness <0.05 (before sample removal); subject missingness <0.02; autosomal heterozygosity deviation ($|\text{Fhet}| < 0.2$); SNP missingness <0.02 (after

sample removal); difference in SNP missingness between cases and controls <0.02; SNP Hardy-Weinberg equilibrium ($P > 10^{-6}$ in controls or $P > 10^{-10}$ in cases) and male subjects with heterozygosity rate for chromosome X > 0.5 and females subjects <0.5.

13 subjects were excluded due to SNP missing >0.02. 11 subjects were excluded as population outliers in a principal component analysis (with principal component 1 < −0.1 and two with principal component 2 > 0.1) (Lett et al., 2020).

Genotype imputation was performed using the pre-phasing/imputation stepwise approach implemented in EAGLE (Loh et al., 2016)/MINIMAC3 (Das et al., 2016; Howie et al., 2012) (with a variable chunk size of 132 genomic chunks and default parameters). The imputation reference set consisted of 54,330 phased haplotypes with 36,678,882 variants from the publicly available HRC reference (European Genome-Phenome Archive, 2016; Lett et al., 2020).

The relatedness was tested using a subset of 65,833 SNPs (common between both studies, i.e. MooDs and IntegraMent) obtained with a stringent quality criterion (INFO >0.8, missingness <1 %, minor allele frequency > 0.05) and by applying a LD pruning (r2 > 0.02). The analysis revealed 13 pairs of related and 19 overlapping samples (20 pairs within each study and 12 pairs between both studies).

2.4. Calculation of PRS for anhedonia

We obtained the summary statistics of the largest available anhedonia GWAS (sample size 375,275) (Ward et al., 2019). The summary statistics were then LD-pruned and clumped by discarding variants within 500 kb of, and in r2 ≥ 0.1 with another (more significant) marker. These LD-independent SNPs were used as weights to perform PRS estimation in subjects from both cohorts. The PRS was calculated for each subject using the -score and -q-score-range function in Plink v2.0 (Chang et al., 2015; Purcell, 2015). Scores were calculated for 10 different *p*-value thresholds, ranging from $p = 1$ to $p < 5e^{-8}$ (≈0.0017). Lower p-value thresholds include fewer SNPs, resulting in a more specific score, but might not include all relevant SNPs. The threshold yielding the highest model fit (R^2) with the anhedonia score was selected for the subsequent fMRI analyses. For the best model fit, the first 6 genetic principal components (to account for population stratification), age, site, sample, sex, and diagnostic subgroups for whole group analysis were included as covariates.

2.5. Experimental paradigm

In this study, the MID task was used as an experimental paradigm to evoke reward anticipation and reward feedback phases (Fig. S1). This task is adapted from a well-established reward task of Kirsch et al. (Kirsch et al., 2003). In the adapted task, subjects are presented in each trial with a cue that announces either monetary reward (arrow upwards), monetary loss (arrow downwards), no reward/neutral cue (double-headed horizontal arrow) or a cue for verbal trials (double-headed vertical arrow). Subjects had then to react to a visual target with a button press. In the neutral trials, no button press was required. After that, subjects are presented with their reward feedback (reward or loss of 2€; feedback of missed reward; feedback of loss omission; neutral feedback; verbal feedback ("you reacted fast" or "you reacted slow"). Each condition is presented 10 times in a pseudorandomized order and the response time window was adapted to individual reaction times to assure that all subjects had a similar amount of rewarding and loss trials.

2.6. fMRI data acquisition and preprocessing

Functional MRI data were acquired using 3 T Siemens Trio scanners (Siemens Medical Systems) at the Central Institute of Mental Health Mannheim, at Charité - Universitätsmedizin Berlin and at the Life and Brain Centre of the University of Bonn. All sites followed the same imaging protocol. Functional images were acquired using an echo-planar imaging (EPI) sequence (TE: 30 ms, TR: 2 s, α: 90°, matrix: 64 × 64, FOV: 192 × 192 mm, in-plane resolution: 3 × 3 mm, slice thickness: 4 mm, gap: 1 mm, 28 axial slices, 267 volumes).

Images were preprocessed by using HALFpipe, a software that uses fmriPrep for preprocessing and NiPype as its working engine (HALFpipe, 2022; Waller et al., 2022). Preprocessing steps included motion correction, normalization, slice timing, smoothing with a kernel of FWHM of 6 mm, grand mean scaling with a factor 10,000 and applying a high pass band filter of 125 s.

Quality control was performed in HALFpipe and excluded subjects with a mean voxel-based framewise displacement (FD) >3 mm.

2.7. fMRI analysis

First level and group level analysis of fMRI data were performed in SPM12 (SPM12, 2014).

