

Distinct risk factors for obsessive and compulsive symptoms in chronic schizophrenia

Emilio Fernandez-Egea^{1,2,3,4}, Yulia Worbe⁵, Miguel Bernardo^{4,6,7,8}
and Trevor W. Robbins^{3,9}

Original Article

Cite this article: Fernandez-Egea E, Worbe Y, Bernardo M, Robbins TW (2018). Distinct risk factors for obsessive and compulsive symptoms in chronic schizophrenia. *Psychological Medicine* **48**, 2668–2675. <https://doi.org/10.1017/S003329171800017X>

Received: 30 September 2017
Revised: 17 December 2017
Accepted: 11 January 2018
First published online: 19 February 2018

Key words:

Antipsychotics; habit formation; clozapine; schizophrenia; obsessive compulsive disorder.

Address for correspondence:

Emilio Fernandez Egea,
E-mail: ef280@cam.ac.uk

¹Clozapine Clinic, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK; ²Department of Psychiatry, University of Cambridge, Cambridge, UK; ³Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK; ⁴Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain; ⁵Sorbonne Université, 75005 Paris, France; Department of Physiology, Neurophysiology Unit, Hospital Saint-Antoine, Paris, France; Institute du Cerveau et de Moelle Epigniere, Paris, France; ⁶Barcelona Clinic Schizophrenia Unit, Neuroscience Institute, Hospital Clinic of Barcelona, Barcelona, Spain; ⁷Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ⁸Department of Psychiatry, University of Barcelona, Barcelona, Spain and ⁹Department of Psychology, University of Cambridge, Cambridge, UK

Abstract

Background. Obsessive-compulsive disorder (OCD) is common in clozapine-treated patients although the actual prevalence, phenomenology and risk factors remain unclear. The aim of the present study was to address the three aforementioned questions.

Methods. The electronic records of a large cohort of clozapine-medicated schizophrenia patients routinely screened for OCD were used. The Obsessive Compulsive Inventory Revised version (OCI-R) was available from 118 cases and a 21 points cut-off threshold for OCD was defined.

Results. OCD prevalence was 47%, higher in patients on poly-pharmacy than on monotherapy (64% vs 31%; $p = 0.001$). Two OCI-R factors had significantly higher scores and distinct risk factors: checking behaviour (mean = 5.1; SD = 3.6) correlated with length of clozapine treatment ($r = 0.21$; $p = 0.026$), and obsessing factor (mean = 4.8; SD = 3.6) correlated with psychosis severity ($r = 0.59$; $p = 0.001$). These factors along with total OCI-R, did not correlate with either clozapine dose or plasma levels, after correcting for psychosis severity.

Conclusions. Screening for OCD in clozapine patients, and probably in those treated with structurally similar drugs with potent antiserotonergic properties, should be widely adopted by clinicians. Further research is needed to understand the pathophysiology underlying repetitive behavior onset in clozapine-treated patients.

Background

Obsessive-compulsive disorder (OCD) is common in schizophrenia patients treated with anti-psychotics with significant anti-serotonergic action (Swets *et al.* 2014; Grillault Laroche & Gaillard, 2016). Clozapine was the first drug reported (Baker *et al.* 1992) and is still the medication more frequently associated with OCD (Poyurovsky *et al.* 2001), along with olanzapine (Schirmbeck *et al.* 2011). However, the prevalence, phenomenology and pathophysiology of clozapine-induced OCD remain unclear.

In the literature, the prevalence of clozapine-induced OCD ranges from <5% (Mahendran *et al.* 2007) to over 70% (Schirmbeck *et al.* 2011). This discrepancy reflects the heterogeneity in the methodology used, such as the diagnostic instrument (structured clinical interview *v.* scale score threshold) and the sample characteristics, among others. For instance, some studies only included patients on clozapine monotherapy (Lin *et al.* 2006; Schirmbeck *et al.* 2011), whereas others broaden the scope to cases using concomitant medication (Poyurovsky *et al.* 2001; Mukhopadhaya *et al.* 2009). Noteworthy, medications like antidepressants or antipsychotics are also prescribed for treating OCD and therefore could potentially mask OCD prevalence and severity.

From the point of view of phenomenology, degree of insight should help to distinguish between delusions and obsessions (Poyurovsky *et al.* 2004), but this can be difficult to disentangle in the presence of chronic positive symptoms in clinical practice (Leung & Palmer, 2016). Most studies of prevalence have not taken into account psychosis severity (Poyurovsky *et al.* 2001; Lin *et al.* 2006; Faragian *et al.* 2009; Mukhopadhaya *et al.* 2009). When psychosis is considered, most (Guillem *et al.* 2009; Sa *et al.* 2009) but not all (Faragian *et al.* 2009) studies have associated delusions and OCD severity, which suggests an overlap between them. Clinically, a predominantly compulsion profile was initially described in clozapine-associated OCD (Ongür & Goff, 2005; Guillem *et al.* 2009; Kim *et al.* 2012), but this has not always been replicated (Schirmbeck *et al.* 2011; Doyle *et al.* 2014). The type of compulsion also varies across studies, as the predominance of checking (Poyurovsky *et al.* 2004; Mukhopadhaya *et al.* 2009; Schirmbeck *et al.* 2011) and also cleaning and washing (Poyurovsky *et al.* 2001; Faragian

© Cambridge University Press 2018. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

et al. 2009; Guillem *et al.* 2009) compulsions have been reported. Nevertheless, there is a high concordance of the obsession–compulsion pair: contamination with washing (Poyurovsky *et al.* 2001; Ongür & Goff, 2005; Faragian *et al.* 2009; Sa *et al.* 2009) and doubting with checking (Leung & Palmer, 2016).

