BMC Medicine

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Exploratory analysis of the relationship between striatal connectivity and apathy during phosphodiesterase 10 inhibition in schizophrenia: findings from a randomized crossover trial

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Abstract

Background Negative symptoms in schizophrenia remain a challenge with limited therapeutic strategies. The novel compound RG7203 promotes reward learning via dopamine D1-dependent signaling and therefore holds promise, especially to improve the apathy dimension of negative symptoms. When tested as add-on to antipsychotic medication, apathy did not change significantly with RG7203 versus placebo. However, the response varied across patients, and a subset showed clinically relevant improvement of apathy. It remains unclear if these interindividual differences are related to neurobiological correlates.

Methods Due to the predominant binding of RG7203 in the striatum, we investigated how apathy changes with RG7203 are related to changes in cortico-striatal connectivity by computing rank correlations (r_s). In a post hoc exploratory analysis, we focused on cortico-striatal circuits that have been associated with apathy and previously showed connectivity alterations in schizophrenia. In a double-blind, 3-way randomized and counterbalanced crossover study, resting-state functional magnetic resonance imaging was acquired from 24 individuals with schizophrenia following a 3-week administration of placebo, 5 mg, or 15 mg of RG7203 as an add-on to antipsychotics.

Results We found that 5 mg or 15 mg of RG7203 did not lead to significant changes in striatal connectivity. However, changes in the apathy response across individuals were reflected by striatal connectivity changes. Apathy improvement with 5 mg and 15 mg RG7203 vs. placebo was associated with increased striatal connectivity to paracingulate ($r_s = -0.58$, $p = 0.047$ for both doses) and anterior cingulate regions ($r_s = -0.56$, $p = 0.047$ for both doses). Such associations were not observed for the negative symptom dimension of expressive deficits. We additionally observed that lower striatal connectivity to paracingulate and anterior cingulate regions during placebo was linked to greater apathy improvement during RG7203 treatment at both doses ($r_s = 0.61$–0.79 and $p = 0.0002$–0.02 across regions and doses).

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Conclusions These findings suggest that striatal connectivity with the paracingulate gyrus and anterior cingulate cortex may be associated with apathy modulation under RG7203 treatment. Replication and further elaboration of these findings in larger clinical studies could help to advance biologically informed and personalized treatment options for negative symptoms.

Trial registration NCT02824055, registered on ClinicalTrials.gov (2016–06-21).

Keywords Schizophrenia, Negative symptoms, Apathy, Striatal connectivity, Phosphodiesterase 10 inhibitor

Background

Negative symptoms in schizophrenia are a therapeutic challenge [1, 2]. While traditional antipsychotics treat positive symptoms, their effectiveness against negative symptoms is limited [1, 3]. This creates a crucial gap in treatment options, as negative symptoms are considered one of the main drivers of impaired functional outcomes and reduced quality of life [4].

Factorial analyses of psychometric scales suggest that negative symptoms can be mapped onto the two dimensions apathy and diminished expression [5–7]. While the diminished expression dimension includes the domains blunted affect and alogia, the apathy dimension subsumes the domains avolition, asociality, and anhedonia [8]. Both apathy and diminished expression can be assessed using interview-based, observer-rated scales, such as the Brief Negative Symptom Scale (BNSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS) [9–11]. Individuals with schizophrenia show impaired learning from rewards which is mediated by dopamine-dependent D1 receptor signaling in the striatum [12] and related to the apathy dimension of negative symptoms [8, 13–18]. Evidence from behavioral tasks and computational modeling suggests that apathy-related deficits in reward-driven learning involve difficulties in representing expected reward values and estimating the costs of effortful behavior [17–22]. The recent phosphodiesterase 10 inhibitor RG7203 primarily targets the striatum and promotes reward learning by enhancement of D1-signaling [12, 23]. RG7203 therefore holds promise, particularly to improve the apathy dimension of negative symptoms [23]. While RG7203 has shown small, but consistent positive effects across four different paradigms probing reward functioning in healthy volunteers [24], an add-on three-way, placebo-controlled cross-over study in schizophrenia patients with negative symptoms and stable antipsychotic treatment was negative overall [23]. While a subset of participants showed clinically relevant apathy improvement, there were also patients with clinically relevant worsening of apathy. Instead of random longitudinal apathy fluctuations, these interindividual differences could reflect a heterogeneous effect of RG7203 across patients. In addition to enhancing D1-signaling, RG7203 dampens D2-signaling, a mechanism that can contribute to secondary negative symptoms [25, 26]. Depending on patient-specific D1/D2-signaling and D2 receptor blockade from background antipsychotics, the additional D2-dampening of RG7203 could have led to deleterious effects in some patients, while the beneficial effects of enhanced D1-signaling may have prevailed in others [23]. Striatal functional connectivity during rest, a neurobiological indicator of synchronized neural activity in intrastriatal and cortico-striatal circuits, is related to negative symptoms of schizophrenia as well as to D1/D2 receptor signaling [27–37]. The strength of functional connections within resting-state networks is supposed to be promoted by D1-signaling [34], but can also be reduced by dampening of D2-signaling [37] and is additionally modulated by the regional ratio of D1 and D2 receptors [35].

We therefore asked how the variable apathy changes with RG7203, for example, due to patient-specific D1/D2-signaling features, are related to striatal connectivity with different brain regions. Multimodal evidence from functional and structural MRI suggests that striatal, anterior cingulate, ventromedial, and dorsolateral prefrontal regions are key structures implicated in the pathophysiology of apathy [8]. Within this prefrontal-striatal network, psychosis patients show aberrant functional connectivity that correlates with negative symptom severity and involves ventral as well as dorsal striatum [28, 32, 38]. Hence, we expected that different apathy changes with RG7203 will be related to connectivity changes in those cortico-striatal circuits that have been associated with apathy and showed aberrant connectivity in schizophrenia patients. Specifically, we hypothesized that apathy improvement with RG7203 versus placebo will be associated with the restoration of previously aberrant striatal connectivity. Given that diminished expression has been primarily associated with brain regions distinct from those linked to apathy [8], we expected striatal connectivity changes in apathy-related structures to show weaker associations with alterations in diminished expression.

