“Not Just Right Experiences” as a psychological endophenotype for obsessive-compulsive disorder: Evidence from an Italian family study

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A B S T R A C T

The heart of the obsessional process may be considered the subject’s underlying impression that “something is wrong” or “that something is not just as it should be”. This phenomenon, labeled “not just right experiences” (NJREs), has increasingly been receiving attention as a possible marker of obsessive-compulsive disorder (OCD). The present study sought to add to the evidence that NJREs may be a putative endophenotype of obsessional symptoms. To this aim, measures of NJREs, obsessive-compulsive (OC) symptoms and psychological distress were compared in offspring of parents with and without OC symptoms. The offspring of parents with OC symptoms (N = 120) reported higher frequency and severity of NJREs compared to offspring of parents without OC symptoms (N = 106). Such differences remained significant for NJREs frequency and close to significance for NJREs severity, when general distress (i.e., anxiety and depression) was controlled. The possible role of NJREs as an endophenotype for OCD is discussed in reference to Gottesman and Gould criteria and the National Institute of Mental Health RDoC initiative.

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1. Introduction

Obsessive-Compulsive Disorder (OCD) is a serious mental condition characterized by the presence of persistent, intrusive, and distressing obsessions or compulsions, with marked impairment in quality of life (Eisen et al., 2006; Kugler et al., 2013; Parkin, 1997). Obsessions are uncontrolled, unpleasant and unwanted thoughts, impulses or images accompanied by a feeling of urgency or catastrophe, leading to repetitive, time-consuming or ritualistic behaviors (compulsions). OCD represents one of the most incapacitating psychiatric disorders owing to its intensity, the continuous and unchanging or deteriorative course of its symptoms, and the disturbance in psychosocial functioning that they cause (Albert et al., 2010; Mancebo et al., 2008; Visser et al., 2014).

OCD is characterized by a clinical diversity reflected in a wide range of symptoms, and the clinical presentation can vary both within and across patients over time. Actually, many studies have provided strong evidence that OCD is clinically heterogeneous and that this clinical heterogeneity is likely due to etiologic heterogeneity (e.g., Abramowitz and Jacoby, 2015; Bloch et al., 2008; McKay et al., 2004).

Behavioral genetic (twin) research shows that OCD arises from a mix of genetic and environmental factors, but much remains to be learned about the nature of these etiologic influences (e.g., Pauls et al., 2014). In particular, recent genetic studies demonstrated that OCD is associated with multiple genes, with most having a modest association with OCD, suggesting a polygenic model in which multiple genes make small, incremental contributions to the risk of developing the disorder (e.g., Taylor, 2012; Taylor and Jang, 2011; see also Stewart et al., 2013 on the null results in genome-wide association study of OCD).

Unfortunately, little is known about the predictors and moderators of response to therapies in OCD, despite extensive research on this topic (see review by Knopp et al., 2013).

Like all psychiatric disorders, gaining a complete understanding of what comprises OCD and the underlying etiological mechanisms will probably require a change in how the disorder is conceptualized. In particular, the notion of endophenotype has been proposed as a means of facilitating research into the etiology of complex and heterogeneous disorders such as OCD. Endophenotypes may be considered intermediary between etiologic factors (bottom-level) and phenotypic manifestations (top-level) of a given disorder (see Gottesman and Gould, 2003; Kendler and Neale, 2010). An endophenotype may be a variable from any of a number of levels of organization, including biochemical,
neuropsychological, neuroanatomical, cognitive, or other variables, including those obtained from self-report measures (Cannon and Keller, 2006; Gottesman and Gould, 2003). Importantly, an endophenotype can be a risk factor for a disorder even if the person is not currently symptomatic; in addition, it should be found in unaffected family members at a higher rate than in the general population (for a broad discussion about the role of endophenotypes in psychopathology, see Hasler et al., 2004).

In the last few years, several scholars have considered the lack of a sense of satisfaction and presence of feelings of doubt as central features of obsessions and associated compulsions. In fact, the heart of the obsessional process seems the subject's underlying impression that "something is wrong". In other words, obsessions may be thought of as the perception of a mistake and/or error in certain behavioral situations (see Sica et al., 2015). Based on various empirical data, the construct of “not just right experiences” (NJREs; Coles et al., 2003) has been proposed as a candidate endophenotype for OCD (see also Miguel et al., 2005).

What evidence supports NJREs as an endophenotype? First, the cross-sectional association between NJREs and OCD or obsessive-compulsive (OC) symptoms appears robust for both in nonclinical and clinical populations (e.g., Ferrão et al., 2012; Ghisi et al., 2010; Ghisi et al., 2013; Taylor et al., 2012). In addition, Coles et al. (2012) investigated patients' reports of various factors that may have played a role in the transition from the presence of obsessions and compulsions to full-blown OCD. Increases in the strength of urges for things to feel 'just right' were commonly viewed as contributing to the onset of OCD. Importantly, associations between sensory phenomena (i.e., NJREs) and OCD were also noted in a pediatric OCD population (Lewin et al., 2015).