A general linear model was set up with four cue regressors (reward anticipation, loss anticipation, neutral cue, verbal cue), a target and balance regressor (for neutral trial, when no button press is required) and six feedback regressors (reward feedback, loss feedback, verbal reward feedback, verbal loss feedback, feedback of missed reward and feedback of loss omission). All regressors were convolved with a canonical hemodynamic response function (HRF) and the model was adjusted with six motion regressors.

Since some subjects did not have reward or loss feedback trials, we decided to separately run and analyse anticipation and feedback phases. In the anticipation model, data was available for 517 subjects and in the outcome model, data was available for 497 subjects. The two models had identical task regressors in the general linear model (four cue regressors, target, balance and six feedback regressors), only the analysed contrasts differed. For the anticipation model, the analysed contrasts were cue_win>cue_loss and cue_win>cue_control for reward anticipation, cue_loss>cue_control for loss anticipation, and cue_win+cue_loss>cue_control for salience processing. Neutral cues and verbal cues were combined as control cues to increase statistical power. For the outcome model, the contrasts were defined as hit>miss (reward feedback+omission of loss feedback > feedback of missed reward+loss feedback), win>no_win (reward feedback > feedback of missed reward), loss>no_loss (loss feedback > feedback of loss omission), win>loss (reward feedback > loss feedback). The verbal feedback trials were not analysed in our study.

2.8. Statistical analysis

Contrast images from first level analyses were entered in multiple regression analyses in SPM12 (SPM12, 2014) with PRS as well as the first six genetic principal components, site, sex, age, and subgroup status as covariates. Multiple regressions were performed on the entire sample and if significant, further multiple regressions were also run for the different subgroups. Direct correlation analyses between task activation and self-reported anhedonia scores in our sample will be reported elsewhere (Daniels et al., 2025).

We additionally performed multiple regression analyses between clusters of task activation that correlated with PRS and anhedonia scores, as well as multiple regression analysis between PRS and anhedonia scores.

Clusters of task activations were extracted in SPM12 by cluster extraction function and mean parameter estimates of these clusters were entered into multiple regressions with anhedonia scores in R Statistical Software v4.2.0 (R Core Team, 2021). Finally, we also tested for correlations between structural volume size of a priori defined ROIs (only caudate, putamen and Ncl. accumbens) and PRS by using partial correlation analysis, controlling for intracranial volume, sex, age, subgroup status and the first six genetic principal components. Structural volume sizes were extracted by procedures explained in an earlier study (Lett et al., 2020) and correlation analyses were performed in R Statistical

Software v4.2.0 (Abé et al., 2021; R Core Team, 2021).

A priori ROIs were defined as Ncl. accumbens, caudate, putamen and middle frontal gyrus (MFG), which is part of the dorsolateral prefrontal cortex (DLPFC) (Fig. S2). We chose these ROIs, as previous evidence relates these ROIs to anhedonia (Zhang et al., 2016), and their volume correlated with the anhedonia-PRS in the previous study by Ward et al. (Ward et al., 2019). The ROI masks were extracted from the MNI-template MNI125NLin2009cAsym with the help of a software tool that provides templates for alignment (Ciric et al., 2021).

Multiple Regression analyses were small volume corrected for the predefined masks, with a p(FWE) < 0.05 threshold. Since we tested four ROIs on both brain hemispheres, which equals 8 tests, we had to correct for multiple comparisons. This was done by Bonferroni correction by dividing the significance level of 0.05 by the number of tests.

As medication is a potential confounder in psychiatric subgroups, we analysed if results correlated with medication status. For this we employed a similar approach to Hassel et al. and Schwarz et al. (Hassel et al., 2008; Schwarz et al., 2022). For antipsychotic drugs, we calculated chlorpromazine dose equivalents (CPZ-e) for the mean effective daily dose (ED50), as has been investigated by Davis and Chen (Davis and Chen, 2004). Drugs were coded as zero if absent, if a drug was below or the same as the ED50 of chlorpromazine, it was coded as low (= 1), and if a drug was above the ED50 of chlorpromazine, it was coded as high (= 2). Antidepressant and other psychotropic drugs were similarly coded as absent = 0, low dose = 1, high dose = 2, based on scores by Sackeim (Sackeim, 2001). This resulted in two scores, CPZ-e scores and total medication load for each subject. However, the medication status was only available for the Mannheim subsample (n = 59). We then correlated these two scores with second-level cluster estimates of the significant results, using Spearman's correlation (alpha = 0.05).