Length of clozapine treatment is a replicated risk factor for developing OCD (Lin *et al.* 2006; Boyette *et al.* 2011; Schirmbeck *et al.* 2011; Scheltema Beduin *et al.* 2012). However, the evidence for OCD being a clozapine dose-dependent side effect is still inconclusive. For instance, one study found that patients with clozapine-associated OCD were treated with higher drug doses (Mukhopadhyaya *et al.* 2009), and another study (Schirmbeck *et al.* 2011) showed a correlation between dose and OCD symptoms but failed to correlate with clozapine plasma levels. Noteworthy, plasma level is considered as a more accurate measure, as it is not affected by patients' compliance or pharmacokinetic factors (i.e. smoking). To date, no study has found a correlation between clozapine plasma levels and obsessive and compulsive symptom (OCS) severity (Lin *et al.* 2006; Schirmbeck *et al.* 2011).

Aims of the study

The aims of this study was to address three aforementioned questions of OCD prevalence, clinical profile and associated severity factors, using electronic records of a large cohort of clozapine-medicated schizophrenic patients. Patients were routinely screened for OCD using standardised scales as well as relevant clinical, psychometric and demographic data.

Material and methods

Study design

This is a cross-sectional, single-centre study of a cohort of clozapine-treated schizophrenia patients at the Cambridgeshire and Peterborough NHS Foundation Trust, a community mental health trust in the UK. The study included electronic clinical records of more than 200 cases from August 2015 to June 2017. The anonymised clinical records were embedded in an ethically approved database for research and clinical purposes (13/EE/0121). All cases were reviewed by the same care consultant (EFE).

Study sample

All records of clozapine-treated schizophrenia cases were initially included, regardless of other medication status. The only exclusion criterion was not suffering with a primary psychotic disorder (i.e. off label use of clozapine). All cases were included for the prevalence and phenomenology analyses. Stricter criteria were defined for the analysis of the role of clozapine dose and plasma level on OCD severity, i.e. only cases on clozapine monotherapy, with clozapine plasma levels available and with evidence of adequate medication compliance measured by the clozapine:norclozapine ratio, were included.

Clinical assessment

Assessment includes full psychiatric history, mental state examination, current medication list, smoking, legal and illegal drugs habits, comprehensive clozapine side effects assessment, physical health assessment and psychopathological scales (see below), among others. Per protocol, clozapine and norclozapine plasma levels are assessed every 3 years, unless otherwise required for

clinical reasons (i.e. change in smoking status, side effects or compliance queries). Levels were determined at the Toxicology Department, King's College Hospital, London, UK.

Psychopathological scales

All assessment included Global Assessment of Functioning (GAF) and Clinical Global Impression for Schizophrenia (Haro *et al.* 2003), which measures severity of positive, negative, depressive, cognitive symptoms domains as well as an overall score, all ranging from 1 (no symptoms) to 7 (extremely severe). The Short version of the Warwick-Edinburg Wellbeing scale was performed annually (Brown *et al.* 2016).

Since August 2015, the Obsessive Compulsive Inventory-Revised (OCI-R) (Foa *et al.* 2002) was added to the routine assessment while subjects were doing the routine plasma level control, in order to screen subjects with obsessive symptoms that might require intervention. OCI-R is a widely used 18-item self-rated questionnaire easy to implement in clinical settings. Each question has a five-point Likert-type score that measures the degree of distress or being bothered with common OCD phenomena, ranging from 0 ('not at all') to 4 ('extremely'). The cut-off point for OCD diagnosis is 21 for the total OCI-R. The scale is composed of six factors of three items each, evaluating washing behaviour, obsessing thinking, hoarding, ordering, checking behaviour and mental neutralisation. For OCD diagnosis, a cut-off point for the obsessive factor of 5 has been defined (Foa *et al.* 2002). As there are no specific cut-off points for the other five factors, here we have used the same five-point cut-off for clinically significant symptoms to reach the disorder threshold.

Concomitant medication assessment

Poly-pharmacy is common in treatment-resistant schizophrenia. Some of these drugs can potentially influence obsessive symptoms. For instance, clozapine augmentation with aripiprazole is common for persistent psychotic symptoms (Cardinal *et al.* 2015) but can also be added as therapy for OCD (Englisch *et al.* 2009; Eryilmaz *et al.* 2013), sedation (Perdigués *et al.* 2016) or metabolic complications (Zimbron *et al.* 2016). Similarly, antidepressants are primarily used for depression, anxiety or OCD. Rather than excluding cases on poly-pharmacy, we adopted a pragmatic approach by recording dichotomic (yes/no) variable for medication use, regardless of the primary indication: use of any drug with potential effect on OCD (aripiprazole, selective serotonin reuptake inhibitor, SSNRI or tricyclics), which for simplification in this manuscript we termed as anti-OCD medication.

Statistical analysis

All statistical analyses were conducted using SPSS v23.0 for Mac, with a two-tail 0.05 significance level. As described in the Results section, χ^2 , Student's *t* test, analysis of variance and bivariate correlation using Pearson *r* coefficient were used according to the analysis needs. Partial correlation was used for controlling the role of a third factor on bivariate correlations. An exploratory factor analysis was also carried out to compare our data structure with the six-factor component of the OCI-R.