Second, experimental studies have demonstrated that NJREs elicited in the laboratory predicted OC symptoms. For instance, in a sample of undergraduate students, affective response to clutter (i.e., NJREs) was uniquely predictive of hand-washing duration when controlling for pre-wash anxiety (Cougle et al., 2011). Moreover, measures of incompleteness predicted urges to check following a stove checking task (Cougle et al., 2013; see also, Summers et al., 2014). Buse et al. (2014) assessed reaction times (RT) to harmonic and disharmonic chord sequences as well as their emotional appraisal in 64 healthy young adults. The participants clearly indicated that disharmonic chord sequences sounded not just right and incomplete and rated them as unpleasant, arousing, and irritating. This effect tended to be greater among participants who reported stronger general experiences of incompleteness as an underlying core dimension of OCD-like symptoms.

Third, in a one-year longitudinal study on undergraduates, NJREs predicted OC symptom variation even when looming style (a specific cognitive mechanism for anxiety, Rachman et al., 2005) was accounted for (Sica et al., 2012).

Lastly, NJREs appear specific to OCD. In several studies, NJREs were significantly more strongly correlated with OC symptoms than other domains of psychopathology (e.g., social anxiety, worry, depression; Coles et al., 2003; Coles et al., 2005; Ecker and Gönger, 2008; Ghisi et al., 2010; Taylor et al., 2012). Sica et al. (2015) who found that a group of OCD patients reported higher levels of NJRE severity than groups of patients with either gambling (GD) or eating disorders (ED) recently corroborated this evidence. In the same study, while a measure of NJREs did not discriminate between OCD patients and patients with hair-pulling disorder, this last group did not have higher scores of NJREs severity than GD and ED counterparts.

It is not surprising therefore that the DSM-5 newly acknowledged NJREs as one of the “affective responses” seen in OCD (American Psychiatric Association, APA, 2013, p. 239). Despite the substantial evidence that indicate NJREs as a possible mechanism involved in OCD, no published studies have investigated whether NJREs are present in relatives of individuals with OCD or OC symptoms (unaffected family members) at a higher rate than in the general population. Providing data about this important issue would strengthen the evidence for NJREs as a putative endophenotype for OCD and OC symptoms.

1.1. The current study

We speculated that the frequency and/or severity of NJREs should be higher in offspring of parents with OC symptoms compared to offspring of parents without OC symptoms. This supposition is in fact coherent with the idea that NJREs might be a liability factor for the OCD. To test our hypothesis, measures of NJREs, OC symptoms, anxiety, and depression were collected from a sample of college students and their parents. Then, we identified two groups of college students: those with at least one parent with some OC symptoms (as measured by the Obsessive-Compulsive Inventory, see below) and those with no parents with OC symptoms. The first group of students was considered an “at-risk group” for OC symptoms whereas the second one was considered not at risk for OC symptoms.

We chose a nonclinical sample because we believe that, in case of OCD, it has certain advantages compared to clinical counterparts. For example, those seeking treatment for OCD represent a minority of the OCD population (Grabe et al., 2000), and likely differ from non-help seekers on social, economic, attitudinal, and personality factors. Confounding factors such as prior treatment types and treatment effects and, above all, comorbidity, also pose challenges for studies of OC phenomena in clinical populations. In addition, OCD is a chronic disorder, especially if not treated in the appropriate way (Sica et al., 2010): we do not know how a chronic OCD affects the psychological (and neurobiological) functions of people in the long-term. Also, since OCD occurs in only 2–3% of the population, it can be time intensive and costly to recruit clinical samples of an adequate size.

On the other hand, OC symptoms do occur in the general population (e.g., Adam et al., 2012; de Bruijn et al., 2010; Grabe et al., 2000), allowing researchers to recruit larger samples with relative convenience. As a matter of fact, researchers have pursued various forms of analogue research in order to study OC phenomena. Let us consider the evidences in favor of such choice.

1) Studies of analogue samples (i.e., student and community participants) highlight the prevalence of subclinical OC symptoms. According to surveys, up to 90% of people report that they at least occasionally experience intrusive thoughts that are similar in form and content to clinical obsessions (e.g. Clark, 1992; Freeston et al., 1991). Several studies of student or community samples have reported the prevalence of “caseness” as assessed by the Obsessive Compulsive Inventory-Revised (OCI-R; Foa et al., 2002) (e.g., Cuttler and Taylor, 2012; Kaczurkin, 2013). Therefore, OC symptoms are present to some degree in the nonclinical samples, providing initial evidence for a continuum of severity.

