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From brain to body: exploring the connection between altered reward processing and physical fitness in schizophrenia

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ABSTRACT

Understanding the underlying mechanisms that link psychopathology and physical comorbidities in schizophrenia is crucial since decreased physical fitness and overweight pose major risk factors for cardio-vascular diseases and decrease the patients' life expectancies. We hypothesize that altered reward anticipation plays an important role in this. We implemented the Monetary Incentive Delay task in a MR scanner and a fitness test battery to compare schizophrenia patients (SZ, $n = 43$) with sex- and age-matched healthy controls (HC, $n = 36$) as to reward processing and their physical fitness. We found differences in reward anticipation between SZs and HCs, whereby increased activity in HCs positively correlated with overall physical condition and negatively correlated with psychopathology. On the other handy, SZs revealed stronger activity in the posterior cingulate cortex and in cerebellar regions during reward anticipation, which could be linked to decreased overall physical fitness. These findings demonstrate that a dysregulated reward system is not only responsible for the symptomatology of schizophrenia, but might also be involved in physical comorbidities which could pave the way for future lifestyle therapy interventions.

1. Introduction

Schizophrenia, a severe and chronic mental disorder characterized by a range of cognitive, emotional, and behavioral disturbances, has long been associated with numerous physical health complications (Ryan and Thakore, 2002). In recent years, research has been indicating a strong link between schizophrenia and metabolic abnormalities, including obesity and decreased physical fitness (Ostermann et al., 2013), which – in turn - increase the risk of developing cardio-metabolic diseases, comprising type II diabetes or hypertension. While the patients' quality of life is already greatly reduced by symptoms such as disorganized thinking, psychosis or anhedonia, this co-occurrence of mental and physical health conditions poses significant challenges for patients, as it can exacerbate their overall well-being and lower their life expectancies (Ryan and Thakore, 2002; Hennekens et al., 2005; Schmitt et al., 2018).

Up to now, research has identified many potential mechanisms underlying this association between schizophrenia and reduced physical fitness, in particular obesity. Antipsychotic medication plays an important role as it has been shown to increase appetite and reduce sensation of satiety (Newcomer, 2007), thus resulting in weight gain, especially during the first 4 to 12 weeks of treatment (Tschoner et al., 2007). However, there is a growing body of evidence, indicating weight gain in drug-naive or first-episode psychosis patients (Thakore et al., 2002), shifting focus more to lifestyle, genetic factors and the illness neurobiology itself that render patients more susceptible and vulnerable to gaining weight (Grimm et al., 2017; Minichino et al., 2017). Reward functioning has emerged as a promising avenue of investigation, as it is known to be impaired in individuals with schizophrenia and further associated with positive and negative symptomatology (Juckel et al., 2006; Waltz et al, 2009). Dysfunctional reward processing in schizophrenia can manifest as altered sensitivity to reward and punishment (Moustafa et al., 2015), impaired reinforcement learning (Deserno et al., 2013), and disrupted functional connectivity patterns within reward circuitries (Koch et al., 2014; Sheffield et al., 2016). Research indicates that anhedonia, a core negative symptom of schizophrenia, is particularly related to diminished responses during reward anticipation rather than the outcome phase - the receipt of the reward (Strauss et al., 2014; Wulff et al., 2020; Zeng et al., 2022). This further underlines the impact of motivational deficits of patients in terms of decision making and

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seeking pleasure. Moreover, this motivational aspect of reward functioning plays a vital role in shaping behaviors and responses to stimuli, including food intake and physical activity (Gorrell et al., 2022).

Viewed from a molecular perspective, research has shown that the neurotransmitter dopamine plays a crucial role by mediating motivation towards rewards. While it is responsible for a variety of symptoms in schizophrenia – delusions and hallucinations amongst others – its dysregulation reduces the incentive properties of rewards in patients (McCutcheon et al., 2020). Due to its elevated background level, the phasic dopamine release during reward anticipation is overshadowed resulting in blunted striatal activity in patients with schizophrenia (Grace, 2016). Besides that, dopaminergic neurons, which originate in the ventral tegmental area, and its mesocorticolimbic projections to the ventral striatum and the ventromedial prefrontal cortex encode effort demands. This refers to the weighing of costs and benefits in decision-making and thus the motivational aspect controlling voluntary physical movement and eating behavior (Treadway et al., 2012; Ruiz--Tejada et al., 2022), which both include a rewarding component to ensure reinforcement. This explains engaging in motor activity and consecutive physical health requires a certain motivational drive.

However, no study has yet attempted to establish a link between altered dopaminergic reward processing, symptom severity and decreased physical fitness in schizophrenia.

We propose that altered reward processing influences the way individuals with schizophrenia respond to external stimuli, leading to maladaptive behaviors such as overeating and sedentary lifestyles. Therefore, by making use of a frequently used and well-established functional magnetic resonance imaging task (fMRI-task) - the Monetary Incentive Delay task (MID task; Knutson et al., 2000) - and a fitness test battery (Ruiz et al., 2011), we hypothesize that patients show a blunted activity in the reward system during reward anticipation, which further correlates with reduced physical fitness and increased symptom severity, compared to healthy controls.

Ultimately, a comprehensive understanding of the complex interplay between altered reward functioning, obesity, and decreased physical fitness is crucial to identify potential targets for future therapeutic lifestyle interventions that can improve the overall health and well-being of patients.

2. Methods

2.1. Participants

We matched 43 patients with schizophrenia (SZ) and 36 healthy controls (HC) as to sex and age. Demographics can be taken from Table 1. SZs were mainly recruited from the department of Psychiatry, Psychosomatic Medicine and Psychotherapy of the university clinic in Frankfurt am Main, Germany and psychiatric institutions of surrounding areas using flyers and web pages. Psychiatric diagnoses were based on DSM-V criteria and established by registered psychiatrists. SZs were included in the study if the following criteria were met: 1) diagnosis of schizophrenia; 2) no intake of benzodiazepines within the last two weeks; 3) history of stable medication for at least 4 weeks; 4) no physical impairments that would hinder the performance in the fitness test; 5) no history of neurological disorders; 6) no current alcohol or drug abuse; 7) no magnetic resonance imaging (MRI) contraindications. Inclusion criteria for HCs were the same, except for criteria 1) no history of psychiatric disorders in which case criterion 3 also becomes invalid. All participants provided written consent to the study protocol, approved by the institutional review board of the Goethe University Frankfurt. The study was registered at the German clinical study register (www.drks.de) with the number DRKS00023907.

2.2. Psychopathology assessment

To assess psychopathology and especially negative symptoms in both groups, we utilized the Chapman Scale for Physical and Social Anhedonia (PAS, SAS) (Chapman et al., 1976), the World Health Organization Disability Assessment Schedule (WHODAS) (Üstün, 2010) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993). Clinical symptoms within the patient group were additionally recorded by means of the standardized and structured Positive and Negative Syndrome Scale (PANSS) interview (Kay et al., 1987). All interviews were conducted by trained raters. All clinical characteristics of the study sample are summarized in Table 1.

Table 1
Sample characteristics with two-sample t-test and Mann-Whintey U test results, displaying group differences between patients and healthy controls.