Results

Two hundred and one patients on clozapine and with primary diagnosis of non-affective psychosis were included. Of those,

Table 1. Samples sociodemographic and clinical variables, expressed as mean and standard deviation

	Total sample	Monotherapy	Poly-therapy	<i>p</i>
N	118	63	55	
Gender male n (%)	98 (83%)	54 (85.7%)	44 (80.0%)	0.28
Age (in years)	44.3 (11.0)	43.3 (12.1)	45.5 (9.7)	0.29
Clozapine treatment (in years)	14.6 (7.1)	14.6 (7.4)	14.5 (6.8)	0.93
Clozapine dose (mg/day)	346 (141)	337.1 (144.7)	356.8 (138.3)	0.45
Clozapine plasma level (mg/dL)	0.42 (0.22)	0.39 (0.22)	0.45 (0.23)	0.20
Norclozapine plasma levels (mg/dL)	0.27 (0.13)	0.26 (0.13)	0.29 (0.13)	0.28
GAF score	70.1 (12.9)	71.5 (14.0)	68.4 (11.4)	0.19
CGI-positive	2.8 (1.6)	2.51 (1.5)	3.13 (1.6)	0.03
CGI-negative	3.0 (1.3)	2.98 (1.4)	3.09 (1.2)	0.65
CGI-overall	2.7 (1.0)	3.27 (1.3)	3.67 (1.0)	0.22
On aripiprazole	24%		51%	
On antidepressants (SSRI/SNRI)	33%		71%	

p represents *p*-significance group differences (monotherapy *v.* poly-therapy) using Student's *t* or χ^2 tests.

SSRI, selective serotonergic reuptake inhibitor (fluoxetine, paroxetine, fluvoxamine, citalopram, sertraline and escitalopram); SNRI, serotonin and norepinephrine reuptake inhibitors (venlafaxine and duloxetine).

122 (60.7%) completed the OCI-R scale during the clinical review. Three patients were excluded from the analyses as OCD predated psychosis (two cases) and another case due to lack of reliability in the answers, reaching a final sample of 118 cases.

Prevalence of OCD

Among the 118 cases, the mean OCI-R total score was 20.3 (s.d. = 13.7) and 47% ($n = 55$) reached threshold criteria for OCD. Fifty-five of the 118 cases (47%) were on anti-OCD medication. As shown in Table 1, patients on poly-pharmacy had significantly higher OCI-R scores (24.6 s.d. = 13.2 *v.* 16.2 s.d. = 12.2; $t = 3.465$; $p = 0.001$) and OCD prevalence (64% *v.* 31%; $\chi^2 = 12.001$; $p = 0.001$) as well as higher clinical global impression (CGI)-positive scores (3.1 s.d. = 1.6 *v.* 2.5 s.d. = 1.5; $t = 2.184$; $p = 0.031$).

OCS profile

We tested if our OCI-R responses fit the original OCI-R factor structure, as its validity has not been formally tested before in schizophrenia patients. To this aim, we used an exploratory factor

analysis of the individual answers, fixing a six-factor model and choosing a maximum likelihood as extraction method with no rotation. A χ^2 measure of goodness-of-fit, testing the null hypothesis that six factors were adequate to explain 76% of the co-variances in our data, showed a $\chi^2 = 112.67$, with a $p < 0.001$.

Mean scores of the six factors were (from higher to lower): checking 5.1 (s.d. = 3.6); obsessing 4.8 (s.d. = 3.6); hoarding 3.2 (s.d. = 3.2); ordering 2.9 (s.d. = 3.0); neutralising 2.4 (s.d. = 3.0) and washing 1.8 (s.d. = 2.4). All six factors showed significant greater severity in the poly-medicated group (Table 2). When a cut-off point of 5 was applied to indicate 'disorder', about half of patients reported significantly distressing checking compulsions and obsessive thinking (Fig. 1). In order to improve readability, we will report here only checking and obsessing factors, although online Supplementary Table shows analyses with all six factors.

Role of severity of schizophrenia-positive symptoms in OCS

OCI-R is a self-rated questionnaire and some questions illustrate the overlap of obsessive and psychotic phenomena. For instance, question 6 (obsessing factor) states: 'I find difficult to control my

Table 2. Mean score and standard deviation (s.d.) of the OCI-R total and six factors

	Total sample	Monotherapy	Polypharmacy	<i>p</i> significance
Sample size	118	63	55	
OCI-R total score	20.3 (13.7)	16.5 (12.2)	24.6 (13.2)	0.001
Checking factor	5.1 (3.6)	4.3 (3.4)	5.8 (3.6)	0.018
Obsessing factor	4.8 (3.6)	3.4 (3.1)	6.5 (3.5)	<0.001
Hoarding factor	3.2 (2.8)	2.4 (2.5)	4.1 (2.9)	0.001
Ordering factor	2.9 (3.0)	2.8 (2.9)	3.1 (3.1)	0.614
Neutralising factor	2.4 (3.0)	2.0 (2.6)	2.8 (3.3)	0.133
Washing factor	1.8 (2.4)	1.5 (2.1)	2.2 (2.8)	0.137

p Significance indicates the Student's *t* test comparison between clozapine monotherapy and poly-pharmacy groups.

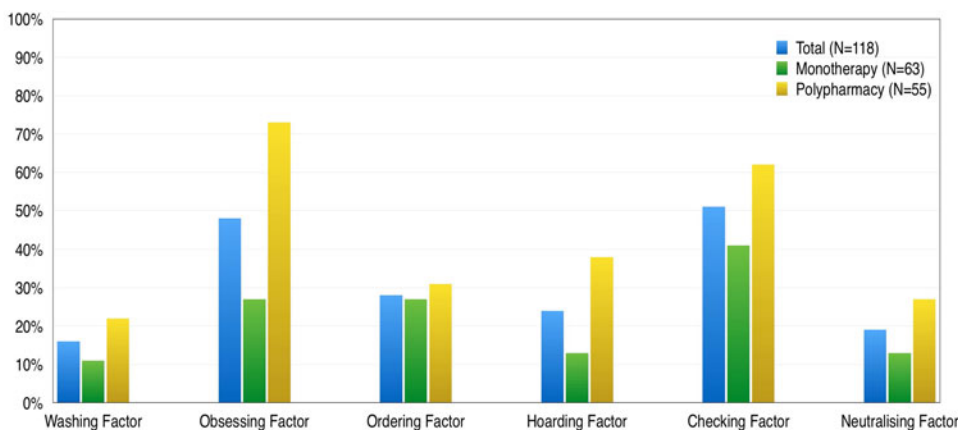


Fig. 1. Percentage of significant (cut-off point of 5) of the six OCI-R factors, in the total sample (dark grey), monotherapy (light grey) and poly-pharmacy (black) groups.

own thoughts'. In turn, some positive symptoms of schizophrenia might lead to patient's repetitive behaviour (Faragian *et al.* 2009), so we explored the effect of psychosis on the OCI-R sub-scales.

