Phenomenology and genetic moderators of excessive checking after antipsychotic treatment

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Abstract

A significant proportion of antipsychotic-treated schizophrenia patients develop *de novo* checking compulsions, a phenomenon that is yet to be understood. Informed by models of habit formation developed in the cognitive neurosciences, we hypothesised that excessive checking could be understood as the by-product of psychosis, promoted by clozapine's strong anti-serotoninergic action. Using the anonymised electronic records of a cohort of 204 clozapine-treated patients, including longitudinal assessments of obsessive-compulsive symptoms (OCS) and psychosis (n=724 face-to-face assessments), we performed longitudinal multi-level mediation and multi-level moderation analyses to explore OCS' associations with psychosis and with patient genotype respectively. We found OCS to be common in clozapine-treated patients (54%), with checking being the most prevalent symptom. Mediation models showed psychosis severity to indirectly effect checking behaviour by inducing obsessions [0.08 (IC 0.05, 0.12); p<0.001). No direct effect of psychosis on checking was identified [-0.06 (IC -0.13, 0.02); p=0.145]. After psychosis remission, checking compulsion directly correlated with both clozapine plasma levels (r=0.33; p=0.005) and dose (r=0.30; p=0.010). The transition from psychosis to obsession and compulsion was moderated by glutamatergic genetic variants (*GRIN2B*). We also identified novel associations with the serotoninergic pathway (*SLC6A4*, *HTR2A and HTR2C*). Understanding the different phases of the complex transition from psychosis to compulsion may inform clinicians' therapeutic decisions.

Introduction

A significant proportion of patients with schizophrenia develop obsessive-compulsive symptoms (OCS). Some patients fully transition from a psychotic to an obsessive-compulsive disorder (OCD), whilst others enter an intermediate state combining psychosis and OCS [1]. However, there is no clear understanding of this phenomenon.

OCS and OCD is common in those with schizophrenia, with prevalence increasing from 12.5% in subjects at-risk mental state, to 25% in early schizophrenia [2], and up to 47% in clozapine-treated patients [2]. There is plausible biological overlap between schizophrenia with OCS and patients with pure OCD. Both feature orbitofrontal cortex over-activation [4] and exhibit similar traits of cognitive inflexibility, reduced processing speed and memory deficits [5–7]. Further, patients with schizophrenia and OCS share a genetic background with 'pure' 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 [8]. However, association with serotoninergic (5-HT) pathways has not been explored, despite the role of *SLC6A4* (serotonin transporter), *HTR2A* and *HTR2C* (serotonin receptors) in pure OCD [9]. Some authors advocate for inclusion of schizo-obsessive disorder as a schizophrenia subtype in which pre-existing OCS/OCD is unmasked after psychosis remission [3]. However, this proposal is contradicted by work showing a correlation between OCS and psychosis severity [10–12].

Others argue *de novo* OCS in schizophrenia to be an antipsychotic-related event [13]. Epidemiologically, *de novo* OCS are over-represented in patients treated with clozapine, olanzapine, or risperidone compared with patients prescribed with aripiprazole, amisulpride or haloperidol [11, 14, 15]. This likely reflects these drugs' different 5-$HT_{2A/2C}$ receptor affinity. OCS is also associated with higher clozapine dose and length of treatment [15], suggesting a dose-dependent relationship, although there exists conflicting results disagreement in the literature [16]. However, no previous work has found associations between clozapine plasma levels and OCS [15], despite plasma level being considered a more accurate measure of clozapine effect [17].

We have previously identified psychosis severity and length of treatment as distinct risk factors for obsessions and checking compulsions respectively [2]. However, more work is needed to understand the development of de novo OCS/OCD in schizophrenia. Most studies show a predominance of compulsions over obsessions in this patient group [18, 19], with excessive checking being the most frequently reported repetitive behaviour [15, 20, 21]. Informed by models of habit formation developed in the cognitive neurosciences, we hypothesise that these checking compulsions may arise as the by-product of psychosis. Specifically, repetition in the context of a diminished ability to consider an action's outcome may lead to automatisation of behaviour ('habit formation'). Further, a decreased 5-HT activity may enhance habit development [22–24]. Applying this framework, we hypothesised a two-phase model of OCS and OCD development. Firstly, an initial phase of checking as a goal-directed behaviour due to psychotic hypervigilance occurs. After psychosis remission, achieved with anti-psychotic treatment, a second 'habit' phase occurs in which clozapine ameliorates psychosis but promotes checking compulsions via serotonin antagonism in those genetically vulnerable.