	SZ $n = 43$		HC $n = 36$	
characteristics	mean	SD	mean	SD
males	28		26	
females	15		10	
age [years]	35.3	± 12.3	34.5	± 12.2
Smoking [packyears]	6.6*	± 11.8	1.8*	± 4.5
CPZeq	503.6	± 465.4		
PANSS	62.0	± 16.2		
PAS	12.2*	± 7.1	7.9*	± 4.6
SAS	11.7*	± 7	7.8*	± 5
WHODAS	34.5**	± 18.1	9.6**	± 9.5
CDSS	4.7**	± 3.3	1.4**	± 1.9
BMI	27.6*	± 5.1	25*	± 4.5
total body fat [%]	30.4*	± 8.2	25.2*	± 8.2
jump [cm]	147*	± 41	177*	± 42
handgrip [kg]	35.3*	± 10.2	40.8*	± 9.5
VO2max [ml O2/kg/min]	35.1*	± 10	41.1*	± 10
physical condition	0.27*	± 1	- 0.32*	± 0.86
physical fitness	- 0.28*	± 0.93	0.33*	± 1

Note: SZ, schizophrenia patients; HC, healthy controls; SD, standard deviation; CPZeq, chlorpromazine equivalent; PANSS, Positive and Negative Syndrome Scale; PAS/SAS, Physical and Social Anhedonia Scales; WHODAS, World Health Organization Disability Assessment Schedule; CDSS, Calgary Depression Scale for Schizophrenia.
*≤ .05; **≤ .001

2.3. Physical fitness test battery

Body fat was evaluated by using a skinfold caliper on seven anatomical points throughout the body, including the triceps, subscapular, biceps, abdominal, suprailiac, thigh, and calf. To apply the caliper about 1 cm away from the fingers the skin was pinched between thumb and index finger. Each skinfold was taken twice bilaterally throughout the body to calculate mean values, used for further analyses. Overall body fat percentage was determined, calculating body density first using age-specific formulas based on four skinfold measurements (triceps, biceps, subscapular, and suprailiac) following the methods and equations of Durnin and Womersley (1974), Siri (1993) and Brožek (Brožek et al., 1963).

The physical exercise segment involved two tests to assess muscular strength. The first test was a handgrip test using a Takei dynamometer (Takei Analogue Hand Grips Dynamo Meter, PS219A). Participants were instructed to squeeze the dynamometer as tightly as possible with one hand while keeping their arms extended next to their body. The test was repeated twice for each hand, and the average strength in kilograms was recorded.

To evaluate the muscular strength of the lower body, participants performed a standing long jump test. They started from behind a marker on the floor and were asked to engage their entire body to jump off using both legs simultaneously and landing on both feet at the end. Two attempts were made, and the better result in centimeters, measured from the marker to the back heel, was recorded.

To determine the participants' maximal oxygen capacity (VO2max), the Chester step test (Sykes and Roberts, 2004) was used. A pulse band was placed below the chest to monitor resting heart rate before the test.

Participants stepped on a 30 cm-step, moving one foot after the other according to a metronome's rhythm, which started at 60 beats per minute (bpm). The test consisted of five levels, with each level lasting for 2 minutes. The metronome's speed increased by 20 bpm with each level, reaching 140 bpm in level 5. The test was stopped if the participant completed a level where their heart rate reached 80 % of their age-related maximum heart rate (calculated as 0.8 x (220 - age)) or if they felt too exhausted to continue. Participants' exhaustion levels were assessed using the Borg Rating of Perceived Exertion (Borg, 1970) at each completed level. The aerobic capacity (VO2max in ml O2/kg/min) was then manually estimated by plotting the exercise heart rates from each level on a graphical datasheet and determining the intersection with the line of maximum heart rate (Sykes and Roberts, 2004).

The fitness test battery resulted in the following variables, used for further analysis: sum of all 7 skinfolds (mm), Body Mass Index (BMI), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), total body fat percentage (BF, %), handgrip strength (kg), standing long jump distance (cm) and maximal oxygen capacity (ml O2/kg/min).

To include all variables acquired during the fitness test in the analysis but to reduce redundancy at the same time, a principal component analysis (PCA) was performed. The 8 variables acquired during the fitness test and included in the PCA are listed in Table 4 of the supplementary section. Further analysis was performed using the two factors - physical fitness and physical condition (describing the participants' physical appearance) - which resulted from the PCA. A detailed description of the statistical analysis is included in the statistical analysis section.

2.4. Monetary Incentive Delay task

A well-validated implementation of the MID task was used to assess reward processing (Plichta et al., 2012; Boecker et al., 2014; Grimm et al., 2014). In our study, the MID task consisted of two different trials, which both included a reward cue, a target stimulus, a reaction time window and a reward outcome phase (Fig. 1A). During the win trial, indicated by a yellow smiley (reward cue), participants had the opportunity to win 50 cents, if they reacted fast enough (250 ms reaction time window) to the target stimulus. A color and form-matched circle (Fig. 1) indicated the neutral trials. With a 200 ms delay, the total amount of money earned was always displayed during the reward outcome phase. The trials were jittered by 2 seconds plus the excess reaction time with a black screen. Prior to the experiment, participants were instructed to react as fast as possible to the target stimulus, which occurred as a white flash of the screen after the reward cue disappeared, by pressing a button on a remote device in their hands. Fig. 1 depicts the chronological time frame of the trials, in case of a positive outcome. If the participants did not react fast enough, the reward outcome window displayed "Too slow!". The trials occurred in a random order, but never more than three of the same kind in a sequence, resulting in a total of 40 trials each. The threshold for a fast response was adaptive for each subject and each trial to ensure that all participants had an approximate 66 % chance to win and work on their maximum performance level. The adaptive algorithm was a simple increase of the reaction time window after a slow response and a decrease after a fast response by 5 % each (maximum reaction time 1000 ms). If participants missed more than 10 trials, because they did not react to the target stimulus, they were excluded from further analysis. The total amount of money won during the win trials was paid out to the participants after the measurement. On average, patients earned 12,25 € (± 1.73 €) and healthy controls 12,35 € (± 1.43 €).

2.5. fMRI data acquisition and preprocessing

The functional MR images were obtained using the 3 Tesla MRI scanner (Siemens Magnetom Prisma) of the Brain Imaging Center of the Goethe University Frankfurt with a 64-channel head coil. The participants' heads were stabilized with a small pillow and equipped with ear plugs. They were instructed to rest quietly and not to move, especially their heads. During the anatomical scans they were given the choice to close their eyes, if preferred. With a mirror attached to the head coil the participants were able to see a screen, placed behind the scanner and used to display the MID task. Responses were given using a remote device inside of the scanner. All participants practiced the MID task on a computer before entering the scanner rooms. The 390 volumes were acquired using a gradient-echo planar imaging (EPI) sequence with the

