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# Understanding the mechanisms underlying cognitive control in psychosis

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## Abstract

**Background.** Cognitive control (CC) involves a top–down mechanism to flexibly respond to complex stimuli and is impaired in schizophrenia.

**Methods.** This study investigated the impact of increasing complexity of CC processing in 140 subjects with psychosis and 39 healthy adults, with assessments of behavioral performance, neural regions of interest and symptom severity.

**Results.** The lowest level of CC (Stroop task) was impaired in all patients; the intermediate level of CC (Faces task) with explicit emotional information was most impaired in patients with first episode psychosis. Patients showed activation of distinct neural CC and reward networks, but iterative learning based on the higher-order of CC during the trust game, was most impaired in chronic schizophrenia. Subjects with first episode psychosis, and patients with lower symptom load, demonstrate flexibility of the CC network to facilitate learning, which appeared compromised in the more chronic stages of schizophrenia.

**Conclusion.** These data suggest optimal windows for opportunities to introduce therapeutic interventions to improve CC.

## Original Article

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## Introduction

Cognitive control (CC) alludes to conscious control (Posner & Snyder, 1975) over multiple incoming streams of information, that are processed simultaneously (McClelland, Rumelhart, & Hinton, 1988), and create a conflict for decision making. Emotional processing influences CC, judgments and reasoning, and motivate actions either by perceptual vigilance, i.e. increasing the salience of the information, or by perceptual defense i.e. directing attention away from anxiety provoking information (Henley, 1986; Posner & Snyder, 1975).

CC can be conceptualized and studied at various levels of relational complexity of incoming information (Badre, 2013). We propose a distinction into three levels of CC with increasing complexity of information. Level 1-CC involves inhibition of responses in presence of simple distractors without any emotional component; the Stroop task is an example of initial level 1-CC (Freund, Bugg, & Braver, 2021), representing a classical measure of top–down control.

An intermediate Level 2-CC represents response inhibition in the presence of explicit emotional information, where the emotional information changes the rule of the task, i.e. distractors become cues and vice versa. The subject thus needs to learn the new rule from the feedback presented. Thus, feedback learning is involved in assessing when to ignore the emotional information and when to respond to it, and CC is needed to regulate automatic emotional impulses (Saunders, Milyavskaya, & Inzlicht, 2015).

A higher-order Level 3-CC involves response selection in interactions with others, integrating implicit emotional information. Social decision making paradigms such as the trust game (Berg, Dickhaut, & McCabe, 1995), involve CC in the context of rule learning as well as emotion processing and reward learning by predicting the reciprocation based on previous feedback of the game partner. In this process, judgments are made about the other's trustworthiness, requiring higher-order CC including processing of implicit complex emotional information (Lahno, 2020), that guides decision making (Declerck, Boone, & Emonds, 2013). Thus, in this level 3-CC task, both emotional information and reward learning

modulate top–down CC (Lee & Shomstein, 2014; Ochsner, Silvers, & Buhle, 2012), while reward learning alone also modulates bottom–up CC (Lee & Shomstein, 2014).

Above mentioned CC tasks (inhibition tasks with or without rule changes, and social decision making paradigms) are associated with activation of neural regions within the cognitive control network (CCN), also referred to as the fronto-parietal control network (FPN) overlapping with the dorsal attention, ventral attention and default mode network (Yeo et al., 2011). The CCN includes anterior cingulate cortex/pre-supplementary motor area (ACC/pSMA), dorsolateral prefrontal cortex (dlPFC), inferior frontal junction (IFJ), anterior insular cortex (AIC), dorsal pre-motor cortex (dPMC), and posterior parietal cortex (PPC). These areas, however, are not all simultaneously active for every CC task (Cole & Schneider, 2007).

Deficits in CC are found in schizophrenia and along the psychosis continuum (Alústiza, Radua, Pla, Martin, & Ortuño, 2017) leading to inadequate filtering of stimuli, an overload of information, and the inability to integrate that information (Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009). Deficits in level 1-CC are well-documented across the psychosis spectrum, and do not seem to improve over time. They are seen in patients with first episode psychosis (FEP) (Avery et al., 2019), in individuals at high-risk of developing psychosis (Guo et al., 2020), and in individuals with treatment resistant psychosis (Thomas et al., 2021). Level 2-CC impairments show that emotional cues impair decision making (Anticevic, Repovs, & Barch, 2012; Averbeck & Duchaine, 2009; Tully, Lincoln, & Hooker, 2014), is compromised by symptom severity in early stages of psychotic illness (Horne et al., 2022).