Methods

Participant criteria and experimental design

Patients aged between 15 and 50 years with a confirmed DSM-5 diagnosis of schizophrenia were enrolled. Participants were required to have a minimum score of 18

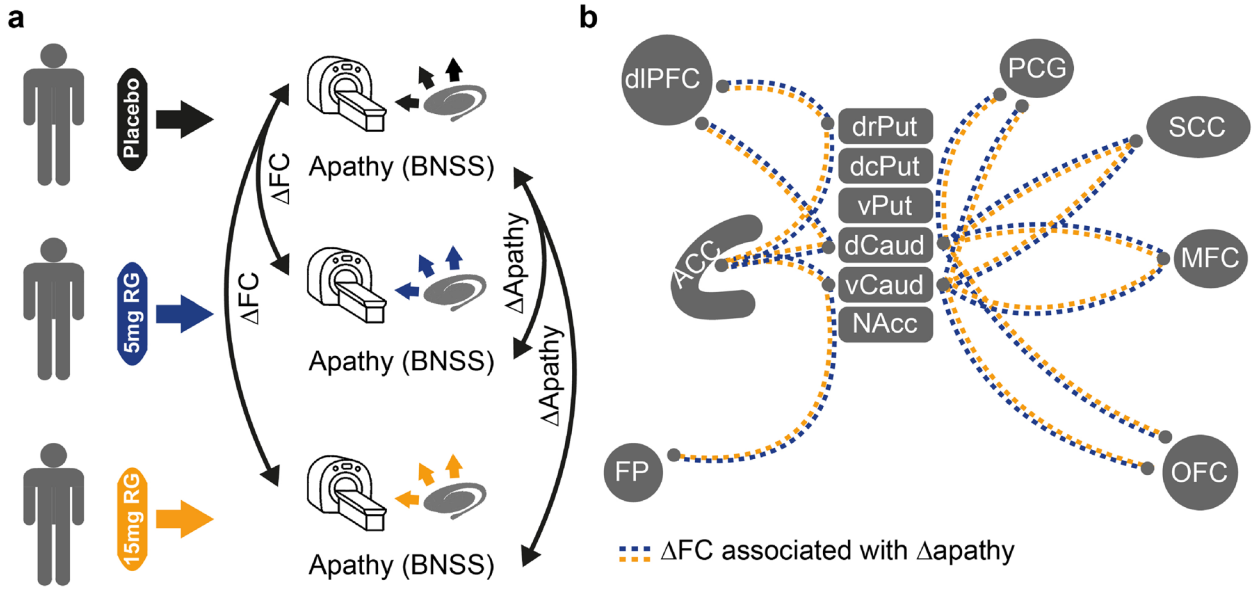

Fig. 1 Hypotheses about effects of RG7203. **a** Placebo, 5 mg, or 15 mg RG7203 are given to individuals with schizophrenia, in addition to antipsychotic background medication. After placebo, 5 mg, or 15 mg RG7203 have been given for 3 weeks, individuals with schizophrenia underwent fMRI and BNSS testing. Apathy scores were computed from the BNSS subdimensions avolition, asociality, and anhedonia. ΔApathy was defined as the treatment effect on apathy and computed for 5 mg RG7203 (5 mg RG7203 minus placebo) and 15 mg RG7203 (15 mg RG7203 minus placebo). The treatment effect on cortico-striatal functional connectivity during rest was defined as ΔFC and computed for 5 mg RG7203 (5 mg RG7203 minus placebo) and 15 mg RG7203 (15 mg RG7203 minus placebo). **b** Cortico-striatal circuitry that has been associated with apathy [8] and that showed altered functional connectivity in individuals with schizophrenia and first-episode psychosis across previous studies [32]. We hypothesized that ΔFC in this circuitry correlates with Δapathy at 5 mg (blue dotted line) and 15 mg RG7203 (orange dotted line). Abbreviations: dr, dorsorostral; dc, dorsocaudal; v, ventral; d, dorsal; Put, putamen; Caud, caudate; NAcc, nucleus accumbens; FP, frontal pole; dlPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; PCG, paracingulate gyrus; SCC, subcallosal cortex; MFC, medial frontal cortex; OFC, orbitofrontal cortex

on the PANSS (Positive and Negative Syndrome Scale) negative symptom factor score [39] during the initial screening and to be in a symptomatically stable state. Participants on antipsychotic treatment were included if the dosage did not surpass the equivalent of 6 mg risperidone. Other inclusion criteria included a score of 3 or above on the Clinical Global Impression Severity scale (indicating at least mildly ill); a PANSS depression score (G6) of 4 or below (indicating moderate or mild symptoms); and a score of 8 or below on the Calgary Depression Rating Scale for Schizophrenia. Exclusion criteria encompassed a score exceeding 2 (indicative of mild conditions) on any of the Clinical Global Impression Severity scale items of the Extrapyramidal Symptom Rating Scale and treatment with either olanzapine or clozapine within the preceding 3 months. An exhaustive list of eligibility criteria can be found in the Supplementary Material.

This study was a three-way, placebo-controlled crossover study. Individuals with schizophrenia underwent randomization to one of six treatment sequences that were fully counterbalanced and characterized by three treatment periods with placebo, 5 mg, or 15 mg of RG7203 (Fig. 1a, daily applied in identical oral capsules). Timeline and treatment sequences are shown in Additional file 1: Table S1. Each sequence had about 8 participants and RG7203 was given as add-on treatment to stable antipsychotic background medication [23]. During the period of 15 mg treatment, dosing was progressively increased to the set target over the initial week. A single treatment phase spanned 3 weeks, succeeded by a 2-week wash-out period. fMRI scans and behavioral tasks were conducted on the concluding day of each treatment phase (day 22, Fig. 1a). At the end of a session, participants received the rewards earned during the behavioral tasks [23]. Weekly evaluations were conducted to determine safety, compatibility, and psychological condition. A subsequent follow-up was performed approximately 2 weeks post the final medication dose. Adherence to the regimen was tracked using a mobile application. This is a double-blind study, i.e., the study patients, the investigators, and all individuals in direct contact with the study patients at the investigative sites were blinded as well as the Roche SMT. In total, 33 patients diagnosed with schizophrenia were recruited across three study centers in the USA (study start: 2016–06–27; study completion: 2017–04–24). The sample comprised 30 males and

included 21 African American, 9 Caucasian, and 3 Asian individuals, with a mean age of 36.6 ± 7.0 years (see Additional file 1: Table S2 for further patient characteristics). Of these, 24 patients completed the study. Two patients discontinued due to adverse events (dystonic reactions), and seven discontinued for other reasons, including non-compliance with the study drug, withdrawal by the participant, and loss to follow-up. The two patients with dystonic reactions were withdrawn during the 5 mg RG7203 treatment period. One experienced severe dystonia, while the other experienced mild dystonia. The data from the 24 patients who completed the study were included in the initial analysis. Additional information about the study plan/protocol can be found at https://clinicaltrials.gov/study/NCT02824055.

