The role of psychosis and clozapine load in excessive checking in treatment-resistant schizophrenia

Running title: clozapine excessive checking

Emilio Fernandez-Egea[1,2,3 *]
Shanquan Chen[2]
Estela Sanguesa[4]
Patricia Gassó[5]
Marjan Biria[3,6]
James Plaistow[1]
Isaac Jarratt-Barnham[1]
Nuria Segarra[1]
Sergi Mas[5]
Maria-Pilar Ribate[4]
Cristina B. Garcia[4]
Naomi Fineberg[8,9]
Yulia Worbe[10,11,12]
Rudolf N. Cardinal[1,2]
Trevor W. Robbins[3,6]

Words: 3,324	Abstract: 246	References: 23
Tables: 2	Figures: 2	Supplementary materials: 3

Author details:
1 Cambridgeshire and Peterborough NHS Foundation Trust. Cambridge, UK
2 Department of Psychiatry, University of Cambridge. Cambridge, UK
3 Behavioural and Clinical Neuroscience Institute, University of Cambridge. Cambridge, UK
4 Faculty of Health Sciences, Universidad San Jorge. Villanueva de Gállego (Zaragoza). Spain
5- Department of Basic Clinical Practice, University of Barcelona, Spain. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Spain.
6 Department of Psychology, University of Cambridge. Cambridge, UK
7 Department of Public Health and Primary Care, University of Cambridge
8 Hertfordshire Partnership University NHS Foundation Trust, University of Hertfordshire. Welwyn Garden City, UK
9 School of Life and Medical Sciences, University of Hertfordshire. Hatfield, UK
10 Sorbonne Université. Paris 05, France
11 Department of Neurophysiology, Saint-Antoine Hospital. Paris, France
12 INSERM U 1127, CNRS UMR 7225, Institute du Cerveau et de la Moelle Epinière. Paris, France

*__Corresponding author__
Emilio Fernandez-Egea
Cambridge Psychosis Centre
Cambridgeshire and Peterborough NHS Foundation Trust
128 Tenison Road
Cambridge, CB1 2DP, UK
Email: ef280@cam.ac.uk
Phone: (+44) 01223 227501
Fax: (+44) 01223 227501

Abstract

Background: A significant proportion of patients with clozapine-treated schizophrenia develop checking compulsions, a phenomenon yet to be understood. We use habit formation models developed in the cognitive neurosciences to conceptualise the complex relations between psychosis, clozapine action and compulsions.

Aims: The main research question investigated the dynamic interplay between psychosis, clozapine dose and obsessive– compulsive symptoms (OCS).

Method: Using the anonymised electronic records of a cohort of clozapine-treated patients, including longitudinal assessments of OCS and psychosis, we performed longitudinal multi-level mediation and multi-level moderation analyses to explore associations of psychosis with obsessiveness and excessive checking. Classical bivariate correlation tests were used for assessing clozapine load and checking compulsions. The influence of specific genetic variants was tested in a subsample.

Results: A total of 196 subjects and 459 face-to-face assessments were included. We found significant OCS to be common in clozapine-treated patients (37.9%), with checking being the most prevalent symptom. In mediation models, psychosis severity mediated checking behaviour indirectly by inducing obsessions [0.07 (Confidence interval 0.04, 0.09); p<0.001). No direct effect of psychosis on checking was identified [−0.28 (IC −0.09, 0.03); p=0.340]. After psychosis remission (n=65), checking compulsions correlated with both clozapine plasma levels (r=0.35; p=0.004) and dose (r=0.38; p=0.002). None of the glutamatergic and serotoninergic genetic variants found moderating the effect of psychosis on obsession and compulsion (*SLC6A4, SCL1A1 and HTR2C*) survived the multiple comparisons correction.

Conclusions: We elucidated different phases of the complex interplay of psychosis and compulsions, which may inform clinicians' therapeutic decisions.

Keywords:
habit formation; clozapine; treatment-resistant schizophrenia; serotonin; compulsion

Introduction

A significant proportion of patients with schizophrenia develop obsessive–compulsive symptoms (OCS). Some patients experience an obsessive–compulsive disorder (OCD) after remission of psychosis, whilst others enter an intermediate state combining psychosis and OCS[1]. However, there is no clear understanding of this phenomenon.

Schizophrenia and OCS/OCD

OCS and OCD are common among those with schizophrenia, with prevalence increasing from 12.5% in subjects with at-risk mental states for psychosis, to 25% in early schizophrenia, and up to 47% in clozapine-treated patients[2]. There is a plausible biological overlap between schizophrenia with OCS and patients with classical OCD. Both feature orbitofrontal cortex over-activation[3] and exhibit similar traits of cognitive inflexibility, reduced processing speed and memory deficits[4]. Further, patients with schizophrenia and OCS share a genetic background with OCD. Specifically, single nucleotide polymorphisms (SNPs) and other genetic variants in the glutamate pathway, such as *SLC1A1* (glutamate transporter) and *GRIN2B* (glutamate receptor), are associated with OCS in clozapine patients[5]. However, associations with serotonergic (5-HT) pathways have not been explored, despite the role of *SLC6A4* (a serotonin transporter), *HTR2A* and *HTR2C* (serotonin receptors) in OCD[6]. Some authors advocate for including schizo-obsessive disorder as a schizophrenia subtype in which pre-existing OCS/OCD is unmasked after psychosis remission[4]. However, this hypothesis is undermined by work showing a correlation between OCS and psychosis severity[5]. Others argue that *de novo* OCS in schizophrenia is an antipsychotic-related event[1]. Epidemiologically, *de novo* OCS are over-represented in patients treated with clozapine, olanzapine, or risperidone when compared to patients prescribed aripiprazole, amisulpride or haloperidol[6]. This likely reflects these drugs' different 5-$HT_{2A/2C}$ receptor affinity. OCS are also associated with higher clozapine dose and length of treatment and clozapine plasma levels[7], suggesting a dose-dependent relationship. This is challenged, however, in the literature, with some suggesting that these findings be confounded by the higher antipsychotic doses typically required by those with psychosis of greater severity[8].