Deficits in level 3-CC are also found throughout the spectrum, in individuals at high-risk for psychosis, in patients with FEP (Lemmers-Jansen, Fett, Hanssen, Veltman, & Krabbendam, 2019), and in chronic schizophrenia (Campellone, Fisher, & Kring, 2016; Fett et al., 2012; Gromann et al., 2013; Hanssen, van Buuren, Van Atteveldt, Lemmers-Jansen, & Fett, 2021; Sutherland et al., 2020). Our everyday decisions often involve higher-order CC, hence deficits in level 3-CC perhaps play a significant role in functional impairment. Previous fMRI research with the trust game task, have demonstrated that regions important for reward learning, cognitive control and emotional processing are involved (Bellucci, Chernyak, Goodyear, Eickhoff, & Krueger, 2017; Delgado, Frank, & Phelps, 2005; Fett, Gromann, Giampietro, Shergill, & Krabbendam, 2014; King-Casas et al., 2005; Krueger, Grafman, & McCabe, 2008; Krueger et al., 2007; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004; van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2009) offering a paradigm to compare functioning of CCN and reward network separately for level 3-CC.

In the present study, we examined how level 1 and 2-CC impacted level 3 CC across the stages of psychotic illness. We used behavioral data from level 1 and 2 CC and both behavioral and fMRI data from level 3-CC tasks. We also explored whether plasticity, defined as the ability to learn by reorganizing neural networks (Fandakova & Hartley, 2020; Zatorre, Fields, & Johansen-Berg, 2012) differs between the two groups at level 3-CC. We hypothesized that (a) individuals with FEP and chronic psychosis would show impaired CC compared to healthy individuals at all three levels, and that CC deficits in the presence of emotional information (level 2 and level 3) would be more impaired in individuals with chronic schizophrenia compared to individuals with FEP; (b) individuals with FEP and chronic schizophrenia would show reduced neural activation in CCN and reward processing networks during level 3-CC, compared to healthy individuals, and that this reduction of activation would be most marked in chronic schizophrenia; and finally (c) that level 2 and 3 CC would be associated with increased plasticity i.e. ability to learn, in FEP as opposed to chronic schizophrenia. An exploratory analysis examined the impact of psychosis symptoms on CC performance.

## Methods

### Participants

In our study, 46 patients with schizophrenia (SZ), 107 patients with first episode psychosis (FEP) and 46 healthy adults were recruited as part of the MUTRIPS study (Thomas et al., 2021). We excluded five SZ, eight FEP and seven HC due to incomplete or missing scanning data on the trust game. Exclusion criteria for all patients were a history of neurological illness, current major physical illness, and drug dependency over the last six months. Exclusion criteria for HC were a history of psychiatric illness or having a first-degree relative with a current or previous psychotic disorder. The final sample consisted of 41 SZ, 99 FEP and 39 HC. Diagnoses in the FEP group were mainly acute and transient psychotic disorder and unspecified nonorganic disorder, and in the SZ group mainly schizophrenia. Ethics approval was provided by the London Camberwell St Giles REC. All experiments were compliant with the Declaration of Helsinki. Participants provided informed written consent and compensated for their time and travel.

### Materials

Levels of CC were operationalized using three previously established experimental paradigms in psychosis: The trust game for level 3-CC (King-Casas et al., 2005; Lemmers-Jansen et al., 2019); the faces task for level 2-CC (Averbeck & Duchaine, 2009; Evans, Fleming, Dolan, & Averbeck, 2011a; Vanes, Mouchlianitis, Collier, Averbeck, & Shergill, 2018) and the Stroop task for level 1 CC (Stroop, 1935). A concise synopsis of the three tasks is provided below. For a more detailed description, please see the Supplementary Materials.

### Stroop task

In the computerized Stroop task (Stroop, 1935), participants were required to name the font color of words which was either congruent (same color) or incongruent (different color) with the written word meaning. The task consisted of 33 congruent, 33 incongruent, and 34 fixation trials, presented in randomized order. Behavioral data of Stroop reaction time (RT; calculated as mean RT on incongruent minus mean RT on congruent trials; in milliseconds) and the accuracy Stroop effect (defined as accuracy on congruent minus accuracy on incongruent trials) were used in the analyses.

### Faces task

The Faces task consisted of four blocks of 30 trials each, with two faces presented each trial with a neutral or an emotional expression (angry or happy). One face was associated with a 60% and the other with a 40% reward probability (Averbeck & Duchaine, 2009; Vanes et al., 2018). Behavioral data were the proportion

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of choices for an emotional face, when that would be the higher reward option according to the model (Vanes et al., 2018); the proportion of correct choices for a neutral face; the proportion of correct (overall) choices; and the emotional bias, defined as the difference between the proportion of choices for the happy and for the angry faces, when the opposite expression would have been the ideal choice, as an indication of CC separate from emotion processing (Averbeck & Duchaine, 2009).

### Trust game

In this multi-round trust game, participants were given £10, of which they could choose to invest an amount in the second player. The amount was tripled, and the second player could return part of the amount to the participant. Behavioral parameters of baseline trust (the first investment) and mean trust (mean investment over 20 trials) were used in the analyses. Plasticity, i.e. the learning over trials based on the feedback of the second player, calculated as every participant's own regression coefficient over the 20 trials in the interaction 'trial number × group' on investment, called 'slope'). In addition, fMRI analyses were also performed on neural activation during the investment and repayment phases (see below).