Cognitive functions, such as reward-driven effortful behavior, probabilistic learning, and working memory, were assessed via fMRI (employing MID and n-back) in addition to behavioral tasks (the working memory reinforcement learning task [WMRLT] and effort-cost–benefit task [ECBT]). Results of these behavior tasks were presented previously [23]. Symptomatology was assessed with the PANSS, BNSS and CGI (Clinical Global Impression) scores. The negative symptom dimensions apathy and diminished expression were derived from the BNSS [10].

The research protocol was registered on ClinicalTrials.gov (NCT02824055) and obtained approvals from responsible ethics oversight bodies (see Declarations below for further details). Informed consent to participate in the study was obtained from all participants.

Results of the primary and secondary objectives/outcome measures have been reported previously [23]. The analyses in this study are post hoc exploratory analyses that were not pre-specified on the ClinicalTrials.gov page. Using a hypothesis-driven approach, we aimed to investigate whether apathy changes with RG7203 were associated with connectivity changes in cortico-striatal circuits previously linked to apathy and known to exhibit aberrant connectivity in schizophrenia.

MRI data collection

Three different 3 T scanner models (GE 3 T Discover 750w 25.0 by GE Healthcare; Siemens 3 T MAGNETOM Trio and Siemens 3 T Verio by Siemens Healthineers) were used. Across all locations, BOLD (blood oxygenation level dependent) fMRI information was gathered using a T2-weighted echo-planar imaging protocol (with parameters: repetition time of 2000 ms, echo time of 27 ms, flip angle set at 90°, 39 slices, and a voxel dimension of 3 × 3 × 3 mm with a 1 mm gap). For each patient, a conventional structural T1-weighted scan (1 × 1 × 1 mm) was also captured for alignment aims using default sequences at every imaging facility.

fMRI data processing

The fMRI datasets underwent preprocessing via the CONN toolbox [40] and were also analyzed using MATLAB (R2023a version by The MathWorks, Inc.). Preprocessing included realignment for motion and distortion correction, co-registration to structural scans, followed by standardization to the Montreal Neurological Institute coordinates, masking of non-gray matter voxels, and application of a 6 mm full width at half maximum Gaussian smoothing kernel. We applied a comprehensive detection and correction of artifacts including despiking using the Artifact Detection Tools (ART) implemented in the CONN toolbox [40, 41]. This also included scrubbing of frame-wise displacement above 0.9 mm and of global signal intensity changes between successive volumes above 5 standard deviations, along with additional regressing out of motion parameters as well as of physiological noise [40, 41]. In addition, all participants whose median frame-wise displacement or median global signal intensity changes exceeded twice the average of these measures across all 24 participants were excluded from further analysis. The last criterion, introduced to ensure a homogeneous dataset and prevent artifacts from artificially elevating connectivity values, led to the exclusion of two participants. The remaining 22 participants who constituted the final analysis group for this study showed homogeneous frame-wise displacement and global signal intensity changes in all conditions before the above-mentioned artifact correction procedures were applied (Additional file 1: Table S3). The fisher-transformed striatal connectivity values of the remaining 22 participants (Additional file 1: Fig. S1) fell within the typical range observed in patients with psychosis [42]. We finally conducted an analysis of functional connectivity during rest using the CONN toolbox in Matlab (MathWorks, version R2023a). All participants were analyzed according to their original assignment to the placebo, 5 mg RG7203, or 15 mg RG7203 groups, with each participant serving as their own control due to the crossover design.

Statistical analyses and hypotheses

In a hypothesis-driven approach, we investigated the effect of RG7203 vs. placebo on functional connectivity in preselected components of the cortico-striatal circuit. Cortico-striatal components were selected if they have been implicated in apathy [8] and showed consistent alteration of functional connectivity in schizophrenia and first-episode psychosis according to prior studies [32]. Apathy has been associated with the following cortico-striatal components: anterior cingulate cortex (ACC),

orbitofrontal cortex (OFC), ventromedial prefrontal cortex, dorsolateral prefrontal cortex (dlPFC) as well as the ventral and dorsal striatum [8]. Our definition of the ventromedial prefrontal cortex thereby included frontal pole (FP), medial frontal cortex (MFC), subcallosal cortex (SCC), paracingulate gyrus (PCG), ACC, and OFC [43]. The striatum was subdivided into ventral rostral putamen (vPut), dorsal rostral putamen (drPut), dorsal caudal putamen (dcPut), ventral caudate (vCaud), and nucleus accumbens (NAcc) according to previously established coordinates [27]. The criteria above resulted in 14 connectivities between cortico-striatal component pairs that have been implicated in apathy and showed consistent connectivity alteration in schizophrenia and first-episode psychosis (Fig. 1b). Of the 14 connectivities (Fig. 1b), prior studies indicated that 13 were reduced in schizophrenia and first-episode psychosis compared to healthy controls; only the connectivity between the ventral caudate (vCaud) and OFC was reported to be increased [32]. Our primary hypothesis was that improvement of apathy during treatment with RG7203 would be associated with the restoration of aberrant striatal connectivity. For all 13 component pairs with reduced connectivity in psychosis, we therefore expected that improvement of apathy would be linked with connectivity increases while worsening of apathy would be associated with further connectivity reductions. For the connectivity between vCaud and OFC with increased connectivity in psychosis [32], we expected that improvement of apathy would be linked with a connectivity decrease while worsening of apathy would be associated with further connectivity enhancement. Compared to apathy which has been primarily linked to ACC, ventromedial prefrontal cortex, dlPFC, OFC, and striatal regions, diminished expression has been more strongly associated with the amygdala, ventrolateral prefrontal cortex, and the rostral anterior cingulate cortex [8]. We therefore also hypothesized that connectivity changes between apathy-related structures would be more associated with apathy changes when compared to alterations in diminished expression.