The present study aimed to test this two-phase hypothesis using a large cohort of longitudinally assessed clozapine-treated patients. Specifically, we hypothesised that: 1) checking compulsion is a goal-directed behaviour associated with psychosis severity, 2) checking severity is correlated with clozapine plasma levels in those on psychosis remission. Finally, we also explored the moderating effects of specific genetic variants on the transition from psychosis to obsession and compulsion.

Method

Study design and setting

This was a naturalistic, observational longitudinal study using anonymised electronic records gathered by Cambridgeshire and Peterborough NHS Foundation Trust (CPFT). CPFT is the primary public mental health care provider for approximately 860,000 people in a mixed urban/rural area in the East of England, UK.

Participants and electronic records

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 [25]. Extracted data maintained patient anonymity by removing all identifiable data. All clinical assessments in the CRD were performed by an experienced psychiatrist (EFE) or self-rated by the patient during routine clinical appointments. This study covers information from 24th August 2012 to 1st November 2020. The CDR includes 2,560 face-to-face assessments of 241 patients taking clozapine. For this study, only assessments with a standardised evaluation of OCS were included (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), 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).

Relevant psychopathology scales included in the CRD include the Clinical Global Impression for schizophrenia (CGI-SCH), [26] completed at every appointment since 2012, the Obsessive-Compulsive Inventory-Revised version (OCI-R; [27] self-reported annually from 2016 (and blinded to other scales) and the positive subscale of the Positive and Negative Symptoms Scale (PANSS-positive) [28] rated every two years since 2017.

Psychopathology scales

OCS severity was measured using the OCI-R, 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). 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 and scores of 5 or above in any subscale to be clinically significant [2].

The overall severity of schizophrenia symptoms was assessed using the CGI-SCH, a sensitive, clinician-rated scale comprising four domains determined by a single item: positive/psychosis (CGI-positive), negative, depressive, cognitive, and overall severity [29]. The CGI-SCH utilises a 7-point scale to rate symptom severity, ranging from 1(=absence) to 7(=extreme), with higher scores indicating greater symptoms.

Psychosis severity was also measured using the positive subscale (items P1 to P7) of the Positive and Negative Symptoms Scale (PANSS, ref). The PANSS is a clinician-rated scale including 7 items referring to psychotic symptoms rated on a 7-point scale where 1(=absence) and 7(=extreme). The PANSS offers a richer assessment of psychosis than the CGI, including a capturing a greater range of symptoms and symptom severities.

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 18/NW/0581). The study aimed to replicate previously described genetic variants associated with clozapine side effects, including OCD [8] and metabolic complications [30]. Specifically, we explored genetic variants affecting the serotonin pathway, including single nucleotide polymorphisms (SNP): *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 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 with 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 PCR and RFLP conditions previously described (Wendland JR, Mol Psychiatry 2006). 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). 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 [31].

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. For multiple comparisons, we applied the Bonferroni correction.

A multi-level mediation model was used to assess the longitudinal direct and indirect (via obsessing) association between psychosis severity and checking compulsion. This is the preferred method for exploring longitudinal changes in samples in which time between assessments is not fixed, as in our study. Psychosis severity (measured by PANSS-positive) was included as both a fixed-effect and a (per-subject) random-effect variable and duration of clozapine treatment was controlled for, as previously used in similar studies [2].

Multi-level moderation models were also conducted to explore if specific genetic variants moderated the association between psychosis severity (measured by CGI-Positive) and checking compulsion 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.

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).

