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ORIGINAL RESEARCH

Altered reward-related neural responses in non-manifesting carriers of the Parkinson disease related *LRRK2* mutation

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Abstract

Disturbances in reward processing occur in Parkinson's disease (PD) however it is unclear whether these are solely drug-related. We applied an event-related fMRI gambling task to a group of non-manifesting carriers (NMC) of the G2019S mutation in the *LRRK2* gene, in order to assess the reward network in an "at risk" population for future development of PD. Sixty-eight non-manifesting participants, 32 of which were non-manifesting non-carriers (NMNC), performed a gambling task which included defined intervals of anticipation and response to both reward and punishment in an fMRI setup. Behavior and cerebral activations were measured using both hypothesis driven and whole brain analysis. NMC demonstrated higher trait anxiety scores ($p = 0.04$) compared to NMNC. Lower activations were detected among NMC during risky anticipation in the left nucleus accumbens (NAcc) ($p = 0.05$) and during response to punishment in the right insula ($p = 0.02$), with higher activations among NMC during safe anticipation in the right insula ($p = 0.02$). Psycho-Physiological Interaction (PPI) analysis from the NAcc and insula revealed differential connectivity patterns. Whole brain analysis demonstrated divergent between-group activations in distributed cortical regions, bilateral caudate, left midbrain, when participants were required to press the response button upon making their next chosen move. Abnormal neural activity in both the reward and motor networks were detected in NMC indicating involvement of the ventral striatum regardless of medication use in "at risk" individuals for future development of PD.

Keywords LRRK2 · Genomic vulnerability · Reward · Anticipation · fMRI

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Introduction

Disturbances in reward processing are common in Parkinson's disease (PD) and take the form of both impulse control disorders (ICD) (hypersexuality, hoarding, gambling and food craving) and dopamine dysregulation syndrome (a tendency to take excessive amounts of dopaminergic medications). While initially thought to be related to dopamine agonist therapy, ICD have recently been recognized to occur with either dopamine agonist or levodopa treatment (Antonini et al. 2017).

The ventral striatum, which includes the nucleus accumbens (NAcc), is one of the main hubs of the reward network (Haber and Knutson 2010), receiving cortical inputs from the orbitofrontal cortex, ventral-medial prefrontal cortex, the anterior cingulate cortex and the anterior insula, together with dopaminergic midbrain inputs (Haber and Knutson 2010). Indeed, fMRI studies that have focused on reward and motivation repeatedly have demonstrated activations in these

regions (Liu et al. 2011). However, this network is not completely independent and interacts with other basal ganglia networks (cognitive and motor) in order to maximize performance (Haber and Knutson 2010). Efferent projections from the ventral striatum reach the pallidum and midbrain. The mesolimbic and mesocortical dopaminergic systems, connecting the ventral tegmental area in the midbrain with the ventral striatum and with frontal cortical areas respectively, are considered to be less affected by the early neurodegenerative process of PD, compared to the motor related nigrostriatal system (Kish et al. 1988). Dopamine has been linked to stimulus-outcome associations, tracking and responding to rewarding or punishing outcomes and motivation (Dagher and Robbins 2009) and plays a role in certain personality traits as well. A Parkinsonian personality, described as inflexible, cautious, introverted and non-impulsive has been proposed (Menza et al. 1993).

The elucidation of the genetic basis of PD and the identification of non-manifesting mutation carriers (NMC) who are at an increased risk for future development of PD provides an opportunity for better understanding the pre-motor stage of the disease. NMC of the G2019S mutation in the *LRRK2* gene differ from non-manifesting non-carriers (NMNC) in both gait (Mirelman et al. 2011), motor imagery (van Nuenen et al. 2012), cognition (Thaler et al. 2012; Thaler et al. 2015) and demonstrated altered intrinsic cortico-striatal connectivity (Helmich et al. 2015), while maintaining cerebral structural integrity (Thaler et al. 2014). While untreated PD patients were not found to have more symptoms of any ICD compared to healthy controls (Antonini et al. 2011), it is yet unknown whether "at risk" populations for future development of PD demonstrate altered behavior, or neural responses, during motivational processing. Addressing this question, we designed an fMRI study utilizing a risky choice event related task (Kahn et al. 2002; Assaf et al. 2009) expecting to find reduced risk taking and reduced activations in the NAcc among NMC when anticipating and obtaining rewarding outcomes, compared with NMNC, reflecting the aforementioned pre-motor personality characteristics of patients with PD.

Materials and methods

Participants

Non-manifesting first degree relatives of Ashkenazi Jewish PD patients, heterozygote carriers of the G2019S mutation in the *LRRK2* gene were recruited to this study through their affected PD family members. Inclusion criteria included Unified Parkinson Disease Rating Scale part III (UPDRS) (Fahn 1987) < 5, Montreal Cognitive Assessment test (MoCA) (Nasreddine et al. 2005) > 23, Beck Depression Inventory (BDI) (Schrag et al. 2007) <10. Exclusion criteria included history of head trauma, treatment with medications for PD or with dopamine depletion medications, any neurodegenerative disease, carrying a mutation in the β-glucocerebrosidase (*GBA*) gene (Gan-Or et al. 2008) and general exclusion criteria for MRI scanning. The study was approved by the Tel-Aviv Medical Center IRB committee. All participants provided written informed consent and were divided into groups based on an examination of the 6055G_A (G2019S) mutation in exon 41 of the *LRRK2* gene (for further details regarding the genomic analysis please refer to (Orr-Urtreger et al. 2007). Participants and researchers were unaware of the genetic status during recruitment, scanning and initial data analysis.

Demographic, clinical and personality measures

Basic demographic data and medical history were collected; participants completed the following standardized questionnaires: Cloningers' Tridimensional Personality Questionnaire (TPQ) (Menza et al. 1993) and Spielberger State Trait Anxiety Inventory (STAI) (Mondolo et al. 2007) as well as a computerized cognitive test battery (Mindstreams, NeuroTrax Corp., NY) (Hausdorff et al. 2006) designed to evaluate multiple cognitive domains including attention, memory, executive function and motor skills. All tests were run in the same fixed order on a computer using a mouse and a keyboard. Indices were normalized for age and years of education and are presented similarly to an IQ-like scale (mean ± SD: 100 ± 15) (Thaler et al. 2012). The program generates a global cognitive score (GCS), a composite of all the cognitive sub-scores.