In light of the limited evidence linking the amygdala-insula-hippocampus-striatum network to apathy or, more broadly, negative symptoms [44–46], we conducted an additional exploratory analysis investigating striatal connectivity with the amygdala, hippocampus, and insula. Similar to the connectivity pairs in our primary hypothesis, striatal regions were selected based on Sabaroedin et al. [32] for connectivity with the amygdala and hippocampus. Regions connected to the insula were identified according to Peters et al. [47], as Sabaroedin et al. [32] did not report consistent psychosis-related connectivity alterations involving the insula.

Changes in resting-state connectivity and apathy with 5 mg or 15 mg RG7203 vs. placebo were tested using a Wilcoxon signed-rank test. Correlations between changes in apathy and connectivity with 5 mg or 15 mg RG7203 vs. placebo were computed using the Spearman correlation coefficient (r_s). The Spearman correlation coefficient is rank-based, does not assume linearity, and is robust against deviations from normality and outliers. These properties make it a conservative and robust measure of association, particularly advantageous for small sample sizes and when possible non-linear relationships between variables are considered. The 95% confidence intervals of the Spearman correlation coefficients were calculated using bootstrapping with 1000 resamples. All Spearman correlation analyses were conducted on 22 independent data points from 22 independent participants, ensuring the avoidance of pseudoreplication [48]. To further investigate connectivity pairs where changes in apathy and striatal connectivity showed a significant Spearman correlation, we applied a linear mixed model (LMM) to analyze their relationship under 5 mg and 15 mg RG7203. The model was designed to assess whether striatal connectivity changes predict apathy changes and whether apathy responses differ between the two dose conditions. The model was specified as follows:

$$\triangle\text{Apathyij} = \beta 0 + \beta 1 \triangle\text{Connectivityij} + \beta 2\text{Doseij} + (1|\text{Subjecti}) + \epsilon ij$$

where ΔApathy_{ij} represents the change in apathy for subject i under condition j (5 mg minus placebo or 15 mg minus placebo). β_0 is the intercept, representing the mean apathy change at 5 mg RG7203 vs. placebo when the connectivity change is 0. β_1 captures the effect of striatal connectivity changes ($\Delta\text{Connectivity}_{ij}$) on apathy. β_2 captures the effect of dose (coded as categorical variable: 5 mg minus placebo vs. 15 mg minus placebo), indicating whether apathy changes differ between doses. $(1|\text{Subject}_i)$ is a random intercept per subject, accounting for interindividual variability in apathy responses. ϵ_{ij} represents residual variability. For all analyses with multiple comparisons, p values were corrected according to the Benjamini–Hochberg procedure as implemented in the Matlab mafdr-function.

Results

Across participants, apathy did not change significantly for 5 mg or 15 mg of RG7203 vs. placebo (Fig. 2a). In the context of the BNSS scale from 0 (absence of symptoms) to 6 (severe symptoms), apathy changes spanned a clinically relevant range of 3.43 (SD: 0.86) and 3.71 (SD: 0.93) for 5 mg and 15 mg of RG7203 vs. placebo, respectively (Fig. 2a).

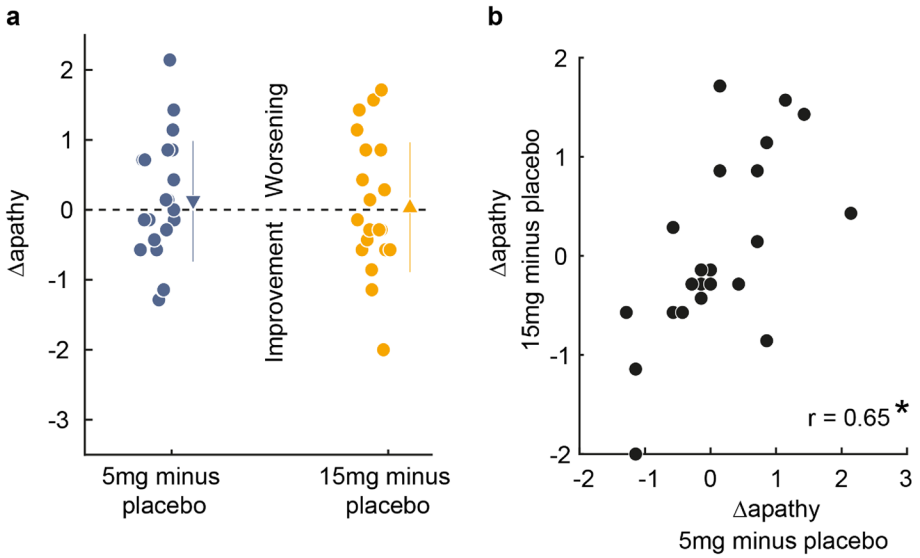

Fig. 2 Apathy changes with RG7203 vs. placebo. **a** Apathy changes (Δapathy) when 5 mg or 15 mg RG7203 are given instead of placebo (blue: 5 mg minus placebo; orange: 15 mg minus placebo); filled circles represent individual participants; triangles with error bars show means and standard deviations. **b** Correlation between Δapathy at 5 mg and 15 mg RG7203. Asterisk indicates $p < 0.05$

At 5 mg RG7203 compared to placebo, 23% of patients showed an improvement of more than 0.5 points on the BNSS scale, while 32% experienced a worsening of more than 0.5 points. At 15 mg RG7203, 27% of patients improved by more than 0.5 points, and an equal proportion (27%) worsened by more than 0.5 points. Apathy changes at 5 mg and 15 mg RG7203 versus placebo were positively correlated across the 22 participants ($r_s = 0.65$; $p = 9.9{*}10^{-4}$, Fig. 2b), indicating that participants who showed greater apathy changes at one dose versus placebo tended to show greater apathy changes in the same direction at the other dose versus placebo. If these apathy changes in each participant were purely driven by random longitudinal fluctuations across the placebo, 5 mg, and 15 mg RG7203 conditions, we would expect no correlation between apathy changes at 5 mg and 15 mg RG7203 versus placebo across participants. Due to the interindividual differences of apathy changes and their similarity at both doses of RG7203, we further explored their potential relationship to cortico-striatal connectivity.