Using the habituation model to understand the interplay between psychosis, OCS and clozapine

We have previously identified that, in clozapine-treated patients, psychosis severity and length of treatment are distinct risk factors for obsessions and checking compulsions respectively[9]. Most studies show a predominance of compulsions over obsessions in this patient group with excessive checking being the most frequently reported repetitive behaviour[10]. Informed by models of habit formation developed in the cognitive neurosciences, we conceptualised these checking compulsions as arising as the by-product of psychosis. Specifically, repetition in the

context of a diminished ability to consider an action's outcome may lead to the automatisation of behaviour ('habit formation'). Further, decreased 5-HT activity may enhance habit development.[11] We have applied this framework to hypothesise a two-phase model of OCS and OCD development. Firstly, an initial phase of checking as a goal-directed behaviour may occur due to psychotic hypervigilance. After psychosis remission, achieved with antipsychotic treatment, a second 'habit' phase may occur in which clozapine ameliorates psychosis but promotes checking compulsions via serotonin antagonism in those vulnerable.

In the present study, we investigated the dynamic interplay between psychosis, clozapine dose and OCS. We aimed to test this two-phase hypothesis using a large cohort of clozapine-treated patients assessed longitudinally. Specifically, we hypothesised that:
1) checking compulsion is related to psychosis severity;
2) checking severity correlates with clozapine plasma levels in those in remission from psychosis.
Finally, we also explored the moderating effects of specific genetic variants on the effect of psychosis on obsession and the development of compulsions.

Methods

Study design and setting

This naturalistic, observational longitudinal study used anonymised electronic records gathered by Cambridgeshire and Peterborough NHS Foundation Trust (CPFT). CPFT is the primary public mental health care provider for approximately 890,000 people in a mixed urban/rural area in East England, UK.

Ethics, Participants and electronic records

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

We used the Clinical and Research Database (CRD) for Persistent Schizophrenia under NHS Research Ethics Committee (REC) approvals (ref. 13/EE/0121; 18/EE/0239). This database contains anonymised routine clinical data from the CPFT Clozapine Clinic.

Extracted data maintained patient anonymity by removing all identifiable data. All clinical assessments in the CRD were performed by an experienced psychiatrist (EFE) and the database also contained measures self-rated by the patient during routine clinical appointments.

This study covers information from 24th August 2012 to 31st Dec 2022. The CRD includes 3,126 face-to-face assessments of 254 patients taking clozapine. For this study, assessments were only included that had a standardised evaluation of OCS and scores from the Positive and Negative Syndrome Scale (PANSS), positive subscale (PANSS-positive) (see below).

Routine clinical assessments

All annual care plan assessments (CPAs) in the electronic record include relevant sociodemographic data (age, gender, age of illness onset, date clozapine start date), a review and confirmation of prescribed medication (with dose), current smoking habit (average number of cigarettes per day), alcohol use (average number of alcohol units per week) and latest clozapine and norclozapine plasma levels results (including date of test). All patients are evaluated with all the scales.

For this study, relevant psychopathology scales included in the CRD include the Obsessive–Compulsive Inventory—Revised (OCI-R), self-reported annually from 2016 (and independently done to other scales) and the PANSS-positive, rated every two years since 2017.

Psychopathology scales

OCS severity was measured using the OCI-R[12], a self-reported, 18-item measure featuring six subscales (washing, checking, ordering, obsessing [e.g. having obsessional thoughts], hoarding, and mental neutralising). The impact of each item on a respondent's function is reported via a 5-point scale, ranging from 'not at all' (0) to 'extremely' (4). The total score, therefore, ranges from 0 to 72, with higher scores indicating greater OCS severity. As in previous work, we considered a total score of 21 or above, or 5 or above in any subscale, as clinically significant 9 .

Psychosis severity was also measured using the positive subscale (items P1 to P7) of the PANSS. The PANSS is a clinician-rated scale including 7 items referring to psychotic ("positive") symptoms rated on a 7-point scale (1 absence, 7 extreme). Patients were considered in remission from psychosis when none of these items scored 3 or above, as the main goal of the study was to explore whether active symptoms (PANSS score of 3 or above) were associated with OCS/OCD.

Using plasma levels for assessing clozapine load.

We used blood clozapine levels as a measure of clozapine load, rather than clozapine dose, as dose (typically ranging from 75–900 mg/day) is an inaccurate measure of clozapine load[14]. This is because clozapine metabolism is influenced by various factors, including concordance,

gender, cytochrome polymorphisms, concurrent medication, and smoking habits.]. Blood levels, therefore, represent a more precise measure.