3. Results

3.1. Sample characteristics

The sample included 517 subjects in four diagnostic subgroups (n (Control) = 373, n(MDD) = 57, n(BPD) = 48, n(SCZ) = 39). Groups differed significantly in their distribution of age, site, handedness and anhedonia scores (Table 1). In the outcome model of the MID task, data were only available for 497 subjects (n(Control) = 360, n(MDD) = 52, n (BPD) = 48, n(SCZ) = 37) (Table S1). No relevant differences in the distribution of sample characteristics were present between the anticipation and the outcome model.

3.2. Task effects

The MID task elicited the expected task activation during reward anticipation and feedback, as has been published in previous studies (Knutson et al., 2000). For reward anticipation, we observed significant activations in the ventral and dorsal striatum, thalamus, anterior cingulate cortex (ACC), OFC, MFG, supplementary motor cortex and visual cortex. For reward feedback, we found activation in the ventral and dorsal striatum, thalamus, ACC, OFC, MFG, and visual cortex.

The analysis of group differences in task activations and relationship between self-reported anhedonia and task activations has been analysed in our sample group in a previous paper (Daniels et al., 2025). They showed group differences in the task activation clusters, particularly in the bilateral putamen and between the control and SCZ group. Further, they showed an interaction effect between diagnostic group and self-reported anhedonia in the left putamen. This effect was primarily accounted for by a pronounced negative association between left putamen activity and anhedonia in MDD patients.

3.3. PRS correlation effects

The Polygenic Risk Score (PRS) did not correlate with the anhedonia score, which was based on a self-reported state anhedonia factor score. The best model fit explained 0.00157 R^2 variance, at a p-value-threshold of $p < 0.01$, but this was not significant ($p = 0.258$).

The PRS did not correlate with volumes of bilateral putamen, caudate or Ncl. accumbens (Table S2).

3.4. PRS correlation - anticipation model

During reward anticipation, PRS correlated negatively with left (T = 4.08, $p = 0.010$, FWE-ROI corrected) and right putamen ($T = 3.74$, p = 0.038, FWE-ROI corrected) activity and left MFG ($T = 3.82$, $p = 0.034$, FWE-ROI corrected) activity (Fig. 1, Table S3). The effect in the putamen was particularly pronounced in the BPD group and the effect in the MFG in the MDD group (Table S3).

Also, the PRS correlated negatively with MFG activity during loss anticipation ($T = 4.28$, $p = 0.006$, FWE-ROI corrected) and salience processing ($T = 4.42$, $p = 0.004$, FWE-ROI corrected) (Fig. 2, Tables S4 and S5). This effect survived correction for multiple comparisons ($p <$ 0.006). None of these correlation clusters was associated with the anhedonia score. Results of direct correlation analyses between self-reported anhedonia and task activity will be reported elsewhere (Daniels et al., 2025).

3.5. PRS correlation - outcome model

During reward feedback, PRS negatively correlated with right caudate activity ($T = 3.67$, $p = 0.032$, FWE-ROI corrected) (Fig. 3 and Table S6). This was particularly pronounced in the Control Group (Table S6).

During loss feedback, PRS positively correlated with right caudate (T = 3.90, $p = 0.015$, FWE-ROI corrected) and bilateral putamen (left putamen: $T = 3.69$, $p = 0.041$, FWE-ROI corrected and right putamen: T = 3.67, $p = 0.042$, FWE-ROI corrected) activity (Fig. 4 and Table S7). This effect was particularly strong in the Control Group and survived correction for multiple comparisons in the right caudate and putamen (p < 0.006).

Table 1
Sample characteristics in the anticipation model.

	Control (n = 373)	MDD (n = 57)	BPD (n = 48)	SCZ (n = 39)	Group differences
Age	31.83 ± 10.62	36.51 ± 12.45	36.46 ± 11.31	33.87 ± 9.35	$p < 0.001$ (F)
Sex (M / F)	216 / 157	35 / 22	24 / 24	24 / 15	$p = 0.079$ (x^2)
Site (Bonn / Berlin1 / Berlin2 / Mannheim)	181 / 127 / 41 / 24	0 / 0 / 33 / 24	0 / 0 / 28 / 20	0 / 0 / 25 / 14	$p < 0.001$ (x^2)
Handedness (R / L / A)	342 / 22 / 7	45 / 6 / 5	41 / 2 / 5	31 / 5 / 2	$p = 0.004$ (x^2)
CPZ-e (n = 59, only from Mannheim sample)	–	0.33 ± 0.64	1.29 ± 0.78	1.79 ± 0.66	p < 0.001(F)
Total medication load (n = 59, only from Mannheim sample)	–	1.50 ± 1.18	1.67 ± 1.06	0.50 ± 0.94	p < 0.001 (F)
Anhedonia score	−0.43 ± 0.39	1.31 ± 1.22	0.75 ± 1.49	0.61 ± 0.95	p < 0.001 (F)
PRS	0.12 ± 0.07	0.13 ± 0.07	0.13 ± 0.07	0.11 ± 0.08	$p < 0.368$ (F)

Values are presented as mean and standard deviation or n. For comparison of nominal data, chi-squared tests were performed and for ordinal data, Kruskal-Wallis tests were performed with an alpha-level of 0.05.
MDD: major depressive disorder, BPD: bipolar disorder, SCZ: schizophrenia, CPZ-e: chlorpromazine dose equivalents, PRS: polygenic risk score.