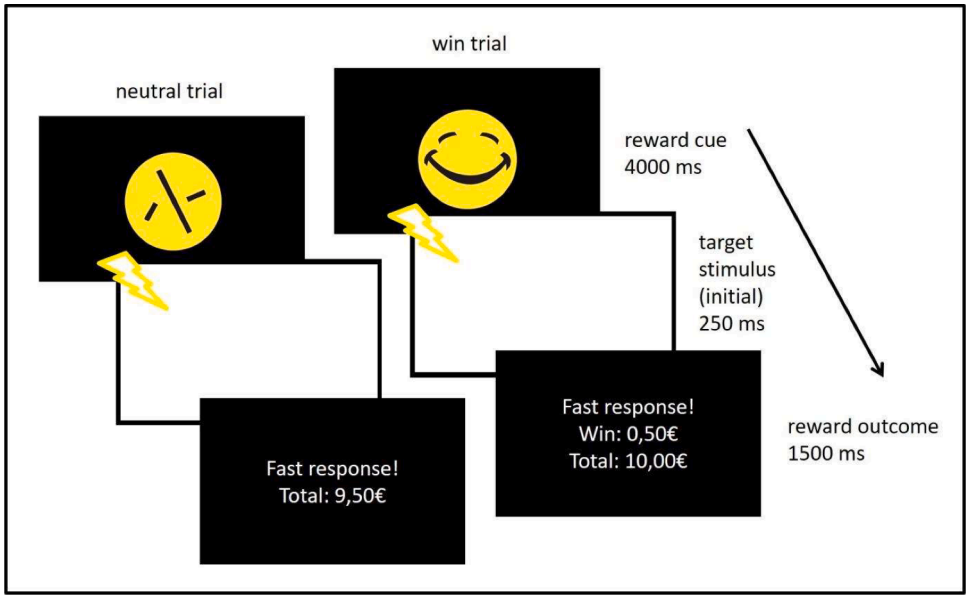

Figure 1. Monetary Incentive Delay (MID) task. The figure shows the chronological time frame of the MID task for both possible trials that occur in a random order throughout the task. In both trials the participants are presented with a reward cue for 4 seconds. After the reward cues disappears, a target stimulus occurs as a white flash of the screen, indicating the start of the reaction time window, during which the participants are supposed to press a button as fast as possible. In case of the win trial, they can then win 50 cents. In case of the neutral trials they will only receive a feedback, whether they were fast enough. The reward outcome is displayed for 1.5 seconds, before a new trial begins. If the participants react too slowly, the reward outcome window displays "Too slow". The current balance of the total amount of money earned is, however, always displayed.

following parameters: repetition time (TR) 1800 ms, echo time (TE) 30 ms, flip angle 90°, 52 transversal slices, slice thickness 2.8 mm, field of view (FoV) 224 mm (voxel size 2.8×2.8×2.8 mm). This resulted in a total sequence length of 11 minutes and 42 seconds. To compensate for distortions and to improve image quality, the EPI sequence was followed by a short field-map, with the same parameters consisting of only 3 images obtained in the opposite phase encoding direction - from posterior to anterior (Andersson et al., 2003; Smith et al., 2004; Shrestha et al., 2018). The according anatomical scans were obtained using a T1-weighted anatomical 3D magnetization-prepared rapid gradient echo sequence with the following parameters: TR = 2000 ms, TE = 2.12 ms, FoV = 256, 176 sagittal slices, voxel size = 1 × 1 × 1 mm, flip angle = 8°, resulting in a total length of 5 minutes and 52 seconds.

Prior to preprocessing, image distortions were corrected by the fieldmap images with fsl topup (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup, last accessed 2023/09/25). Preprocessing was then performed using the MATLAB toolbox SPM12 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK), including motion- and slice-time correction, spatial normalization into Montreal Neurological Institute [MNI] space, resampling to 2×2×2 mm^3 and smoothing using an 8 mm full-width at half-maximum Gaussian kernel. Scans including movement spikes above 3 mm were additionally motion corrected using the interpolation method of ArtRepair. If participants moved more than 5 mm or had more than 25 % of images interpolated, they were excluded from further analysis.

2.6. Statistical analyses

For the PCA of the fitness test data, the factors were expected to be independent and thus a varimax rotation was used. Item loadings below 0.30 were not considered. Two principal factors were chosen a priori, which explained 75 % of the data's variance. The according scree plot can be found in Figure 3 of the supplementary section and the factor loadings after rotation can be obtained from Table 4 of the supplementary section.. The two factors resulting from the PCA were used for further analysis, such as correlations. Factor 1 was defined as physical fitness, representing the participants' sportiness, and factor 2 as physical condition, describing the participants' physical appearance. Higher values of factor 1 can be interpreted as better physical fitness, while higher values of factor 2 are to be understood as poorer physical condition.

The fMRI analysis was performed in SPM 12. BOLD responses for each participant were modeled using the default hemodynamic response function and seven paradigm regressors including phase (anticipation or feedback), trial type (win or neutral), outcome of the feedback phase (fast enough/too slow) and the target stimulus (flashing screen) as well as six motion parameters. The second-level analysis was performed, using a two-sample t-test, including age, sex and chlorpromazine equivalent as nuisance variables. As we were interested exclusively in reward anticipation, the following contrasts were computed: anticipation > feedback (win + neutral anticipation > win + neutral feedback), referred to as anticipation > outcome, and reward anticipation > neutral anticipation (anticipation win trial > anticipation neutral trial). Group results are displayed using a binarized whole brain mask, with a voxel threshold of $p \leq .001$ (uncorrected) and a cluster threshold of $p \leq .05$ (Family Wise Error-corrected; FWE-corr.).

We tested for normality using the Shapiro-Wilk-Test. Normally distributed variables were further analyzed using parametric tests (two-sample t-test; Pearson correlation). Otherwise, non-parametric tests were applied (Mann-Whitney U-test; Spearman correlation).

To calculate correlations between the fMRI results, psychopathology and physical fitness data, the mean beta-values from the voxels within significant clusters were extracted. Correlations were performed across diagnostic groups within the whole sample. All results were corrected for multiple testing using Bonferroni-correction.

3. Results

3.1. Sample characteristics

Sample characteristics are summarized in Table 1. Five SZs had to be excluded from further analysis due to excessive head movement in the scanner and 4 SZs and 2 HCs were excluded because of more than 10 task omissions, resulting in a final sample size of 43 SZs and 36 HCs. According to the Mann-Whitney U test, SZs obtained significantly higher scores in all questionnaires assessing psychopathology, including PAS (Mann-Whitney $U = 1093.5$; $p = .002$), SAS (Mann-Whitney $U = 1058$; $p = .005$), CDSS (Mann-Whitney $U = 1261$; $p \leq .0001$) and WHODAS (Mann-Whitney $U = 1393.5$; $p \leq .0001$). The PANSS interview was conducted within the patient group only (Table 1). In the fitness test, HCs performed significantly better in all disciplines ($t = 2.423$; $p = .018$). As to the body measures, SZs showed significantly higher BMIs (Mann-Whitney $U = 1058$; $p = .005$) and significantly higher amounts of body fat ($t = -2{,}82$; $p = .006$) compared to HCs. These results are also reflected by the PCA components, where SZs revealed a significantly lower overall physical fitness (Mann-Whitney $U = 473$; $p = .003$) and overall physical condition ($t = -2{,}71$; $p = .008$) compared to HCs.

To compare task performance, we employed an independent t-test to determine whether there were significant differences in task performance. The results showed no significant difference between the groups ($t(77) = -1.54$, $p = 0.13$) in terms of money won.

To evaluate medication effects, we calculated correlations between demographic measure, brain activation, psychopathology, and anthropometric measures. There were no significant correlations between medication (daily CPZ equivalent) and age ($p=0.12$), sex ($p=0.16$), physical fitness or any anthropometric measure ($p>0.30$), as well not with psychopathology parameters, or brain activation ($p>0.07$).

3.2. fMRI results

To identify brain regions that are more activated in HCs compared to SZs during reward anticipation of the MID task, we computed the contrast anticipation > outcome. HCs showed significantly higher BOLD activation during anticipation in the left anterior insula (Table 2, Fig. 2). We further found that SZs activated more in the bilateral posterior cingulate cortex (PCC; Table 2, Fig. 2) and the left cerebellum (vermal lobules VI-VII; Table 2, Fig. 2) during anticipation compared to HCs. To reveal brain areas more sensitive to reward anticipation in win compared to neutral trials of the MID task, we used the contrast reward anticipation > neutral anticipation. Compared to the patient group, HCs activated significantly higher in the right angular gyrus (Table 2, Fig. 2), the right occipital cortex (Table 2, Fig. 2), the right cerebellum (vermal lobules V-VI and VIII-X; Table 2, Fig. 2) and the left cerebellum (vermal lobules VIII-X; Table 2, Fig. 2). We found no significant clusters in SZs compared to HCs (win > neutral, SZ > HC). All results are summarized in Table 2 and Fig. 2, displayed with a voxel threshold of $p \leq .001$ (uncorrected) and a cluster threshold of $p \leq .05$ (FWE-corr.). Group specific results for contrast one can be found in the supplementary section.

