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Quantifying dimensional severity of obsessive-compulsive disorder for neurobiological research

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ABSTRACT

Current research to explore genetic susceptibility factors in obsessive-compulsive disorder (OCD) has resulted in the tentative identification of a small number of genes. However, findings have not been readily replicated. It is now broadly accepted that a major limitation to this work is the heterogeneous nature of this disorder, and that an approach incorporating OCD symptom dimensions in a quantitative manner may be more successful in identifying both common as well as dimension-specific vulnerability genetic factors. As most existing genetic datasets did not collect specific dimensional severity ratings, a specific method to reliably extract dimensional ratings from the most widely used severity rating scale, the Yale-Brown Obsessive Compulsive Scale (YBOCS), for OCD is needed. This project aims to develop and validate a novel algorithm to extrapolate specific dimensional symptom severity ratings in OCD from the existing YBOCS for use in genetics and other neurobiological research. To accomplish this goal, we used a large data set comprising adult subjects from three independent sites: the Brazilian OCD Consortium, the Sunnybrook Health Sciences Centre in Toronto, Canada and the Hospital of Bellvitge, in Barcelona, Spain. A multinomial logistic regression was proposed to model and predict the quantitative phenotype [i.e., the severity of each of the five homogeneous symptom dimensions of the Dimensional YBOCS (DYBOCS)] in subjects who have only YBOCS (categorical) data. YBOCS and DYBOCS data obtained from 1183 subjects were used to build the model, which was tested with the leave-one-out cross-validation method. The model's goodness of fit, accepting a deviation of up to three points in the predicted DYBOCS score, varied from 78% (symmetry/order) to 84% (cleaning/contamination and hoarding dimensions). These results suggest that this algorithm may be a valuable tool for extracting dimensional phenotypic data for neurobiological studies in OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a complex neurobiological condition characterized by the presence of obsessions, or intrusive, unwanted thoughts, which cannot be suppressed, and compulsions or repetitive behaviors or mental acts (APA, 2013; Shavitt et al., 2014). The etiology of this disorder is complex, with a strong genetic element based on heritability estimates of approximately 40–65%, depending on early versus post-adolescent age of onset (Mataix-Cols et al., 2013; Pauls, 1992, 2010), presence of tics (Pauls et al., 1995), and sporadic or

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familial form (Pauls et al., 2014). In addition, rare variations (Cappi et al., 2016) and epigenetic factors have been reported as relevant to the clinical manifestations of OCD (Yue et al., 2016). Moreover, there is robust evidence that different symptoms of this disorder may have overlapping but distinct neurobiological substrates corresponding to specific genetic features (Alonso et al., 2011; Cavallini et al., 2002; Hasler et al., 2007; Katerberg et al., 2010a; Kohlrausch et al., 2016; Lennertz et al., 2014; Taj et al., 2013).

Addressing the OCD phenotype for genetic studies has been a challenge for researchers in the field and many studies have emphasized the relevance of using a dimensional approach (Aleman et al., 2016; Lecrubier, 2008; Waszczuk et al., 2017). To this date, most studies have emphasized a four-factor model comprising: (I) repugnant/harm obsessions (i.e. sexual, religious, harm-related, somatic) and checking compulsions; (II) symmetry obsessions and repeating, counting, and ordering compulsions; (III) contamination obsessions and cleaning compulsions; and (IV) hoarding obsessions and compulsions (Bloch et al., 2008). This biological heterogeneity based on primary symptom dimensions has been supported by functional neuroimaging, family history, age of onset, and response to pharmacotherapy (De Luca et al., 2011; Harrison et al., 2013; Jhung et al., 2014; Mataix-Cols et al., 2004; Pertusa et al., 2010; Rosario-Campos et al., 2001; Via et al., 2014). Additional support is conferred from reports of individuals' symptoms staying within the same symptom groups over time (shown in adults and children) (Delorme et al., 2006; Mataix-Cols et al., 2002; Rufer et al., 2005), despite the observation in clinical practice that specific symptom types may change over the course of the disease. Despite the delineation of distinct OCD subgroups obtained by exploratory factor analyses (EFA) of data from the Yale-Brown Obsessive-Compulsive Scale [YBOCS] (Goodman et al., 1989a; Goodman et al., 1989b); (Mataix-Cols et al., 2004; Leckman et al., 1997), one issue that remains unresolved with this methodology is to what extent the severity of each symptom dimension contributes to the observed phenotype. Furthermore, within a given individual, symptoms may coexist from two or more factors simultaneously. Therefore, individuals cannot easily be assigned to one predominant symptom "class". Consequently, there is a clear need for a novel, practical, readily available, and standardized way to quantitatively assess OCD symptoms across the differing dimensions present in a given individual, particularly for any exploration of genetic vulnerability.