Imaging data acquisition

Participants underwent brain MRI scanning performed on a General Electric 3 Tesla Signa HDxt scanner (GE Signa EXCITE, Milwaukee, WI, USA) using a standard 8-channel head coil. MRI protocol included high resolution three-dimensional spoiled gradient echo sequence (3D-SPGR): field of view (FOV) 250 × 250 mm; matrix size 256 × 256; and 1 mm slice thickness, resulting in a voxel size of 0.98 × 0.98 × 1; Repetition Time (TR)/Echo Time (TE) = 9/3.6 ms. Functional MRI images were acquired using a single shot gradient EPI sequence with the following parameters: FOV 200 × 200 mm, TE/TR = 35/2.5 ms, 40 axial slices, matrix size = 64 × 64 no gap, scanning time 15 min with a total of 360 images.

fMRI paradigm

During fMRI, participants played a two-player risky choice gambling game designed in our lab and commonly used to study neural response during different stages of risk taking

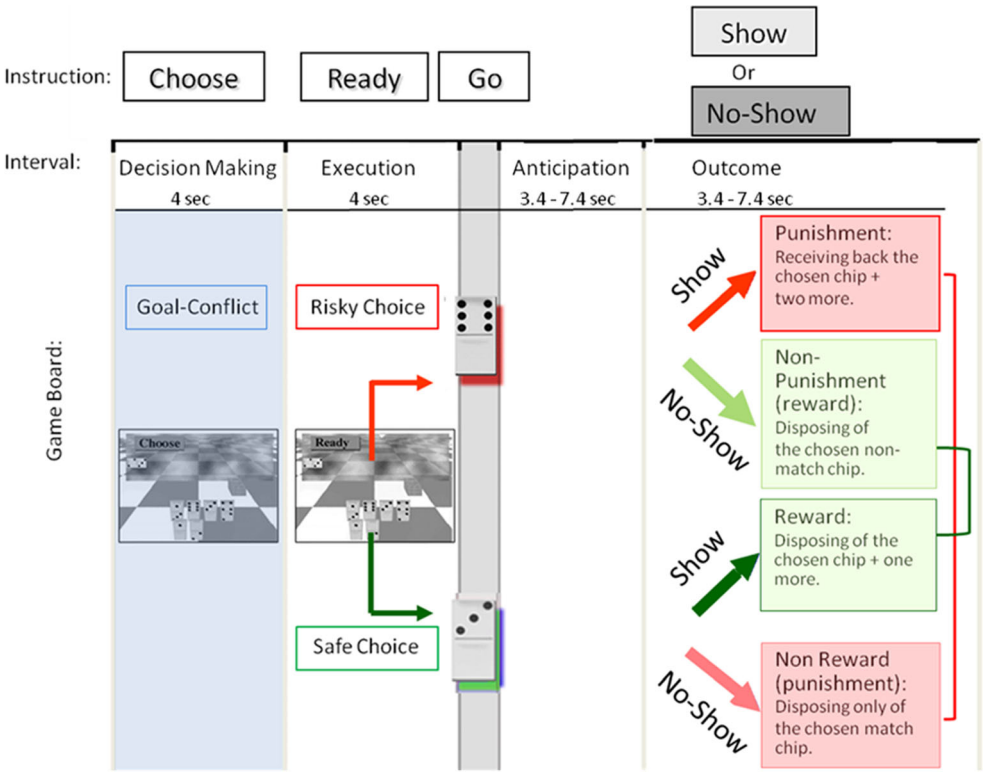

Fig. 1 Domino game paradigm. Each round of the game is composed of 5 intervals: the player chooses which chip to play next, ('Choose' interval, lasting 4 s), moves the cursor to the chosen chip ('Ready' interval lasting 4 s) and places it facing down adjacent to the master chip ('Go' interval). The player then waits for the opponent's response ('Anticipation' which is jittered randomly 3.4, 5.4, 7.4 s) and sees whether the opponent challenges this choice by uncovering the chosen chip or not ('Outcome' which is jittered randomly 3.4, 5.4, 7.4 s). Player's choices and opponent's responses are interactively determined by the flow of the game round after round, creating a natural progression of a game situation that lasts 4 min or until the player wins the game by disposing of all his chips. Each player played consecutively for 14 min

process (Kahn et al. 2002; Assaf et al. 2009) (Fig. 1). The scanned participant was the player, while a computer randomly generated the opponent's responses in a predetermined pattern to allow a balanced design. Participants, however, were told that their opponent was the experimenter and that their choices could increase their chances of winning the game by beating their rival. At the beginning of each round, 12 random domino chips were assigned to the participant together with one master chip. In each round of the game the participant had to choose one chip, place it facing down adjacent to the master chip and wait for the opponent's response (i.e., anticipation) to see whether the opponent challenged this choice by uncovering the chosen chip or not (i.e., outcome). Each assigned chip could either match the master chip or not. Since the master chip was constant throughout the game, it was only possible to win by choosing both matching and non-matching chips.

In the game context, matching chips were considered 'safe' since they were associated with rewards and non-matching chips were considered 'risky' as they were associated with punishments if uncovered. Based on the participant's choice and opponent's response, there were four possible consequences per game round (i.e. 'outcome' possibilities). 1) Show of a non-match chip: the choice of a non-match chip was exposed and the participant was punished by receiving back the selected chip plus two additional chips from the deck. 2) No show of a non-match chip: the choice of a non-match chip remained unexposed and only the selected chip was disposed of, so the participant was relatively rewarded as he got away with a non-match choice. 3) Show of match chip: the choice of a match chip was exposed and the participant was rewarded by disposal of the selected chip and one additional random chip from the game board. 4) No show of a match chip: the choice of a match chip was not exposed and only the selected match chip was disposed of, so the participant was relatively punished as he could have disposed of a non-match chip instead. In the context of the game, rewarding outcomes were made up of both the 'no show of non-match' and the 'show of match' events while punishing outcomes were made up of 'no show of match' and 'show of non-match' event.