3.3. Atlas-based Region-of-Interest analysis of the ventral striatum

An atlas-based analysis of the bilateral ventral striatum revealed significant group differences in neural activation patterns. During the anticipation > outcome contrast, SZs exhibited lower contrast estimates compared to HCs ($t[77] = 2.84$, $p = 0.0057$). Similarly, in the reward anticipation > neutral anticipation contrast, patients again showed lower contrast estimates than controls ($t[77] = 2.73$, $p = 0.0079$). These findings demonstrate reduced ventral striatal response to reward-related cues within the patient group.

Table 2
Significant fMRI results of the Monetary Incentive Delay task.

Contrast	brain region	cluster *p*-value (FWE-corr)	cluster size [voxels]	peak *t*-value	peak MNI coordinates [mm]		
anticipation > outcome					x	y	z
HC > SZ	left anterior insula	0.006	227	3.87	-28	26	-8
				3.84	-40	18	-10
				3.84	-34	28	-6
				3.52	-40	6	-8
SZ > HC	left cerebellum, VL VI-VII	0.05	151	4.25	-26	-88	-30
	posterior cingulate cortex	≤ 0.001	544	4.11	-4	-58	34
				3.86	14	-50	38
				3.78	6	-58	32
reward anticipation > neutral anticipation							
HC > SZ	left cerebellum, VL VIII-X	0.013	184	4.25	-34	-74	-52
				3.55	-18	-74	-50
	right cerebellum, VL V-VI	≤ 0.001	459	4.35	28	-72	-20
				4.0	20	-84	-20
	right cerebellum, VL VIII-X	≤ 0.001	585	4.46	18	-68	-52
				3.87	4	-80	-40
				3.78	38	-70	-54
	right angular gyrus	0.039	147	3.76	42	-50	50
	right occipital cortex	≤ 0.001	357	4.12	28	-86	18
				4.02	34	-94	18
				3.68	34	-96	8

Note: SZ, schizophrenia patients; HC, healthy controls; VL, vermal lobules; MNI, Montreal Neurological Institute.

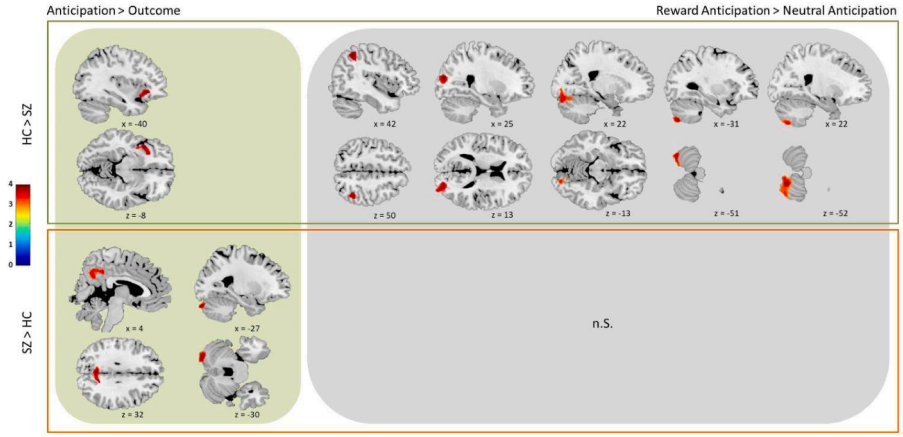

Figure 2. Significant fMRI results of the Monetary Incentive Delay task. The left shows significant clusters resulting from the contrast anticipation > receipt of reward of the MID task, while the right displays significant clusters resulting from the contrast reward anticipation > neutral anticipation. The top part surrounded by the green square depicts brain areas that are significantly stronger activated in healthy controls (HC) compared patients (SZ; HC > SZ). The bottom part surrounded by the orange square indicates brain regions which are significantly stronger activated in SZs compared to HCs (SZ > HC). During anticipation HCs show increased activity in the left anterior insula compared to SZs and SZs reveal significantly higher activity in posterior cingulate cortex (x = 4, z = 32) and the left cerebellum (vermal lobules VI-VII; x = -27, z = -30). During reward trials compared to neutral trials, HCs activate more in the right angular gyrus (x = 42, z = 50), the right occipital gyrus (x = 25, z = 13), the right cerebellum (vermal lobules V-VI; x = 22, z = -13), the left cerebellum (vermal lobules VIII-X; x = -31, z = -51) and the right cerebellum (vermal lobules VIII-X; x = 22, z = -52) compared to SZs. The color bar on the left indicates t-values. *Note*: n.S., no significance.

3.4. Correlation between fMRI-, behavioral- and fitness data

To relate altered reward anticipation with physical fitness and psychopathology, we performed exploratory correlations across groups between the eight significant clusters resulting from the fMRI analysis, the fitness test variables and the questionnaire scores of the PAS, SAS, CDSS, WHODAS and the PANSS. All correlation results that remained significant after Bonferroni-correction are summarized in Table 3. Decreased activity in the anterior insula during anticipation, as well as decreased activity in the left and right cerebellum, the right angular gyrus and the right occipital gyrus during reward compared to neutral trials correlated with symptom severity and decreased physical condition (Table 3). Furthermore, increased activation during anticipation in the left cerebellum negatively correlated with physical fitness (Table 3).

4. Discussion

Consistent with our hypothesis, we could demonstrate reduced overall brain activity during reward anticipation in SZs compared to HCs, which correlated with different psychopathology parameters, overall physical fitness, and condition.

Nevertheless, it should be mentioned that the activations, we found in both groups, are not primarily limited to the striatum, as assumed, but in brain areas associated with reward processing.

During anticipation, our findings revealed decreased BOLD activity in the left anterior insula of SZs compared to HCs, which further correlated with symptom severity and reduced physical condition. The anterior insula is a cortical structure, associated with emotional processing of interoceptive awareness showing connections to sensory cortices but also limbic areas (Wylie and Tregellas, 2010). It further provides sensory input to the ventral striatum (Haber, 2011). In line with our findings, many studies found activity in the anterior insula

Table 3
Correlation results between significant fMRI clusters, psychopathology and fitness data.

Cluster	PANSS	PAS	SAS	CDSS	WHO	Physical fitness	Physical condition
anticipation > outcome							
HC > SZ		ρ = -.270		r = -.311	r = -.283		r = -.249
left anterior insula							
		.0320*		.0156*	.0349*		.0266*
SZ > HC							
PCC							
SZ > HC						ρ = -.243	
left CBM, VL VI-VII							
						.0312*	
reward anticipation > neutral anticipation							
HC > SZ				ρ = -.321	ρ = -.293		ρ = -.352
left CBM, VL VIII-X							
				.0197*	.0442*		.0015*
HC > SZ					ρ = -.348		ρ = -.382
right CBM, VL VIII-X							
					.0083**		.0005**
HC > SZ					ρ = -.294		ρ = -.293
right CBM, VL V-VI							
					.0430*		.0087*
HC > SZ			ρ = -.312				
right angular gyrus							
			.0103*				
HC > SZ		ρ = -.289			ρ = -.335		ρ = -.258
right occipital gyrus							
		.0485*			.0126*		.0220*

during reward anticipation (Knutson and Greer, 2008; Krebs et al., 2012; Zeng et al., 2022), which has led to a discussion of its role in goal-directed behavior, including the integration of internal and external stimuli, such as rewards (Jauhar et al., 2021) - an ability impaired in schizophrenia. Moreover, the insula represents a structure implicated in food intake and taste (Verdejo-Román et al., 2017; Li et al., 2023). In their review Li et al. (2023) summarize its role derived from MRI studies with obese patients, indicating reduced grey matter volumes and hyperactivity during food or monetary reward evaluation. Therefore, the association between decreased insular activity and reduced physical condition we found in this study seems valid but needs further clarification.