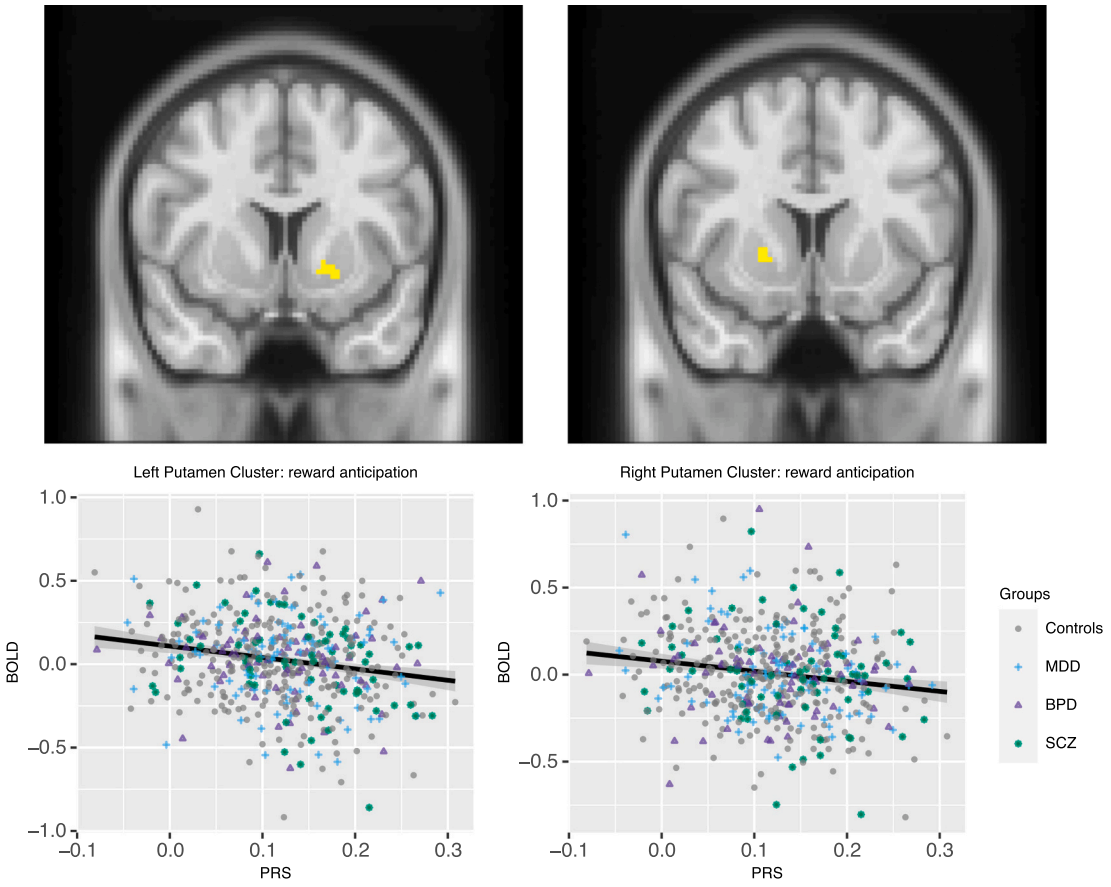

Fig. 1. Association between bilateral putamen activity and PRS for anhedonia during reward anticipation. The dark gray area in the regression plot represents 95 % confidence interval.