Five intervals were defined: The decision-making interval lasted from the 'choose' command onset to the 'ready' command onset. The ready interval was defined from the onset of the 'ready' command to the onset of the 'go' command; during this interval the participant moved the cursor to the chosen chip. These two intervals lasted 4 s each. The go interval, lasted from the appearance of the 'go' command until the participant pressed the response button, this interval represents the task's reaction time (RT). The anticipation interval started after the selected chip was placed face down beside the opponent's master chip and ended with the opponent's response. The last interval, outcome, began after the opponent's response and ended with the next 'choose' command.

The interval between the participant's choice and reward delivery was jittered so that the participant could not foresee the reward onset. Participant's choices and opponent's

responses were interactively determined by the flow of the game, round after round, creating a natural progression of the game situation that lasted until the participant won the round, or four minutes had passed, without the participant being explicitly aware of the length of time that each round lasted. If the participant completed a full round (disposed of all chips) before 4 min had elapsed, a "You won!" sign appeared on the screen, otherwise after 4 min a "Game over!" screen was presented and a new round began automatically. Each participant played consecutively for 14 min, while the scan lasted 15 min with the first minute used as baseline. Participants practiced the game before entering the scanner until the experimenter ensured that they understood the rules of the game and could appropriately manipulate the cursor with a four-button control box used with both hands.

Behavioral analysis of the game

A non-match index was defined as the ratio between the number of instances in which a participant chose a match chip over the total number of choices throughout the entire game. This index represents a choice bias for safe matching chips when smaller than 0.5 or for risky non-matching chips when greater than 0.5.

fMRI data preprocessing

fMRI data was preprocessed using BrainVoyager QX 2.3 software package (Brain Innovation, Maastricht, The Netherlands). The first six functional volumes, before signal stabilization, were excluded from analysis. A standard sequence of preprocessing was performed: 3D motion correction using trilinear interpolation, linear trend removal and high-pass filtering. A 6-mm full-width at half-maximum Gaussian smoothing was used to overcome differences in inter-subject localization. Functional maps were manually aligned and co-registered with 3D anatomical data, which were normalized into Talairach space. To account for the hemodynamic response, predictors were convolved with 6-s hemodynamic response filter.

fMRI data analyses

Brain Voyager QX 2.3 (Brain Innovation, Maastricht, Netherlands) was used for all fMRI data analyses. The size of the effect for each condition for each participant was computed by a general linear model (GLM) that included all the conditions of the game; choose, ready, go, no show match, no show non-match, picked match, picked non-match, show match and show non-match. GLM regressors of the anticipation interval were sorted into "safe" and "risky" (i.e. "match" and "non-match") according to the player's choice; and those of the outcome interval based on the computers' response (i.e. "show" or "no show") to derive the four related task conditions: safe anticipation, risky anticipation, rewarding outcome and punishing outcome (Fig. 1). If only matching chips or only non-matching chips remained to choose from, a condition in which the participant had no actual choice, the events were discarded ("don't care"). To avoid the confounding effect of fluctuations in the whole-brain BOLD signal, the whole brain global mean signal was entered to the model as a nuisance regressor, and so was the mean white-matter signal. MNI coordinates were transformed to Talairach coordinates using the Brett transform.

fMRI whole brain analyses

We performed a whole brain two-factor (within-subject, between-groups) ANOVA with repeated measures, assessing each condition of interest separately and according to our hypotheses, contrasting the anticipation and outcome conditions between the two groups while correcting for multiple comparisons at the voxel level (whole-brain $p = 0.05$, FDR corrected).

fMRI regional analyses

We defined six regions of interest (ROI) for anticipation and outcome, based on a functional neuroimaging meta-analysis of reward (Liu et al. 2011) and our experience with this task (Admon et al. 2012; Gonen et al. 2012; Admon et al. 2013) (Table 1). For regional response effect we extracted GLM mean parameter estimates (beta weights) within a $5 \times 5 \times 5$ mm cube.

Functional connectivity analysis

A whole brain psychophysiological interaction (PPI) random effects GLM analysis was conducted to test for task-specific changes in whole-brain connectivity between NMC and NMNC(O'Reilly et al. 2012). Regressors included the psychological variable (all the original regressors of the experiment condition), the physiological variable (time course activity in the seed ROI) and the interaction variable (an element-by-element product of the psychological and physiological variables). Seed regions were delineated as a 125 mm cube. Significance threshold was corrected for multiple comparisons at voxel level (FDR $p = 0.05$).

Statistical analysis

Means and standard deviations were calculated for all dependent variables that were collected outside the scanner. The relationship between genetic status and behavioral indices was examined using the Student's t-test or χ^2 for continuous and dichotomous variables,

Table 1 Region of Interest coordinates based on Liu et al. for anticipation and outcome

Anticipation of reward	X	Y	Z	NMNC	NMC	P	T (df)
Right NAcc	12	10	−4	−0.004 (0.101)	−0.002 (0.067)	0.98	−0.17(66)
Left NAcc	−12	9	−6	0.179 (0.079)	−0.003 (0.056)	0.05	1.95 (66)
Right Insula	38	19	−8	0.413 (0.073)	−0.053 (0.077)	0.02	−2.35 (66)
Left Insula	−32	17	−6	0.159 (0.067)	−0.058 (0.058)	0.09	−1.69 (66)
Right Thalamus	4	−11	12	0.032 (0.068)	−0.007 (0.059)	0.66	0.44 (66)
Left Thalamus	−10	−21	12	0.021 (0.066)	0.015 (0.052)	0.95	0.06 (66)
Rewarding outcome							
Right NAcc	12	9	−6	−0.480 (0.204)	−0.630 (0.146)	0.54	0.60 (66)
Left NAcc	−10	8	−4	−0.878 (1.71)	−0.652 (0.157)	0.33	−0.97 (66)
Right Medial Orbitofrontal cortex	−2	54	−8	−0.201 (0.227)	−0.535 (0.125)	0.19	1.32 (66)
Left Medial Orbitofrontal Cortex	2	46	−14	0.196 (0.205)	−0.212 (0.138)	0.09	1.68 (66)
Right Amygdala	26	−1	−13	−0.204 (0.191)	−0.440 (0.159)	0.34	0.95 (66)
Right Insula	36	21	−8	0.289 (0.148)	−0.381 (0.141)	0.02	2.39 (66)