In the monotherapy sub-sample, psychosis severity (measured with CGI-positive symptoms score) significantly correlated with total OCI-R ($r = 0.38$; $p = 0.002$) and obsessing factor ($r = 0.59$; $p < 0.001$) but not with checking behaviour factor ($r = 0.17$; $p = 0.18$). Similar results were seen in the poly-medicated group, where psychosis significantly correlated with total OCI-R ($r = 0.32$; $p = 0.018$) and obsessing factor ($r = 0.46$; $p < 0.001$) but not checking factor ($r = 0.20$; $p = 0.15$).

We further explored the role of psychosis by dividing the 118 cases into those with positive symptoms (GCI-positive symptoms >1 ; $n = 84$) and those with complete psychosis remission (GCI-positive symptoms = 1; $n = 34$). Patients with active psychosis presented a significantly higher total OCI-R score (22.5 s.d. = 13.5 v. 14.8 s.d. = 10.9; $t = 2.955$; $p = 0.004$) and higher obsessing factor (5.9 s.d. = 3.5 v. 2.3 s.d. = 2.5; $t = 5.277$; $p < 0.001$) but not checking factor (5.4 s.d. = 3.7 v. 4.3 s.d. = 3.2; $t = 1.542$; $p = 0.126$). The result made us consider positive symptoms severity as a confounding factor that should be taken into consideration in subsequent analyses.

Factors associated with OCD

We assessed length of clozapine treatment and degree of clozapine exposure as risk factors for OCD onset, as both have been

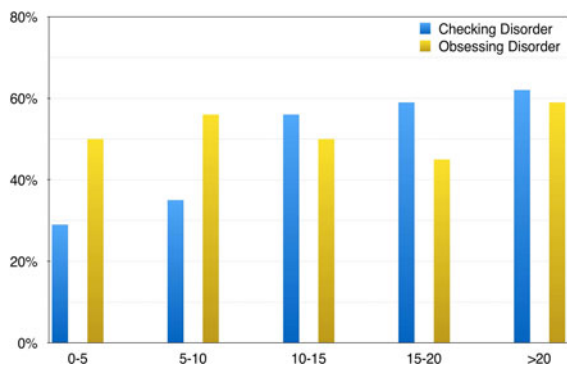


Fig. 2. Percentage of significant 'obsessive' and 'checking behaviour' using the OCI-R factor and a five-point cut-off threshold and length of clozapine treatment in 5-year intervals.

described in the literature (Lin *et al.* 2006; Boyette *et al.* 2011; Schirmbeck *et al.* 2011; Scheltema Beduin *et al.* 2012).

In our sample, length of clozapine treatment significantly correlated with checking severity ($r = 0.21$; $p = 0.026$), but not with total OCI-R ($r = 0.15$; $p = 0.10$) or obsessing factor ($r = 0.02$; $p = 0.86$). A partial correlation of length of treatment and checking factor, controlled by psychosis severity, showed a stronger correlation ($r = 0.25$; $p = 0.006$). Figure 2 plots length of clozapine treatment and significant checking and obsessing factors (cut-off point ≥ 5).

With regard to the influence of clozapine dose on OCD, we controlled for three confounders that have not been considered together before: (i) clozapine plasma levels, as dose is markedly influenced by pharmacokinetic factors (i.e. smoking) (Couchman *et al.* 2010); (ii) poor compliance with medication, which can be irregular so we used the plasma clozapine:norclozapine ratio, as it is a proxy for compliance (Couchman *et al.* 2010) and (iii) as in our sample, positive symptoms significantly correlated with clozapine dose ($r = 0.22$; $p = 0.015$) and plasma levels ($r = 0.25$; $p = 0.007$), we used partial correlation to co-variate for psychosis severity.

Therefore, for this analysis, we included cases on monotherapy, with no change in dose or smoking habit during the prior 3 months and showing adequate medication compliance, measured as clozapine:norclozapine ratio between 0.5 and 1.0, to a final sample of 37. Table 3 shows the direct correlation between OCS and clozapine dose and plasma levels as well as partial correlation of these parameters controlling for psychosis.

Discussion

In our study, with the largest sample studied so far, about half of the 118 cases of clozapine-treated schizophrenia patients reported OCD measured with the OCI-R. Crucially, we were able to identify the distinct risk factors associated with the two main OCD subscales. Checking compulsions, the most prevalent group of symptoms, were associated with the length of clozapine treatment, whereas obsessions, the second most common group of symptoms, were associated with psychosis severity. None of the symptoms were associated with clozapine dose or plasma level.

