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## Original articles

# G protein gene variants in schizophrenia

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## Abstract

**Background:** Various studies demonstrating enhanced vulnerability to apoptosis may contribute to the pathobiology of schizophrenia. **Objective:** Thus, G proteins may provide an intriguing link between the signal transduction, and apoptotic hypotheses of schizophrenia. In the light of these findings, we investigated whether G protein gene polymorphisms (GNAS1-T393C and GNB3-C825T) accounted for an increased risk of schizophrenia. **Methods:** The present analyses were based on 100 subjects diagnosed with schizophrenia, and on 100 unrelated healthy controls. The genotyping of GNAS1-T393C, and GNB3-C825T gene polymorphisms were performed using the polymerase chain reaction- restriction fragment length polymorphism (PCR-RFLP). **Results:** We demonstrated the positive association of GNB3-C825T gene variants with schizophrenia risk (p: 0.023). In our study, more prevalent CC genotype frequencies were detected in GNB3 in patients compared with the frequencies in the controls. The individuals with GNB3-C825T CC genotype had 2 fold increased risk for schizophrenia (p: 0.011, $\chi^2$: 6.39, OR:2.14, 95% CI: 1.18-3.90). **Discussion:** Our study results suggested that GNB3-C825T polymorphism might be associated with schizophrenia.

*Gokce Yavuz HH et al. / Arch Clin Psychiatry. 2020;47(2):31-4*

**Keywords:** G protein, GNB3, GNAS1, schizophrenia, polymorphisms.

## Introduction

Schizophrenia is a common psychiatric illness that is characterized by psychotic phenomena such as delusions, hallucinations, and thought disorder, along with impairment in emotions and social function[1]. The lifetime morbidity risk is approximately 1% in schizophrenia[2]. Schizophrenia is a complex biological disorder whose pathogenesis is likely to be governed by a number of different risk factors. It is well-established that the heritability of schizophrenia was over 80%[1,2]. Family, twin, and adoption studies over the past century strongly indicated that predisposition is largely genetically determined. Several environmental risk factors such as perinatal viral infections, obstetric trauma, and maternal malnutrition have been identified as risk factors for schizophrenia[3]. The prevalence of schizophrenia is similar among men, and women[4]. However, the course of schizophrenia is often more severe in men with earlier onset of the disease[5]. The diagnosis relies on clinical observation and self-reports because there is no available diagnostic laboratory tests for schizophrenia.

Heterotrimeric guanine nucleotide binding proteins (G proteins) play key roles in the conversion of external receptor signals into intracellular response. G proteins are composed of a, b, and g subunits, and each subunit is coded by various different genes[6]. Many studies showed that the dysregulation of neurotransmitters signal transduction pathways[7], and enhanced vulnerability to apoptosis may both contribute to the pathobiology of the schizophrenia[8]. Thus, G proteins may provide an intriguing link between the signal transduction, and apoptotic hypotheses of schizophrenia. In an animal study, a G protein signaling gene knockout or mutant mice has been reported to develop abnormal involuntary movements[9]. In addition, G-protein measurements were suggested to be a biochemical marker for schizophrenia[10].

The synonymous T393C polymorphism in the GNAS1 gene was reported to be possibly significantly affect Gas mRNA expression, with TT genotypes displaying highest Gas expression and greater apoptotic vulnerability in several different cell types[11]. The GNB3 gene codes the b-subunit 3 of G-proteins, and (*GNB3*) C825T polymorphism (T-allele) results in increased intracellular signal transduction in G-protein coupled receptors[12]. The T-allele results in an in-frame deletion of 41 amino acids, and has been associated with major depression[13]. Moreover, the C/T or T/T genotype has been reported to be associated with seasonal affective disorder[14].

The aim of the present study was to investigate the possible association between GNB3-C825T and GNAS1-T393C polymorphisms with the presence of schizophrenia.

## Material and methods

### Subject selection

The study sample comprised of 100 patients with schizophrenia, and 100 healthy controls with no personal or family history of psychiatric disorders. All patients had psychotic or active symptoms at the time of the study. Most patients were receiving antipsychotic medication at the time of scan. Each patient was given a diagnostic assessment based on the clinical interviews using a Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[15]. The mean age was 41.25 ± 10.98 years for

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schizophrenia patients, and 40.54 ± 12.83 years for controls. No significant difference was detected between the study, and control groups in terms of mean age and sex distribution.

To minimize the effect of ethnic differences in gene frequencies, the study participants were selected among the Turkish population living in the western region of Turkey. The study was approved by the Medical Ethics Committee of Istanbul Medical Faculty, and all participants (i.e. controls, patients or unaffected family members (on behalf of some patients) gave written informed consents.