NMNC- Non-Manifesting Non-Carriers, NMC - Non-Manifesting Carriers, NAcc – nucleus accumbens

respectively. Spearman rank-order correlation was used to assess the relationship between behavioral data, activations (beta weights) and connectivity measures. Two regression analyses were performed with RT and the non-match index as the dependent variables. The model included age, STAI-T, STAI-S, BDI, MoCA UPSIT and UPDRS III as independent variables. SPSS version 20 was used for all statistical analyses.

Results

Group characterization

One hundred participants were recruited to this study, however only 68 were included in this report for the following reasons: excessive head movements ($n = 8$), technical problems with the generated protocol ($n = 11$), panic attack (n = 1), presence of a GBA mutation ($n = 3$), BDI score above 10 (n = 3), MoCA score bellow 23 (n = 3) and UPDRS motor scores above 5 (n = 3). This cohort of participants has already been previously reported on by our group utilizing different fMRI tasks. Thirty-six of the 68 study participants were NMC. Behavioral results are presented in Table 2, no significant between-group differences were noted on any of the scales assessed.

Behavioral results

Regression analysis revealed that STAI-T (B = −0.40, CI -0.16 – 0.00, $p = 0.05$), STAI-S (B = 0.51, CI 0.00–0.01, $p = 0.04$) and MoCA scores (B = 0.54, CI 0.01–0.05, $p < 0.01$)

Table 2 Participants' characteristics

	Non-carriers	Carriers	P
Number	32	36	
Age	45.83 ± 10.45	49.08 ± 11.62	0.23
Gender F/M	15/17	20/16	0.63
Handedness R/L	29/3	33/3	0.88
Years of education	16.53 ± 1.94	16.35 ± 2.32	0.99
STAI-T	29.87 ± 5.61	34.23 ± 10.20	0.04
STAI-S	30.03 ± 7.85	31.73 ± 9.98	0.45
BDI	2.75 ± 2.92	2.44 ± 3.38	0.69
Novelty Seeking	14.41 ± 5.29	15.82 ± 5.83	0.32
Reward Dependence	14.51 ± 3.28	15.02 ± 3.48	0.55
Harm Avoidance	14.34 ± 4.71	14.11 ± 5.38	0.86
UPDRS III	1.62 ± 1.41	2.05 ± 2.15	0.34
MoCA	26.50 ± 2.06	27.05 ± 2.36	0.31
UPSIT	32.41 ± 3.78	32.31 ± 3.66	0.91
Global Cognitive Score	102.75 ± 8.74	102.29 ± 6.74	0.81
Memory	100.65 ± 8.91	100.76 ± 9.65	0.96
Executive Function	102.64 ± 11.06	100.66 ± 10.55	0.41
Go no-Go	102.42 ± 16.99	101.09 ± 15.34	0.74
Stroop	100.14 ± 16.23	96.69 ± 15.31	0.38
Catch game	106.01 ± 11.99	104.25 ± 11.97	0.55
Visuospatial	103.68 ± 14.36	106.97 ± 12.91	0.33
Attention	100.88 ± 12.86	98.87 ± 8.67	0.46
Motor Skills	106.38 ± 8.86	105.49 ± 6.25	0.64
Non-match Index	0.42 ± 0.14	0.47 ± 0.11	0.12
Reaction Time	1.02 ± 0.71	1.33 ± 1.19	0.19

F/M: female/male, R/L right/left, STAI: State-Trait Anxiety Inventory, BDI: Beck Depression Inventory, UPDRS: Unified Parkinson's Disease Rating Scale part III (motor), MoCA: Montreal Cognitive Assessment, UPSIT: University of Pennsylvania Smell Identification Test

predicted the non-match index in NMNC (F = 2.45, $p = 0.05$). The same analysis did not reveal any significant findings among NMC. Regression analysis of RT as the dependent variable using the same model did not reveal any findings in either group.

Region of interest analysis

Two regions demonstrated group effects during general anticipation of reward as hypothesized; the left NAcc (p = 0.05, $t = 1.95$) and the right insula ($p = 0.02$ $t = 2.39$). The NAcc demonstrated a trend towards a between-group interaction effect of anticipation (F (2,66) = 3.62, $p = 0.06$) with NMC showing lower activity (0.059 ± 0.036 [mean ± SEM]) during risky anticipation compared to NMNC (0.214 ± 0.073 [mean ± SEM]) (Fig. 2a). In the right insula no interaction effect between groups and conditions was detected. However, post-hoc examination of simple effects revealed that NMC (0.279 ± 0.045 [mean ± SEM]) trended to higher activation patterns during safe anticipation compared to NMNC (0.112 ± 0.055 [mean ± SEM]) (T(66) = −2.35, $p = 0.02$, Fig. 2c). Correlations between beta weights of risky anticipation in the left NAcc and the non-match index within each group were significant (NMNC: $r = -0.397$, $p = 0.024$, NMC: $r = 0.410$, $p = 0.013$; Fig. 2b) with a trend for a correlation between safe anticipation in the right insula and the non-match index (NMC: $r = 0.301$, $p = 0.07$). The right insula demonstrated between-group difference in activation patterns during the outcome phase ($p = 0.02$) with an interaction effect between groups and outcomes (F (2,66) = 13.97, $p < 0.001$). NMC showed reduced activations (−0.079 ± 0.105 [mean ± SEM]) compared to NMNC (0.310 ± 0.123 [mean ± SEM]) during punishing outcomes (p = 0.02) (Fig. 2d, Table 1).