The British National Formulary still considers OCD as a rare (one out of 10 000) clozapine side effect. In our sample, the OCS prevalence was 47%, a mid-point between 5% and 74% (de Haan *et al.* 1999; Lin *et al.* 2006; Mahendran *et al.* 2007; Mukhopadhyaya *et al.* 2009; Schirmbeck *et al.* 2011) among the

Table 3. Correlation of clozapine dose, plasma levels and norclozapine v. total OCI-R score and obsessing and checking factor in 37 cases on clozapine monotherapy and adequate compliance

	Direct correlation			Correlation mediated by positive symptoms		
	Clozapine dose	Clozapine plasma level	Norclozapine plasma levels	Clozapine dose	Clozapine plasma level	Norclozapine plasma levels
OCI-R total score	$R = 0.14$; $p = 0.40$	$R = 0.29$; $p = 0.08$	$R = 0.25$; $p = 0.14$	$R = -0.02$; $p = 0.89$	$R = -0.06$; $p = 0.71$	$R = -0.11$; $p = 0.54$
Obsessing factor	$R = 0.18$; $p = 0.28$	$R = 0.46$; $p = 0.004$	$R = 0.37$; $p = 0.024$	$R = 0.09$; $p = 0.60$	$R = 0.22$; $p = 0.19$	$R = 0.25$; $p = 0.14$
Checking factor	$R = -0.01$; $p = 0.96$	$R = 0.33$; $p = 0.048$	$R = 0.29$; $p = 0.08$	$R = 0.10$; $p = 0.57$	$R = 0.18$; $p = 28$	$R = 22$; $p = 0.19$

First using bivariate correlation and then a partial correlation mediated by psychosis severity.

reported ranges in clozapine-treated patients. This prevalence is three times the OCD prevalence in non-clozapine patients (Swets *et al.* 2014) and suggests a stronger effect in clozapine-treated patients. To limit a potential prevalence overestimation, we used a 21-point cut-off for OCD diagnosis, instead of the less restrictive 18 points suggested by OCI-R (Foa *et al.* 2002). Consistent with previous reports (Guillem *et al.* 2009), we also found a higher prevalence in the poly-medicated and more severe cases (64%) compared with those with monotherapy (31%). In summary, our results might help to raise awareness of OCD in clozapine-treated patients among clinicians.

Importantly, independent OC factors were adequately measured with the OCI-R, as seen in the contrast of the six-factor structure in our sample and the original OCI-R validation (Foa *et al.* 2002), which is relevant taking into account it is a self-rated scale. This is in line with prior factor analyses using Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman *et al.* 1989) where the same five-factor structure was found in 51 cases of antipsychotic-induced OCD (Kim *et al.* 2012) and in 110 cases of comorbid OCD in schizophrenia (Faragian *et al.* 2009). Our findings support the use of standardised OCD symptom scales in clinical settings for screening and monitoring of OCS in this population (Doyle *et al.* 2014; Swets *et al.* 2014).

Clinically, we found a shift towards predominantly compulsive behaviours after prolonged (a decade) treatment with clozapine. Checking was the most prevalent OCD symptom with half of patients reporting significant distress, which is consistent with prior studies in both clozapine- (Kim *et al.* 2012) and non-clozapine-treated (Faragian *et al.* 2009) patients. In our sample, checking gradually increased over time (Fig. 2), with 29% prevalence among the cases with <5 years of treatment to 69% in those with more than 20 years of treatment. This replicates prior reports (Lin *et al.* 2006; Boyette *et al.* 2011; Schirmbeck *et al.* 2011; Scheltema Beduin *et al.* 2012) associating longer clozapine exposure to more checking compulsion.

We also found that obsessing was associated with severity of positive symptoms, but not with treatment duration or clozapine dose/plasma level. Our results replicate prior studies using Y-BOCS that shown a specific correlation between delusion severity and obsessions (Guillem *et al.* 2009; Sa *et al.* 2009). A study also using OCI-R (Kumbhani *et al.* 2010) did not report a correlation, but included only 29 patients on full remission of psychosis, which can account for the difference in the findings.

Nevertheless, discerning whether an unwanted thought is an obsession or a delusion with partial insight in a patient with active psychosis can be on occasion clinically challenging but also

relevant for treatment decisions (Leung & Palmer, 2016). Of note, these conceptual debates are not exclusive to schizophrenia. For instance, the distinction of whether specific repetitive behaviour represents complex tics or compulsions in Tourette disorder have been studied (Kim *et al.* 2012) and about 20% of cases present both symptoms at the same time. For our study, we decided a pragmatic approach, measuring both phenomena independently, whereas others have excluded subjects, in whom OCD symptoms might be attributed to psychotic experience (Poyurovsky *et al.* 2001; Poyurovsky *et al.* 2004). The OCI-R factor structure in our sample mimics the six factors structure in pure OCD cases, and therefore we are relatively confident that the obsessing factor was adequately measured. However, further study of the overlapping phenomenology is required.

To date, no studies had found a direct correlation between clozapine plasma levels and OCD symptoms or severity. In one study of 26 patients on clozapine monotherapy (Schirmbeck *et al.* 2011), a correlation of OCD severity with dose, but not plasma levels was found. Significantly, dose is not an accurate measure of exposure to clozapine, as this is also influenced by compliance or pharmacokinetic factors. Another study showed that clozapine schizophrenia patients with OCD had higher clozapine plasma levels (Lin *et al.* 2006). However, this study did not account for other pharmacological interactions as clozapine patients with OCD group were treated with fluvoxamine, an antidepressant for OCD that significantly increases clozapine plasma levels (Couchman *et al.* 2010). Finally, none of these studies controlled for psychosis severity, which in our sample strongly correlated with clozapine dose. We initially found a direct bivariate correlation between plasma levels and obsessing and checking behaviour. However, this correlation became non-significant when controlled by level of psychosis (see Table 3), suggesting that severity of positive symptom could be a confounding factor.

Nevertheless, the absence of correlation of clozapine dose and OCD in our study should be considered cautiously as these results relied on a cross-sectional evaluation. Indeed, some previous findings also pointed to OCD improvement after clozapine reduction or withdrawal (Englisch *et al.* 2009; Leung & Palmer, 2016). A potential explanation would be that OCD symptoms were triggered by a high clozapine dose. If the dose was later reduced due to other factors (i.e. sedation or metabolic side effects), we would not have seen a correlation in our study. A long-term follow-up study before and after clozapine would help to understand this particular aspect.