In the apathy-related cortico-striatal circuit, striatal connectivity did not change significantly for 5 mg or 15 mg RG7203 vs. placebo (Fig. 3a, b). Striatal connectivity changes at 5 mg and 15 mg RG7203 versus placebo were positively correlated across the 22 participants for all circuit connections ($p = 1.22{*}10^{-4}$, Wilcoxon signed-rank test for $n = 14$ correlation values, Additional file 1: Fig. S2), and the highest correlation was found for the connectivity pair vCaud-PCG ($r_s = 0.7$, $p = 4{*}10^{-3}$). These positive correlations between striatal connectivity changes at 5 mg and 15 mg RG7203 versus placebo indicate that individuals with larger striatal connectivity changes at one dose versus placebo also tended to exhibit larger changes in the same direction at the other dose versus placebo. If striatal connectivity changes at 5 mg and 15 mg RG7203 versus placebo were purely driven by random longitudinal fluctuations across the placebo, 5 mg, and 15 mg RG7203 conditions, we would expect no correlation between striatal connectivity changes at 5 mg and 15 mg versus placebo across participants. Due to the interindividual differences of connectivity changes and their similarity at both doses of RG7203, we then investigated if apathy changes with 5 mg or 15 mg of RG7203 versus placebo (Fig. 2a) are reflected by corresponding changes in striatal connectivity (Fig. 3a, b): For 5 mg of RG7203, there was a negative correlation with connectivity changes between vCaud-PCG ($r_s = -0.58$, $p = 0.047$) and vCaud-ACC ($r_s = -0.56$, $p = 0.047$, Fig. 3c, Additional file 1: Fig. S3a). For 15 mg of RG7203, we also found a negative correlation between changes in apathy and vCaud-PCG/ACC connectivity (Fig. 3c, Additional file 1: Fig. S3b, vCaud-PCG: $r_s = -0.58$, $p = 0.047$; vCaud-ACC: $r_s = -0.56$, $p = 0.047$). Both for vCaud-PCG and vCaud-ACC, the additional LMM analysis confirmed that striatal connectivity changes were negatively correlated with apathy changes (vCaud-ACC: $\beta = -3.14$, SE = 0.66, tStat = −4.76, $p = 4.87{*}10^{-5}$; vCaud-PCG: $\beta = -2.71$, SE = 0.63, tStat = −4.3, $p = 1{*}10^{-4}$) while no other effects reached statistical significance. In summary,

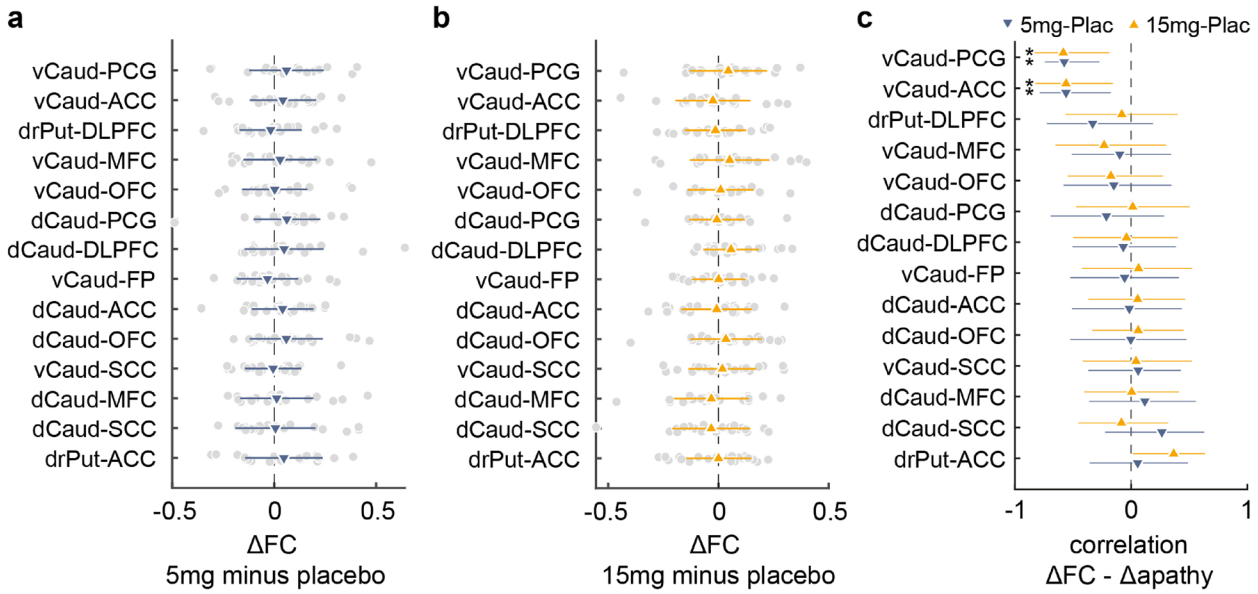

Fig. 3 Correlation between changes in apathy and functional connectivity at 5 mg and 15 mg of RG7203. **a** Functional connectivity changes (ΔFC) in the cortico-striatal circuit when 5 mg RG7203 are given instead of placebo; filled circles (gray) represent individual participants; blue downward-pointing triangles with error bars show mean and standard deviation. **b** Functional connectivity changes (ΔFC) in the cortico-striatal circuit when 15 mg RG7203 are given instead of placebo; filled circles (gray) represent individual participants; orange upward-pointing triangles with error bars show mean and standard deviation **c** Correlation between Δapathy (apathy changes with 5 mg or 15 mg RG7203 vs. placebo) and ΔFC is illustrated for the cortico-striatal circuit. The error bars correspond to the 95% confidence interval. Asterisks indicate $p < 0.05$ after FDR-correction

improvement in apathy during treatment with 5 mg and 15 mg of RG7203 was correlated with increased vCaud-PCG/ACC connectivity and vice versa.