Genetics of clozapine-induced OCS

One hundred patients also consented to participate in the ethically approved 'Genetics of common clozapine-induced side effects' study (REC reference 18/NW/0581). The study aimed to replicate previously described genetic variants associated with clozapine side effects, including OCD and metabolic complications.

Specifically, we explored serotonin pathway genetic variants, including single nucleotide polymorphisms (SNPs): *SLC6A4* (rs4795541, rs25531), *HTR2A* (rs6313, rs6314) and *HTR2C* (rs3813929, rs1414334). Variants within the glutamate pathway were also included: *SLC1A1* (rs2228622) and *GRIN2B* (rs890). Samples were collected during routine blood monitoring at the clozapine clinic, using Whatman® FTA® (Flinders Technology Associates) cards by Sigma-Aldrich, allowing storing, transporting, stability and deoxyribonucleic acid (DNA) purification from samples at room temperature.

Genotyping was conducted at San Jorge University in Zaragoza and within the Pharmacology Unit of Barcelona University Medical School, both in Spain. Using a paper puncher previously sterilised with alcohol and flame, 3 mm discs of dried blood were obtained from the card. DNA was extracted following the manufacturer's instructions. The concentration and quality of DNA were measured spectrophotometrically using a NanoDrop 2000 (Thermo Fisher Scientific, Surrey, UK). Genetic variants of the *SLC6A4* gene, rs4795541 (also known as 5-HTTLPR) and rs25531, were genotyped using MJ Mini Thermal Cycler (Bio-Rad, Hercules, CA, USA) following polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) conditions described previously . CFX Connect Real-Time PCR System (Bio-Rad, Hercules, CA, USA) was used to genotype rs6313 and rs6314 (*HTR2A*) with predesign rhAmp SNP Genotyping assays (Integrated DNA Technologies, Coralville, Iowa. USA). The polymorphisms rs3813929and rs1414334 (*HTR2C*), rs2228622 (*SLC1A1*) and rs890 (*GRIN2B*) were genotyped using MJ Mini Thermal Cycler (Bio-Rad, Hercules, CA, USA) following PCR and RFLP conditions previously described.

The STROBE guidelines checklist was followed and can be found in the submission.

Statistical analysis

For basic description, categorical variables are reported in the format “number (percentage %)”, and continuous variables in the format “mean (standard deviation [SD])”.

Pearson correlation coefficients were used to measure the strength and direction of associations between continuous variables. To account for multiple comparisons, we applied a Bonferroni correction.

A multi-level mediation model assessed the longitudinal association between psychosis severity and checking compulsions, directly and indirectly via obsessing. This is the preferred method for exploring longitudinal changes in samples where the time between assessments is not fixed, as in our study. Psychosis severity (measured by the PANSS-positive subscale) was included as both a fixed-effect and a (per-subject) random-effect variable, and the duration of clozapine treatment was controlled for, as in previous similar studies. Further analyses used PANSS-positive items associated with reality distortion (items P1, P3 and P6).

For assessing the effect of clozapine load on psychosis severity, we selected a subgroup of patients to avoid factors confounding previous research. These patients were 1) on clozapine monotherapy (no other antipsychotic or antidepressant) for more than a year, 2) were in remission from psychosis, 3) and had plasma levels taken within 28 days of the OCS evaluation (without intervening medication changes) that), which were within the upper limit of the therapeutic range (0.6 mg/L or 600 ng/mL).

Multi-level moderation models were also conducted to explore if specific genetic variants moderated the association between psychosis severity and checking compulsions via obsessions. The models were fitted with psychosis severity and genetic variant as both fixed-effect and (per-subject) random-effect variables. Duration of clozapine use was controlled for. This was performed in a sub-group of patients for whom genetic data were available (n=97, 235 face-to-face assessments).

All statistical analyses were performed using R (version 3.5.0), including the packages lmerTest (version 3.1-2) and Mediation (version 4.5.0).

Access to code and database will made available upon request to the corresponding author.

Results

Sample description

The final sample consisted of 196 patients and 459 OCI-R/PANSS-positive pair assessments, each patient being followed for an average of 2.7 years. **Table 1** shows key sociodemographic and clinical variables at baseline: 74 individuals (37.9%) had an OCI-R score at or above the OCD cut-off of 21. Obsessing and checking compulsions were the most common OCS. Among those in psychosis remission (n=60 out of 196), 25 patients (12.8% of the total) exhibited significant checking behaviours (indicated by a score >4 on the checking subscale).

Thirty-five patients (17.9%) exhibited negligible OCS (total score <5 and checking factor <2) after five years or more on clozapine treatment. The **supplementary material** expands on the details of the prevalence of OCS severity by psychosis remission.

--------Insert table 1 here -------

The role of psychosis and reality distortion in OCS

Psychotic symptoms significantly correlated with overall OCS severity and with the obsessing and checking compulsion subscales of the OCI-R (**Table 2**). This association was significantly stronger for obsessing (r=0.419) than compulsion (r=0.116). **Table 2** also shows the associations with the individual psychotic symptoms.

-------- insert table 2 -------

The effect of psychosis on checking behaviour was indirect, mediated by obsessional symptoms. No direct effect of psychosis on checking compulsions was identified (**Figure 1**). The length of clozapine treatment was controlled for in this model. In further models (see **supplementary figures 1 and 2**), an indirect effect of psychosis on compulsion was only found for those patients with active paranoid/psychotic symptoms (n=198; those in which the sum of PANSS items P1+P3+P6 > 4). Similar results were found when additional confounds, including clozapine dose, were included in the models.