Unlike other studies, we found increased activity in SZs during anticipation in the PCC and the left cerebellum. As a core component of the default mode network (DMN), usually active during resting-state and deactivated during task-based fMRI measures (Whitfield-Gabrieli, 2009), the PCC is not involved in reward processing. Thus, we assume that its relative hyperactivity in SZs during anticipation of our study reflects an insufficient suppression of the DMN related to cognitive dysfunction of SZs (Harrison et al., 2007; Leech and Sharp, 2014). Accordingly, there is evidence that attention deficits in schizophrenia are coped by enhanced activity in the left cerebellum (Eyler et al., 2004). Habas et al. (2009) found cerebellar connectivity networks, with vermal lobule VI as part of the salience network responsible for deactivating the DMN in HCs. Insufficient DMN suppression may contribute to left cerebellum hyperactivity in SZs, but we did not observe associations with psychopathology in this study.

During anticipation of reward trials compared to neutral trials, HCs activated significantly more in several cerebellar regions, the right angular gyrus and the right occipital gyrus compared to SZs. In line with our findings, Singh et al. (2013), who assessed reward processing in bipolar disorder using the MID task, found increased activity in the angular gyrus of HCs during anticipation of gain compared to no gain trials. The angular gyrus, part of the parietal cortex, is implicated in signaling surprising outcomes, as demonstrated by previous studies (Farrer et al., 2008; Gläscher et al., 2010; Segarra et al., 2016). This could be related to the adaptive algorithm implemented in our MID task to ensure a 66 % chance of winning during win trials, instead of 100 %. Further, there is evidence that the parietal cortex is modulated by dopamine during reward processing (Medic et al., 2014). Notably, dysfunction of the angular gyrus appears to be specific to schizophrenia, since parietal hypoactivity related to outcome uncertainty has been observed (Paulus et al., 2003).

We did a complementary ROI-based analysis of the ventral striatum (VS) which provides a valuable reference point when interpreting our whole-brain results. While we observed significant group differences in the cerebellum with notably larger effect sizes, the VS findings offer a baseline for understanding the magnitude of reward-related differences: We observed a significant reduction in striatal activation in a ROI-based analysis of the VS among SZs during both contrasts. This finding aligns with previous studies demonstrating blunted striatal responses in both patients (Esslinger et al., 2012) and their first-degree relatives (Grimm et al., 2017), reinforcing its potential role as an endophenotype. However, compared to our whole-brain analysis, the effect size within the VS was less pronounced. Notably, the cerebellum exhibited substantially larger effect sizes, suggesting that while the reward/salience network may be altered in schizophrenia and influenced by physical fitness, the VS may not be the sole or primary region of dysfunction.

Our findings regarding the cerebellum, support the hypothesis of its involvement in reward processing, motivation and the psychopathology of schizophrenia (Wilson et al., 2018; Holloway et al., 2019). It is connected to the substantia nigra, the anterior cingulate cortex, the anterior insula, the dorsal striatum and the amygdala, contributing to the salience network and the reward circuitry (Kruithof et al., 2023; Washburn et al., 2024). This connectivity with both networks indicates the cerebellum's role as a detector of potentially relevant information during reward tasks. Specifically, vermal lobule VI may be linked to reward anticipation (Wilson et al., 2018), revealing reduced activity in schizophrenia patients (Kruithof et al., 2023). Recent findings of Washburn et al. (2024) underpin the assumption that the cerebellum encodes reward value by directly modulating dopamine levels in the basal ganglia via the mesolimbic pathway. Moreover, cerebellar dysfunction correlates with a range of cognitive deficits in patients, referred to as the Cognitive Dysmetria Theory of Schizophrenia (Andreasen et al., 1998): previous MRI and PET studies created a model highlighting the significance of connectivity among prefrontal regions, thalamic nuclei, and the cerebellum. Disruptions in this network result in cognitive difficulties as to effectively prioritizing, processing, coordinating, and responding to information. These impairments in mental coordination are core cognitive deficits in schizophrenia. Our findings of

a correlation between the SZs' self-rated disability and reduced cerebellar activity are in line with this model.

Furthermore, besides its involvement in the regulation of appetite and voluntary movement, the cerebellum is also implicated in the hedonic aspect of food intake due to its projections to reward mediating nuclei (Iosif et al., 2023). This could explain the association found in this study between stronger cerebellar activity and better physical condition and again underlines the importance of the cerebellum in terms of a holistic view of psychiatric conditions.

Our study does not only detect the cerebellum as a major hub of the reward system altered in schizophrenia and diminished physical fitness, but it also points to the more general link between the reward system, motivation and motor activity. The relationship between motivation, physical fitness, and their neurobiological underpinnings is complex, particularly when considering the impact on schizophrenia. Engaging in physical activity has been found to be inherently rewarding, which is supported by studies showing that voluntary exercise can lead to an increase in BDNF-mediated striatal dopamine release (Bastioli et al., 2022). This enhanced 'reward drive' can incentivize individuals to pursue more physical activity. In animal models, there is evidence that the reward system is closely tied to motivation and physical activity, with wild type mice demonstrating a preference for running in a wheel over constant sucrose consumption—a behavior that shifts when dopamine transmission is pharmacologically blocked (Correa et al., 2016).

Human neuroimaging studies corroborate these findings, suggesting that attributes such as a smaller anterior cingulate cortex volume can predict a higher likelihood of engaging in physical activity, though the size of the nucleus accumbens does not show a direct correlation with physical activity levels, which points to the necessity of using functional imaging to assess reward system changes more sensitively (Miró-Padilla et al., 2023). Moreover, motivational syndromes linked to lower physical activity are seen in conditions like depression, where anhedonia and a loss of motivation—which may arise from dopaminergic dysfunction—shows transdiagnostic similarities between depression and schizophrenia (Taylor et al., 2022).

Physical fitness and motivation share a complex relationship that is deeply influenced by the neurobiological mechanisms within the brain, particularly involving the neurotransmitter dopamine. Dopamine's central role in motivation is well-documented, affecting not only various cognitive processes but also playing a critical role in the psychopathology of schizophrenia, contributing not only to symptoms such as anhedonia (McCutcheon et al., 2020). The blunted response of the reward system – ranging from the VS to the cerebellum – was verified in our study. A likely mechanism is less phasic dopamine activity from the background of an elevated, noisier tonic dopamine background. These dopaminergic neurons from the ventral tegmental area project to critical regions involved in motivation, such as the VS, which are instrumental in encoding the effort required for actions. These neurons are responsible for evaluating the cost-benefit ratio in decision-making, thus influencing the motivational drive behind voluntary physical movement and eating behavior — both of which are intrinsically rewarding and necessary for survival (Treadway et al., 2012).

The dopaminergic system must maintain an intricate balance to support healthful engagement with rewarding activities. However, dysregulated dopamine function can contribute to a lack of motivation, which can manifest in a reluctance to engage in physical activity, as often seen in motivational impairments related to schizophrenia and depression (Gold et al., 2013).

While our study underscores the importance of the reward system in the interplay between motivation and physical fitness and highlights potential targets for therapeutic interventions, particularly in the context of compromised physical activity in schizophrenia, it comes with some limitations.