Whole brain analysis

Whole brain analysis revealed significant main effect for group in the 'go' condition when participants were required to press the

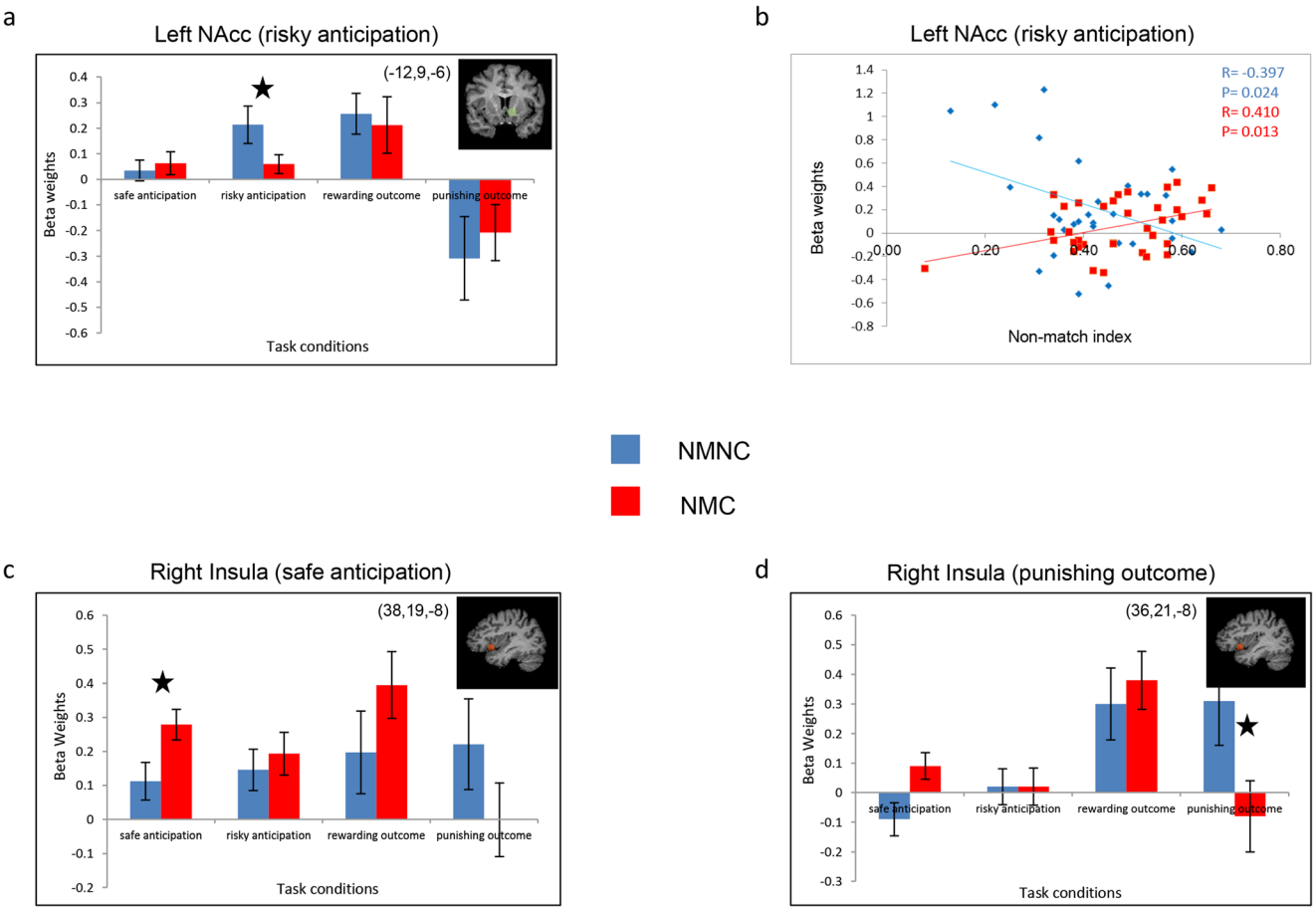

Fig. 2 Region of Interest analysis. **a** Differential activation patterns between NMNC (blue) and NMC (red) during risky anticipation in the left NAcc. **b** Scatter plots of correlation analysis between the non-match index and beta weights during risky anticipation in the NAcc for both NMC (red) and NMNC (blue) groups. **c** Differential activation patterns between NMNC (blue) and NMC (red) during safe anticipation in the right insula. **d** Differential activation patterns between NMNC (blue) and NMC (red) during punishing outcome in the right insula. NAcc - nucleus accumbens, NMNC - non-manifesting non-carriers, NMC - non-manifesting carriers, star indicates significant between groups differences in beta weights ($p < 0.05$)

Table 3 Between group main effect of the 'go' condition

		X	Y	Z	T	P
right precentral	BA9	38	25	36	6.12	<0.001
right middle frontal gyrus	BA10	38	58	6	7.17	<0.001
right inferior parietal lobe	BA40	35	−32	33	6.45	<0.001
right parahippocampal gyrus	BA19	35	−41	−3	5.59	<0.001
right insula	BA13	26	28	9	6.23	<0.001
right middle occipital gyrus	BA18	32	−83	−9	5.92	<0.001
right medial frontal lobe	BA6	14	7	54	8.64	<0.001
right middle frontal gyrus	BA6	29	−2	48	6.00	<0.001
right parahippocampal gyrus	BA28	20	−26	−6	−7.87	<0.001
right superior frontal gyrus	BA8	20	43	46	6.31	<0.001
right caudate body		8	16	15	7.54	<0.001
left paracntral lobe	BA6	−7	−29	63	6.17	<0.001
left midbrain		−10	−29	−9	−7.66	<0.001
left caudate body		−22	22	9	6.91	<0.001
left lingual gyrus	BA19	−10	−56	−6	−7.10	<0.001
left precuneus	BA7	−13	−44	54	5.72	<0.001
left cingulate	BA32	−16	10	36	7.42	<0.001
left cingulate	BA31	−22	−53	24	6.54	<0.001
left parahippocampal gyrus	BA30	−31	−47	12	6.56	<0.001
left middle frontal gyrus	BA8	−28	22	39	6.92	<0.001
left postcentral gyrus	BA3	−58	−14	21	−6.41	<0.001
left inferior parietal lobe	BA40	−61	−29	27	−5.77	<0.001

BA - Broadmann's Area

response button after preparing their next move. Diffuse cortical as well as left midbrain and bilateral caudate body with NMC demonstrated higher activations in most regions compared to NMNC ($p = 0.05$, FDR corrected; Table 3, Fig. 3a,b).