-------- insert figure 1 -------

The role of clozapine on the persistence of excessive checking after psychosis remission

]**Figure 2** shows the significant correlations between checking compulsions and clozapine dose (n=65, r=0.378, p=0.002), clozapine plasma level (r=0.353; p=0.004) and norclozapine level

(r=0.270; p=0.030). There was no correlation between obsessing and either clozapine dose or levels (p>0.21).

-------- insert figure 2 -------

Within this group of patients in remission, we compared those with excessive checking (OCI-R checking subscale >4; n=28) to those without checking (n=37). Those with excessive checking had a higher clozapine dose (t=2.956; p=0.04), higher clozapine levels (t=2.973; p=0.04) and higher norclozapine levels (t=2.363; p=0.021).

Across the whole sample (thus, including those with any severity of psychosis or non-monotherapy; n=313), there were not significant correlations between checking severity and clozapine dose (r=0.071; p=0.213) or plasma level (r=0.021; p=0.709).

Genes moderating psychosis-to-obsession and obsession-to-compulsion effects.

We found the association of psychosis with obsessions to be moderated by serotonergic genes in uncorrected tests, but this did not survive correction for multiple comparisons. In the uncorrected tests, genotype GC for the HTR_{2C} (rs1414334) moderated the effect, and genotype GA *SCL6A4* (rs25531) and genotype AA for *SLC1A1 (rs2228622)* moderated the effect from obsession to compulsion, but none of the other SNPs studied did. **Supplementary table 1** details the eight SNPs studied.

Discussion

OCS is common in clozapine-treated patients and is associated with both psychosis severity and clozapine load, albeit at different phases. Mediation analyses suggested that psychosis severity generates checking behaviour indirectly by inducing obsessions. After remission from psychosis, checking compulsion correlated with clozapine plasma levels. We also found indications that serotonergic and glutamatergic variants might moderate the effect of psychosis on obsessions and compulsions, although our sample size was too small for these findings to be considered conclusive.

This study has some limitations. Firstly, its naturalistic design is inferior to an experimental study. Experimental methodologies, however, are unfeasible as the potentially lethal side effects of clozapine generally prohibit its chronic administration to healthy volunteers. Long-term longitudinal studies in patients with schizophrenia after clozapine initiation could provide a more detailed characterisation, but the latency of the onset of OCS (up to a decade) may render such

studies impractical. Given this, we consider this study's large sample and longitudinal follow-up to represent a balance between practical feasibility and rigour. Secondly, OCS were evaluated using a self-rated scale and further work might benefit from replication using a clinician-rated scale such as Y-BOCS. Again, however, this may be impractical in a clinical environment. Thirdly, the patient sample included in this study's genetic analyses was small (n=97), and these findings should therefore be taken as exploratory and in need of replication.

Our results broadly align with previous research regarding OCS prevalence (here, 37.1%) and the predominance of checking and obsessing symptoms. Our sample is representative of a typical clozapine-treated cohort, with male predominance (79%), an average prescribed clozapine dose of ~330 mg/day and a typical treatment length (~14 years). Importantly, however, this study's sample size (196 cases), longitudinal nature and volume of standardised OCS and PANSS-positive assessments (457 face-to-face assessments) are more extensive than any previous research.

This work builds on a hypothesis was established *a priori* and and developed during our previously published cross-sectional publication. We have conceptualised clozapine-associated OCS as a dynamic phenomenon that fluctuates in intensity according to psychosis severity, in line with recent work by Schirmbeck and colleagues[16], and clozapine load. We uncoupled OCS into its two main components (obsessions and compulsions) and applied a mediation model that identified an association of psychosis severity (particularly the severity of reality distortion symptoms, such as delusions, hallucinations, or suspiciousness/persecutory beliefs) with obsessive thoughts. Obsessive thoughts, in turn, triggered checking behaviour. This may initially be understood as goal-directed, safety-seeking behaviour in acutely psychotic, paranoid patients. As one patient in this cohort reported, '*I need to check everything is in place as my upstairs neighbour comes to steal my stuff*'. Then, in patients achieving psychosis remission, we found checking severity to be significantly correlated with clozapine plasma levels, suggesting a role of clozapine in perpetuating checking as a non-goal-directed action or habit. Indeed, persistently impaired safety signalling has been described in OCD[16], limiting patients' ability to assign safety valuations after verification.

Appreciating the distinct roles of psychosis and clozapine in OCS development is essential to understanding the apparent discrepancies in previous cross-sectional studies. The point prevalence of OCS (measured via questionnaire) may fluctuate according to the severity of the psychosis (**Figure 1, Table 2**), clozapine load (**Figure 2**), concomitant medications (e.g. antidepressants) or even the tools used to assess the symptoms. For instance, psychosis-

driven, goal-directed checking might not be considered OCS but part of a delusion. Here we circumvented this risk by using a patient-reported OCS questionnaire.

Our hypothesised two-phase model of OCS development[9], is based on cognitive neuroscience framework habit formation[11] and shows the potential for embedding cognitive neuroscience into clinical practice. In our context, clozapine-treated patients in psychosis remission might experience checking compulsions as an antipsychotic-induced habit. A notable strength of our two-phase model is its integration of present results, previous studies and patients' narratives, in which psychosis-induced goal-directed behaviour becomes habitual. This model is also flexible in regarding the content of the repetitive behaviour, as we found checking, but others reported washing as the most common compulsion.[17] Therefore, it can accommodate other triggers, such as the influence of stressful eventsClick or tap here to enter text., cognitive dysfunctions or affective symptoms (not included in this study as they were not part of the *a priori* hypothesis).