While the MID paradigm is routinely employed to investigate reliably reward processing, it is important to acknowledge the striatum's functions extend beyond hedonic pleasure: habit formation, goal-directed behavior, and decision-making are all highly relevant to the motivational deficits observed in schizophrenia. Other paradigms than the MID task might be useful in exploring these other non-hedonic aspects of striatal function.

The striatum, particularly the VS, plays a central role in reward processing. Our findings of reduced striatal activation during reward anticipation in SZs directly align with this understanding.

Another limitation comes from considering the impact of chronic neuroleptic medication, particularly dopamine-blocking antipsychotics, on the reward system. While our study did not reveal a direct correlation between chlorpromazine equivalent dosage and striatal activation (and corrected for CPZ as covariate), this measure might be too simplistic. Future studies should investigate the effects of long-term medication use with more nuanced measures. It is plausible that the blunted reward response observed in chronic schizophrenia is partially mediated by antidopaminergic medication.

The interesting activity in the cerebellum, we found, is becoming increasingly important in the context of reward anticipation and schizophrenia. However, SPM12, we used for our analysis, does not include a reference brain atlas with MNI coordinates of cerebellar regions. Therefore, the identified regions in the cerebellum may differ slightly from other works specifically focused on analyses in the cerebellum. To substantiate our findings, we suggest performing the same analysis in future studies using a cerebellar brain map. Finally, regarding the comparison of reward and neutral anticipation, further analyses are needed to provide more precise statements about group differences. Currently, we do not know whether SZs generally activate less or actually discriminate less between win and neutral trials. Follow-up analyses should shed more light on this question.

In conclusion, our results clearly indicate a link between psychopathology and reduced physical fitness, which includes reward-mediating brain areas in schizophrenia. Further, the decreased activity in cerebellar regions is consistent with recent studies linking reward processing and motivational behavior to cerebellar function, supporting the long-controversial role of the cerebellum in "cognitive dysmetria" in schizophrenia (Andreasen et al., 1999). Finally, our study not only highlights the role of the reward system as to physical fitness in schizophrenia, but also suggests the cerebellum as a neuromodulatory target for interventional studies.

CRediT authorship contribution statement

Lara Hamzehpour: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tamara Bohn:** Investigation, Formal analysis, Data curation. **Valentin Dutsch:** Investigation, Formal analysis, Data curation. **Lucia Jaspers:** Investigation, Formal analysis, Data curation. **Oliver Grimm:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.115877.

References

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: the calgary depression scale. Br. J. Psychiatry, Suppl. (22), 39–44. https://doi.org/10.1192/S0007125000292581.

Andersson, J.L.R., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: Application to diffusion tensor imaging. Neuroimage 20 (2), 870–888. https://doi.org/10.1016/S1053-8119(03)00336-7.

Andreasen, N.C., Paradiso, S., O'Leary, D.S., 1998. Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr. Bull. 24 (2), 203–218. https://doi.org/10.1093/oxfordjournals.schbul.a033321.

Andreasen, N.C., Nopoulos, P., O'Leary, D.S., Miller, D.D., Wassink, T., Flaum, M., 1999. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol. Psychiatry 46 (7), 908–920. https://doi.org/10.1016/s0006-3223(99)00152-3.

Bastioli, G., Arnold, J.C., Mancini, M., Mar, A.C., Gamallo-Lana, B., Saadipour, K., Rice, M.E., 2022. Voluntary exercise boosts striatal dopamine release: evidence for the necessary and sufficient role of BDNF. J. Neurosci. 42 (23), 4725–4736.

Boecker, R., Holz, N.E., Buchmann, A.F., Blomeyer, D., Plichta, M.M., Wolf, I., Baumeister, S., Meyer-Lindenberg, A., Banaschewski, T., Brandeis, D., Laucht, M., 2014. Impact of early life adversity on reward processing in young adults: EEG-fMRI results from a prospective study over 25 years. PloS one 9 (8), e104185. https://doi.org/10.1371/journal.pone.0104185.

Borg, G., 1970. Perceived exertion as an indicator of somatic stress. Scand. J. Rehabil. Med. 2 (2), 92–98.

Brožek, J., Grande, F., Anderson, J.T., Keys, A., 1963. Densitometric analysis of body composition. revision of some quantitative assumptions. Ann. N.Y. Acad. Sci. 110, 113–140. https://doi.org/10.1111/j.1749-6632.1963.tb17079.x.

Chapman, L.J., Chapman, J.P., Raulin, M.L., 1976. Scales for physical and social anhedonia. J. Abnorm. Psychol. 85 (4), 374–382. https://doi.org/10.1037//0021-843x.85.4.374.

Correa, M., Pardo, M., Bayarri, P., López-Cruz, L., San Miguel, N., Valverde, O., Ledent, C., Salamone, J.D., 2016. Choosing voluntary exercise over sucrose consumption depends upon dopamine transmission: effects of haloperidol in wild type and adenosine A_2AKO mice. Psychopharmacology 233 (3), 393–404. https://doi.org/10.1007/s00213-015-4127-3.

Deserno, L., Boehme, R., Heinz, A., Schlagenhauf, F., 2013. Reinforcement learning and dopamine in schizophrenia: dimensions of symptoms or specific features of a disease group? Front. Psychiatry 4, 172. https://doi.org/10.3389/fpsyt.2013.00172.

Durnin, J.V., Womersley, J., 1974. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br. J. Nutr. 32 (1), 77–97. https://doi.org/10.1079/bjn19740060.

Eyler, L.T., Olsen, R.K., Jeste, D.V., Brown, G.G., 2004. Abnormal brain response of chronic schizophrenia patients despite normal performance during a visual vigilance task. Psychiatry Res 130 (3), 245–257. https://doi.org/10.1016/j.pscychresns.2004.01.003.

Esslinger, C., Englisch, S., Inta, D., Rausch, F., Schirmbeck, F., Mier, D., Kirsch, P., Meyer-Lindenberg, A., Zink, M., 2012. Ventral striatal activation during attribution of stimulus saliency and reward anticipation is correlated in unmedicated first episode schizophrenia patients. Schizophr. Res. 140 (1-3), 114–121. https://doi.org/10.1016/j.schres.2012.06.025, 2012.

Farrer, C., Frey, S.H., Van Horn, J.D., Tunik, E., Turk, D., Inati, S., Grafton, S.T., 2008. The angular gyrus computes action awareness representations. Cereb. Cortex 18 (2), 254–261. https://doi.org/10.1093/cercor/bhm050.

Gläscher, J., Daw, N., Dayan, P., O'Doherty, J.P., 2010. States versus rewards: dissociable neural prediction error signals underlying model-based and model-free reinforcement learning. Neuron 66 (4), 585–595. https://doi.org/10.1016/j.neuron.2010.04.016.

Gold, J.M., Strauss, G.P., Waltz, J.A., Robinson, B.M., Brown, J.K., Frank, M.J., 2013. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. Biol. Psychiatry 74 (2), 130–136. https://doi.org/10.1016/j.biopsych.2012.12.022.

Gorrell, S., Shott, M.E., Frank, G.K.W., 2022. Associations between aerobic exercise and dopamine-related reward-processing: Informing a model of human exercise engagement. Biol. Psychol. 171, 108350 https://doi.org/10.1016/j.biopsycho.2022.108350.

Grace, AA., 2016 Aug. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nat Rev Neurosci 17 (8), 524–532. https://doi.org/10.1038/nrn.2016.57. Epub 2016 Jun 3. PMID: 27256556; PMCID: PMC5166560.