2) Distress, impairment, and reduced quality of life are also part of the diagnostic criteria for OCD (APA, 2013). Accordingly, studies also reveal some degree of impairment and treatment seeking even among non-clinical groups, and thus support the dimensional model of OC symptoms (Adam et al., 2012; de Bruijn et al., 2010; Grabe et al., 2000). Even more important, two taxometric studies have found support for a dimensional latent structure for OC symptoms globally (Haslam et al., 2005; Olatunji et al., 2008).

3) A large body of research indicates that for the most part, the themes, content, and form of intrusive distressing (obsession-
like) thoughts are the same among non-clinical (analogue) and clinically diagnosed OCD samples (e.g., Belloch et al., 2004; Garcia-Soriano et al., 2011; Julien et al., 2009; Rasmussen and Eisen, 1989). Moreover, Rachman and de Silva (1978) found that even trained clinicians could not distinguish between the content of obsession-like intrusive thoughts reported by people with and without a diagnosis of OCD. Likewise, most types of compulsions observed in clinical OCD samples (e.g., checking, counting, repeating, washing) are also observed in nonclinical samples (Flament et al., 1988; Henderson and Pollard, 1988).

4) Numerous studies have used factor and cluster analysis of OC symptom measures to elucidate the thematic structure of OC symptoms in non-clinical and clinical samples. In general, findings indicate structural invariance between clinical and non-clinical samples across different measures of OC symptoms (Maudsley Obsessional Compulsive Inventory; Hodgson and Rachman, 1977; Padua Inventory, Saniovio, 1988; van Oppen et al., 1995; OCI-R; Foa et al., 2002; Overduin and Furnham, 2012; Schedule of Obsessions Compulsions and Pathological Impulses, Watson and Wu (2005); Yale-Brown Obsessive Compulsive Scale; Goodman et al., 1989a, 1989b; Katerberg et al., 2010; Wu et al., 2007; López-Solà et al., 2014).

5) A recent meta-analysis compared the pattern of results from twin studies in which one or both twins were diagnosed with OCD versus twin studies of non-clinical samples in which twins completed measures of OC symptom severity (Taylor, 2011). Results indicated that all the findings from clinical samples were replicated in non-clinical samples (see also Taylor et al., 2010). These findings suggest that OC symptoms, as assessed in analogue samples, are etiologically related to the diagnosis of OCD.

6) Psychological processes and mechanisms hypothesized to govern the development and maintenance of OC symptoms do overlap across types of samples. This is true both for NJREs (as previously illustrated) and for alternative models of OCD development. Regarding the latter, for instance, researchers have identified six domains of dysfunctional beliefs (i.e., “obsessive beliefs”) thought to be associated to OC phenomena. Numerous correlational, prospective, and experimental studies demonstrate that obsessive beliefs are present and associated with OC symptom severity in both clinical and non-clinical analogue samples (e.g., Abramowitz et al., 2006; Abramowitz and Deacon, 2006; Obsessive Compulsive Cognitions Working Group, 2003, 2005).

7) Various experimental paradigms have found the presence of attentional biases in individuals with OCD and in analogue samples. In a meta-analytic study, Bar-Haim et al. (2007), examined 50 studies using samples of non-clinical individuals: they found that a threat-related attentional bias is an overlapping feature of individuals with clinical and nonclinical levels of OC symptoms (see also Coles et al., 2006; Dek et al., 2010; van den Hout and Kindt, 2003).

8) Contemporary treatment development continues to rely on analogue samples for the initial evaluation of potentially effective interventions (e.g., Amir et al., 2009; Najmi and Amir, 2010). Analogue treatment research is also useful for answering important scientific questions such as the process of change, the specific efficacy of different treatment components, and the manner in which treatments might be modified to optimally target different OCD symptom presentations. For example, Cougle et al. (2007) found that the process and outcome of exposure to a feared contaminant differed according to whether non-clinical analogue OC participants were concerned with illness or other threats. In contrast to participants with illness-related concerns, those with non-illness concerns (e.g., loss of control) did not experience a reduction in the urge to wash following a single session of exposure therapy (see also, Olatunji et al., 2009).

To conclude, research supports the idea that OC-related phenomena among non-clinical analogue samples are milder variants of those observed among individuals with symptoms severe enough to meet the criteria for a diagnosis of OCD (for a review, see Abramowitz and Jacoby, 2014).

2. Method

2.1. Participants and procedure

A portion of the current sample participated in a previous study of the familiarity of NJREs (see, Sica et al., 2013). Approximately 600 undergraduates of Health Sciences (Psychology and Medicine) and Sciences (Computer Science and Engineering) from two different Italian universities in Central and Northern Italy were approached during lectures by faculty to participate in a study “on the psychology of family relationships”. To be eligible for the study, individuals had to have been raised by their biological parents and have lived at the family home until they were at least 18 years old. These restrictions were included to reduce variability in upbringing and to reflect the typical home situation for children in Italy.