A plausible mechanism for the persistence of repetitive behaviour following remission from psychosis may be clozapine's antagonism of 5-HT_{2A} and 5-HT_{2C} receptors. A decrease in serotonin neurotransmission causes perseveration in reversal learning tasks, the hallmark of cognitive inflexibility in compulsive behaviours including OCD[19]. In humans, dietary tryptophan depletion (which reduces serotonin in the brain acutely) promotes habitual over goal-directed control[20]. Remarkably, a recent mouse-model study showed similar results. Mice receiving clozapine increased their grooming time significantly (as a proxy of compulsion). This behaviour then reverted on the administration of fluoxetine, a selective serotonin reuptake inhibitor. Interestingly, the same effects were seen in both wild-type and *Sapap3*-knockout mice (a well-known animal model of OCD), albeit with significantly greater intensity in the knockout mice, suggesting a genetic vulnerability to clozapine-induced habit formation.[21]

Nevertheless, it is also interesting to note that individual factors might increase vulnerability. For instance, 35 patients (17.9%) exhibited negligible OCS after five years or more on clozapine treatment. Variations in vulnerability was explored in this work, in which we suggest a distinct role of serotoninergic and glutamatergic SNPs on psychosis-to-obsession and obsession-to-compulsion influence, respectively (**supplementary material**). We found evidence to support previous findings involving the glutamate pathway[22], such as *SCL1A1*. More importantly, we report the first indication of serotonin pathway involvement, as described in pure OCD. However, drawing firm conclusions about the role of specific variants will require work with larger samples. Nevertheless, our identification of several genetic variants in the serotonin pathway (*SCL64A*, *5HTR2C*) moderating the psychosis–obsession–compulsion pathway is notable, and may offer

clues to future preventative or therapeutic approaches. The converging evidence from this study, and others, indicates that interventions directed to enhancing serotonin function are crucial for the effective treatment of clozapine-induced OCS[23], as in pure OCD. Nevertheless, we did not specifically explore the effect of medication modifications on OCS severity, and further research is needed in this area.

In conclusion, the onset of significant OCS in clozapine-treated patients is a puzzling phenomenon in which people suffering from one disorder (schizophrenia) seem to transition to a second (OCD). Here, we offer an explanatory model for this phenomenon informed by the insight provided by cognitive neuroscience into habit formation. This suggests that compulsions arise as a by-product of florid paranoid psychosis and are then perpetuated in predisposed subjects (after remission of psychosis) by clozapine's anti-serotonergic action. A better understanding of the different phases of the phenomenon (associated either with psychosis or clozapine load) may inform clinicians' therapeutic decisions.

Declaration of Interest

EFE is the deputy editor of BJPsych but did not take part in this paper's review or decision-making process. EFE has received consultancy honoraria from Boehringer-Ingelheim (2022), Atheneum (2022) and Rovi (2022–23), speaker fees by Adamed (2022–23) and Otsuka (2023) and training and research material from Merz (2020). All other co-authors have no conflict of interest relevant to this work.

Funding

An intramural research award from Universidad San Jorge supported ES. MB, IJB, and NS were supported by a studentship from the Mental Health Research UK. SC's and RNC's research was funded by the UK Medical Research Council (grant MC_PC_19213, MR/W014386/1). Dr. Fernandez-Egea is supported by the 2022 MRC/NIHR CARP award (MR/W029987/1), and this research was supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014, NIHR203312). The views expressed are those of the author(s) and not necessarily of the NIHR or the Department of Health and Social Care.

Acknowledgements We would like to thank all those patients who contributed to the study and to Pedro Fernandez-Bruna for his creative support with the figures.

Author Contribution

Conceptualise: EFE, IJB, YB, NF and TWR
Design Study: EFE, YB, TWR, MB, JP, NS
Assessing: EFE
Genotyping: ES, PG, SM, MPR, CBG
Statistical analysis: EFE, SC, RNC
Writing article: EFE, SC, RNC, TWR
All authors approved final version.

Transparency declaration

The lead author (EFE) affirms that the manuscript is honest, accurate and transparent. No important aspects of the study have been omitted.

Data availability

Data are available from the corresponding author upon reasonable request.

Figure 1. Obsessive–compulsive symptoms (OCS) and psychosis. Mediation model for exploring causality. Psychosis was measured with the Positive and Negative Syndrome Scale (PANSS), positive subscale (n=195, with 459 face-to-face assessments).

Figure 2. Correlation of checking severity with clozapine dose and plasma levels in the subgroup (n=65) on clozapine monotherapy and in remission from psychosis. Clozapine plasma levels were taken within 28 days of the assessment and with no intervening medication changes.

Reference list

1 Schirmbeck F, Zink M. Comorbid obsessive-compulsive symptoms in schizophrenia: Contributions of pharmacological and genetic factors. Front Pharmacol 2013; 4 AUG: 1–14.

2 Mawn L, Campbell T, Aynsworth C, Beckwith H, Luce A, Barclay N, *et al.* Comorbidity of obsessive-compulsive and psychotic experiences: A systematic review and meta-analysis. J Obsessive Compuls Relat Disord. 2020; **26**. doi:10.1016/j.jocrd.2020.100539.