Grimm, O., Heinz, A., Walter, H., Kirsch, P., Erk, S., Haddad, L., Plichta, M.M., Romanczuk-Seiferth, N., Pöhland, L., Mohnke, S., Mühleisen, T.W., Mattheisen, M., Witt, S.H., Schäfer, A., Cichon, S., Nöthen, M., Rietschel, M., Tost, H., Meyer-Lindenberg, A., 2014. Striatal response to reward anticipation: evidence for a systems-level intermediate phenotype for schizophrenia. JAMA psychiatry 71 (5), 531–539. https://doi.org/10.1001/jamapsychiatry.2014.9.

Grimm, O., Kaiser, S., Plichta, M.M., Tobler, P.N., 2017. Altered reward anticipation: Potential explanation for weight gain in schizophrenia? Neurosci. Biobehav. Rev. 75, 91–103. https://doi.org/10.1016/j.neubiorev.2017.01.029.

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., Greicius, M. D., 2009. Distinct cerebellar contributions to intrinsic connectivity networks. J. Neurosci. 29 (26), 8586–8594. https://doi.org/10.1523/JNEUROSCI.1868-09.2009.

Haber, S.N., 2011. Neuroanatomy of reward: a view from the Ventral striatum. Ed.. In: Gottfried, J.A. (Ed.), Neurobiology of Sensation and Reward. CRC Press/Taylor & Francis. Chapter 11.

Harrison, B.J., Yücel, M., Pujol, J., Pantelis, C., 2007. Task-induced deactivation of midline cortical regions in schizophrenia assessed with fMRI. Schizophr. Res. 91 (1-3), 82–86. https://doi.org/10.1016/j.schres.2006.12.027.

Hennekens, C.H., Hennekens, A.R., Hollar, D., Casey, D.E., 2005. Schizophrenia and increased risks of cardiovascular disease. Am. Heart J. 150 (6), 1115–1121. https://doi.org/10.1016/j.ahj.2005.02.007.

Holloway, Z.R., Paige, N.B., Comstock, J.F., Nolen, H.G., Sable, H.J., Lester, D.B., 2019. Cerebellar modulation of mesolimbic dopamine transmission is functionally asymmetrical. Cerebellum 18 (5), 922–931. https://doi.org/10.1007/s12311-019-01074-w.

Iosif, C.I., Bashir, Z.I., Apps, R., Pickford, J., 2023. Cerebellar prediction and feeding behaviour. Cerebellum 22 (5), 1002–1019. https://doi.org/10.1007/s12311-022-01476-3.

Jauhar, S., Fortea, L., Solanes, A., Albajes-Eizagirre, A., McKenna, P.J., Radua, J., 2021. Brain activations associated with anticipation and delivery of monetary reward: A systematic review and meta-analysis of fMRI studies. PloS one 16 (8), e0255292. https://doi.org/10.1371/journal.pone.0255292.

Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenia. NeuroImage 29 (2), 409–416. https://doi.org/10.1016/j.neuroimage.2005.07.051.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276. https://doi.org/10.1093/schbul/13.2.261.

Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. NeuroImage 12 (1), 20–27. https://doi.org/10.1006/nimg.2000.0593.

Knutson, B., Greer, S.M., 2008. Anticipatory affect: neural correlates and consequences for choice. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 363 (1511), 3771–3786. https://doi.org/10.1098/rstb.2008.0155.

Koch, K., Rus, O.G., Reeß, T.J., Schachtzabel, C., Wagner, G., Schultz, C.C., Sorg, C., Schlösser, R.G., 2014. Functional connectivity and grey matter volume of the striatum in schizophrenia. Br. J. Psychiatry 205 (3), 204–213. https://doi.org/10.1192/bjp.bp.113.138099.

Krebs, R.M., Boehler, C.N., Roberts, K.C., Song, A.W., Woldorff, M.G., 2012. The involvement of the dopaminergic midbrain and cortico-striatal-thalamic circuits in the integration of reward prospect and attentional task demands. Cereb. Cortex 22 (3), 607–615. https://doi.org/10.1093/cercor/bhr134.

Kruithof, E.S., Klaus, J., Schutter, D.J.L.G., 2023. The human cerebellum in reward anticipation and outcome processing: An activation likelihood estimation meta-analysis. Neurosci. Biobehav. Rev. 149, 105171 https://doi.org/10.1016/j.neubiorev.2023.105171.

Leech, R., Sharp, D.J., 2014. The role of the posterior cingulate cortex in cognition and disease. Brain 137 (Pt 1), 12–32. https://doi.org/10.1093/brain/awt162.

Li, G., Hu, Y., Zhang, W., Wang, J., Ji, W., Manza, P., Volkow, N.D., Zhang, Y., Wang, G. J., 2023. Brain functional and structural magnetic resonance imaging of obesity and weight loss interventions. Mol. Psychiatry 28 (4), 1466–1479. https://doi.org/10.1038/s41380-023-02025-y.

McCutcheon, R.A., Krystal, J.H., Howes, O.D., 2020. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World psychiatry 19 (1), 15–33. https://doi.org/10.1002/wps.20693.

Medic, N., Ziauddeen, H., Vestergaard, M.D., Henning, E., Schultz, W., Farooqi, I.S., Fletcher, P.C., 2014. Dopamine modulates the neural representation of subjective value of food in hungry subjects. J. Neurosci. 34 (50), 16856–16864. https://doi.org/10.1523/JNEUROSCI.2051-14.2014.

Minichino, A., Ando', A., Francesconi, M., Salatino, A., Delle Chiaie, R., Cadenhead, K., 2017. Investigating the link between drug-naive first episode psychoses (FEPs), weight gain abnormalities and brain structural damages: Relevance and implications for therapy. Prog. Neuropsychopharmacol. Biol. Psychiatry 77, 9–22. https://doi.org/10.1016/j.pnpbp.2017.03.020.

Miró-Padilla, A., Adrián-Ventura, J., Cherednichenko, A., Monzonís-Carda, I., Beltran-Valls, M.R., MolinerUrdiales, D., Ávila, C., 2023. Relevance of the anterior cingulate cortex volume and personality in motivated physical activity behaviors. Commun. Biology 6 (1), 1106.

Moustafa, A.A., Kéri, S., Somlai, Z., Balsdon, T., Frydecka, D., Misiak, B., White, C., 2015. Drift diffusion model of reward and punishment learning in schizophrenia: Modeling and experimental data. Behav. Brain Res. 291, 147–154. https://doi.org/10.1016/j.bbr.2015.05.024.

Newcomer, J.W., 2007. Antipsychotic medications: metabolic and cardiovascular risk. J. Clin. Psychiatry 68 (Suppl. 4), 8–13.

Ostermann, S., Herbsleb, M., Schulz, S., Donath, L., Berger, S., Eisenträger, D., Siebert, T., Müller, H.J., Puta, C., Voss, A., Gabriel, H.W., Koch, K., Bär, K.J., 2013. Exercise reveals the interrelation of physical fitness, inflammatory response, psychopathology, and autonomic function in patients with schizophrenia. Schizophr. Bull. 39 (5), 1139–1149. https://doi.org/10.1093/schbul/sbs085.

Paulus, M.P., Frank, L., Brown, G.G., Braff, D.L., 2003. Schizophrenia subjects show intact success-related neural activation but impaired uncertainty processing during decision-making. Neuropsychopharmacology 28 (4), 795–806. https://doi.org/10.1038/sj.npp.1300108.

Plichta, M.M., Schwarz, A.J., Grimm, O., Morgen, K., Mier, D., Haddad, L., Gerdes, A.B., Sauer, C., Tost, H., Esslinger, C., Colman, P., Wilson, F., Kirsch, P., Meyer-Lindenberg, A., 2012. Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. NeuroImage 60 (3), 1746–1758. https://doi.org/10.1016/j.neuroimage.2012.01.129.