The pathophysiological mechanisms of clozapine-induced OCD are beginning to be elucidated. Recent studies support a

biological plausibility based on similarities in cognitive deficits (Patel *et al.* 2010; Schirmbeck *et al.* 2011), brain circuits (Schirmbeck *et al.* 2015) and genetic variants (Kwon *et al.* 2009) to those with pure OCD. Specifically, similarly to pure OCD patients, clozapine-treated schizophrenia patients with OCD consistently showed abnormal impulse inhibition, a tendency to response perseveration and difficulties in set-shifting abilities (Patel *et al.* 2010; Schirmbeck *et al.* 2011) associated with abnormal activation of orbitofrontal cortex (Schirmbeck *et al.* 2015) and linkage with significant variants of the SLC1A1 gene (Kwon *et al.* 2009).

The nature of the compulsive symptoms arising from chronic clozapine treatment, with its predominance in checking compulsion and obsessions, is a relevant observation. We would like to hypothesise a cognitive interpretation. In our sample, the two symptoms were associated with distinct risk factors: 'obsessing' correlated with positive symptoms and 'checking' with longer treatment. We suggest that abnormal habitual *v.* goal-directed behavioural control might be a coherent explanation as it integrates the content of psychotic symptoms and clozapine's mechanism of action. Briefly, the abnormal habit-formation model posits that OCD might result from an imbalance between excessive formation of stimulus–response associations and a diminished ability for goal-directed actions (Gillan *et al.* 2016). Thus, repetition in the context of a diminished ability for consideration of action outcome, leads to automatization of behaviour. Indeed, schizophrenia patients exhibit deficits in goal-directed actions, likely representing a failure of cortical control over striatum (Morris *et al.* 2015), which might also increase vulnerability to OCD.

Using this conceptual framework, our hypothetical model suggests two OCD stages in clozapine-treated schizophrenia patients. Initially, goal-directed checking behaviour would be driven by psychosis (i.e. checking due to delusional hypervigilance). Then, a second phase characterised by 'obsessions' ameliorated by clozapine treatment but with a persisting (habitual) repetitive checking behaviour. A plausible mechanism for the persistence of repetitive behaviour would be clozapine's antagonism of 5-HT_{2A} and 5-HT_{2C} receptors (Schirmbeck & Zink, 2012). Decrease in serotonin neurotransmission in the brain causes perseveration in reversal learning tasks, the hallmark of cognitive inflexibility in compulsive behaviours including OCD (Robbins *et al.* 2012). For instance, in non-human primates, selective reduction in prefrontal serotonin is associated with cognitive inflexibility (Clarke *et al.* 2004). Similarly in rodents either reduction of 5-HT_{2A} binding in the orbitofrontal cortex (Barlow *et al.* 2015) or 5-HT_{2A} receptor antagonism (Boulougouris *et al.* 2008) is associated with impaired reversal learning. In humans, a dietary tryptophan depletion (a technique that acutely reduces serotonin in the brain) promotes habitual over goal-directed control (Worbe *et al.* 2015) and affects goal-directed learning (Worbe *et al.* 2016). Moreover, schizophrenia patients on clozapine who develop OCD present selective perseveration, as seen in the extra-dimensional set-shifting task (Patel *et al.* 2010). Taken together, these results suggest several plausible mechanisms such as impaired cognitive flexibility, impaired goal-directed behavioural control and reliance on habits by which clozapine antagonism to serotonin receptors might induce repetitive behaviour. This, our model integrates not only the present results but also the results of previous studies (Lin *et al.* 2006; Boyette *et al.* 2011; Schirmbeck *et al.* 2011; Scheltema Beduin *et al.* 2012; Schirmbeck & Zink, 2012) and patients' narratives. Others have described that non-clozapine patients present a profile characterised by higher contamination obsessions and washing

compulsions (Krüger *et al.* 2000; Faragian *et al.* 2009), consistent with the proposed model of abnormal habit formation.

There are limitations to our study. The first limitation is the inability to replicate our findings experimentally on healthy volunteers. As a drug with potentially lethal side effects, clozapine cannot be tested in healthy volunteers and it is only available for severe cases of schizophrenia, which limits experimental studies in humans. Second, despite that our sample is the largest studied to date, due to the complexity of the disorder, the amount of confounding factors and the staged approach proposed, a replication using an even larger sample is warranted. Additionally, this was a cross-sectional study, whereas a prospective design would address some of limitations of our approach such as the specific time of onset of checking behaviour. However, the feasibility of such study might be compromised by the fact that we found that OCD prevalence increased only after 10 years treatment with the same medication. Finally, OCD symptoms were evaluated using a self-rated scale and the study might benefit of replication using a clinician-rated scale such as Y-BOCS. However, we found that the responses followed the five-factor structure, suggesting that the answers were, at least, similar to other population such as OCD patients. There are some other inherent limitations related to the current diagnostic classification, as perhaps using two distinct nosologic categories (schizophrenia and OCD) does not fully capture or explain the phenomena. In line with the recent National Institute of Mental Health (NIHM) Research Domain Criteria (RDoC) initiative (Insel, 2014), checking behaviour in clozapine-treated patients might be better characterised in schizophrenia patients as a drug-enhanced habit, possibly mediated by the striatum.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S003329171800017X>

Acknowledgements. To patients, Anita Torossian for assistance during preparation and to Carme Colmenar for conceptual insights. Dr Fernandez-Egea was supported by 2009 Young investigator award and intramural funding from CPFT/NIHR-CRN supported setting the database. Professor Bernardo is funded by the Spanish Ministry of Science and Education, the Spanish Ministry of Economy and Competiveness, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), from the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2014SGR441), from the Foundation European Group for Research In Schizophrenia (EGRIS), and from the Seventh Framework Program of the European Union. Dr Y Worbe is supported by the Association Française du syndrome de Gilles de la Tourette, Fondation de recherche Médicale and Dystonia Foundation for Medical Research (USA). Professor TW Robbins' research is funded by a Wellcome Senior Investigator Award (104631/Z/14/Z). Work was completed at the Behavioural and Clinical Neuroscience Institute, which was supported by a joint award from the Medical Research Council and Wellcome Trust (G00001354).