3 Schirmbeck F, Mier D, Esslinger C, Rausch F, Englisch S, Eifler S, *et al.* Increased orbitofrontal cortex activation associated with "pro-obsessive" antipsychotic treatment in patients with schizophrenia. *Journal of Psychiatry and Neuroscience* 2015; **40**: 89–99.

4 Poyurovsky M, Weizman A, Weizman R. Obsessive-compulsive disorder in schizophrenia: Clinical characteristics and treatment. CNS Drugs. 2004; **18**. doi:10.2165/00023210-200418140-00004.

5 Guillem F, Satterthwaite J, Pampoulova T, Stip E. Relationship between psychotic and obsessive compulsive symptoms in schizophrenia. *Schizophr Res* 2009; **115**. doi:10.1016/j.schres.2009.06.004.

6 Grillault Laroche D, Gaillard A. Induced Obsessive Compulsive Symptoms (OCS) in schizophrenia patients under Atypical 2 Antipsychotics (AAPs): review and hypotheses. *Psychiatry Res* 2016; **246**: 119–28.

7 Gürcan G, Şenol ŞH, Yağcıoğlu AEA, Ertuğrul A. Clinical risk factors, phenomenology and the impact of clozapine induced obsessive compulsive symptoms. *Psychiatry Res* 2021; **296**. doi:10.1016/j.psychres.2020.113665.

8 Kim DD, Barr AM, Stewart SE, White RF, Honer WG, Procyshyn RM. Relationship between clozapine dose and severity of obsessive-compulsive symptoms. *Med Hypotheses* 2021; **148**. doi:10.1016/j.mehy.2021.110506.

9 Fernandez-Egea E, Worbe Y, Bernardo M, Robbins TW. Distinct risk factors for obsessive and compulsive symptoms in chronic schizophrenia. *Psychol Med* 2018. doi:10.1017/S003329171800017X.

10 Mukhopadhaya K, Krishnaiah R, Taye T, Nigam A, Bailey AJ, Sivakumaran T, *et al.* Obsessive-compulsive disorder in UK clozapine-treated schizophrenia and schizoaffective disorder: A cause for clinical concern. *Journal of Psychopharmacology* 2009; **23**: 6–13.

11 Gillan CM, Robbins TW, Sahakian BJ, van den Heuvel OA, van Wingen G. The role of habit in compulsivity. *European Neuropsychopharmacology* 2016; **26**. doi:10.1016/j.euroneuro.2015.12.033.

12 Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, *et al.* The obsessive-compulsive inventory: Development and validation of a short version. *Psychol Assess* 2002; **14**. doi:10.1037/1040-3590.14.4.485.

13 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987. doi:10.1093/schbul/13.2.261.

14 Rostami-Hodjegan A, Amin AM, Spencer EP, Lennard MS, Tucker GT, Flanagan RJ. Influence of Dose, Cigarette Smoking, Age, Sex, and Metabolic Activity on Plasma Clozapine Concentrations: A Predictive Model and Nomograms to Aid Clozapine Dose Adjustment and to Assess Compliance in Individual Patients. *J Clin Psychopharmacol* 2004; **24**: 70–8.

15 Schirmbeck F, Esslinger C, Rausch F, Englisch S, Meyer-Lindenberg A, Zink M. Antiserotonergic antipsychotics are associated with obsessive-compulsive symptoms in schizophrenia. *Psychol Med* 2011; **41**: 2361–73.

16 Schirmbeck F, Konijn M, Hoetjes V, Zink M, de Haan L. Obsessive–compulsive symptoms in psychotic disorders: longitudinal associations of symptom clusters on between- and within-subject levels. *Eur Arch Psychiatry Clin Neurosci* 2019; **269**: 245–55.
17 Poyurovsky M, Hramenkov S, Isakov V, Rauchverger B, Modai I, Schneidman M, *et al.* Obsessive-compulsive disorder in hospitalized patients with chronic schizophrenia. *Psychiatry Res* 2001; **102**. doi:10.1016/S0165-1781(01)00238-4.
18 Schirmbeck F, Konijn M, Hoetjes V, Vermeulen J, Zink M, Dekker J, *et al.* Stressful experiences affect the course of co-occurring obsessive-compulsive and psychotic symptoms: A focus on within-subject processes. *Schizophr Res* 2020; **216**: 69–76.
19 Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. Neurocognitive endophenotypes of impulsivity and compulsivity: Towards dimensional psychiatry. *Trends Cogn Sci* 2012; **16**: 81–91.
20 Worbe Y, Savulich G, de Wit S, Fernandez-Egea E, Robbins TW. Tryptophan depletion promotes habitual over goal-directed control of appetitive responding inhumans. *International Journal of Neuropsychopharmacology* 2015; **18**. doi:10.1093/ijnp/pyv013.
21 Kang S, Noh HJ, Bae SH, Kim YS, Lew H, Lim J, *et al.* Clozapine generates obsessive compulsive disorder-like behavior in mice. *Mol Brain* 2020; **13**. doi:10.1186/s13041-020-00621-5.
22 Cai J, Zhang W, Yi Z, Lu W, Wu Z, Chen J, *et al.* Influence of polymorphisms in genes SLC1A1, GRIN2B, and GRIK2 on clozapine-induced obsessive-compulsive symptoms. *Psychopharmacology (Berl)* 2013; **230**: 49–55.
23 Englisch S, Esslinger C, Inta D, Weinbrenner A, Peus V, Gutschalk A, *et al.* Clozapine-induced obsessive-compulsive syndromes improve in combination with aripiprazole. *Clin Neuropharmacol* 2009; **32**: 227–9.