Among those recruited, 542 students qualified and agreed to participate, corresponding to an average participation rate of 90%, similar to rates in our previous studies with other college-recruited samples. All students were Caucasian and single.

Participants were given a general description of the purpose of the study, signed a consent form, and completed a questionnaire on background information and several self-report measures (see below). Each participant was given two sealed envelopes to take home, one for the father and one for the mother. In the instructions, we specified that parents, after signed a consent form, had to fill in questionnaires packages independently of one another and that students would remind parents that this was an important requirement of the study. A few days later, a research assistant collected the parents’ questionnaires—securely sealed in a signed envelope—from the students.

Participation was voluntary and no payment or course credits were offered to participants. Data were collected at different times throughout the academic year (between October 2011 and December 2012) to avoid effects due to timing of the assessment. Ethical approval was obtained from the institutional ethics committee.

Eighty-seven percent of students (n = 470; 47% female) returned at least one of their parent’s questionnaires (96% mothers, 80% fathers). Two percent of the questionnaires were excluded due to missing data. The final sample was composed of 460 undergraduates (43.2% females), 435 mothers and 360 fathers. All undergraduates included valid information from at least one of the parents. Students who did not have their parents participate were not different from remaining participants on demographic characteristics (age, percentage of females, education levels) or on any of the variables examined in this study (all ps > 0.05).

Seven percent of students (n = 33) reported having obtained mental health professional advice and/or pharmacotherapy for the following: anxiety (30%), depression (34%), eating disorders (25%), systemic disorders (7%) or self-harm (4%). Likewise, 10% of mothers (n = 45) and 5% (n = 18) of fathers reported having received professional advice (mothers: 55% for depression, 31% for anxiety, 14% for systemic disorders; fathers: 43% for depression, 20% for systemic disorders, 29% for anxiety, 8% for neurological disorders).

The mean age was 21.7 years (SD 2.7; range 18–35) for the students, 51.7 years (SD 5.1; range 38–66) for the mothers, and
54.2 years (SD 5.2; range 36–70) for the fathers. Mothers had an average education of 12.6 years (SD = 3.7) and 11% reported being separated or divorced; fathers had an average education of 12.9 years (SD = 4.3) and 6% were separated or divorced. Most student participants still lived with their parents (83.4%); the remainder had lived on their own for an average of about 17 months.

2.1.1. Selection of offspring groups

Two groups of parents were selected. The OCD group (n = 141, mothers = 82; fathers = 59; 18% of all parents) included those who scored 40 or higher on the Obsessive-Compulsive Inventory (OCI) Total score (in 21 cases both parents had a score equal or above this threshold). This threshold corresponds to the 85th percentile for Italian OCI norms (Marchetti et al., 2010). The Control Group (n = 115, mothers = 68; fathers = 47; 14.4% of all parents) was composed of parents among whom at least one scored 6 or less on the OCI Total score and the other one (if data were available for both) scored below 40 (in 9 cases both parents had a score equal or below 6). The threshold of six or less corresponds to the 30th percentile for Italian OCI norms (Marchetti et al., 2010). Demographic and psychopathology scores for the two groups of parents are shown in Table 1.

The offspring of the OCD group were denoted as “at risk” for OC symptoms (At-Risk Offspring, ARO; n = 120; 26% of student sample), whereas the offspring of the CG were not considered at risk (Control Offspring, CO; n = 106; 23% of student sample). As shown in Table 2 the two groups of students were equivalent in gender proportion and age, but the ARO exhibited a higher level of OCD, anxiety and depression symptoms (Table 2).

2.2. Measures

All participants completed a background information questionnaire and the following measures:
The Not Just Right Experiences-Questionnaire-Revised (NJRE-Q-R; Coles et al., 2005) has 19 items in three parts. The first part presents 10 NJREs (e.g., “I have had the sensation of getting dressed that parts of my clothes did not feel just right”, “I have had the sensation while organizing my desk that my papers and other things didn’t look just right.”) and instructs respondents to indicate whether they experienced these within the past month. The second part (2 items) asks respondents to indicate which NJRE occurred most recently and when it last occurred (past few hours to past month). In the third part (7 items), respondents rate frequency, intensity, immediate distress, delayed distress, rumination, urge to respond, and sense of responsibility associated with the most recent NJRE on a scale from 1 (absence) to 7 (extreme). This measure yields two overall indices: the NJRE-Q-R-total (i.e. the sum of the first 10 items) and the NJRE-Q-R severity scale (i.e. the sum of ratings for the last seven items; see, for instance Taylor et al., 2012). The Italian version of the NJRE-Q-R demonstrated good psychometric properties in several studies (e.g., Ghisi et al., 2010; Sica et al., 2012, 2013, 2015). In the present study, the alpha coefficient for the total score was 0.60 for students, 0.73 for mothers and 0.71 for fathers, and the alpha coefficient for the severity score was 0.93 for students, 0.94 for mothers and 0.93 for fathers.