Declaration of Interest. Dr Fernandez-Egea has no conflict of interest to disclose. Dr Worbe has received research grants from Mertz. Dr Bernardo has received fees for consultant and/or research grants from ABbiotics, Adamed, Ferrer, Forum Pharmaceuticals, Gedeon, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche, Servier. Professor Robbins consults for Cambridge Cognition, Lundbeck, Mundipharma and Unilever. He receives royalties for CANTAB from Cambridge Cognition and editorial honoraria from Springer-Verlag and Elsevier.

References

Baker RW, Chengappa KN, Baird JW, Steingard S, Christ MA and Schooler NR (1992) Emergence of obsessive compulsive symptoms during treatment with clozapine. *The Journal of Clinical Psychiatry* 53, 439–442.

- Barlow RL, Alsö J, Jupp B, Rabinovich R, Shrestha S, Roberts AC *et al.* (2015) Markers of serotonergic function in the orbitofrontal cortex and dorsal Raphé nucleus predict individual variation in spatial-discrimination serial reversal learning. *Neuropsychopharmacology* **40**, 1619–1630.
- Boulougouris V, Glennon JC and Robbins TW (2008) Dissociable effects of selective 5-HT_{2A} and 5-HT_{2C} receptor antagonists on serial spatial reversal learning in rats. *Neuropsychopharmacology* **33**, 2007–2019.
- Boyette L, Swets M, Meijer C, Wouters L and Authors G (2011) Factor structure of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) in a large sample of patients with schizophrenia or related disorders and comorbid obsessive-compulsive symptoms. *Psychiatry Research* **186**, 409–413.
- Brown JEH, Mezquida G and Fernandez-Egea E (2016) Well-being in clozapine-treated schizophrenia patients: the significance of positive symptoms. *Comprehensive Psychiatry* **68**, 140–146.
- Cardinal RN, Savulich G, Mann LM and Fernandez-Egea E (2015) Association between antipsychotic/antidepressant drug treatments and hospital admissions in schizophrenia assessed using a mental health case register. *NPJ Schizophrenia* **1**, 15035.
- Clarke HF, Dalley JW, Crofts HS, Robbins TW and Roberts AC (2004) Cognitive inflexibility after prefrontal serotonin depletion. *Science* **304**, 878–880.
- Couchman L, Morgan PE, Spencer EP and Flanagan RJ (2010) Plasma clozapine, norclozapine, and the clozapine:norclozapine ratio in relation to prescribed dose and other factors: data from a therapeutic drug monitoring service, 1993–2007. *Therapeutic Drug Monitoring* **32**, 438–447.
- de Haan L, Linszen DH and Gorsira R (1999) Clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disorders. *The Journal of Clinical Psychiatry* **60**, 364–365.
- Doyle M, Chorcorain AN, Griffith E, Trimble T and O'Callaghan E (2014) Obsessive compulsive symptoms in patients with schizophrenia on clozapine and with obsessive compulsive disorder: a comparison study. *Comprehensive Psychiatry* **55**, 130–136.
- Englisch S, Esslinger C, Inta D, Weinbrenner A, Peus V, Gutschalk A *et al.* (2009) Clozapine-induced obsessive-compulsive syndromes improve in combination with aripiprazole. *Clinical Neuropharmacology* **32**, 227–229.
- Eryilmaz G, Hızlı Sayar G, Ozten E, Gögceğöz Gül I and Karamustafaloğlu O (2013) Aripiprazole augmentation in clozapine-associated obsessive-compulsive symptoms in schizophrenia. *Annals of General Psychiatry* **12**, 40.
- Faragian S, Pashinian A, Fuchs C and Poyurovsky M (2009) Obsessive-compulsive symptom dimensions in schizophrenia patients with comorbid obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **33**, 1009–1012.
- Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G *et al.* (2002) The obsessive-compulsive inventory: development and validation of a short version. *Psychological Assessment* **14**, 485–496.
- Gillan CM, Robbins TW, Sahakian BJ, van den Heuvel OA and van Wingen G (2016) The role of habit in compulsivity. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* **26**, 828–840.
- Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL *et al.* (1989) The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry* **46**, 1006–1011.
- Grillault Laroche D and Gaillard A (2016) Induced obsessive compulsive symptoms (OCS) in schizophrenia patients under atypical 2 antipsychotics (AAPs): review and hypotheses. *Psychiatry Research* **246**, 119–128.
- Guillem F, Satterthwaite J, Pampoulova T and Stip E (2009) Relationship between psychotic and obsessive compulsive symptoms in schizophrenia. *Schizophrenia Research* **115**, 358–362.
- Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A *et al.* (2003) The clinical global impression-schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta Psychiatrica Scandinavica* **107**(S416), 16–23.
- Insel TR (2014) The NIMH Research Domain Criteria (RDoC) project: precision medicine for psychiatry. *The American Journal of Psychiatry* **171**, 395–397.
- Kim JH, Ryu S, Nam HJ, Lim M, Baek JH, Joo YH *et al.* (2012) Symptom structure of antipsychotic-induced obsessive compulsive symptoms in schizophrenia patients. *Progress in Neuropsychopharmacology & Biological Psychiatry* **39**(1), 75–79.
- Krüger S, Bräunig P, Höffler J, Shugar G, Börner I and Langkrämer J (2000) Prevalence of obsessive-compulsive disorder in schizophrenia and significance of motor symptoms. *The Journal of Neuropsychiatry and Clinical Neurosciences* **12**, 16–24.
