European Psychiatry 30 (2015) 309–316

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Are stressful life events causally related to the severity of obsessive-compulsive symptoms? A monozygotic twin difference study

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ARTICLE INFO

Article history:
Received 2 July 2014
Received in revised form 17 September 2014
Accepted 9 November 2014
Available online 12 December 2014

Keywords:
Twin study
Obsessive-compulsive symptoms
Life events
Abuse

ABSTRACT

Traumatic or stressful life events have long been hypothesized to play a role in causing or precipitating obsessive-compulsive symptoms but the impact of these environmental factors has rarely been investigated using genetically informative designs. We tested whether a wide range of retrospectively-reported stressful life events (SLEs) influence the lifetime presence and severity of obsessive-compulsive symptoms (OCS) in a large Swedish population-based cohort of 22,084 twins. Multiple regression models examined whether differences in SLEs within twin pairs were significantly associated with differences in OCS. In the entire sample (i.e., both monozygotic [MZ] and dizygotic twin pairs), two SLEs factors, "abuse and family disruption" and "sexual abuse", were significantly associated with the severity of OCS even after controlling for depressive symptoms. Other SLEs factors were either not associated with OCS ("loss", "non-sexual assault") or were no longer associated with OCS after controlling for depression ("illness/injury"). Within MZ pair analyses, which effectively control for genetic and shared environmental effects, showed that only the "abuse and family disruption" factor remained independently related to within-pair differences in OCS severity, even after controlling for depressive symptoms. Despite being statistically significant, the magnitude of the associations was small; "abuse and family disruption" explained approximately 3% of the variance in OCS severity. We conclude that OCS are selectively associated with certain types of stressful life events. In particular, a history of interpersonal abuse, neglect and family disruption may make a modest but significant contribution to the severity of OCS. Further replication in longitudinal cohorts is essential before causality can be firmly established.

1. Introduction

Controlled family studies have consistently found that obsessive-compulsive disorder (OCD) is a familial disorder. For example, first-degree relatives of OCD probands are approximately 4 to 5 times more likely to have OCD themselves, compared to relatives of unaffected controls [53,69,44,52]. This familial risk decreases as the genetic distance with the proband increases. For example, second- and third-degree relatives are approximately 2 and 1.5 times more likely to have OCD, respectively, compared to relatives of unaffected controls, strongly suggesting a genetic component to OCD [44]. Twin studies primarily conducted in population-based (non-clinical) samples estimate the genetic contribution to be in the region of 40–50% [69,44,72]. Consistently, gene-searching efforts are well underway [67] and, though they have met with limited success to date, they are likely to continue [53].

Both family and twin studies also converge to suggest that shared environmental factors (e.g. growing up in the same neighbourhood) are unlikely to play a major role in causing OCD. Instead, the types of environmental influences that seem important in OCD are thought to be of the "non-shared" type, that is, environmental factors that affect specific individuals rather than families [72,28]. Such non-shared environmental factors could be biological (e.g. infections) or psychosocial (e.g. traumatic and

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http://dx.doi.org/10.1016/j.eurpsy.2014.11.008

stressful life events [SLEs], like being involved in an accident, being physically or sexually abused, or the death of one's partner). While the link between such SLEs and the pathogenesis of depression has been well-established [31,34], the evidence supporting a link between SLEs and OCD is much less conclusive because most studies have been conducted in clinical samples, based on retrospective reports and using designs that did not permit causal inferences. For example, research in clinical samples has shown that the association between OCD and post-traumatic stress disorder (PTSD) is larger than expected by chance [20,38]. One study [47] found that, compared to a control group, adults with OCD retrospectively-reported a greater number of SLEs one year before symptom onset. Similarly, in a large clinical sample of 265 adults with OCD, Cromer et al. [13] found that retrospectively-reported SLEs were associated with higher severity of OC symptoms (OCS) after controlling for a range of variables including depression severity. Similar findings have been reported in clinical samples of pediatric OCD [23,63]. However, clinical and convenience samples are liable to referral and Berkson's type biases, which may result in an overestimation of the associations.