We next computed connectivity alterations for all possible combinations of cerebrum structures at 5 mg and 15 mg RG7203 and explored their correlation with changes in apathy (Fig. 4a, b). This resulted in 1770 unique correlations (i.e., only the left lower triangle without the diagonal part from Fig. 4a, b, left panel). As a further test of the significance of our findings, we compared the correlation between changes in apathy and vCaud-PCG/ACC connectivity with all possible correlations of changes

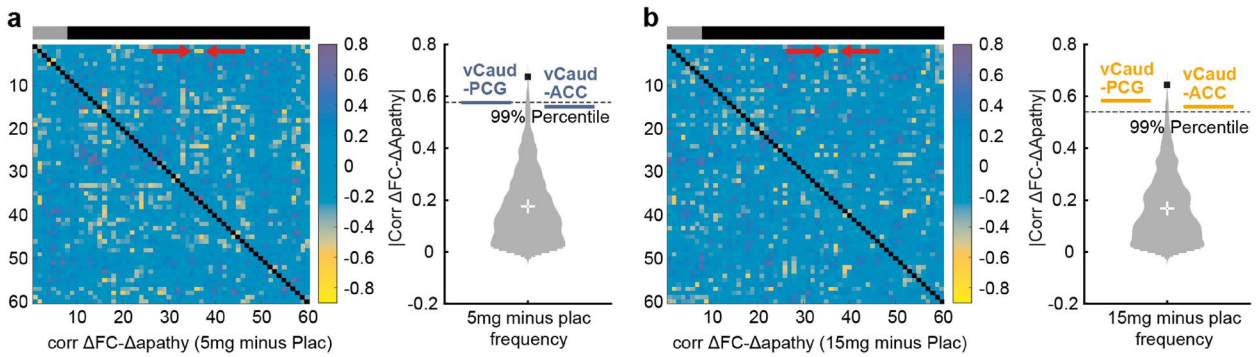

Fig. 4 Relationship between changes in apathy and connectivity with RG7203 vs. placebo for all combinations of cerebrum structures. **a** 5 mg RG7203 compared to placebo. Left panel: Functional connectivity changes at 5 mg RG7203 (ΔFC) has been computed for all possible combinations of the 60 anatomical cerebrum structures and correlated with corresponding apathy changes (Δapathy); gray bar indicates striatal regions, black bar extrastriatal regions; correlation of Δapathy and ΔFC between vCaud and PCG/ACC is indicated by red arrows. Right panel: Violin plot showing the absolute value of all 1770 unique correlations between ΔFC and Δapathy; correlation between Δapathy and ΔFC for the connectivity vCaud-PCG and the connectivity vCaud-ACC is indicated by blue bars. The black square indicates the maximum of all correlations. **b** 15 mg RG7203 compared to placebo: Same computations and conventions as in **a**, but correlation between Δapathy and ΔFC for vCaud-PCG/ACC is indicated by orange instead of blue bars in the right panel

in apathy and connectivity between all cerebrum structures. For this analysis, only the absolute value of correlations was used (Fig. 4a, b, right panel). The correlation between changes in apathy and vCaud-PCG/ACC connectivity was around the 99th percentile of all possible correlations for 5 mg RG7203 vs. placebo, and above the 99th percentile for 15 mg RG7203 vs. placebo (Fig. 4a, b, vCaud-PCG: 5 mg minus placebo: 99th percentile; 15 mg minus placebo: 99.7th percentile; vCaud-ACC: 5 mg minus placebo: 98.7th percentile; 15 mg minus placebo: 99.2th percentile).

To further contextualize our findings, we then added several explorative analyses. First, connectivity changes with 5 mg or 15 mg RG7203 versus placebo did not correlate with changes in diminished expression (Additional file 1: Fig. S4a, b). We then investigated if striatal connectivity under placebo (Additional file 1: Fig. S5a) is related to apathy changes when 5 mg or 15 mg RG7203 are given versus placebo. As increased vCaud-PCG/ACC connectivity with 5 mg of RG7203 was a correlate of better apathy response, we hypothesized that better apathy response at RG7203 would also be associated with lower and more pathological [32] vCaud-PCG/ACC connectivity under placebo. As expected, connectivity between vCaud and PCG as well as between vCaud and ACC during placebo treatment was positively correlated with apathy changes at 5 mg and 15 mg RG7203 (vCaud-PCG: 5 mg minus placebo, $r_s = 0.65$; $p = 0.02$; 15 mg minus placebo: $r_s = 0.71$; $p = 2^{*}10^{-3}$; vCaud-ACC: 5 mg minus placebo: $r_s = 0.61$; $p = 0.02$; 15 mg minus placebo: $r_s = 0.79$; $p = 2^{*}10^{-4}$; Additional file 1: Fig. S5b, Additional file 1: Fig. S6a, b). Thus, lower vCaud-PCG/ACC connectivity under placebo was associated with a better apathy response at 5 mg and 15 mg RG7203 vs. placebo. With regard to the correlation with apathy alterations at RG7203, we also compared vCaud-PCG/ACC connectivity under placebo with connectivity of all other cerebrum structures under placebo. The correlations between apathy changes and vCaud-PCG/ACC connectivity under placebo were well above the 99th percentile of all possible correlations, both at 5 mg and 15 mg of RG7203, or even represented the maximal correlation (Additional file 1: Fig. S7a, b, vCaud-PCG: 5 mg minus placebo: 99.9th percentile and second largest value; 15 mg minus placebo: 99.9th percentile and second largest value; vCaud-ACC: 5 mg minus placebo: 99.8th percentile and fifth largest value; 15 mg minus placebo: maximal correlation of all possible connectivity pairs). Thus, the correlation magnitudes for the connections vCaud-PCG and vCaud-ACC under placebo were the two greatest for apathy changes at 15 mg and among the top five for apathy changes at 5 mg of RG7203 vs. placebo when compared to all other 1768 connections of cerebrum structures. Given the limited evidence consistent with an association between the insula-hippocampus-striatum network and apathy, or more broadly, negative symptoms, we finally investigated striatal connectivity with the amygdala, hippocampus, and insula (see Methods). Neither 5 mg nor 15 mg of RG7203, compared to placebo, was associated with significant changes in striatal connectivity to these regions (Additional file 1: Fig. S8a, b). Moreover, changes in apathy with 5 mg or 15 mg of RG7203 versus placebo did not significantly correlate with changes in striatal connectivity to these regions (Additional file 1: Fig. S8c). Finally, we investigated whether changes in apathy or striatal connectivity with 5 mg or 15 mg RG7203 were correlated with the risperidone equivalents of the stable antipsychotic background medication administered during the study. However, no significant associations were found between risperidone equivalents and changes in apathy or striatal connectivity under 5 mg or 15 mg of RG7203 (Additional file 1: Fig. S9).