Functional connectivity analysis

Five regions with between-group divergent activation patterns that were detected in the whole brain and ROI analysis; left and right caudate during the 'go' condition, left NAcc for risky anticipation and right insula for both safe anticipation and punishing outcome, were used as seed regions in a PPI analysis (Table 4, Fig. 4), with results corrected for multiple comparisons at the voxel level (FDR $p = 0.05$).

The left caudate displayed stronger connectivity to the frontal cortex in NMC and stronger connectivity to the right temporal lobe in NMNC (Fig. 4a). A correlation between the left caudate-right frontal cortex connectivity and part III UDPRS among NMC ($r = -0.359$, $p = 0.032$) was detected. However, no significant findings were detected while performing the same analysis using the right caudate as seed region.

The left NAcc demonstrated stronger connectivity with the pregenual anterior cingulate cortex (pgACC) in NMNC and stronger connectivity to the dorsal anterior cingulate cortex (dACC) in NMC (Fig. 4b). Significant correlations between the left NAcc-dACC connectivity in NMNC and the non-match index ($r = 0.434$, $p = 0.013$) was detected.

PPI analysis of the right insula detected stronger connectivity with the right medial frontal lobe among NMNC while the left insula demonstrated stronger connectivity with the right insula in NMNC (Table 4).

Discussion

We tested for differential reward related neural activity and connectivity between NMC and NMNC of the G2019S mutation in the *LRRK2* gene, using an interactive game that evokes behavioral states of safe and risky anticipation to reward, as well as acceptance of rewarding or punishing outcomes. NMC demonstrated reduced BOLD activations when faced with risky anticipation and punishment in the left NAcc and right insula, respectively and higher BOLD activation when faced with safe anticipation in the right insula as well. Exploratory whole brain analysis revealed between-group differences when pressing the response box in cortical motor regions as well as in bilateral caudate and left midbrain regions.

Differential response to both reward anticipation and to rewarding outcomes

The ventral striatum is part of the reward system with a role in integrating cognitive, motor and affective information and in influencing goal-directed behavior (Haber and Knutson 2010). It is considered to be relatively preserved in early PD compared to the dorsal striatum (Kish et al. 1988). According to the dopamine overdose theory, the dopamine levels needed to treat the motor symptoms of PD, which result from the severely depleted dorsal striatum, overdose the relatively intact ventral striatum resulting in both cognitive and behavioral impairments including impulse control disorders (Cools et al. 2001). While non-medicated patients with PD do not have higher rates of ICD compared with healthy controls (Weintraub et al. 2015), encoding of both reward and punishing outcomes have been found to be reduced in non-medicated PD patients; with lower response magnitude to reward compared to healthy controls in the ventral putamen, caudate, ventral tegmental area and insula (van der Vegt et al. 2013). The reduction is reward response prior to dopamine treatment could potentially explain the tendency for ICD among PD patients when medicated, similarly to findings among gamblers who demonstrate reduced response to reward in mesolimbic regions prior to gambling and an exaggerated response once they begin gambling (Cilia et al. 2011). This might be the explanation for the increase of