The Obsessive Compulsive Inventory (OCI; Foa et al., 1998) is a widely used 42-item self-report questionnaire assessing the distress and frequency of OC symptoms on 5-point Likert scales. Items are grouped into seven rationally derived subscales (washing, checking, ordering, obsessing, doubting, mental neutralizing, and hoarding). Initial reports supported the reliability and validity of this instrument, and showed strong convergence with established measures of OCD, moderate to high internal consistency across the seven subscales, and adequate to high test-retest stability (e.g., Foa et al., 1998; Wu and Watson, 2003). The Italian version of the OCI indicated good internal consistency and 30-day retest reliability, as well as good convergent, divergent, and criterion validity (Marchetti et al., 2010; Sica et al., 2009). The present study assessed only distress associated with obsessions and compulsions since the two scales (distress and frequency) yield redundant information (e.g., Foa et al., 2002; Wu and Watson, 2003). In the present study, the alpha coefficient for the total OCI distress was 0.94 for students, 0.96 for mothers, and 0.91 for fathers. Consistent with the Italian validation study, alpha coefficients for the OCI-R subscales exceeded 0.70 in all groups.

The OCI was preferred over the shorter 18-item version (OCI-R) because previous investigations showed that the brevity of the OCI-R scales might be of concern especially for an excessive restriction of score range (Ghisi et al., 2010; Sica et al., 2012).

The Beck Anxiety Inventory (BAI; Beck et al., 1988) is a 21-item self-report measure of anxiety severity with excellent psychometric properties. The Italian version of the BAI has shown good internal consistency (Cronbach’s alpha = 0.89) and a 30-day retest reliability of 0.62, as well as good convergent, divergent, and criterion validity (Sica et al., 2006; Sica and Ghisi, 2007). In the present study, the alpha coefficient for the BAI was 0.88 for students, 0.92 for mothers and 0.94 for fathers.

The Beck Depression Inventory-Second Edition (BDI-II; Beck et al., 1996) is a 21-item self-report scale that assesses the severity of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data and symptomatology for parents selected for high and low levels of OC symptoms.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Parents high in OC symptoms (141)</td>
</tr>
<tr>
<td>Age</td>
<td>52.9 (3.3)</td>
</tr>
<tr>
<td>% of females</td>
<td>58.1</td>
</tr>
<tr>
<td>BAI</td>
<td>16.2 (12.0)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>15.5 (9.1)</td>
</tr>
<tr>
<td>OCI-Total</td>
<td>64.1 (20.8)</td>
</tr>
<tr>
<td>OCI-Washing</td>
<td>12.0 (6.5)</td>
</tr>
<tr>
<td>OCI-Checking</td>
<td>13.4 (6.1)</td>
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<tr>
<td>OCI-Doubting</td>
<td>4.7 (2.8)</td>
</tr>
<tr>
<td>OCI-Ordering</td>
<td>8.8 (4.1)</td>
</tr>
<tr>
<td>OCI-Obsessing</td>
<td>11.6 (6.0)</td>
</tr>
<tr>
<td>OCI-R Mental Neutralizing</td>
<td>7.5 (3.9)</td>
</tr>
<tr>
<td>OCI-R Hoarding</td>
<td>5.8 (2.8)</td>
</tr>
</tbody>
</table>

Notes: standard deviations in brackets; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression inventory-II; OCI = Obsessive-Compulsive Inventory.

Table 2 | Demographic data and symptomatology for at-risk offspring (ARO) and control offspring (CO). |
<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>ARO (120)</td>
</tr>
<tr>
<td>Age</td>
<td>21.8 (2.2)</td>
</tr>
<tr>
<td>% of females</td>
<td>52</td>
</tr>
<tr>
<td>BAI</td>
<td>13.3 (9.3)</td>
</tr>
<tr>
<td>BDI-II</td>
<td>9.6 (7.2)</td>
</tr>
<tr>
<td>OCI-Total</td>
<td>33.6 (26.9)</td>
</tr>
<tr>
<td>OCI-Washing</td>
<td>5.3 (5.9)</td>
</tr>
<tr>
<td>OCI-Checking</td>
<td>6.8 (6.6)</td>
</tr>
<tr>
<td>OCI-Doubting</td>
<td>2.6 (2.7)</td>
</tr>
<tr>
<td>OCI-Ordering</td>
<td>4.7 (3.0)</td>
</tr>
<tr>
<td>OCI-Obsessing</td>
<td>7.3 (6.7)</td>
</tr>
<tr>
<td>OCI-R Mental Neutralizing</td>
<td>3.7 (3.7)</td>
</tr>
<tr>
<td>OCI-R Hoarding</td>
<td>3.2 (2.9)</td>
</tr>
</tbody>
</table>

Notes: standard deviations in brackets; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression inventory-II; OCI = Obsessive-Compulsive Inventory.