Discussion

Here we tested the relationship between changes in apathy and striatal connectivity during treatment with the PDE10 inhibitor RG7203 which was given as add-on to antipsychotic medication. Compared to placebo, treatment with neither 5 mg nor 15 mg of RG7203 resulted in significant changes in apathy or striatal connectivity. However, the effect of RG7203 on apathy showed clinically relevant variation that was reflected in striatal connectivity. With 5 mg and 15 mg RG7203 vs. placebo, increased connectivity between vCaud and PCG as well as between vCaud and ACC was associated with apathy improvement and vice versa. Importantly, such correlations were not observed for the negative symptom dimension of diminished expression.

The relationship between changes in apathy and vCaud-PCG/ACC connectivity supports the association of these cortico-striatal components with apathy [8] and aligns with current theories about the functions of the vCaud, ACC, and PCG. The network of the vCaud, ACC, and PCG has been implicated in the integration of cognitive and reward processing, and impairment in these domains is assumed to be a primary driver of apathy [8, 49–55]. A recent study proposed that parts of the ACC and ventral striatum play a key role in the generation of apathy across neurological disorders [56]. A foregrounded relevance of the ventral striatum and ACC for apathy would be in line with our finding that changes in apathy and the vCaud-ACC are correlated but may also explain why we did not find a relationship between changes in apathy and connectivity for most of the other tested connectivity pairs. The only other connectivity with a significant relationship to apathy changes was the connectivity between

the vCaud and PCG. Interestingly, the ACC and PCG are adjacent structures in the medial part of the brain. Apart from that, correlations between changes in functional connectivity and apathy rarely showed high magnitudes in our cerebrum-wide analysis. This aligns with recent theories that view schizophrenia as a disorder of discrete neural circuits rather than a diffuse brain dysfunction [32, 57, 58].

We also observed that lower vCaud-PCG/ACC connectivity during placebo treatment was associated with larger improvement of apathy during treatment with RG7203. This is in line with our main finding that increased vCaud-PCG/ACC connectivity is a correlate of improved apathy with RG7203 vs. placebo. Additionally, an interesting hypothesis could be that lower vCaud-PCG/ACC connectivity increases the probability that patients benefit from RG7203 (with the caveat that the placebo condition is not exactly the same as a baseline condition). The relationship between changes in apathy with RG7203 and striatal connectivity at baseline could be investigated in larger clinical studies that are designed for this purpose. If resting-state striatal connectivity at baseline would inform the benefit patients can expect from RG7203, this would advance biologically informed treatment options for apathy and pave the way for more personalized treatments in schizophrenia. Nevertheless, RG7203, as an adjunctive treatment to antipsychotics, did not demonstrate an improvement in negative symptoms in the overall group of schizophrenia patients. By contrast, a recent placebo-controlled phase 2 trial reported that adjunctive treatment with pimavanserin, a selective 5-HT_{2A} receptor inverse agonist and antagonist, was associated with a significant, albeit modest, improvement in negative symptoms [59]. Similarly, a phase 2 study demonstrated that the acetylcholine receptor agonist xanomeline, combined with a peripheral anticholinergic, was associated with improvements in negative symptoms compared to placebo [60]. While preliminary results for these and other novel compounds are promising, their definitive efficacy across diverse patient populations and in the long term remains uncertain. Notably, several previous compounds, such as glycine reuptake inhibitors, failed to demonstrate efficacy in phase 3 trials despite showing potential in earlier phases [1]. In this context, a greater emphasis on personalized treatment approaches has been suggested to achieve meaningful benefits for patients [1]. It is also notable that we did not observe significant differences in apathy improvement or worsening when comparing the 5 mg and 15 mg doses of RG7203 to placebo. A potential explanation is that the higher dose of RG7203 may amplify its effects in each patient, with greater enhancement of D1-signaling and stronger dampening of D2-signaling compared to the lower dose. While increased D1-signaling at the higher dose may add positive effects on apathy, this effect could be counteracted by the higher dampening of D2-signaling, which has been implicated in the promotion of secondary negative symptoms [25, 26]. As a result, both doses of RG7203 may produce similar net effects on apathy in individual patients.

There are several limitations to our study. First, the sample size in the final analysis is relatively small, which may constrain the reliability of the findings. However, the study design as a randomized, placebo-controlled crossover trial helps mitigate some of these concerns. By allowing each participant to act as their own control, this design reduces the influence of between-participant variability, enhances consistency across treatment conditions, and provides robust within-participant comparisons. These features strengthen the reliability of the observed effects, even in the context of a limited sample size. Additionally, the consistency of our findings across different doses of RG7203 and multiple analyses supports the robustness of the results. Notably, we observed significant correlations between apathy improvements and specific changes in striatal connectivity, suggesting that the results reflect meaningful neurobiological associations rather than random variation. Apart from that, we cannot rule out the possibility that apathy changes with RG7203 vs. placebo simply reflect longitudinal apathy fluctuations with no relation to RG7203. The extent of interindividual differences in apathy modulation and the similar apathy response to both doses of RG7203 provide arguments against this possibility. Considering the limited test–retest reliability of functional connectivity [61, 62], it is also possible that the observed changes in functional connectivity with RG7203 vs. placebo reflect longitudinal connectivity fluctuations with no relation to RG7203. The observed consistency in connectivity alterations across both doses of RG7203, especially for the connectivity pairs vCaud-PCG and vCaud-ACC, may at least indicate that this is less probable. Moreover, the treatment duration was relatively short, and it is unknown whether we would have found significantly altered apathy and striatal connectivity after a longer treatment course with RG7203. Another potential concern with crossover designs is the risk of medication-related carry-over effects. However, in this study, each treatment period was separated by a 2-week washout period, providing a substantial safety margin based on RG7203's terminal half-life of approximately 14 h to eliminate residual pharmacological effects. Additionally, the fully counterbalanced randomization to six treatment sequences further mitigates the likelihood that any potential carry-over effects introduced systematic bias into the results. Finally, the complexity of brain circuitry and its interaction with

pharmacological agents calls for a cautious interpretation of the observed correlations. Future studies with larger sample sizes, longer treatment durations, and comprehensive assessments of striatal connectivity are required to substantiate and expand upon these findings.