### PANSS

The 30-item Positive and Negative Syndrome Scale (PANSS; (Kay, Fiszbein, & Opler, 1987)) semi-structured interview was used for rating symptoms in the 2 weeks prior to testing by trained researchers. Variables used for analysis are the positive, negative, and general subscales, and the PANSS total score.

### MRI acquisition

#### Scanning parameters

Functional scans were acquired using a T2* echo planar sequence (370 volumes, TR = 2000 ms, TE = 35 ms, field of view = 24 cm, slice thickness = 3 mm, matrix = 64 × 64, flip angle = 75°) sensitive to blood oxygenation level-dependent (BOLD) contrast on a 3T GE Excite II MR scanner (GE Healthcare, USA). A structural image was acquired for each subject with a T1-weighted magnetization prepared rapid acquisition gradient echo (MP RAGE) sequence (TR = 7321 ms, TE = 3 ms, TI = 400 ms, field of view = 240 mm, slice thickness = 1.2 mm, 196 slices).

#### fMRI paradigm

The trust game consisted of 20 experimental and 20 control trials. A trial consisted of: an investment cue (2 s); the investment period (4 s, regardless of reaction times); presentation of the invested amount (2 s); a waiting period (jittered, 2–4 s) and a fixation cross (500 ms); display of the returned amount (3 s) and the final totals of both players (jittered, 2.5–4.5 s); a fixation cross (500 ms). Every trial lasted 18.5 s in total. Both the investment and repayment period were considered, as the former requires maximal cognitive control when making a decision, and the latter reflects reward learning.

### Statistical analyses

#### Behavioral analyses

Group differences were calculated with regression analyses (reg); multilevel random regression analyses (xtreg) to account for multiple observations [investments (level 1), within participants (level 2)]; and a logistic regression (logit) for assessing group differences in sex distribution. All regression analyses were controlled for age and sex. Patients' chlorpromazine (CPZ) equivalent medication dosages were calculated using conversion tables (Thomas et al., 2021).

Of each task, two behavioral parameters were added into a structural equation model (SEM), to investigate if lower-order CC behavior can predict learning in the level 3-CC trust game.

To investigate the associations between tasks, a structural equation model analysis (SEM) was performed, including Stroop accuracy and RT (level 1), proportion ideal choices and emotion bias (level 2) and mean trust and slope (level 3), see Supplementary Materials, Fig. S4.

#### fMRI analyses

fMRI data were pre-processed and analyzed using Statistical Parametric Mapping 12 (Ashburner et al., 2014). The data were spatially smoothed using a 6 mm FWHM (full width half maximum) Gaussian kernel. At first level, a general linear model was used to construct individual time courses for eight different events during the trials, and analyses were controlled for the six standard motion parameters estimated by SPM. For each trial, we defined the investment phase as the period of stimulus onset to the ending of that period, 6 s later, and the repayment phase as the 3 s where the return of the trustee is shown. Experimental events were contrasted with the corresponding period during control trials. At second level, analyses were controlled for age and sex.

A priori region of interest (ROI) analyses were performed. ROIs comprising the CCN and reward learning network were selected based on existing literature. ROIs of the CCN were dorsal ACC (MNI coordinates: 2, 16, 40; (Breukelaar et al., 2017)), dlPFC (36, 14, 43; (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008)), anterior insula (−31, 21, −1; [Vincent et al., 2008]), posterior parietal cortex (angular gyrus. 39, −57, 47; (Cole & Schneider, 2007)) and precuneus (8, −68, 46; (Breukelaar et al., 2017)). ROIs of reward learning network were the OFC (orbito-frontal cortex; −6, 36, −15; (Lin, Adolphs, & Rangel, 2012)), caudate (−8, 2, 10; [Haruno & Kawato, 2006]), putamen (−20, 16, −2; [Haruno & Kawato, 2006]) and VTA (0, −16, −7; [Gu et al., 2010; Hadley et al., 2014]). ROIs were defined as a sphere of 10 mm for cortical regions, and 5 mm for subcortical regions (caudate, putamen and VTA).

We tested group differences using MarsBaR (version0.44; http://marsbar.sourceforge.net). To account for multiple tests, an adjusted $p$ value was calculated, taking the correlation between the $\beta$-values into account by using the Simple Interactive Statistical Analysis Bonferroni tool (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm), resulting in an adjusted $p = 0.034$ for investments and 0.022 for repayments (Lemmers-Jansen et al., 2019; Woudstra et al., 2013). Contrast estimates for each ROI were extracted and further used in correlation analyses.

#### Principal component analysis

Finally, we explored the predictive value of neural activation on learning in the trust game. The neuroimaging data comprised 9 ROIs, measured during investment and repayment totaling 18 variables. We performed a principal component analysis (PCA) to reduce the dimensionality of the data, while preserving as much of the data's variance as possible and discuss 1st and 2nd principal components. Additional behavioral data added to the

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model did not increase the strength of the components and were consequently omitted.

## Results

Demographic characteristics of the participants are presented in Table 1. Patient groups did not differ on the PANSS total score, or the positive and general subscales. SZ reported higher negative symptoms than FEP. However, symptom severity overall was moderate (Leucht et al., 2005).