Factorial analyses allow for the characterization of the phenotype based on the presence/absence of symptoms pertaining to each category (Schooler et al., 2008; Katerberg et al., 2010b), but not on the contribution of the severity of each symptom dimension to the overall clinical severity. In this way, OCD genetic studies have potentially been hampered by the heterogeneity of this illness, and it has been proposed that analyses based on the quantitative measures of specific symptom dimensions may thus be a powerful way to explore more genetically homogeneous subgroups of OCD. To the best of our knowledge, no study in the OCD field has ever tried to extract dimensional data (i.e., how severe?) from large datasets containing only categorical data (present/absent). The novel approach proposed in the present study aims to enable, for the first time, the determination of the severity of individual symptom dimensions for a better delineation of the OCD phenotypes. The approach based on separating the different types of symptoms is a necessary first step in refining the OCD phenotype, but the need to determine which group of symptoms is more relevant to the observed clinical picture remains unattended. It is becoming increasingly clear that all efforts to investigate the genetic basis of this condition should take a symptom dimensional approach, as the few studies that specifically examined genetic risk support both shared and unique genetic vulnerability across these dimensions (Alonso et al., 2011; Cavallini et al., 2002; Katerberg et al., 2010a; Kohlrausch et al., 2016; Taj et al., 2013; Iervolino et al., 2011).

The phenomenology of OCD can be captured by structured interviews that can be self-reported or clinician administered, like the YBOCS (Goodman et al., 1989a; Goodman et al., 1989b) and the Dimensional YBOCS (DYBOCS) (Rosario-Campos et al., 2006). Although the YBOCS is the most widely used instrument in OCD studies internationally, it does not allow for the collection of quantitative data by symptom type. By contrast, the DYBOCS was developed to assess the presence and severity of five individual symptom dimensions and their respective severity in patients with OCD, plus one miscellaneous dimension comprising symptoms of the OCD-related conditions. The DYBOCS enables determination of the clinical relevance and severity of each symptom dimension, as well as an overall OCD severity rating. This dimensional approach seems particularly pertinent to the biological investigation of a complex condition such as OCD. Thus, broad consensus has emerged in the field for the need to explore OCD not as a homogeneous diagnosis, but rather utilizing quantitative assessments of these symptom factors.

Efforts to elucidate genetic risk factors in OCD have been underway by several international centers. The recent genome-wide association studies that searched for common DNA sequence variations predisposing individuals to OCD have not yielded genome-wide significant results, but these datasets did not historically include any dimensional measures to permit analysis based on symptom dimensions (Mattheisen et al., 2014; Stewart et al., 2013). Future exploration with increased attention to phenotypes, especially the consideration of subtypes of this disorder, could result in greater success (Burmeister et al., 2008). If there was a reliable way to extrapolate valid quantitative dimensional data from the most widely used OCD scale (the YBOCS), the existing international datasets could be re-explored in a more refined and symptom-specific fashion.

The aim of this study was to develop and validate a novel, statistical algorithm for the extraction of quantitative, symptom-dimension specific data for all symptoms in a given individual from the most commonly used OCD rating scale, the YBOCS. We used data from 1183 subjects from three independent international samples. We postulate that this algorithm will allow for a more successful way in identifying the neurobiological underpinnings of OCD, such as genetic vulnerability factors associated with specific OCD symptom dimensions.

2. Methods

This work was done with DYBOCS and YBOCS data obtained from 1183 adult patients with primary OCD, diagnosed according to DSM-IV criteria, from three independent groups: the Brazilian OCD Research Consortium (Miguel et al., 2008) (n = 912), the Anxiety Disorders Clinic at the Centre for Addiction and Mental Health and the Frederick W. Thompson Anxiety Disorders Centre at the Sunnybrook Health Sciences Centre, Canada (n = 36) and the Hospital of Bellvitge, Barcelona, Spain (n = 235). Data from the YBOCS and DYBOCS were obtained by trained clinicians at the same point in time. All the work was developed with de-identified data sets built over the years using data from different research projects approved by the local Ethics Committee at each participant Institution. The funding for this study came from a joint grant of the University of Sao Paulo and University of Toronto, process number 13.1.13252.1.6, 2012.

In order to build an algorithm for extraction of a dimensional severity score from the YBOCS, the first step was to recode DYBOCS data into the YBOCS format for the Brazilian sample, since these subjects had the severity ratings but not the symptom checklist from the YBOCS. Table 1 shows the main features of the YBOCS and DYBOCS.

The YBOCS is more general than the DYBOCS in the characterization of symptoms. For example, YBOCS symptom #64 is "I have mental rituals (other than checking/counting)", whereas the DYBOCS has five symptoms related to mental rituals: "I have mental rituals, other than checking, specifically related to: #30-sexual or religious obsessions; obsessions of symmetry, exactness, or just right perceptions (#41); contamination worries (#53); hoarding obsessions (#60) and somatic worries (#64)". Therefore, if a patient scores 2 (present) at YBOCS

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