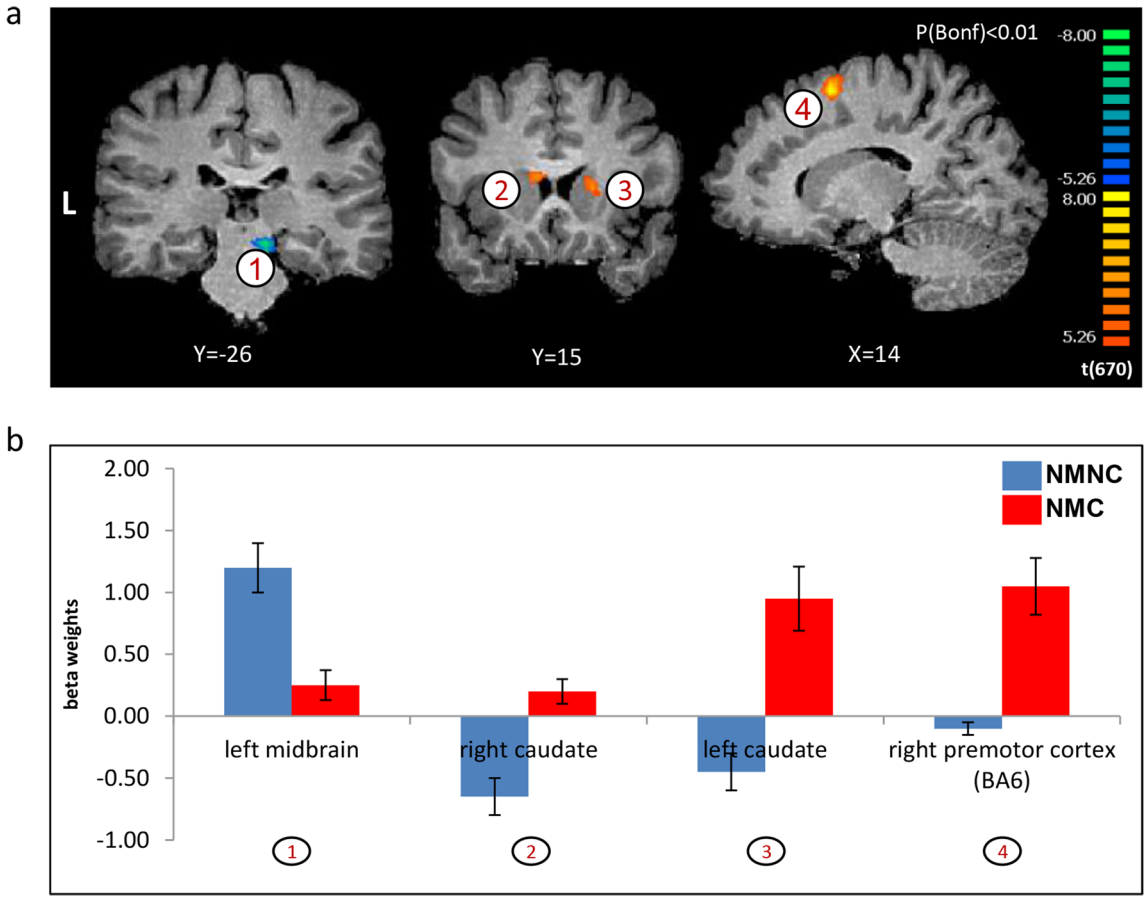

Fig. 3 Whole brain analysis of the 'go' task between the two study groups. **a** Activation maps, contrasting the two study groups during the 'go' condition, multiple corrected using FDR ($p = 0.05$) (for display purposes portrayed at Bonferroni $p = 0.01$). 1- left midbrain, 2- right caudate, 3- left caudate, 4- right dorsal premotor (BA6), higher activations for NMC are shown in orange, for NMNC in blue. **b** Graphical representation of the differential activation patterns between NMC (red) and NMNC (blue) during the 'go' condition (presented in A). 1- left midbrain, 2- right caudate, 3- left caudate, 4- right dorsal premotor (BA6). NMNC- Non-Manifesting Non-Carriers, NMC - Non-Manifesting Carriers, BA - Broadmann's Area

Table 4 PPI analysis for each condition the seed region and differential connectivity regions are presented

		X	Y	Z	T	P
Left caudate 'go'						
right middle temporal gyrus	BA21	66	−17	−9	−5.35	<0.005
right superior temporal gyrus	BA22	47	−17	6	−5.56	<0.005
right precentral gyrus	BA6	38	−8	60	5.39	<0.005
left anterior cingulate	BA32	−10	34	−6	5.37	<0.005
left inferior frontal gyrus	BA45	−49	19	6	4.88	<0.005
Nacc 'risky anticipation'						
right dorsal cingulate	BA 24	5	−5	36	5.67	<0.005
right perigenual cingulate	BA 24	5	31	3	−4.95	<0.005
Right insula 'safe anticipation'						
right medial frontal lobe	BA 6	2	−17	70	−2.87	<0.005
Right insula 'punishment'						
left insula	BA 13	−40	10	−9	−4.77	<0.005

dopamine release that causes impairment in expectancy coding (van Eimeren et al. 2010).

We identified a valence dependent disparity among NMC with increased response to safe anticipation along with reduced response to risky anticipation and punishing outcomes in key reward structures. This finding could be related to the tendency of dopamine to enhance reward-based and impair punishment-based learning in patients with PD (Frank et al. 2004) even if one takes into account that the direct association between the BOLD signal and dopamine is elusive.

NMC trended for higher trait anxiety levels but did not differ from NMNC in the three personality measures assessed herein. Low dopamine levels have been associated with a lack of novelty seeking (NS) in PD patients (Kaasinen et al. 2004). While no correlation was detected between the activation patterns of the NAcc and insula and NS or STAI-T among both groups of participants, a reduced response to threat and

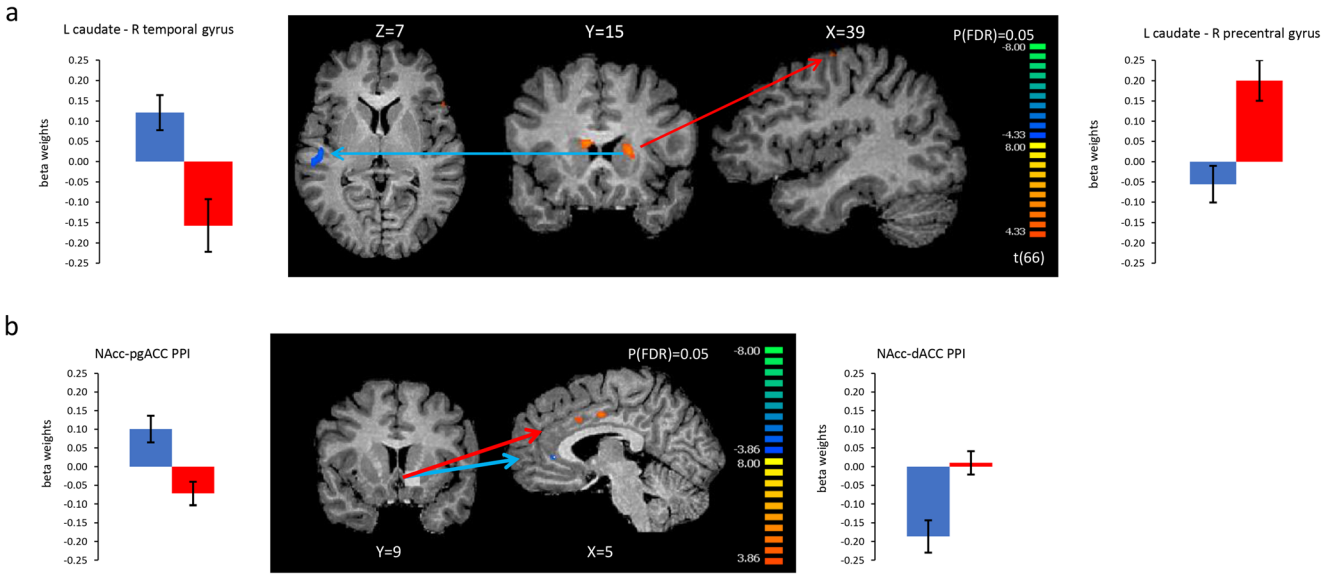

Fig. 4 Psychophysiological interaction (PPI) analyses. **a** Left caudate during the 'go' condition as seed region. Differential connectivity patterns detected; NMNC showed stronger connectivity with the right temporal gyrus (blue), NMC with stronger connectivity with right precentral gyrus (BA6) (red). **b** Left NAcc during risky anticipation as seed region. Differential connectivity patterns detected; NMNC showed stronger connectivity with the anterior pregenual anterior cingulate cortex (blue), NMC demonstrated stronger connectivity with the dorsal anterior cingulate cortex (red). NMNC- Non-Manifesting Non-Carriers, NMC - Non-Manifesting Carriers, BA - Broadmann's Area, NAcc – nucleus accumbens, pgACC - pregenual cingulate cortex, dACC – dorsal anterior cingulate cortex

increased response to reward seems to fit the personality trait associated with PD (Menza et al. 1993).