A range of epidemiological, largely retrospective studies have also found associations between specific SLEs and OCD. For example, Mathews et al. [45] found an association between history of physical abuse, physical neglect and emotional abuse in childhood and OCS in a sample of 938 college students. Saunders et al. [64] and Boudreaux et al. [6] found that reported rape was associated with both lifetime and current OCD in a community sample of 391 women. Grisham et al. [24] found an association between retrospectively-reported sexual and physical abuse before age 11 and a diagnosis of OCD at ages 26 or 32, even after controlling for comorbid post-traumatic stress disorder. While, taken together, these findings are suggestive of an association between SLEs and OCD, they do not help clarifying the nature of this association. In particular, these studies could not control for genetic variability between individuals. This is particularly important as genetic background may not only put people at risk of developing psychopathology but also at risk of exposure to specific SLEs [30]. There is ample evidence that exposure to SLEs is at least partly heritable [30,56]. Therefore, isolating the non-shared variance of both OCS and SLEs is a crucial step to understand their association.

Genetically informative studies, in particular those employing the discordant monozygotic (MZ) twin design, are better suited to test whether the association between an environmental measure and an observed phenotype is likely to be consistent with a causal effect because they provide excellent control of both genetic and shared environmental effects. Because MZ-twins share 100% of their genetic background and grow up largely in the same environment, any observed phenotypic differences between members of a MZ-twin pair (e.g. differences in OCS) may be attributable to non-shared environment (e.g. non-shared SLEs) [73]. To our knowledge, only one previous study employed such design to test the association between SLEs and OCS in a population-based twin sample [12]. The authors selected 25 pairs of MZ-twins discordant for OCS (based on pre-determined cut-offs on a self-report questionnaire) and compared high vs low scoring twins on a number of potential environmental stressors, including retrospectively ascertained SLEs. They found suggestive evidence that SLEs, and particularly sexual assaults, were associated with OCS at the trend level ($P = 0.08$). It should be noted that this study did not adjust for other variables, such as depression, when comparing SLEs within discordant pairs. This is important because, not only there is a strong association between SLEs and depression, but also between depression and OCS [31,5,25]. Given that the evidence for the association between SLEs and OCS is only suggestive, it is plausible that part of this association might be explained by the presence of depressive symptoms. Thus, it is tenable that controlling for symptoms of depression may weaken the association between SLEs and OCS. Nevertheless, the suggestive results of Cath et al. study [12] merit replication in larger samples and expanding the number of SLEs examined.

In the present study, we used a genetically informative design to explore the relationship between a wide range of different SLEs and the severity of OCS in a large population-based sample of twins. Previous studies have often measured a limited range of different SLEs. In order to control for both genetic and shared environment effects and maximize the variance provided in our dataset, we employed the MZ-difference method [73,54]. This approach allows exploring whether the difference in SLEs between twins of a pair is associated with corresponding differences in the severity of OCS. This affords more statistical power than selecting high vs low symptom groups based on categorical cut-offs. Because there is a strong association between SLEs and depression and between depression and OCS [31,5,25], all our analyses controlled for depression severity in order to establish whether the presumed causal effect of SLEs on OCS is independent from depressive symptoms. Based on the previous literature, we made the following predictions:

- there will be a significant association between SLEs and OCS severity in the entire sample of twins (not controlling for genetic or family factors);
- SLEs will remain associated with OCS severity when genetic and shared environmental factors are strictly controlled in the analysis using the MZ-twin difference method;
- the association between SLEs and OCS severity will be generally weakened by the introduction of depression in the models as some of the variance may be explained by the known association between SLEs and depression.

2. Methods

2.1. Participants

Participants were drawn from the study of twin adults: genes and environment (STAGE), a study of 25,381 Swedish twins born between 1959 and 1985 [40]. Further details on the recruitment and data collection methods can be found elsewhere [40,16]. Briefly, twins were sent a letter inviting them to participate in the study and were given a personal login to the study web page. Non-responders were approached with up to three reminders. Twins could also choose to complete the questionnaire by telephone with a trained interviewer using a computer-based data collection method, supplemented with a mailed self-administered paper questionnaire for sensitive topics. Seventy-two percent of participants completed the web-based survey and 28% undertook the telephone interview. One hundred twins were re-contacted after 2 to 5 months in order to compare methods of data collection. For the OCD section, the agreement between the web-based survey and the telephone interview was perfect (Kappa = 1) [40]. The regional ethics committee of the Karolinska Institutet approved the project. All subjects provided informed consent electronically during the web-based survey or orally during the telephone interview.

Out of the original cohort, 22,517 twins completed a measure of OCS (see Measures section below). From these participants, we excluded all those who had at least one missing item on the OCS questionnaire. The final sample consisted of 22,084 twins (87% of the original cohort and 98% of the participants who completed the OCS questionnaire).