Table 1. Baseline socio-demographic and clinical characteristics of the subjects (*n* = 196). OCI-R, Obsessiv
PANSS, Positive and Negative Syndrome Scale.

Variables	Number (percentage %), or
Per person:	
Age (baseline) (years)	47.44 (
Age at first-episode psychosis (FEP)	22.54
Age at starting clozapine	31.41
Gender (= male)	155 (7
Follow-up (years)	2.71 (
Number of face-to-face assessments	
1	47 (24
2	59 (30
3	68 (34
>4	22 (1
OCI-R total ≥ 21	74 (37
Factor 1: washing ≥ 5	27 (13
Factor 2: obsessing ≥ 5	82 (42
Factor 3: hoarding ≥ 5	53 (27
Factor 4: ordering ≥ 5	47 (24
Factor 5: checking ≥ 5	85 (43
Factor 6: neutralizing ≥ 5	39 (20
Duration of clozapine (years)	17.51
Clozapine dose (mg/day)	335.8 (
PANSS positive (psychosis) score	12.59
OCI-R total	18.44 (
Factor 1: washing	1.73 (
Factor 2: obsessing	4.22 (
Factor 3: hoarding	3.06 (
Factor 4: ordering	2.56 (
Factor 5: checking	4.49 (
Factor 6: neutralizing	2.37 (

Table 2. Correlation between obsessive symptoms and psychotic symptoms. OCS was measured usi
obsessing and checking subscales. Psychosis was measured using PANSS-positive (n=457) and PANSS
P7). OCI-R, obsessive–compulsive inventory (revised); PANSS, Positive and Negative Syndrome Scale. Bo
corrected for multiple comparisons (alpha = 0.05/24 = 0.002).

	PANSS-positive	Delusions (P1)	Disorganization (P2)	Hallucinations (P3)	Excitement (P4)	Grandiosi (P5)
OCI-R total score	**r = 0.289 p < 0.001**	**r = 0.264 p < 0.001**	r = 0.025 p = 0.592	**r = 0.297 p < 0.001**	r = 0.027 p = 0.569	r = 0.009 p = 0.852
OCI-R Obsessing	**r = 0.419 p < 0.001**	**r = 0.393 p < 0.001**	r = 0.084 p = 0.074	**r = 0.450 p < 0.001**	r = -0.071 p = 0.131	r = -0.006 p = 0.902
OCI-R Checking	r = 0.116 p = 0.014	r = 0.113 p = 0.016	r = -0.056 p = 0.240	**r = 0.165 p < 0.001**	r = 0.002 p = 0.974	r = -0.044 p = 0.356

Figure 1

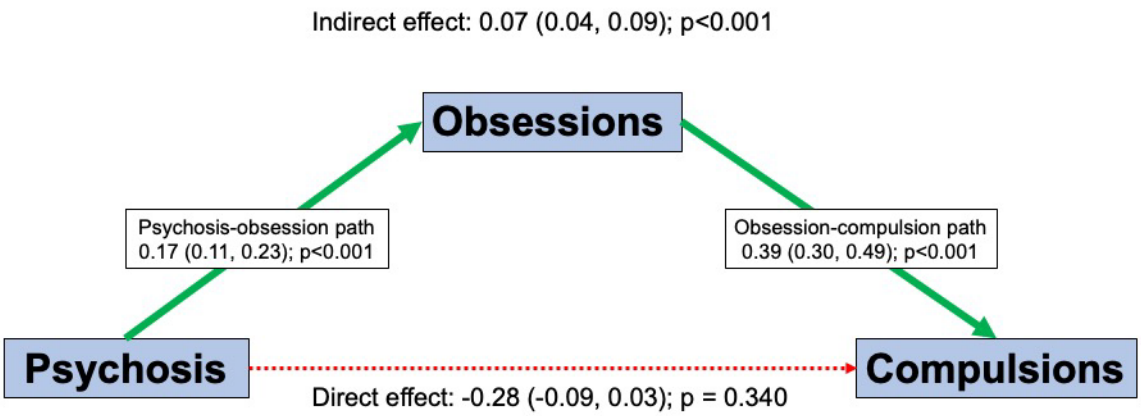
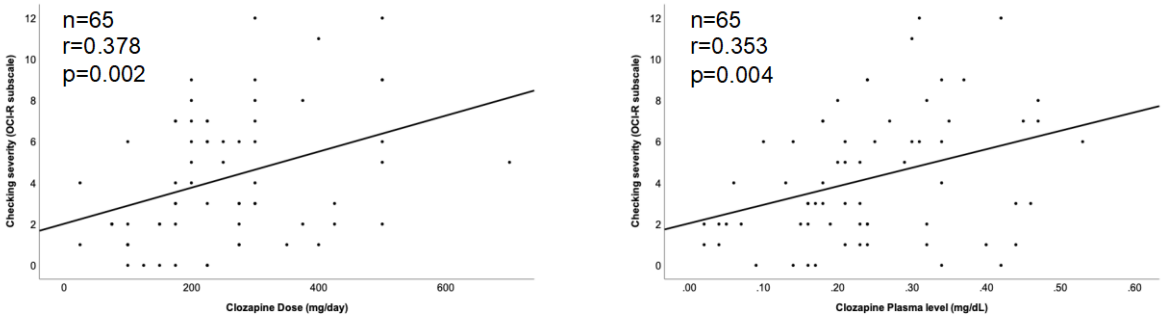
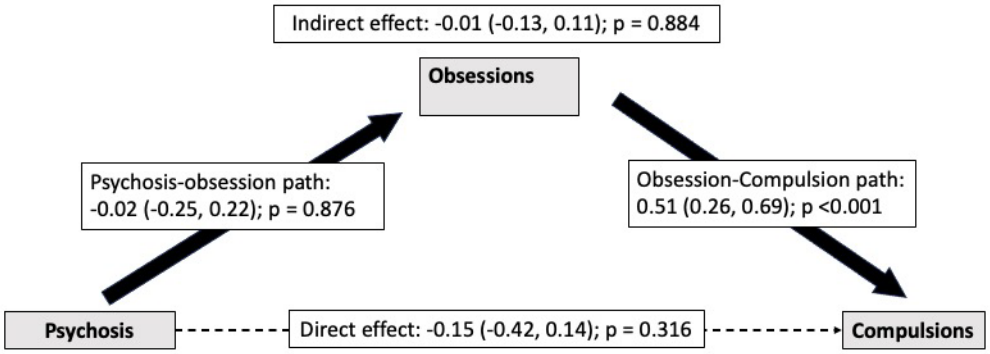