Results

Sample description

The final sample consisted of 204 patients and 734 OCI-R assessments, with each patient being followed for an average of 2.7 years. The CGI-SCH was performed for all patients (n=734). 315 PANSS-positive sub-scales were also recorded. CGI-positive and PANSS-positive scales were highly correlated (r=0.80; p<0.001). Table 1 describes the main sociodemographic and clinical variables, in which 107 (52.5%) individuals had an OCI-R score above the OCD cut-off score of 21. Obsessing and checking compulsion were the most common OCS. Among those in psychosis remission (n=59/204), 25 patients (12.4% of the total sample) exhibited significant checking behaviours (indicated by a score >4 on the checking subscale). 29 patients (14.2%), meanwhile, exhibited negligible OCS (total score <5 and checking factor <2) after five years or more on clozapine treatment.

Table 1
Baseline socio-demographics characteristics of the subjects (*n* = 204).

Variables	Number (percentage %) / Mean (SD)
Per person:	
Age (baseline)	45.6 (10.9)
Age FEP	22.5 (7.0)
Age clozapine	31.7 (9.7)
Gender (= male)	161 (78.9%)
Follow-up (years)	2.7 (1.6)
Second antipsychotic	71 (34.8%)
Number of face-to-face assessments	
1	36 (17.6%)
2	20 (9.8%)
3	30 (14.7%)
>4	118 (57.8%)
OCI-R total >= 21	107 (52.5%)
Factor 1: washing >= 5	54 (26.5%)
Factor 2: obsessing >= 5	116 (56.9%)
Factor 3: hoarding >= 5	94 (46.1%)
Factor 4: ordering >= 5	78 (38.2%)
Factor 5: checking >= 5	118 (57.8%)
Per assessment:	
Duration of clozapine (years)	16.2 (7.6)
Clozapine dose (mg/day)	323.5 (146.7)
CGI-positive	2.5 (1.5)
OCI-R total	19.3 (13.5)
Factor 1: washing	1.8 (2.4)
Factor 2: obsessing	4.4 (3.6)
Factor 3: hoarding	3.2 (2.9)
Factor 4: ordering	2.6 (2.8)
Factor 5: checking	4.7 (3.5)

Table 2

Correlation between obsessive symptoms and psychotic symptoms. OCS measured using OCI-R total score and obsessing and checking subscales. Psychosis was measured using PANSS-positive (n=315) and PANSS individual symptoms (P1 to P7). OCI-R: obsessive-compulsive inventory-revised; CGI: clinical global impression; PANSS: positive and negative syndrome scale. Bold represents significance after being corrected for multiple comparisons.

	PANSS-positive	Delusions (P1)	Disorganization (P2)	Hallucinations (P3)	Excitement (P4)	Grandiosity (P5)	Persecution (P6)	Hostility (P7)
OCI-R total score	r = 0.317 p < 0.001	r = 0.320 p < 0.001	r = 0.042 p = 0.459	r = 0.306 p < 0.001	r = -0.016 p = 0.781	r = 0.026 p = 0.651	r = 0.354 p < 0.001	r = -0.087 p = 0.123
OCI-R Obsessing	r = 0.450 p < 0.001	r = 0.446 p < 0.001	r = 0.067 p = 0.233	r = 0.469 p < 0.001	r = -0.100 p = 0.077	r = 0.014 p = 0.800	r = 0.457 p < 0.001	r = -0.059 p = 0.294
OCI-R Checking	r = 0.114 p = 0.042	r = 0.146 p = 0.009	r = -0.056 p = 0.323	r = 0.141 p = 0.012	r = -0.026 p = 0.641	r = -0.033 p = 0.558	r = 0.189 p = 0.001	r = -0.127 p = 0.025

PANSS: Positive and negative symptoms scale; OCI-R: Obsessive-compulsive inventory -revised version

The role of psychosis in OCS

Psychotic symptoms, measured via PANSS-positive subscale, significantly correlated with overall OCS severity, and with the obsessing and checking compulsion subscales of the OCI-R (Figure 1). This association was significantly stronger for obsessing (r=0.45) than compulsion (r=0.11).