### Behavioral results

All task outcomes data are shown in Table 2.

### Trust game

Baseline trust (first investment) was highest in HC and lowest in FEP, with SZ performing in between. However, only HC and FEP differed significantly ($\beta = 0.21$, $p = 0.04$). SZ patients did not differ significantly from the other two groups ($p > 0.35$). Regarding the mean trust over 20 trials, FEP and SZ showed significantly lower trust than HC ($\beta = -0.36$, $p < 0.001$ and $\beta = -0.21$, $p = 0.034$, respectively), with no significant difference between the patient groups ($p = 0.33$).

The development of trust (slope) over trials was significantly different between groups ($b = 0.024$, CI [−0.044 to −0.005], $p = 0.015$), and post-hoc analyses revealed significant increases of trust over trials in HC and FEP ($\beta = 0.18$, $p < 0.001$ and $\beta = 0.05$, $p = 0.028$, respectively), but not in SZ ($\beta = 0.05$, $p = 0.12$).

### Faces task

The proportion of total ideal choices differed significantly between the three groups ($F$ (4167) = 7.74, $p < 0.001$), with HC making significantly more ideal choices compared to FEP and SZ ($\beta = 0.52$, $p < 0.001$ and $\beta = 0.31$, $p = 0.001$, respectively). Patient groups did not differ significantly ($\beta = 0.16$, $p = 0.14$). When an emotional face was the ideal choice, HC and SZ more often chose the ideal option than FEP ($\beta = 0.44$, $p < 0.001$ and $\beta = 0.23$, $p = 0.045$, respectively).

### Stroop task

For the Accuracy Stroop effect, the regression analysis yielded a statistically significant difference between the three groups ($F$ (4141) = 3.31, $p = 0.013$) and in the RT Stroop effect ($F$ (4141) = 5.43, $p < 0.001$), with HC differing significantly from FEP and SZ, no difference between the patient groups.

**Table 1.** Sample characteristics

| | HC $N = 38$ | FEP $N = 99$ | SZ $N = 41$ | $p$ value | Group difference |
|---|---|---|---|---|---|
| Participant characteristics | | | | | |
| Sex N male (%) | 23 (60.5%) | 69 (70.4%) | 35 (85.4%) | 0.02 | HC < SZ |
| | | | | 0.07 | FEP < SZ |
| Age mean (s.d.) | 33.7 (9.6) | 26.5 (5.9) | 41.3 (10.5) | <0.001 | FEP < HC |
| | | | | | HC < SZ |
| | | | | | FEP < SZ |
| Years education M (s.d.) | 18.1 (3.1) | 15.1 (3.8) | 13.7 (3.7) | <0.001 | HC > FEP |
| | | | | 0.001 | HC > SZ |
| Phonolog verbal M (s.d.) | 13.4 (5.1) | 10.9 (4.2) | 10.9 (3.1) | 0.021 | HC > FEP |
| | | | | 0.001 | HC > SZ |
| Semantic verbal M (s.d.) | 18.6 (5.2) | 15.1 (4.4) | 14.3 (3.7) | <0.001 | HC > FEP |
| | | | | | HC > SZ |
| WASI_IQ M (s.d.) | 118 (11.6) | 99.1 (16.4) | 94.4 (15.8) | <0.001 | HC > FEP |
| | | | | | HC > SZ |
| Illness variables | | | | | |
| Illness duration M (s.d.) | | 1.6 (1.2) | 14.7 (9.4) | <0.001 | FEP < SZ |
| CPZ equivalent M (s.d.) | | 241.9 (141.7) | 342.4 (217.1) | 0.023 | FEP < SZ |
| PANSS total M (s.d.) | | 55.81 (15.80) | 61.37 (18.19) | 0.2 | |
| Positive M (s.d.) | | 13.20 (5.37) | 15.51 (5.54) | 0.1 | |
| Negative M (s.d.) | | 12.95 (5.24) | 16.05 (5.80) | 0.02 | FEP < SZ |
| General M (s.d.) | | 29.36 (7.47) | 30.05 (8.71) | 0.8 | |

FEP, first episode psychosis; SZ, schizophrenia; HC, healthy controls; s.d., standard deviation; Phonolog, phonological subscale of the WASI; WASI_IQ, *estimation of IQ based on the Wechsler Abbreviated Scale of Intelligence* (Wechsler, 1999); Patients' chlorpromazine (CPZ) equivalent medication dosages were calculated using conversion tables (Thomas et al., 2021). For additional details of diagnoses and medication please see Tables S1 and S2 in the Supplementary Material.