*p < 0.01;
affective, cognitive, motivational, vegetative, and psychomotor components of depression. The BDI-II has excellent reliability and validity and is widely used in clinical research. The Italian version of the BDI-II indicated good internal consistency (Cronbach’s alpha = 0.80) and a 30-day retest reliability of 0.76, as well as good convergent, divergent, and criterion validity (Ghisi et al., 2006; Sica and Ghisi, 2007). In the present study, the alpha coefficient for the BDI-II was 0.90 for students, 0.91 for mothers and 0.90 for fathers.

2.3. Statistical analyses

For the entire sample there were about 2% of missing answers to each item of the questionnaires and this figure was the same when offspring, mothers and fathers were examined separately. Maximum likelihood estimates of the missing data (EM algorithm) were then computed and utilized for the subsequent analyses. According to Graham (2009), researchers should use missing data procedures since they are good procedures that are based on strong statistical traditions.

Analyses of variance (ANOVA) and covariance (ANCOVA) were performed to compare the two NJREs scores across the groups (ARO and CO). To evaluate the power of NJREs in discriminating between groups, the magnitude of differences between ARO and CO was computed through eta squared values (\( \eta^2 \)). According to Cohen (1988), \( \eta^2 = 0.01 \) corresponds to a small effect size, \( \eta^2 = 0.06 \) to a medium effect and \( \eta^2 = 0.14 \) to a large effect size.

Lastly, Pearson correlations were used to examine the association between NJREs and OC symptoms within the ARO group. Following Cohen’s (1988) classification, large correlations were defined as 0.50 and above, medium correlations between 0.30 and 0.49, and small correlations between 0.10 and 0.29.

All statistical analyses were conducted using IBM SPSS statistics, version 22.

3. Results

3.1. Preliminary analyses

Eight-seven percent of the ARO group and 74% of the COs reported having experienced at least one of the 10 NJREs described in the NJRE-Q-R. In Table 3 the percentage of individuals who reported having experienced the NJREs listed in the NJRE-Q-R are displayed. For ARO individuals the most common were, “When talking to people, I have had the sensation that my words did not sound just right” (43%), “I have had the sensation while writing something down that the words did not look just how I wanted them to look” (37%). For CO group, the most common were “When talking to people, I have had the sensation that my words did not sound just right” (49%), “I have had the sensation while writing something down that the words did not look just how I wanted them to look” (35%), and “I have had the sensation after getting dressed that part of my clothes (tags, collars, pant legs, etc.) didn’t feel just right” (29%).

Chi-square analyses were computed to evaluate whether the proportions of individuals reporting each NJRE differed between groups. The ARO were more likely to endorse five out ten items than controls, having had that particular experience within the last month.

3.2. Comparison between groups on the NJRE-Q-R indices

Two ANOVAs were performed using the NJRE-Q-R-severity and the NJRE-Q-R-total scores as the dependent variables and the offspring groups as the independent variable (Table 4). For both NJREs scores the ARO group obtained significant higher scores than CO individuals. Results suggested that the magnitude of the differences was generally small to medium.

Since a few previous studies have speculated that NJREs might be more closely associated with some OCD symptoms (e.g., symmetry) than others (Taylor et al., 2014), the correlations between NJREs and the OCI subscales for ARO group were computed. NJREs were significantly associated with all OC symptoms domains measured by the OCI (Washing = 0.35; Checking = 0.42; Doubting = 0.47; Ordering = 0.51; Obsessing = 0.40; Mental Neutralizing = 0.34; Hoarding = 0.33). Such figures are of medium size according Cohen’s classification (1988).

Lastly, since the ARO group reported more symptoms of...
depression and anxiety than COs, we also performed two separate ANCOVAs with the BAI and BDI-II scores as the covariate. This analysis assessed sample effects on NJRE-Q-R severity, and NJRE-Q-R-total, controlling for anxiety and depression. Results showed that one of the NJRE-Q-R indices (total score) remained significantly different between the two groups; in this case the magnitude of differences was small.