In the PPI analysis, NMC showed significant connectivity with the dACC which has been implicated in performance monitoring, value encoding, decision making and learning (Vogt et al. 1992) while NMNC had significant connectivity with the pgACC which is associated with affective and emotional functions (Shenhav et al. 2013). However both regions are related to reward and motivational processing (Vogt 2016). Thus, it could be inferred that while NMNC activate emotional reward areas when faced with risky anticipation, NMC use a more cognitive based approach.

The anterior insula is involved in risk processing (Palminteri et al. 2012) providing a neural marker for negative arousal, and has also been reported to be both functionally and structurally connected with the ventral striatum (Liu et al. 2011). Our findings which suggest the involvement of the right anterior insula, in both safe anticipation and punishing outcomes, with the PPI analysis indicating that NMC had less bilateral insular connectivity compared to NMNC during punishing outcomes, could potentially explain part of the divergent activation pattern of the NAcc in NMC.

The task that was utilized in this study has previously been used to assess differences in motivational processing in healthy controls and among patients with obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). In controls, increased activation in bilateral amygdala was detected when contrasting risky anticipation with safe anticipation. Contrasting unpredicted reward with unpredicted punishment resulted with bilateral NAcc activation as well as ACC, precuneus and inferior parietal lobe activations (Admon et al. 2013). Among patients with PTSD and OCD, reduced NAcc activation during rewarding outcomes was detected (Admon et al. 2012; Admon et al. 2013) but not during risky anticipation and punishment as with NMC. Interestingly, both PTSD and OCD patients tended to take less risks compared with controls while NMC had a higher non-match index which did not reach significance. The NAcc of OCD patients had lower functional connectivity with the dACC (Admon et al. 2012) compared with an increase in connectivity among NMC detected by the PPI analysis. These findings could be explained by the endogenous dopaminergic state, while OCD and PTSD are characterized with increased dopamine levels (Spivak et al. 1999; Eagle et al. 2014), NMC have been found to have reduced dopamine levels in the basal ganglia (Artzi et al. 2017).

Motor performance under stressful conditions

While RT did not differ between the two groups, NMC recruited widespread cerebral regions compared with NMNC while pressing the response box. However, because fMRI data from the midbrain suffers from artifacts related to arterial endogenous motion and partial volume averaging due to its small size (Haber and Knutson 2010), we cannot precisely determine which structures of the midbrain were involved.

Hyper-activations in task related areas as a mean of compensation for latent disease has been reported with both larger areas of activation and stronger activation patterns considered to represent compensation in pre-manifesting participants and tend to reverse the closer the participants are to the diseased state (Scheller et al. 2014). Our results suggest that NMC recruit widespread motor regions while performing the motor part of this task, indicating a reorganization of the motor system in these participants when assessed under threat. These results are in line with both the lack of motor function difference while performing the computerized cognitive assessment and with the gait abnormalities detected in NMC while performing dual tasks (Mirelman et al. 2011), suggesting that motor tasks under stress in NMC could be viewed as potential biomarkers for future development of PD among populations at risk.

Several limitations need be addressed. Penetrance estimations for the G2019S mutation range from 10%–17% at age 50 years to as high as 74% at the age of 79 years (Trinh et al. 2014; Marder et al. 2015; Lee et al. 2017). Currently, there is no method to anticipate which of the carriers will progress to develop PD. Hence, grouping all NMC together might hamper the interpretation of our findings. Future studies will longitudinally follow this important cohort and together with DaT scans that are being collected, will enable the better understanding of the disease related nature of our findings. At present, none of the participants of this study were found to develop motor symptoms of PD. While assessing personality traits, depression and anxiety, we did not collect data regarding apathy and anhedonia which are also dopamine mediated and could influence the result of this study (Santangelo et al. 2015). The absence of a PD group means that no clear relationship between our findings among this "at risk" group and those of patients with PD can be demonstrated. In addition, while no structural analysis was conducted in this study to attest for lack of atrophy in relevant structures, we previously reported that no such differences could be detected among this same cohort of participants (Thaler et al. 2014).

Conclusion

NMC of the G2019S mutation in the *LRRK2* gene exhibit differences in reward-related activations during both anticipation and response to rewarding outcomes, these changes were correlated with the task's non-match index, indicating the motivational aspect of these findings. We found evidence for the involvement of the ventral striatum in NMC indicating that this structure might already be affected in "at risk" individuals for future development of the disease. In addition, differential motor activation patterns were detected suggesting that subtle motor impairments can be relevant even in a motivational task when a simple motor response is required in the context of goal directed decision making.

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AM - conception and design, acquisition and analysis of data.
RCH - conception and design, drafting of manuscript.
TG - drafting of manuscript.
AOU - conception and design.
BB - conception and design.
NG - conception and design, drafting of manuscript.
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Compliance with ethical standards

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Conflict of interest None of the authors report any conflict of interest regarding this study.

Statistical analysis was performed by Dr. Avner Thaler.

Ethical approval This research received our institutions' IRB and was performed in accordance with the ethical standards as laid down in the

1964 Declaration of Helsinki and its later amendments or comparable ethical standards, with each participant signing an informed consent form before initiation as noted in the text.

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