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**Table 2.** Task performance per level of cognitive control and per participant group

| | HC | FEP | SZ | *p* value | Group difference |
|---|---|---|---|---|---|
| Level 3 CC | *N* = 38 | *N* = 99 | *N* = 41 | | |
| Trust game (*N* = 178) | | | | | |
| First investment M (S.D.) | 6.9 (2.5) | 5.9 (2.4) | 6.2 (2.4) | 0.04 | HC > FEP |
| Mean investment M (S.D.) | 7.7 (2.5) | 6.6 (2.8) | 6.7 (2.9) | <0.001[a] | HC > FEP |
| | | | | 0.03 | HC > SZ |
| Slope M (S.D.) | 0.077[b] (0.116) | 0.026[b] (0.114) | 0.027 (0.116) | 0.02 | HC > FEP |
| | | | | 0.06 | HC > SZ |
| Level 2 CC | *N* = 37 | *N* = 95 | *N* = 41 | | |
| Faces task (*N* = 173) | | | | | |
| Ideal choice emotion M (S.D.) | 0.62 (0.12) | 0.54 (0.08) | 0.57 (0.12) | <0.001[a] | HC > FEP |
| | | | | 0.06 | HC > SZ |
| | | | | 0.045 | SZ > FEP |
| Ideal choice neutral M (S.D.) | 0.64 (0.12) | 0.55 (0.08) | 0.55 (0.12) | <0.001[a] | HC > FEP |
| | | | | | HC > SZ |
| Ideal choice total M (S.D.) | 0.63 (0.10) | 0.54 (0.06) | 0.56 (0.10) | <0.001[a] | HC > FEP |
| | | | | 0.001[a] | HC > SZ |
| Emotion bias | 0.09 (0.14) | 0.06 (0.13) | 0.09 (0.19) | >0.4 | N.S. |
| Level 1 CC | *N* = 35 | *N* = 76 | *N* = 35 | | |
| Stroop task (*N* = 146) | | | | | |
| Accuracy Stroop M (S.D.) | 0.02 (0.04) | 0.05 (0.08) | 0.08 (0.08) | 0.012[a] | HC < FEP |
| | | | | 0.01[a] | HC < SZ |
| RT Stroop M (S.D.) | 95.86 (71.27) | 146.42 (105.66) | 181.20 (135.56) | 0.002[a] | HC < FEP |
| | | | | 0.03 | HC < SZ |

FEP, first episode psychosis; SZ, schizophrenia; HC, healthy controls; M, mean; S.D., standard deviation; RT, reaction time; N.S., not significant.
[a] = survives Bonferroni correction.
[b] = Significant slope, e.g. significant increase of investment over trials within group.

The structural equation model analysis (SEM) was performed, including two parameters for every level of CC (see Supplementary Materials, Fig. S4). The model including group had a better fit than the model without group (LR $\chi^2 = 134.4$, $p < 0.001$), and showed significant effects between level 2 and level 3 CC: in HC there was a significant association of emotion bias with mean trust ($b = -6.47$, $p < 0.001$) and with trust slope ($b = 0.38$, $p = 0.009$); in FEP the associations between the proportion ideal choices and mean trust ($b = 5.92$, $p = 0.041$) and between the proportion ideal choices and trust slope ($b = -0.42$, $p = 0.037$) were significant. No significant associations were found in SZ.

## Associations with symptoms

To evaluate the influence of symptoms on task performance, all analyses were repeated separately with PANSS positive, negative and total scores (and the interaction term with group) added to the models. None of the behavioral measures showed a group by symptom interaction, suggesting that symptoms did not drive the group effects. Analyses with the slope, e.g. learning over trials in the trust game revealed a group by symptoms interaction at trend level for positive ($\beta = 0.67$, $p = 0.08$), negative ($\beta = 0.70$, $p = 0.07$) and total symptoms scores ($\beta = 0.77$, $p = 0.06$). Further analysis by group showed that for FEP, negative and total symptoms were significantly negatively associated with slope ($\beta = -0.29$, $\neg p = 0.004$ and $\beta = -0.28$, $\neg p = 0.006$, respectively).

Finally, all patients were grouped in high- and low-symptomatic (Horne et al., 2022). High-symptomatic were those with at least 1 positive symptom item of 5 (moderate severe) or higher, or at least 2 positive symptom items of 4 (moderate) or higher measured using PANSS. The other patients were labeled as low-symptomatic. Again, only slope showed an effect at trend level ($\beta = -0.16$, $p = 0.06$), indicating that patients with lower symptoms showed steeper learning during the trust game, than patients with higher symptoms.

## Neuroimaging outcomes

### Region of interest analyses

During investments, significant group differences were found between HC and FEP, with increased activation in HC in the reward related caudate and putamen and in the CC related precuneus and dACC. Non-significant differences were found between HC and SZ (see Table 3) in both CCN and reward related regions. Patient groups did not differ significantly in ROI activation.