- Kumbhani SR, Roth RM, Kruck CL, Flashman LA and McAllister TW (2010) Nonclinical obsessive-compulsive symptoms and executive functions in schizophrenia. *The Journal of Neuropsychiatry and Clinical Neurosciences* **22**, 304–312.
- Kwon JS, Joo YH, Nam HJ, Lim M, Cho E-Y, Jung MH *et al.* (2009) Association of the glutamate transporter gene SLC1A1 with atypical antipsychotics-induced obsessive-compulsive symptoms. *Archives of General Psychiatry* **66**, 1233–1241.
- Leung JG and Palmer BA (2016) Psychosis or obsessions? Clozapine associated with worsening obsessive-compulsive symptoms. *Case Reports in Psychiatry* **2016**, 2180748–5.
- Lin S-K, Su S-F and Pan C-H (2006) Higher plasma drug concentration in clozapine-treated schizophrenic patients with side effects of obsessive-compulsive symptoms. *Therapeutic Drug Monitoring* **28**, 303–307.
- Mahendran R, Liew E and Subramaniam M (2007) De novo emergence of obsessive-compulsive symptoms with atypical antipsychotics in Asian patients with schizophrenia or schizoaffective disorder: a retrospective, cross-sectional study. *The Journal of Clinical Psychiatry* **68**, 542–545.
- Morris RW, Quail S, Griffiths KR, Green MJ and Balleine BW (2015) Corticostriatal control of goal-directed action is impaired in schizophrenia. *Biological Psychiatry* **77**, 187–195.
- Mukhopadhyaya K, Krishnaiah R, Taye T, Nigam A, Bailey A, Sivakumaran T *et al.* (2009) Obsessive-compulsive disorder in UK clozapine-treated schizophrenia and schizoaffective disorder: a cause for clinical concern. *Journal of Psychopharmacology* **23**, 6–13.
- Ongür D and Goff DC (2005) Obsessive-compulsive symptoms in schizophrenia: associated clinical features, cognitive function and medication status. *Schizophrenia Research* **75**, 349–362.
- Patel DD, Laws KR, Padhi A, Farrow JM, Mukhopadhyaya K, Krishnaiah R *et al.* (2010) The neuropsychology of the schizo-obsessive subtype of schizophrenia: a new analysis. *Psychological Medicine* **40**, 921–933.
- Perdigues SR, Quecuti RS, Mane A, Mann L, Mundell C and Fernandez-Egea E (2016) An observational study of clozapine induced sedation and its pharmacological management. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* **26**, 156–161.
- Poyurovsky M, Hramenkov S, Isakov V, Rauchverger B, Modai I, Schneidman M *et al.* (2001) Obsessive-compulsive disorder in hospitalized patients with chronic schizophrenia. *Psychiatry Research* **102**, 49–57.
- Poyurovsky M, Weizman A and Weizman R (2004) Obsessive-compulsive disorder in schizophrenia: clinical characteristics and treatment. *CNS Drugs* **18**, 989–1010.
- Robbins TW, Gillan CM, Smith DG, de Wit S and Ersche KD (2012) Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends in Cognitive Sciences (Regul Ed)* **16**, 81–91.
- Sa AR, Hounie AG, Sampaio AS, Arrais J, Miguel EC and Elkis H (2009) Obsessive-compulsive symptoms and disorder in patients with schizophrenia treated with clozapine or haloperidol. *Comprehensive Psychiatry* **50**, 437–442.
- Scheltema Beduin AA, Swets M, Machielsen M, Korver N and Investigators GRaOoP (2012) Obsessive-compulsive symptoms in patients with schizophrenia: a naturalistic cross-sectional study comparing treatment with clozapine, olanzapine, risperidone, and no antipsychotics in 543 patients. *The Journal of Clinical Psychiatry* **73**, 1395–1402.
- Schirmebeck F, Esslinger C, Rausch F, Englisch S, Meyer-Lindenberg A and Zink M (2011) Antiserotonergic antipsychotics are associated with obsessive-compulsive symptoms in schizophrenia. *Psychological Medicine* **41**, 2361–2373.
- Schirmebeck F, Mier D, Esslinger C, Rausch F, Englisch S, Eifler S *et al.* (2015) Increased orbitofrontal cortex activation associated with 'pro-obsessive' antipsychotic treatment in patients with schizophrenia. *Journal of Psychiatry & Neuroscience* **40**, 89–99.
- Schirmebeck F and Zink M (2012) Clozapine-induced obsessive-compulsive symptoms in schizophrenia: a critical review. *Current Neuropharmacology* **10**, 88–95.
- Swets M, Dekker J, van Emmerik-van Oortmerssen K, Smid GE, Smit F, de Haan L *et al.* (2014) The obsessive compulsive spectrum in schizophrenia, a

- meta-analysis and meta-regression exploring prevalence rates. *Schizophrenia Research* **152**, 458–468.
- Worbe Y, Palminteri S, Savulich G, Daw ND, Fernandez-Egea E, Robbins TW et al.** (2016) Valence-dependent influence of serotonin depletion on model-based choice strategy. *Molecular Psychiatry* **21**(5), 624–629.
- Worbe Y, Savulich G, de Wit S, Fernandez-Egea E and Robbins TW** (2015b) Tryptophan depletion promotes habitual over goal-directed control of appetitive responding in humans. *The International Journal of Neuropsychopharmacology/ Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)* **18**(10), pyv013.
- Zimbron J, Khandaker GM, Toschi C, Jones PB and Fernandez-Egea E** (2016) A systematic review and meta-analysis of randomised controlled trials of treatments for clozapine-induced obesity and metabolic syndrome. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* **26**(9), 1353–1365.