Conclusions

Our findings indicate that striatal connectivity with the paracingulate gyrus and anterior cingulate cortex may be associated with apathy modulation under RG7203 treatment. Further replication and in-depth exploration of these results in larger clinical studies could enhance the development of biologically informed and personalized treatment options for negative symptoms.

Abbreviations

PANSS	Positive and Negative Syndrome Scale
BNSS	Brief Negative Symptom Scale
CGI-S	Clinical Global Impression—Severity
CAINS	Clinical Assessment Interview for Negative Symptoms
WMRLT	Working memory reinforcement learning task
ECBT	Effort-cost-benefit task
BOLD	Blood oxygenation level dependent
ART	Artifact detection tools
LMM	Linear mixed model
CGI-I	Clinical Global Impression—Improvement
BOLD	Blood oxygenation level dependent
ACC	Anterior cingulate cortex
OFC	Orbitofrontal cortex
dlPFC	Dorsolateral prefrontal cortex
FP	Frontal pole
MFC	Medial frontal cortex
SCC	Subcallosal cortex
PCG	Paracingulate gyrus
vPut	Ventral rostral putamen
drPut	Dorsal rostral putamen
dcPut	Dorsal caudal putamen
vCaud	Ventral caudate
NAcc	Nucleus accumbens

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04004-2.

Additional file 1: Tables S1–S3; Figures S1–S9; Eligibility criteria. Table S1 Timeline and treatment sequences. Table S2 Patient characteristics at baseline. Table S3 Frame-wise displacement and global signal intensity changes before correction procedures. Fig. S1 Striatal connectivity across all subjects and conditions. Fig. S2 Correlation between striatal connectivity alterations at 5 mg and 15 mg RG7203. Fig. S3 Alterations in apathy vs. alterations in striatal connectivity with RG7203 vs. placebo. Fig. S4 Correlation between alterations in diminished expression and striatal connectivity. Fig. S5 Correlation between striatal connectivity under placebo and apathy alterations with 5 mg or 15 mg of RG7203 versus placebo. Fig. S6 Alterations in apathy with RG7203 vs. placebo and striatal connectivity under placebo. Fig. S7 Relationship between apathy changes with RG7203 vs. placebo and connectivity under placebo conditions for all combinations of cerebrum structures. Fig. S8 Relationship of striatal connectivity to amygdala, hippocampus, and insula with apathy changes. Fig. S9 Relationship between risperidone equivalents and changes in apathy and striatal connectivity. Eligibility criteria: inclusion criteria; exclusion criteria.

Additional file 2: CONSORT checklist.

Acknowledgements

We thank Markus Abt, Paul Tamburri, Christopher Chatham, Michael J. Frank, Anne G.E. Collins, David P. Walling, Rick Mofsen, Daniel Gruener, Lev Gertsik, Jeff Sevigny, and Sanjay Keswani for their substantial contributions to the project.

Authors' contributions

W. O. co-conceptualized the data analysis and current study, co-analyzed and interpreted the data, performed the statistical analysis, wrote and refined the manuscript. D.U. conceived, designed, implemented and supervised the original study together with collaborators and contributed to the manuscript. G.C., A.R.M. and G.-Y. H. supported data analysis. G.G. and Š.H. provided the data set. Š.H. and J.D. performed the MRI setup at all study centers, including the MRI sequence setup, operators' training, and the MRI-specific study documentation; and additionally implemented the MRI study in the centers including QC reviews and data transfers and data curation. M.K., T.S., F.R., N.K., A.B. and W.S. reviewed and adapted the manuscript with regard to content. P. H. initiated and co-conceptualized the data analysis and current study, co-interpreted and supervised the study, and refined the manuscript. All authors approved, refined and edited the final version of the manuscript.

Funding

This study was funded and supported by F. Hoffmann-La Roche Ltd. Additionally, P. Homan was supported by a NARSAD grant from the Brain & Behavior Research Foundation (28445), a Research Grant from the Novartis Foundation (20A058) and an ERC Synergy Grant (101118756).

Data availability

The datasets used and analysed are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The following ethics committees approved the experiments: Copernicus Group IRB, P.O. Box 110605, Research Triangle Park, NC 27709, approval given on May 27th 2016; Washington University in St. Louis, Human Protection Office, 660 South Euclid Ave., Campus Box 8089, St. Louis, MO 63110, approval given on 5th August 2016; Alpha IRB, 1001 Avenida Pico, Suite C#497, San Clemente, CA 92673, approval given on 8th July 2016; Integ Review IRB, 3815 S. Capital of Texas Hwy, Suite 320, Austin, TX 78704, approval given on 27th May 2016. Informed consent to participate in the study was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

Co-author D. Umbricht is owner of xperimed LLC that provides consultation on all aspects of clinical drug development for neuropsychiatric indications, works on a contracting basis for Autifony Therapeutics and Gilgamesh pharmaceuticals and holds stocks of Roche, Novartis and Gilgamesh Pharmaceuticals. He has been consulting to Abbvie, Biogen, ERG, Forbion, Healthrhyhms, Kynexis, Psychogenic, Roche and Siesta. Co-author D. Umbricht was a full-time employee of F. Hoffmann-La Roche Ltd., which held the license for RG7203 during the study period. Co-author Š. Holiga is a full-time employee of F. Hoffmann-La Roche Ltd. Co-author G. Garibaldi is the chief medical officer of Noema, which currently holds the license for RG7203, and advisor of Retrotope. P. Homan has received grants and honoraria from Novartis, Lundbeck, Mepha, Janssen, Boehringer Ingelheim, Neurolite outside of this work. No further disclosures were reported.

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Received: 8 August 2024 Accepted: 13 March 2025
Published online: 28 March 2025

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