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**Table 3.** ROI analyses outcomes in the trust game

| Condition Association | ROI | MNI coordinates *X*, *Y*, *Z* | *p* | *T* |
|---|---|---|---|---|
| Investment | | | | |
| HC > FEP | Caudate | −8, 2, 10 | 0.014[a] | 2.22 |
| | Precuneus | 8, −68, 46 | 0.005[a] | 2.62 |
| | Putamen | −20, 16, −2 | 0.006[a] | 2.55 |
| | dACC | 2, 16, 40 | 0.004[a] | 2.66 |
| | Insula | −31, 21, −1 | 0.046 | 1.70 |
| | PPC | 9, −57, 47 | 0.050 | 1.66 |
| | VTA | 0, −16, −7 | 0.047 | 1.68 |
| | dlPFC | 36, 14, 43 | 0.058 | 1.58 |
| HC > SZ | Caudate | −8, 2, 10 | 0.048 | 1.68 |
| | Precuneus | 8, −68, 46 | 0.063 | 1.54 |
| | Putamen | −20, 16, −2 | 0.065 | 1.52 |
| | dACC | 2, 16, 40 | 0.046 | 1.70 |
| Repayment | | | | |
| HC > FEP | PPC | 9, −57, 47 | 0.020[a] | 2.08 |
| | dlPFC | 36, 14, 43 | 0.009[a] | 2.39 |
| FEP > HC | VTA | 0, −16, −7 | 0.003[a] | 2.74 |
| | Putamen | −20, 16, −2 | 0.023 | 2.02 |
| | OFC | −6, 36, −15 | 0.041 | 1.75 |
| FEP > SZ | VTA | 0, −16, −7 | 0.037 | 1.80 |
| SZ > HC | Insula | −31, 21, −1 | 0.008[a] | 2.45 |
| | Putamen | −20, 16, −2 | 0.010[a] | 2.35 |

ROI, region of interest; MNI, Montreal Neurological Institute; FEP, first episode psychosis; HC, healthy controls; SZ, schizophrenia; PPC, posterior parietal cortex; dlPFC, dorso-lateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; VTA, ventral tegmental area; OFC, orbito-frontal cortex.

*Note:* All ROIs were defined as a 10 mm sphere (except caudate, putamen and VTA: 5 mm) around the given MNI coordinates. ROIs in bold indicate reward related regions, other ROIs are cognitive control (FPN) related.

[a]Significant with an adjusted threshold $p = 0.034$ for investments and $p = 0.022$ for repayments. Other results are significant at trend level. Non-significant results are not shown.

During repayments, HC showed greater activation in the CCN regions PPC and dlPFC compared to FEP, but less in reward related regions VTA, and putamen, compared to patients. Whole brain cluster corrected analyses did not reveal any significant group differences. Analyses between high- and low-symptomatic patients did not reveal any significant differences between groups.

All beta values of the ROIs were added in the PCA. The first two components explained most of the variance (Fig. 1) indicating distinct activation patterns, with the first component mainly activating during investments, while the second component largely consists of activation during repayments. This distinction reflects the two distinct phases of the trust game, suggesting no other factors of importance for ROI activation within the task. Online Supplementary Table S3 indicates the means of the components per participant group. Comparing the loading of these components between participant groups revealed a significant difference only in component 1, with higher means in HC than in FEP.

Figure 2 shows the association between the first two principal components. The upward-sloping regression line in HC, and the $\beta = 0.136$ imply a positive linear relationship between principal components 1 and 2. For FEP and SZ patients, the flat regression line implies no such relation in the patient groups.

Analyses of how these components are associated with learning in the trust game, reveal no significant associations between components and slope, and only one significant group difference: The association between component 2 and slope is significantly different in FEP from HC (online Supplementary Table S4).

## Discussion

Our study investigated the interplay between increasing complexity of cognitive control (CC) and disease progression in psychosis as determined by first episode of psychosis (FEP) and schizophrenia (SZ). We conceptualized three levels of CC and combined the behavioral outcomes of these three levels to explore the impact of the hierarchical levels of CC with respect to response inhibition (level 1 – Stroop task), reward learning with explicit emotional information (level 2 – Faces task) and reward learning based on implicit emotional information in the trust game (level 3 – Trust game). Additionally, we investigated the neural activation during the trust game (level 3). Our study showed that CC was impaired in both patient groups (FEP and SZ) compared to healthy individuals. We show that (i) level 1 CC deficits are stable deficits in patients; (ii) level 2 CC distinguishes patients in early and late stages of illness, with impairments being more in the early (FEP) than late stages of psychosis (SZ); (iii) at level 3, both patient groups show reduced neural activation of CCN however they show increased neural activation of reward networks with evidence of decoupling of top–down and bottom–up CC. The same results hold when we stratified the sample with low and high symptoms loading in FEP showing that those with lower symptoms especially lower negative symptoms learnt faster than those with more severe symptoms. Our results indicate that despite CC deficits, plasticity of the CCN network is retained in early stages of psychosis and therefore a possible therapeutic target.

The level 1-CC task was able to differentiate between patients and healthy individuals (Laurenson et al., 2015), showing similar impairments in both patient groups. The impaired performance at CC level 1 was not predictive of performance either at level 2 or 3, indicating that it is perhaps a core deficit in psychosis reflecting CCN resources rather than its plasticity. Level 1-CC does not involve emotional information and does not capture CCN deficits in the context of emotional information such as involving level 2 and 3 CC. This aligns with current literature that shows that non-social and social cognition may be independent in psychosis (Green, Horan, & Lee, 2019) where the former involves CC only while the latter involves CC and emotional information.