Within the PANSS-positive subscale, items assessing reality distortion, such as delusions (P1), hallucinations (P3), and suspiciousness/persecution (P6), significantly correlated with OCS total and obsessing and checking OCI-R subscales. Conceptual disorganisation (P2), excitement (P4), grandiosity (P5) and hostility (P7) were not significantly associated with OCS. After Bonferroni correction for multiple comparisons (p=0.05/24=0.002), obsessing was significantly correlated with P1, P3 and P6. However, checking compulsion was no longer associated with PANSS total score, nor any individual psychotic symptom other than suspiciousness/persecution (P6; p=0.001) (Figure 1).

The direction of this effect was explored using a mediation model. Using 315 responses to the PANSS-positive, we found psychosis' effect on checking behaviour to be indirect, mediated by OCI-R obsessing score. No direct effect of psychosis on checking compulsion was identified (Figure 2). Length of clozapine treatment was controlled for in this model. In further models (see **supplementary results**), an indirect effect of psychosis on compulsion was only found for those patients with active paranoid/psychotic symptoms (n=198; those with the sum of items P1+P3+P6>4). Similar results were found when additional confounds, include clozapine dose (as patients with more severe psychosis might be treated with a higher dose), were included in modelling (results not shown).

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

We then explored compulsion amongst patients in psychosis remission after anti-psychotic treatment, previously an area of controversy [15], by correlating clozapine plasma concentration with checking severity. Clozapine dose, which ranges from 75 to 900 mg daily, was not the main focus as it is an inaccurate measure of clozapine load. This is because Clozapine metabolism is influenced by a variety of factors, including concordance, gender, cytochrome polymorphisms, concurrent medication, and smoking habit [17]. Blood levels, therefore, represent a more precise measure. We selected a subgroup of patients to address factors confounding previous research. These patients were 1) on clozapine monotherapy (no other antipsychotic or antidepressant) for

more than a year, 2) were in psychosis remission (CGI-positive=1), and 3) had had plasma levels taken within 28 days of the OCS evaluation (without medication changes).

Figure 3 shows the significant correlation between checking compulsion and clozapine dose (r=0.305, p=0.010) and clozapine plasma levels (r=0.332, p=0.005). Limiting plasma levels to those not above the therapeutic range (0.6 mg/dL or 600 ng/mL) yielded the same significant results (not shown). There was no correlation between obsessing and either clozapine dose or plasma levels ($p > 0.4$).

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

Finally, we explored if genetic variants moderated OCS using a moderation model linking: 1) psychosis to obsessions, and then 2) obsessions to compulsions. This was performed in a sub-group of patients for whom genetic data was available (n=100, 391 face-to-face assessments). We used CGI-Positive as a measure of psychosis severity. Multi-level analyses accounted for repeated measures effects.

We found the association of psychosis with obsession to be significantly moderated by serotoninergic genes. Genotype AG for *SCL6A4* (rs2531) and AG for the HTR_{2C} (rs813928) significantly moderated the transition. Genotype CC for HTR_{2A} (rs3813298) and genotypes AC and CC for *GRIN2B*_rs890 moderated the transition from obsession to compulsion. **Figure 4** summarises the key results, and **supplementary table 1** details the eight SNPs studied.

Discussion

OCS is both be common in clozapine-treated patients and associated with psychosis severity and clozapine load. Here, mediation analyses suggested that psychosis severity generates checking behaviour indirectly by inducing obsessions. After psychosis remission, checking compulsion correlated with clozapine plasma levels. The transition from psychosis to obsession and compulsion was found to be moderated by genetic variants associated with serotoninergic and glutamatergic transmission. To our knowledge, the association between clozapine-associated OCS/OCD and serotonin genetic variants has not been previously described.

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 prohibit its administration to healthy volunteers. Long-term longitudinal studies in schizophrenia patients after clozapine initiation could provide a more detailed characterisation, but the latency of the OCS onset (up to a decade) may render such studies impractical. Given this, we consider the large sample and longitudinal follow-up of this study a good balance between practical feasibility and rigour. Secondly, OCS were evaluated using a self-rated scale, blind to the clinician, and further work might benefit from replication using a clinician-rated scale such as Y-BOCS. Again, however, this may be impractical in a busy clinical environment. Thirdly, the patient sample included in this study's genetic analyses was relatively small (n=100), and these findings should therefore be taken as exploratory and in need of replication.