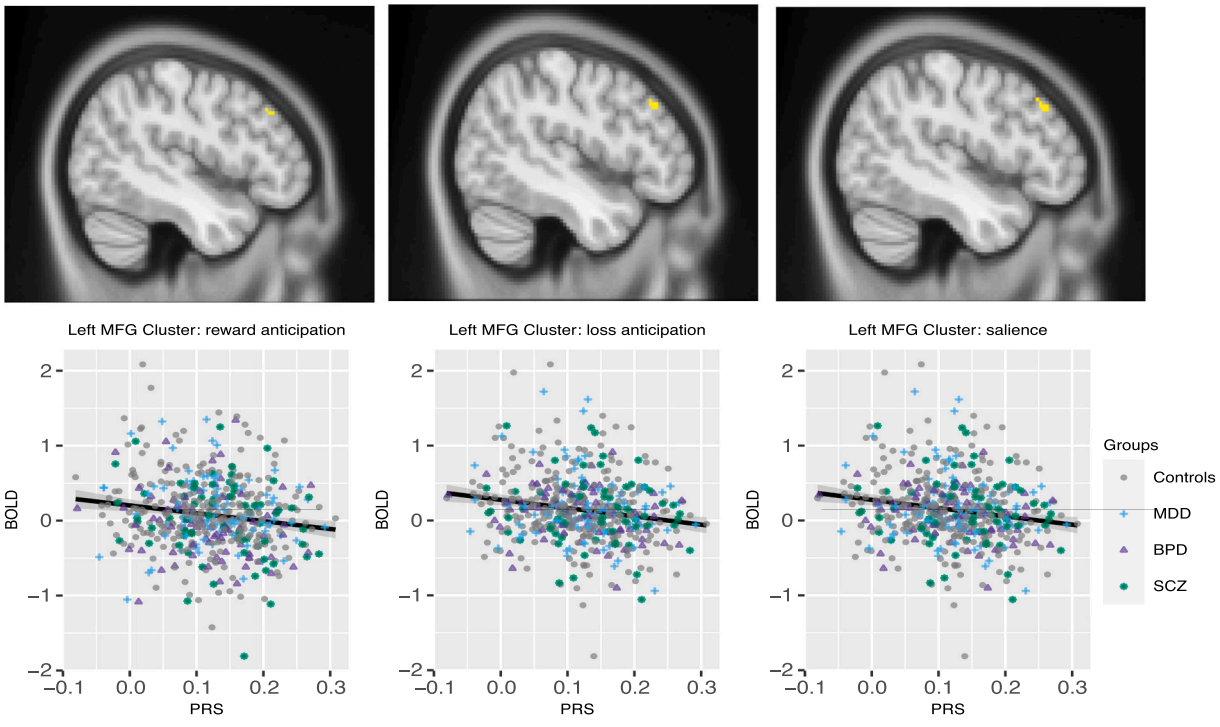

Fig. 2. Associations between PRS for anhedonia and BOLD effect during reward anticipation, loss anticipation and salience processing in left MFG. The dark gray area in regression plot represents 95 % confidence interval.

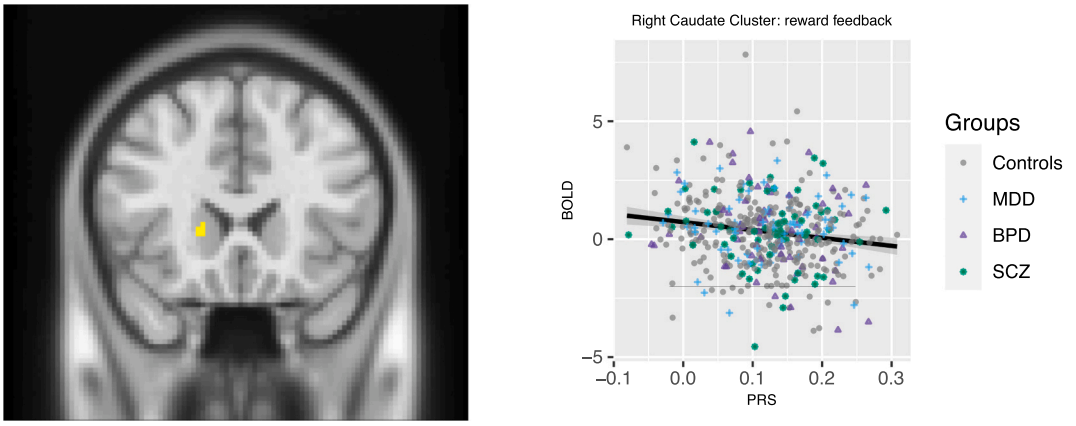

Fig. 3. Association between right caudate activity and PRS for anhedonia during reward feedback. The dark gray area in regression plot represents 95 % confidence interval.