At level 2-CC, both FEP and SZ perform poorly on reward learning with explicit emotional information, but FEP perform worse than SZ. This could indicate that either FEP over-suppress any explicit emotional information or that emotional information is more disruptive to CC in FEP. As previously described, patients show increased susceptibility to emotional information presented as a distractor (Evans et al., 2011b). When categorizing FEP as high and low symptomatic, different activation patterns during this level 2-CC task have been reported despite similar performance, except for similar activation of the ACC (Horne et al., 2022). This unchanged activation of ACC supports our

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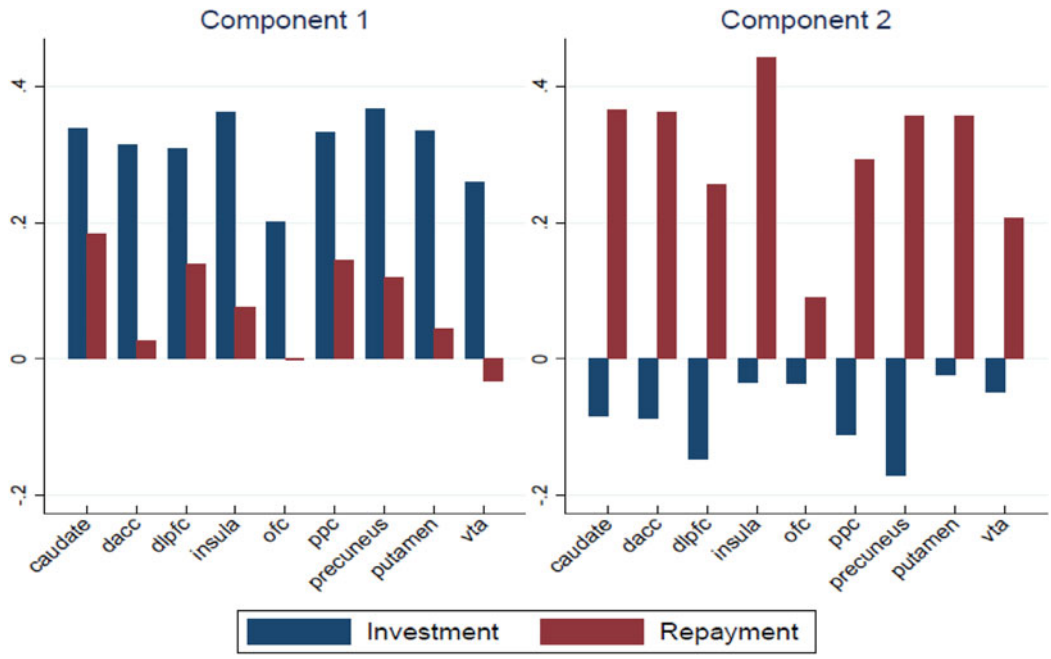


**Figure 1.** Principle component analysis (PCA) of region of interest (ROI) in Trust game.
*Note:* dacc, dorsal anterior cingulate cortex; dlpfc, dorso-lateral prefrontal cortex; ofc, orbito-frontal cortex; ppc, posterior parietal cortex; vta, ventral tegmental area.
The model with two components reflects the two different phases in the task, suggesting no other components influence ROI activation during the task. Component 1 shows clear increased activation of the ROIs during investment, with least pronounced activation in the reward related OFC and VTA. However, activation of the caudate during repayments is quite high in this component, which is in line with the reward signal shifting from the repayment phase towards the investment phase during repeated interactions (becoming reward anticipation) see (King-Casas et al., 2005). Component 2 shows more activation in the ROIs during repayment, with again least activation in the VTA and OFC.

hypothesis that cognitive control may be stronger for emotional information in FEP suppressing explicit emotional information, leading to more inaccuracies in the Faces task in FEP than SZ.

At level 3, exploring CC in the context of implicit emotional information in the trust game, the current study demonstrates that feedback learning during the trust game in FEP was similar

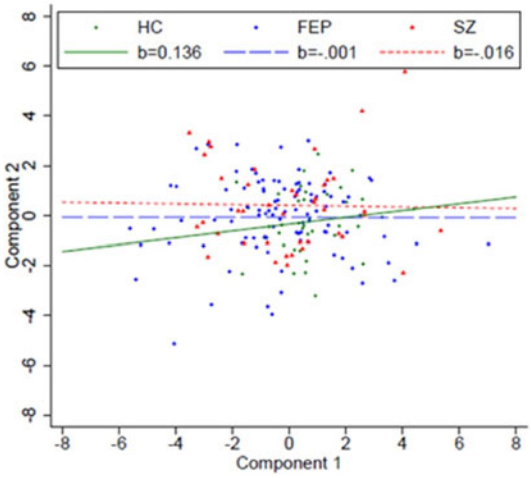


**Figure 2.** Scatterplots and regression slope between principal components.
*Note:* HC, healthy controls; FEP, first episode psychosis; SZ, schizophrenia.
The graph shows an association between component 1 and 2 only in HC, indicating an association between ROI activation between the investment and repayment phase only in healthy controls. In both patient groups, no such association is found, suggesting less integration of investment and repayment phases.