Our results broadly align with previous research in terms of OCS prevalence (52%) 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, typical treatment length (~14 years) and frequent prescription of a second antipsychotic (35%). However, this study's sample size (204 cases) and volume of standardised OCS assessments (734 face-to-face assessments) is more extensive than any previous research.

We considered clozapine-associated OCS as a dynamic phenomenon that fluctuates in intensity according to psychosis severity, in line with recent work by Schirmbeck and colleagues [12], and is associated with the clozapine load. We dissected OCS into its two main components (obsessions and compulsions) and applied a mediation model that identified an association of psychosis severity (particularly severity of reality distortion symptoms, such as persecutory delusions) with obsessive thoughts. Obsessive thoughts, in turn, precipitated checking behaviour. This may initially be understood as a goal-directed, safety-seeking behaviour in acutely psychotic, paranoid patients. As one patient explained; '*I need to check everything is in place as my upstairs neighbour comes to steal my stuff*'. In patients achieving psychosis remission, we found that checking severity 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 in OCD has been described [33], limiting patients' ability to assign safety after verification.

Appreciating the distinct roles of psychosis and clozapine in OCS development is essential to understand the apparent discrepancies in previous cross-sectional studies. Point-prevalence based on questionnaire scores fluctuate according to the severity of the psychosis (figure 1 and 2), clozapine load (figure 3), concomitant medications (e.g. antidepressants) or even the tools used to assess the symptoms. In this sense, for instance, a 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 process of OCS development is based on cognitive neuroscience frameworks of habit formation [23, 24] and shows the potential for embedding cognitive neuroscience into clinical practice. In our context, clozapine treated patients in psychosis remission would experience checking compulsion as an antipsychotic-induced habit. Notably, a two-phased model integrates not only the present results but also the results of previous studies [32][15, 16, 35] and patients' narratives, in which psychosis-induced goal-directed behaviour could become a habit. This model is flexible regarding the content of the repetitive behaviour as it would also accommodate other triggers, such as the influence of stressful events recently reported [36].

A plausible mechanism for the persistence of repetitive behaviour following psychosis remission may be clozapine's antagonism of 5-HT_{2C} and 5-HT_{2A} receptors [1]. A decrease in serotonin neurotransmission causes perseveration in reversal learning tasks, the hallmark of cognitive inflexibility in compulsive behaviours, including OCD [37]. In humans, dietary tryptophan depletion (which acutely reduces serotonin in the brain) promotes habitual over goal-directed control [38]. Remarkably, a recent mouse-model study showed similar results. Mice receiving clozapine significantly increased their grooming time (as a proxy of compulsion). This behaviour then reverted on administration of fluoxetine, a selective serotonin reuptake inhibitor. Interestingly, the same effects were seen in both the wild type and the *Sapap3* knockout mice (a well-known animal model of OCD), suggesting a genetic vulnerability to clozapine-induced habit formation [39].

The genetic vulnerability was explored in this work, in which we identified a distinct role of the serotonin and glutamatergic SNP on psychosis-to-obsession and obsession-to-compulsion transition respectively (**figure 4** and **supplementary material**). We replicated previous findings involving the glutamate pathway [9], such as *GRIN2B*. More importantly, we are here first reporting the serotonin pathway involvement, as described in pure OCD. Importantly, however, drawing firm conclusions about the role of specific variants will require replication in larger samples. Nevertheless, our identification several genetic variants of the serotonin pathway (*SCL64A*, *5HTR2A* and *5HTR2C*) moderating the psychosis-obsession-compulsion transition is notable and may offer clues to future preventative or therapeutic approaches. The converging evidence form this study, and others [39], indicates that interventions directed to enhancing serotonin function are crucial for the effective treatment of clozapine-induced OCS [39], as in pure OCD. Nevertheless, we did not explore specifically the effect of medication modifications in the 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 cognitive neuroscience's insights surrounding habit formation, in which initial compulsions arises as a by-product of florid paranoid psychosis, and are then perpetuated in predisposed subjects after psychosis remission by clozapine's anti-serotoninergic action. Better understanding the different phases of the phenomenon may inform clinicians' therapeutic decisions.