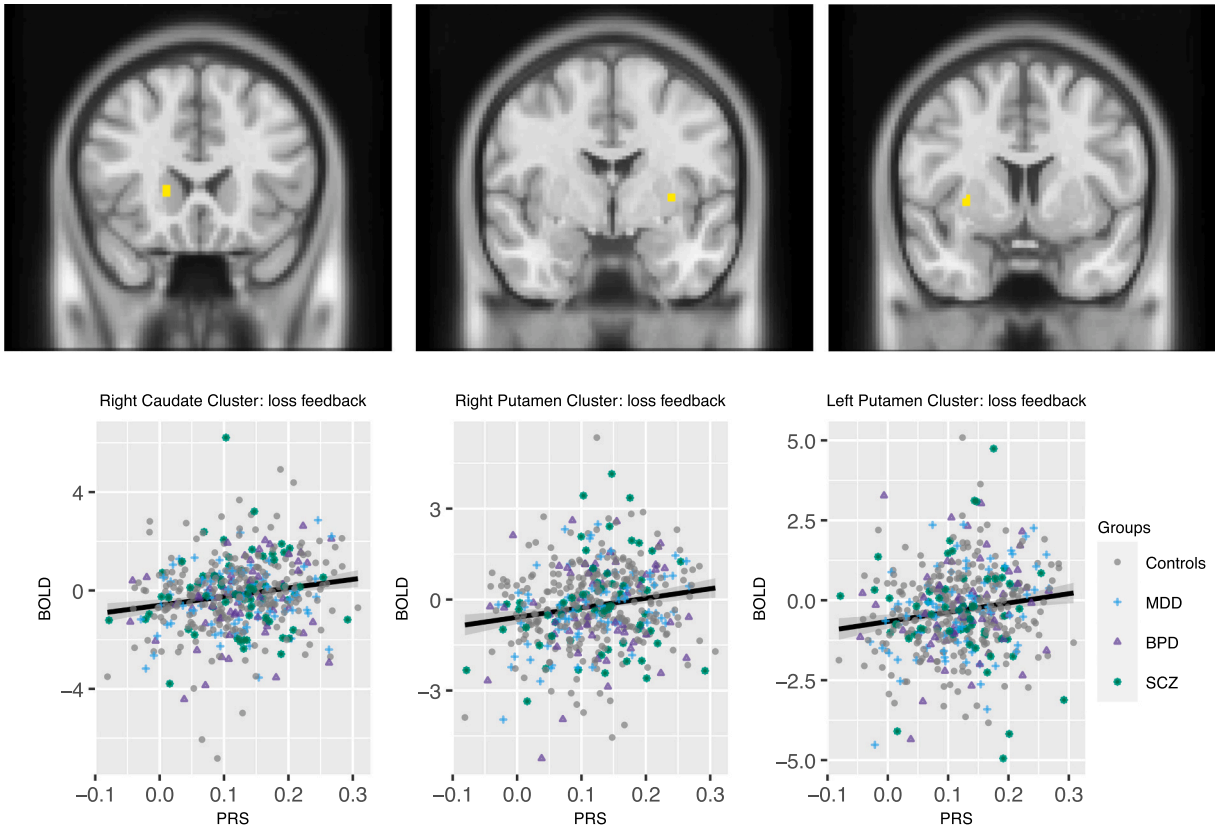

Fig. 4. Association between right caudate and bilateral putamen activity and PRS for anhedonia during loss feedback. The dark gray area in regression plot represents 95 % confidence interval.

Again, none of these correlation clusters were related to anhedonia scores.

3.6. Test for medication effect

Neither total medication load nor CPZ-e correlated with any second-level cluster estimates (Table S8).

4. Discussion

In our study, we attempted to test how polygenic risk for anhedonia affects brain activity during reward processing in a cross-diagnostic sample. We showed that a higher polygenic risk score was associated with attenuated activity during reward and loss anticipation as well as reward and loss outcome.

Our results during reward anticipation and feedback indicate the relevance of the striatum for the genetic risk for anhedonia. Aberrant activity in the striatum, during reward anticipation in the putamen and during reward feedback in the caudate, corresponds to recent findings from other studies. Structural neuroimaging studies have linked anhedonia to reduced volume in the striatum. Reduced Ncl. accumbens volume has been associated with increased anhedonia scores (Auerbach et al., 2017; Wacker et al., 2009). Bilateral putamen volume reduction predicted anhedonia (Auerbach et al., 2017) and correlated with

anhedonia scores in MDD, SCZ, BPD groups, among other psychiatric patient groups (Schaub et al., 2021). Further, reduced gray matter volume in the bilateral caudate was found in MDD (Enneking et al., 2019). In this study, we did not find any correlations between polygenic risk and structural volume size of caudate, putamen and Ncl. accumbens and thereby did not replicate some of the findings of Ward et al. (Ward et al., 2019). This might be due to low sample size, since the effect of polygenic risk for anhedonia on brain structure might be extremely small.

Functional imaging studies have shown that hypoactivity in the striatum during reward anticipation and outcome was associated with higher levels of anhedonia (Corral-Frías et al., 2015; Keller et al., 2013; Kim et al., 2020; Wacker et al., 2009). In a recent meta-analysis of neuroimaging studies of anhedonia in MDD and SCZ patients, anticipatory anhedonia correlated with decreased likelihood of activation in bilateral caudate head and left putamen and consummatory anhedonia with bilateral caudate head and body and left putamen (Zhang et al., 2016).