4. Discussion

OCD is yet to be fully understood, especially in its etiologic features; the high heterogeneity of this disorder represents a challenge for both researchers and clinicians (e.g., Leckman et al., 2010; Summerfeldt et al., 2014). The boundary of OC manifestations is a controversial issue (e.g., Abramowitz and Jacoby, 2015; Lochner and Stein, 2006; Phillips et al., 2010); moreover, the treatment of OCD produces less than optimal results in a significant number of cases (Sica et al., 2010). We are in the need therefore of a better understanding the etiological factors involved in such condition and to determine the association between specific characteristics of OCD and treatment response. From this point of view, NJREs could be considered an underlying vulnerability factor that may cut across overt symptoms in OCD, across its clinical and nonclinical expressions, and perhaps across its boundaries with other disorders (see Abramowitz and Jacoby, 2014).

In the current study, we examined NJREs as a putative endophenotype for OCD, by comparing the offspring of OC symptomatic individuals with the offspring of individuals without OC symptoms. Results confirmed our initial hypothesis: offspring of OC symptomatic individuals reported higher scores on both NJREs frequency and severity. Such differences remained significant for frequency and neared significance for severity when general distress (i.e., anxiety and depression) was controlled. This last finding is important, since controlling for possible covariates in statistical analyses can help to define better candidate endophenotypes that are known to be affected by environmental factors (e.g., Bearden and Freimer, 2006).

Interestingly, in the at-risk individuals NJREs were robustly associated to all the OC domains measured by the OCI: this represents a further demonstration that this construct may underlie most manifestations of OCD.

Overall, the construct of NJREs appears to satisfy at least some of the qualifying features of an endophenotype according Gottesman and Gould (2003): specificity, state independence, and familial association. That is, NJREs are more strongly associated with OCD than with other conditions (specificity); are found among individuals without the full-blown disorder and in nonclinical samples (state independence); and, as evident in the current study, occurred with more frequency and severity among offspring of people reporting OC symptoms compared to those not reporting OC symptoms (familial associations).

In the previous family study on NJREs (Sica et al., 2013), parents’ NJREs correlated with offspring’s NJREs; the magnitude of these correlations was in the small-medium range, a noteworthy result given that our sample was screened for the absence of any psychopathology. This result suggests some form of heritability (a criterion for endophenotype) and/or the influence of environmental factors.

According to Hasler et al. (2004), a putative endophenotype should be selected also with respect to 1) feasibility and reliability of its measurement, and 2) possible relevance for the disorder/subject under study (Hasler et al., 2004). These two additional criteria appear consistent with the available data on NJREs, a measure that has been used for more than ten years in different countries. Empirical results as well as conceptual descriptions of NJREs well fit the clinical account of OCD patients describing their tormenting sense of uncertainty (Sica et al., 2015).

Where do NJREs come from? NJREs seem to be a perceptual phenomenon that is distinct from perfectionistic dysfunctional beliefs and cognitive schema (Coles et al., 2003). In agreement with some scholars, we deem NJREs as the manifestation of a deficit in the ability to use emotional experience and sensory feedback to guide behavior – an emotional indicator that a state has been satisfactorily achieved (e.g., Ecker and Gönner, 2008; Szechtman and Woody, 2004; Summerfeldt et al., 1999). For example, Russo et al. (2014), in a study of transcranial magnetic stimulation in OCD patients, concluded that OCD might be considered the result of a dysfunction of sensory-motor integration. Riesel et al., (2015) proposed that overactive performance monitoring (that is, increased error-related brain activity) might be a candidate endophenotype for OCD. Interestingly, an overactive performance-monitoring system that operates independently of actual outcomes may correspond to the sensation of incompleteness reported by the majority of OCD patients (see also Rotge et al., 2012). Also, Subirà et al. (2015) found a structural correlate of “sensory phenomena” (a construct almost identical to NJREs) in patients with OCD, involving grey matter volume increases within the sensorimotor cortex. They speculated that this peculiarity could precede the onset of the disorder, thus conferring a specific vulnerability to increased sensorimotor activity.

Lastly, the concept of NJREs also provides a point of contact with the National Institute of Mental Health’s Research Domain Criteria (RDoC) initiative (Cuthbert and Kozak, 2013; Insel et al., 2010). The RDoC research initiative calls for a shift in research focus from traditional categorical diagnoses, which represent complex, multidetermined clinical phenotypes, toward more basic symptom dimensions and systems-oriented (e.g., cognitive, emotional arousal, regulatory) constructs for understanding them. NJREs may be a dispositional liability, a unit of analysis (in the realm of self-report behavior) of the construct of “Sustained Threat” within the Negativé Valve Systems domain of the RDoC framework. Sensory dysfunctions or overactive performance-monitoring may well represent other units of analysis of the same construct (e.g., brain circuits and/or physiology). In fact, the RDoC explicitly suggest considering psychopathology phenomena across multiple levels of analysis (i.e., from genetic-cellular through neural circuitry and physiology to observable behavior).