Declarations

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Conflict of Interest

None of the authors declare competing financial interests in relation to the work described.

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Figures

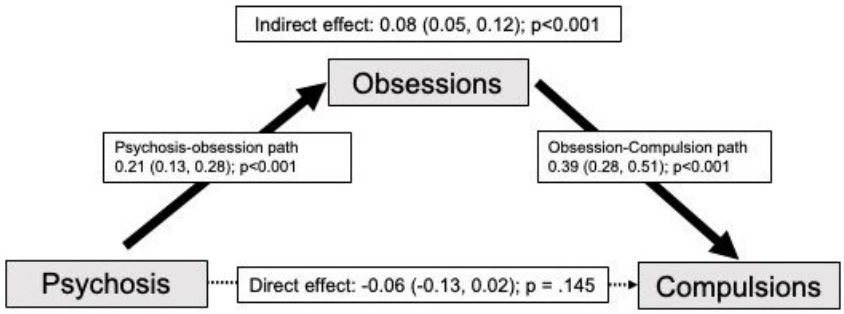

Figure 1

OCS and psychosis. Mediation model for exploring causality. Psychosis was measured with the PANSS-positive subscale.

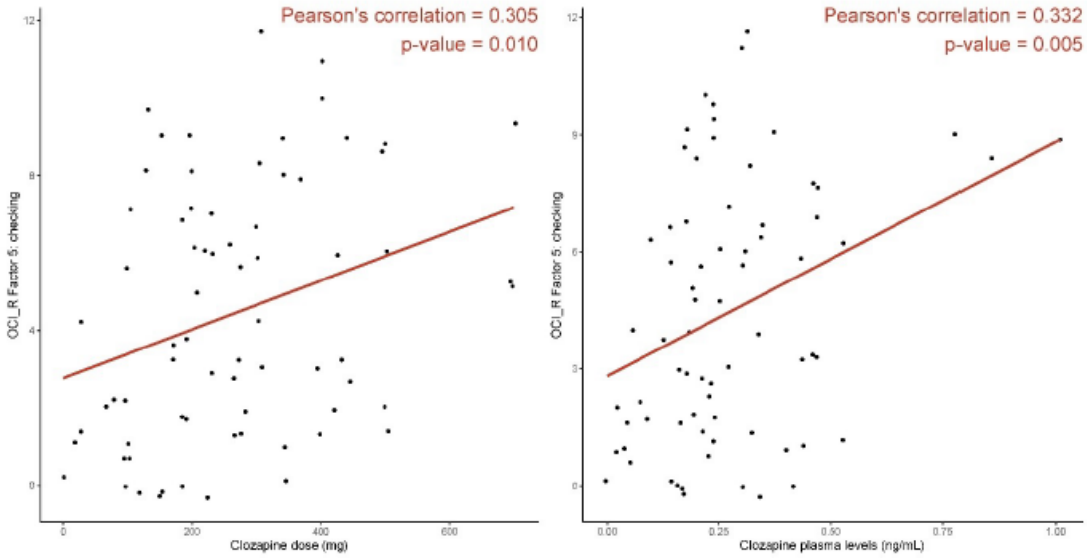

Figure 2

Correlation of checking severity with clozapine dose and plasma levels in the n=47 in the subgroup on clozapine monotherapy and psychosis remission. Clozapine plasma levels were taken with 28 days of the assessment and with no medication changes.

Figure 3

Multi-level moderation model of genetic variants moderating the psychosis to obsessions and obsession to compulsions transition in a group of 100 clozapine treated patients. The models were fitted with psychosis severity (using CGI_positive) and type of genetic variants as both fixed-effect and (per-subject) random-effect variables, controlled for the duration of clozapine use.

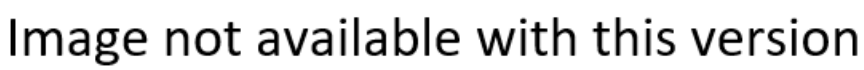

Figure 4

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