to HC (Campellone et al., 2016; Lemmers-Jansen et al., 2019), and greater compared to patients with SZ, while baseline trust was lowest in FEP compared to both HC and SZ. Previous studies show reduced baseline trust over all stages of the illness, including individuals at risk for psychosis (Fett et al., 2014; Gromann et al., 2013; Lemmers-Jansen et al., 2019). Our results show that despite lower baseline trust in FEP, they can learn with feedback, indicating that level 3-CC impairments in FEP occur in the context of a CCN with preserved plasticity, which is lost in SZ. Patients with lower symptoms, especially negative symptoms, showed steeper learning during the trust game. Behavioral outcomes at level 2-CC were predictive for trust behavior in HC and FEP. The unexpected finding that FEP showed lower baseline trust than SZ supports our findings of level 2 CC, indicating a greater suppression of emotional information during CC tasks in FEP.

Neural activation during the trust game demonstrated reduced activation of the CCN in patients compared to HC, especially in the dACC and precuneus. Reduced dACC activation associated with increased cognitive load (Jalbrzikowski et al., 2018) and reduced precuneus activation during cognitive functioning (Soldevila-Matías et al., 2020) is previously reported in FEP. In the reward network, including the caudate and putamen, activation was reduced in patients compared to controls. These findings are consistent with previous trust game (Fett et al., 2019; Gromann et al., 2013) and reward processing studies (Lee et al., 2019; Strauss, Waltz, & Gold, 2013) in psychosis. We found increased activation of VTA in FEP and insula in SZ in the reward networks compared to HC. VTA has been shown to be involved in reward learning (Keiflin, Pribut, Shah, & Janak, 2019). This

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increased activation of VTA may indicate overcoming the greater suppression of emotional information during CC tasks in FEP to facilitate learning in FEP. The insula is involved in detecting deviation from reward expectations (Harlé, Chang, van 't Wout, & Sanfey, 2012; Haufler, Liran, Buchanan, & Pare, 2022) and thus increased activation of insula in SZ may indicate registering the feedback but unable to use it for learning. Although both patient groups have reduced capacity for CC, FEP are able to overcome this limitation to an extent and able to learn with implicit emotional information (trust) using the reward network.

The dynamic relationship of CC and reward processing involves both top–down, i.e. goal driven as well as bottom–up, i.e. stimulus driven (feedback) processes. PCA analysis showed that the activation pattern of the CCN and reward learning areas were distinct during the investment and repayment phases of the trust game. The magnitude of activations in these areas was correlated with performance only in HC indicating integrated top–down and bottom–up modulation of CC (Lee & Shomstein, 2014; Ochsner et al., 2012). In FEP, top–down and bottom–up processes were not integrated in level 3-CC task and a greater suppression of bottom–up explicit emotional information in level 2-CC task (Averbeck & Duchaine, 2009). However, in level 3-CC involving implicit emotional information, PCA – component 2, related to reward network, was predictive for learning over trials in FEP, demonstrating that FEP can use the bottom–up processes using the reward network to modulate CCN.

Top–down and bottom–up processes are also disrupted in SZ, as seen in level 3-CC task, but SZ can use the bottom–up feedback with explicit emotional information in level 2-CC task and perform more accurately than the FEP. We show that FEP can use feedback to learn, i.e. incorporate the bottom–up information in reward network to modulate the CCN, demonstrating preserved plasticity of the CCN. SZ patients fail to show such learning, possibly demonstrating saturation of limited neural resources. In summary, despite disrupted integration of top–down and bottom–up processes of CC, patients with SZ perform better with explicit emotional information although they are limited in their capacity to learn while FEP can learn in the context of implicit emotional information (trust), possibly owing to preserved plasticity of the CCN.

### *Limitations*

Our study focussed on differences in performance in the different levels of cognitive control. As highlighted in Table 1 and Supplementary Materials, the statistical differences in age, education, IQ, types of medication and chlorpromazine equivalent doses between FEP and SZ could also influence task performance in addition to the different stages of illness.

The levels of CC using different task paradigms require increased complexity of CC but also may differ on other aspects, such as emotion recognition, emotion processing, and motor control. This implies that there is a possibility that the results found could be due to other factors we did not consider. Future research could disentangle the processes by designing a single task with different levels of complexity, to minimize confounding factors. In line with this, neuroimaging findings in our study are solely based on the trust paradigm. We did not present a direct comparison of activation of CC and reward learning networks during cognitive control across all three levels of complexity. Furthermore, we have suggested a possible interplay between the CCN and reward network, however, we were not able to establish a causal link between the networks.

## Conclusion

The main finding in our study is that plasticity of CCN, i.e. the ability to learn to modulate cognitive control, is preserved in early stages of psychosis but lost in the later stages of the illness. This plasticity offers cognitive control as a therapeutic target in the early stages of psychotic illness, opening the way to psychological, non-invasive brain modulation, and pharmacotherapeutic approaches.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724001119.

**Competing interests.** None.

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