Among the strengths of the current study is the use of well-validated instruments, a relatively large sample of parents and groups balanced by gender. The inclusion of current psychological disorders and distress requiring intervention aids in the generalizability of the results. There are also a number of limitations. Our sample was relatively restricted in educational level, ethnic background, and socio-economic status. Also, some students returned questionnaires for only one parent, typically the mother. This was expected as in the “traditional” Italian family, the mother raises offspring and fathers may be less involved in family life. In addition, in case of separation or divorce, the offspring usually remain with the mother, making more difficult the contact with fathers. Nonetheless, the response rate of fathers was relatively high. A further limitation is the reliance on self-report measures for practical reasons; future studies may consider other evaluation methods (e.g., diagnostic interview).

Importantly, even though endophenotypes are not etiological factors per se (rather, they provide a means for identifying the ‘downstream’ traits of clinical phenotypes, as well as the ‘upstream’ consequence of genes), it is crucial to demonstrate that they are not an epiphenomenon of the illness. For instance, in the current study we cannot exclude that the differences observed between the offspring in NJREs may be due, in part, to the
possibility that a number of the offspring had already developed OCD and the NJREs developed as a result. On the other side, the choice of a nonclinical sample should limit such eventuality. Moreover, no participant in the current study reported to suffer from OCD. In any case, previous experimental, longitudinal, and cross-sectional studies have provided a relatively strong basis to propose NJREs as a putative endophenotype for OCD.

No doubt, that other studies are needed to establish the construct of NJREs as a possible endophenotype of OCD. For example, cross-sectional studies have provided a relatively strong basis to Moreover, no participant in the current study reported to suffer OCD and the NJREs developed as a result. On the other side, the possibility that a number of the offspring had already developed OCD. Furthermore, examination of whether NJREs can be altered by specific interventions and lead to changes in OC symptoms is an interesting and important avenue for future research for possible early detection of individuals at risk and to develop new treatment targets and strategies.

Lastly, it is also important to consider both limitations and strengths of analogue research. Recruitment methods and the contexts in which assessment and treatment take place might differ in important ways from general clinical settings. For instance, some authors have speculated that such sampling differences also limit the utility of analogue samples in scale development (Reynolds and Steiner, 1998). More generally, there is a need for prospective studies to examine the course of OC symptoms in analogue samples, and predictors of escalation (if any) to clinically severe levels. Understanding such factors could have important implications for clarifying the continuity of OC symptoms as observed in analogue and clinical samples.

On the other hand, although studies using clinical samples often have immediate implications for understanding, assessing, and treating patients with OCD, especially in practical settings, there are a number of advantages to using analogue samples in research on OC-related psychopathology. First, depending on the setting where data are being collected, analogue samples can be more convenient to accrue than clinical samples; this efficiency is especially beneficial in the present era of tight extramural funding and in light of the fact that studies using larger samples can be more reliable than those using smaller samples. Second, given the costs of recruiting large clinical samples, analogue samples are useful for conducting preliminary studies to determine whether a given line of research is fruitful. If the results of such studies appear encouraging, replications can subsequently be attempted using clinical samples. Third, analogue samples are also advantageous in experimental research that tests hypotheses regarding the effects of putative developmental and maintenance factors on OC symptoms (e.g., Deacon and Maack, 2008; Rassin et al., 1999). Indeed, analogue samples afford more precise experimental control (and internal validity) as compared to clinical samples.

Lastly, one might say that is not clear which is the exact nature of the samples selected for the current study, since both are drawn from a nonclinical population. As a matter of fact, between-group designs commonly involve the comparison of groups of participants scoring high or low on some OC-related measure. This is analogous to studies comparing a group of people with OCD to a control group. Both are quasi-experimental designs rather than true experiments, because group allocation (e.g., diagnosis of OCD vs. control) cannot be randomly assigned. Therefore, in our opinion, it is important to demonstrate that the resulting groups of participants have the features of interest. In the current study, all our analyses showed that the two groups of parents and the two groups of offspring were clearly different on the variables of interest. In addition, nor parents nor offspring reported in the dedicated section to suffer a full-blown OCD. Also, OCD typically emerges in adolescence, so it is not probable that any of parents can develop OCD in the future.

Of course, we cannot exclude the presence of differences in OC features inside each group, but this is absolutely true also for clinical samples, whose heterogeneity is well known to be main obstacle to elucidate the underlying psychological as well pathophysiological processes of this disorder.

In conclusion, if endophenotypes are vulnerability factors for developing psychiatric disorders, they could be used as a basis for diagnostic classification, in the same way that vulnerability factors can be important diagnostic factors in general medicine (e.g., hypertension) even when the person is asymptomatic. Such a classification system based on etiology and pathophysiology can facilitate the identification of etiological factors and possibly the development of better preventive strategies and treatments for this disabling disorder (for instance, by systematically defining relatively homogenous OCD subtypes).

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