Further, there is evidence that therapeutic approaches in anhedonia might alleviate anhedonia by reducing hypoactivity in brain areas that were correlated to higher PRS for anhedonia in our study. For example, recent neuroimaging studies have shown that a treatment effect of ketamine is associated with increased activity in Ncl. accumbens and putamen (Kotoula et al., 2022) as well as with increased dACC and putamen activity (Lally et al., 2014). Also, dopaminergic drugs like bupropion (Goodwin et al., 2017) or methylphenidate (Rizvi et al., 2014) have been related to lower anhedonia levels and for the partial dopaminergic agonist drug aripiprazole, anhedonic reductions were correlated with increased striatal activations and functional connectivity between Ncl. accumbens and midcingulate cortex (Admon et al., 2017).

Hypoactivity in reward-related brain areas has been more broadly been described in psychiatric patients with MDD or SCZ (Lambert et al., 2018; Liang et al., 2022), especially in the striatum and prefrontal areas (Zhang et al., 2013). However, in our study we could not find any associations in the MDD and SCZ subgroup, except for a correlation between reward anticipation and right MFG activity in the MDD subgroup. This might be due to small sample sizes in these subgroups, but also anticipatory and consummatory phases of reward, which are tested in the MID task, might not be key to understanding anhedonia in these disorders. In a more refined anhedonia model, reward deficits are discussed to be also influenced by motivational and learning processes (Der-Avakian and Markou, 2012). Particularly, the motivation and effort necessary to obtain rewards, as well as reinforcement learning, e.g. by means of prediction error, might be more important to understand anhedonia in SCZ and MDD (Lambert et al., 2018).

For bipolar disorder, recent works stresses the role of a dysfunctional striatum (Abler et al., 2008; Rizvi et al., 2018). Especially the putamen has been observed to be attenuated and might even be used to differentiate BPD from MDD groups (Redlich et al., 2015; Wakatsuki et al., 2022). Interestingly, negative correlation between putamen activity and polygenic risk score during reward anticipation was particularly pronounced in the BPD subgroup in our sample.

Correlations between PRS and activity in the left middle frontal gyrus were small, but significant, also after correction for multiple comparisons, during reward and loss anticipation as well as salience processing in general. Similarly, in a previous study, left frontal gyrus has been associated with decreased activity during reward anticipation (Zhang et al., 2016).

In addition to our results during reward anticipation and outcome, we also found significant correlations between PRS and putamen and right caudate activity during loss feedback. Interestingly, these correlations were positive and only to be seen in the control group. It could be argued that a higher PRS for anhedonia might contribute to a greater sensitivity to reward loss. This hypothesis is supported by a study in which depressed subjects showed increased activity in the caudate during loss feedback (McCabe et al., 2009). Further, in a recent randomized controlled trial in healthy subjects, it was shown that a single dose of escitalopram decreased activity in the right caudate during loss feedback in the MID task (Lewis et al., 2021). It might be possible that higher caudate activity during reward loss correlates with a higher loss sensitivity, is a risk factor for depression and anhedonia and can be alleviated by antidepressants.

However, our data do not support this hypothesis as we did not find a positive correlation between PRS and brain activity during loss feedback in the psychiatric subgroups. Again, this might be due to small sample sizes in these subgroups in our sample. Also, other studies report no difference in striatal activity (Ubl et al., 2015) or even reduced activity in the caudate during loss outcome (Pizzagalli et al., 2009). Further research in the study of loss processing is needed to explain these diverging results.

Our results mainly strengthen our initial hypothesis that genetic risk for anhedonia might influence reward anticipation and outcome, particularly in the striatum, but also in prefrontal areas. To our knowledge, this is the first study that investigated a genetic risk score for anhedonia on functional activity during reward processing. Currently, there are only a few well-powered GWAS on anhedonia available and even less neuroimaging genetics studies testing the effect of single SNPs or PRS for anhedonia on brain structure and function. In this study, we employed a risk score derived from the largest yet GWAS on anhedonia yet (Ward et al., 2019). In their original paper, Ward et al. investigated a PRS based on their GWAS and found reduced volumes in reward-related areas, mainly in the OFC, MFG, insula, and anterior temporal fusiform cortex, and the but the Ncl. accumbens and caudate at an uncorrected level. Another related GWAS on food liking, i.e. preferring highly palatable food, which again had been associated with higher levels of anhedonia, was associated with lower volumes in bilateral putamen and caudate (May-Wilson et al., 2022).