Ruiz, J.R., Castro-Piñero, J., España-Romero, V., Artero, E.G., Ortega, F.B., Cuenca, M. M., Jimenez-Pavón, D., Chillón, P., Girela-Rejón, M.J., Mora, J., Gutiérrez, A., Suni, J., Sjöström, M., Castillo, M.J., 2011. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. Br. J. Sports Med. 45 (6), 518–524. https://doi.org/10.1136/bjsm.2010.075341.

Ruiz-Tejada, A., Neisewander, J., Katsanos, C.S., 2022. Regulation of voluntary physical activity behavior: a review of evidence involving dopaminergic pathways in the brain. Brain Sci 12 (3), 333. https://doi.org/10.3390/brainsci12030333, 2022.

Ryan, M.C., Thakore, J.H., 2002. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. Life Sci 71 (3), 239–257. https://doi.org/10.1016/s0024-3205(02)01646-6.

Schmitt, A., Maurus, I., Rossner, M.J., Röh, A., Lembeck, M., von Wilmsdorff, M., Takahashi, S., Rauchmann, B., Keeser, D., Hasan, A., Malchow, B., Falkai, P., 2018. Effects of aerobic exercise on metabolic syndrome, cardiorespiratory fitness, and symptoms in schizophrenia include decreased mortality. Front. psychiatry 9, 690. https://doi.org/10.3389/fpsyt.2018.00690.

Segarra, N., Metastasio, A., Ziauddeen, H., Spencer, J., Reinders, N.R., Dudas, R.B., Arrondo, G., Robbins, T.W., Clark, L., Fletcher, P.C., Murray, G.K., 2016. Abnormal frontostriatal activity during unexpected reward receipt in Depression and Schizophrenia: relationship to anhedonia. Neuropsychopharmacology 41 (8), 2001–2010. https://doi.org/10.1038/npp.2015.370.

Sheffield, J.M., Barch, D.M., 2016. Cognition and resting-state functional connectivity in schizophrenia. Neurosci. Biobehav. Rev. 61, 108–120. https://doi.org/10.1016/j.neubiorev.2015.12.007.

Shrestha, M., Hok, P., Nöth, U., Lienerth, B., Deichmann, R., 2018. Optimization of diffusion-weighted single-refocused spin-echo EPI by reducing eddy-current artifacts and shortening the echo time. MAGMA 31 (5), 585–597. https://doi.org/10.1007/s10334-018-0684-x.

Singh, M.K., Chang, K.D., Kelley, R.G., Cui, X., Sherdell, L., Howe, M.E., Gotlib, I.H., Reiss, A.L., 2013. Reward processing in adolescents with bipolar I disorder. J. Am. Acad. Child. Adolesc. Psychiatry 52 (1), 68–83. https://doi.org/10.1016/j.jaac.2012.10.004.

Siri, W.E., 1993. Body composition from fluid spaces and density: analysis of methods. 1961. Nutrition 9 (5), 480–492.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 (Suppl. 1), 208–219. https://doi.org/10.1016/j.neuroimage.2004.07.051.

Sykes, K., Roberts, A., 2004. The Chester step test-a simple yet effective tool for the prediction of aerobic capacity. Physiotherapy 90, 183–188. https://doi.org/10.1016/j.physio.2004.03.008.

Strauss, G.P., Waltz, J.A., Gold, J.M., 2014. A review of reward processing and motivational impairment in schizophrenia. Schizophr. Bull. 40 (Suppl 2), S107–S116. https://doi.org/10.1093/schbul/sbt197.

Taylor, W.D., Zald, D.H., Felger, J.C., Christman, S., Claassen, D.O., Horga, G., Miller, J. M., Gifford, K., Rogers, B., Szymkowicz, S.M., Rutherford, B.R., 2022. Influences of dopaminergic system dysfunction on late-life depression. Mol. Psychiatry 27 (1), 180–191. https://doi.org/10.1038/s41380-021-01265-0.

Thakore, J.H., Mann, J.N., Vlahos, I., Martin, A., Reznek, R., 2002. Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia. Int. J. Obes. Relat. Metab. Disord. 26 (1), 137–141. https://doi.org/10.1038/sj.ijo.0801840.

Treadway, M.T., Buckholtz, J.W., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Kessler, R.M., Zald, D.H., 2012. Dopaminergic mechanisms of individual differences in human effort-based decision-making. J. Neurosci. 32 (18), 6170–6176. https://doi.org/10.1523/JNEUROSCI.6459-11.2012, 2012.

Tschoner, A., Engl, J., Laimer, M., Kaser, S., Rettenbacher, M., Fleischhacker, W.W., Patsch, J.R., Ebenbichler, C.F., 2007. Metabolic side effects of antipsychotic medication. Int. J. Clin. Pract. 61 (8), 1356–1370. https://doi.org/10.1111/j.1742-1241.2007.01416.x.

Ustün, T.B., Chatterji, S., Kostanjsek, N., Rehm, J., Kennedy, C., Epping-Jordan, J., Saxena, S., von Korff, M., Pull, C., WHO/NIH Joint Project, 2010. Developing the world health organization disability assessment schedule 2.0. Bull. World Health Organ., 88 (11), 815–823. https://doi.org/10.2471/BLT.09.067231.

Verdejo-Román, J., Vilar-López, R., Navas, J.F., Soriano-Mas, C., Verdejo-García, A., 2017. Brain reward system's alterations in response to food and monetary stimuli in overweight and obese individuals. Hum. Brain Mapp. 38 (2), 666–677. https://doi.org/10.1002/hbm.23407.

Waltz, J.A., Schweitzer, J.B., Gold, J.M., Kurup, P.K., Ross, T.J., Salmeron, B.J., Rose, E. J., McClure, S.M., Stein, E.A., 2009. Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. Neuropsychopharmacology 34 (6), 1567–1577. https://doi.org/10.1038/npp.2008.214.

Washburn, S., Oñate, M., Yoshida, J., Vera, J., Bhuvanasundaram, R., Khatami, L., Nadim, F., Khodakhah, K., 2024. The cerebellum directly modulates the substantia nigra dopaminergic activity. Nat. Neurosci. https://doi.org/10.1038/s41593-023-01560-9.

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D., Seidman, L.J., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 106 (4), 1279–1284. https://doi.org/10.1073/pnas.0809141106.

Wilson, R.P., Colizzi, M., Bossong, M.G., Allen, P., Kempton, M., , MTAC, Bhattacharyya, S., 2018. The neural substrate of reward anticipation in health: a meta-analysis of fmri findings in the monetary incentive delay task. Neuropsychol. Rev. 28 (4), 496–506. https://doi.org/10.1007/s11065-018-9385-5.

Wulff, S., Nielsen, M.Ø., Rostrup, E., Svarer, C., Jensen, L.T., Pinborg, L., Glenthøj, B.Y., 2020. The relation between dopamine D2 receptor blockade and the brain reward system: a longitudinal study of first-episode schizophrenia patients. Psychol. Med. 50 (2), 220–228. https://doi.org/10.1017/S0033291718004099.

Wylie, K.P., Tregellas, J.R., 2010. The role of the insula in schizophrenia. Schizophr. Res. 123 (2-3), 93–104. https://doi.org/10.1016/j.schres.2010.08.027.

Zeng, J., Yan, J., Cao, H., Su, Y., Song, Y., Luo, Y., Yang, X., 2022. Neural substrates of reward anticipation and outcome in schizophrenia: a meta-analysis of fMRI findings in the monetary incentive delay task. Transl. Psychiatry 12 (1), 448. https://doi.org/10.1038/s41398-022-02201-8.