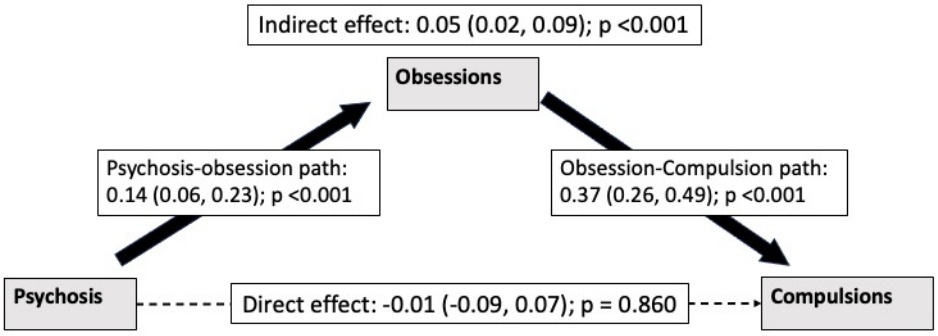
Figure 2



Supplementary figure 2: Non paranoid group



Supplementary figure 1: paranoid group



Supplementary material

Supplementary Table. Rates of obsessive–compulsive disorder (OCD) by psychosis severity at baseline.

		PSYCHOSIS REMISSION		TOTAL
		No	**Yes**	
OCD OVERALL SEVERITY*	*Negligible (0–4)*	18 (62.1%)	11 (37.9%)	29
	Moderate (5–21)	66 (64.1%)	37 (35.9%)	103
	Severe (>21)	51 (81.0%)	12 (19.0%)	63
	Total	135	60	195
EXCESSIVE CHECKING	*No (<5)*	75 (68.2%)	35 (31.8%)	110
	Yes (>5)	60 (70.6%)	25 (29.4%)	85
	Total	135	60	195

*OCD overall severity was calculated using the total OCI-R score. Excessive checking refers to the OCI-R checking subscale (3 items). Psychosis remission refers to all PANSS positive subscale items being scored <3.

Supplementary table. Multi-level moderation analysis of the genetic variants associated with the transitions obsession to compulsion.

gene	Subtype	N of subjects	gene moderates from psychosis to obsessions		gene mo
SCL6A4 rs4795541	SS	10	(reference)	(reference)	(
	SL	48	0.03 (-0.26, 0.32)	0.835	0.1
	LL	36	0.28 (-0.02, 0.59)	0.072	-0.0
SCL6A4 rs25531	AA	82	(reference)	(reference)	(
	GA	11	0.02 (-0.20, 0.24)	0.865	**0.4**
	GG	1	-	-	
SLC1A1 Rs2228622	GG	31	(reference)	(reference)	(
	GA	52	0.17 (-0.01, 0.34)	0.072	0.0
	AA	11	0.09 (-0.16, 0.33)	0.477	**0.4**
GRIN2B rs890	AA	22	(reference)	(reference)	(
	AC	45	-0.04 (-0.24, 0.17)	0.742	-0.0
	CC	27	0.06 (-0.17, 0.28)	0.616	0.1
HTR2C rs3813928	A or AA	20	(reference)	(reference)	(
	GA	4	0.50 (-0.08, 1.07)	0.099	-0.2
	G or GG	70	0.06 (-0.15, 0.27)	0.586	0.0
HTR2C rs1414334	G or GG	81	(reference)	(reference)	(
	GC	2	**2.91 (0.42, 5.39)**	**0.024**	0.1
	C or CC	11	0.14 (-0.14, 0.41)	0.343	0.1
HTR2A rs6313	T or TT	17	(reference)	(reference)	(
	CT	50	0.17 (-0.04, 0.37)	0.111	-0.0
	C or CC	27	0.20 (-0.05, 0.45)	0.128	-0.0
HTR2A rs6314	T or TT	1	-	-	
	CT	14	(reference)	(reference)	(
	C or CC	79	-0.22 (-0.52, 0.06)	0.133	0.2