As stated before, GWAS-supported single SNPs or PRS associated with anhedonia have not yet been tested on their effect in reward processing. However, there are a few imaging genetics studies indicating that SNPs, associated with disorders relevant to anhedonia like MDD, BPD and SCZ, affect striatal activity in a similar pattern as seen in anhedonia neuroimaging studies. For example, a recent PRS approach with 14 SNPs associated with MDD showed an association with reduced activity in Ncl. accumbens and putamen (Guffanti et al., 2019). In a different study, a PRS for SCZ was associated with attenuated striatal activity during reward feedback (Lancaster et al., 2019). Single SNP studies also report associations of risk or protective alleles for MDD, BPD or SCZ and striatal activity (Grimm et al., 2014; Ham et al., 2016; Lancaster et al., 2017; Trost et al., 2016; Wingo et al., 2017). Particularly, dopaminergic genes have also been studied with some robust findings. Risk alleles in dopaminergic genes have been associated with reduced activity in putamen and ventral striatum (Frank et al., 2018; Nikolova et al., 2011), especially alleles in the DRD2 gene. The DRD2 gene could be relevant to anhedonia, since one SNP in this gene was also genome-wide significant in the GWAS on anhedonia (Ward et al., 2019).

In summary, studies with various methodologies report evidence for neurobiological underpinnings of anhedonia and underline the role of deficits in reward-related brain areas. Furthermore, it is evident that genetic factors play a role from twin studies to recent GWAS, but it remains elusive which genes are involved and how they affect brain activity.

4.1. Strengths and limitations

This study has been to our knowledge the first one to investigate the effect of a polygenic risk score for anhedonia on functional activity during a reward-based fMRI task. We used a cross-diagnostic large sample and a well-established reward task to study genetic risk at a symptom-level, a comparably novel approach in line with the RDoC initiative.

However, while our findings generally align with recent

neuroimaging findings, we should point out that we would have expected a more decisive effect in our psychiatric disorder groups and had hoped to replicate some of the findings by Ward et al. (Ward et al., 2019). No correlation with higher genetic risk for anhedonia and brain activity was found for the SCZ subgroup and in the MDD and BPD group we only found an association during reward anticipation. Further, we did not observe any correlation between PRS and anhedonia scores or volumes of three important reward-related brain areas. Also, we could not find any mediation of anhedonia scores by PRS task activation cluster. This might also be related to three important general limitations in imaging genetics studies. First, our anhedonia score was based on SCL-90 questionnaire items and thus different than in the original GWAS study, where anhedonia was asked by a single question (Ward et al., 2019). In general, the construct anhedonia might be imprecise and there have been attempts to differentiate anhedonia for more neurobiologically-informed anhedonic subtypes (Der-Avakian and Markou, 2012; Treadway and Zald, 2011). Second, for studies of polygenic risk, sample sizes are key to obtain robust results. Especially in our psychiatric subgroups, sample sizes might have not been sufficient. Third, the effect of PRS on mediating anhedonia symptoms is likely to be small. Anhedonia is influenced by a wide range of environmental and biological factors, including psychosocial stress, early-life experiences including upbringing, but also inflammatory processes (Bekhbat et al., 2022; Harkness et al., 2022).

Another limitation of the present analysis is that the optimal *p*-value threshold for PRS construction was selected based on model performance within the same target dataset. This approach may lead to a modest overestimation of predictive accuracy due to overfitting. Future studies should include a replication cohort for the optimal p-value threshold.

Our decision to limit the analysis to specific regions of interest was driven by strong support from the literature, particularly in the GWAS discovery sample. This approach also reduced the number of statistical tests compared to a whole-brain analysis, thereby lowering the overall risk of false positive results. However, by limiting the analysis to specific brain regions instead of performing a whole-brain analysis, we might be missing true effects occurring outside our regions of interest.

5. Conclusion

It is becoming evident that genetic risk influences anhedonia and anhedonia itself is strongly related to aberrant reward processing. We tried to link these different strands together and found some evidence that polygenic risk for anhedonia might influence reward and loss anticipation as well as reward and loss feedback. In the future, we need to find better ways to calculate polygenic risk and test these scores on parameters of brain structure and function. In addition, we propose to investigate genetic risk on other anhedonia- and reward-related processes like reward learning and motivation. By this, we hope to find more neurobiologically informed ways to alleviate anhedonia in therapy.

CRediT authorship contribution statement

Nicholas Schäfer: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Swapnil Awasthi:** Writing – original draft, Formal analysis. **Stephan Ripke:** Supervision. **Anna Daniels:** Writing – review & editing, Methodology. **Andreas Meyer-Lindenberg:** Writing – review & editing, Supervision. **Heike Tost:** Writing – review & editing, Supervision. **Andreas Heinz:** Writing – review & editing. **Henrik Walter:** Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Susanne Erk:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

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Declaration of competing 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.jad.2025.120900.

Data availability

The datasets during the current study are not publicly available due to the presence of confidential patient information. However, the data may be made available by the corresponding author upon reasonable request.

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