### Measurements, protocol and procedure

All subjects were examined in accordance with a standardized interview, and examination. Assessment was done using a form which required patient information regarding demographic and personal details of the patients and informants, symptoms of the patients, history of present illness, details of medical or surgical interventions, past history, family history, personal history, premorbid personality, details of physical examination, mental status examination, and the diagnostic formulation. The diagnosis was made using a Structured Clinical Interview for DSM-IV (SCID-I)[16]. The patients were then screened on various rating scales like Brief Psychiatric Rating Scale[17,18] for patients with schizophrenia, Scale for the Assessment of Positive Symptoms (SAPS)[19] and Scale for the Assessment of Negative Symptoms (SANS)[19] for patients with schizophrenia. The subtypes of schizophrenia patients were classified in accordance with the DSM-IV. Relatives and controls with schizophrenia were excluded from the study using the Structured Clinical Interview for DSM-IV[16]. Healthy and unrelated volunteers with no psychiatric disorders were selected as the control group. Control group and first-degree relatives of schizophrenia patients were screened using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version[20,21].

### Inclusion and exclusion criteria

The patients diagnosed with schizophrenia in accordance with the DSM-IV were included in the study. Patients diagnosed with psyhiatric disorders other than schizophrenia were excluded from the study. Patients with a history of neurological or medical disorder that might affect neuropsychological function (seizures, head trauma, stroke, brain tumor, meningitis, etc.) or with a recent history of alcohol abuse or psychoactive drugs were also excluded from the study. In addition, control subjects control subjects with the diagnosis of any physical or psychiatric health problems were excluded from the study. Control subjects had no history of physical health problem.

### Polymorphism analysis

DNA was extracted from white blood cells using the method of Miller *et al.*[22]. GNB3-C825T, and GNAS1-T393C genotypes were determined using the PCR-RFLP method. We used for the GNB3-C825T polymorphism, sense primer 5'- TGACCCACTTGCCACCCGTGC -3' and antisense primer 5'- GCAGCAGCCAGGGCTGGC -3'; for the GNAS1-T393C polymorphism, sense primer 5'- CTCCTAACTGACATGGTGCAA-3'and antisense primer 5'- TAAGGCCACACAAGTCGGGGT -3' (Invitrogen, Carlsbad, CA, USA). The PCR mixture contained 100 ng DNA template, 0.5 µM of each primer, 1.5 mM $MgCl_2$, 2 mM dNTPs (Invitrogen) and 1 U Taq DNA polymerase (Intron Bio, Sungnam, Kyungki-Do, Korea). After denaturing the DNA for 5 min at 94 °C, the reaction mixture was subjected to 35 cycles of denaturing for 1 min at 94 °C, 45 s annealing at 60 °C and 1 min extension at 72°C for the GNB3-C825T. The 268-bp PCR product was digested with BseDI restriction endonuclease and the digested products were separated by electrophoresis on a 3% agarose gel (UltraPure Agarose; Invitrogen, Carlsbad, CA) and visualized using ethidium bromide. The C/C genotype contains a unique restriction site that results in 152- and 116-bp products, and the T/T genotype is not cut (268-bp), allowing the GNB3-C825T genotype to be determined. For the GNAS1-T393C polymorphism, the reaction mixture was subjected to 35 cycles of denaturing for 30 s at 94 °C, 45 s annealing at 58 °C and 1 min extension at 72 °C. The PCR product (345 bp) was digested with BseGI and the digested products were separated and identified as above. Allele T contained no BseGI site whereas C contained the BseGI site, giving rise to 259- and 86-bp products. Each gel was read by two observers unaware of the subject's status. The reactions were repeated for avoiding any possible conflicts.

### Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software package (revision 11.5 SPSS Inc., Chicago, IL, U.S.A.). Data were expressed as mean ± SD. Differences in the distribution of genotypes or alleles of DNA repair gene between cases and controls were tested using the Chi-square statistic. Linkage disequilibrium among DNA repair gene polymorphisms was assessed using $D'$ and $r^2$ values obtained through the haploview program (http://www.broad.mit.edu/mpg/haploview/documentation.php). P value < 0.05 was considered statistically significant.

## Results

Control subjects, and patients were adjusted for age, and sex. Table 1 shows the characteristics of the patients and control groups. The number of smokers was higher in the patient group compared with the numbers in the control group (P: 0.003), and the number of alcohol consumers was higher among the control group compared with number in the patient group (P < 0.001).

There were statistically significant differences in GNB3-C825T genotypes between the controls, and patients ($\chi^2$: 7.52; p: 0.023). However, there were no significant differences for GNB3-C825T allele frequencies between the schizophrenia patients, and controls (p > 0.05) (Table 2).

Frequencies of GNB3-C825T T+ genotype were higher among the controls compared with the frequencies in patients which demonstrating a protective role of T+ genotype against schizophrenia (p: 0.011, $\chi^2$: 6.39, OR: 0.466, 95% CI: 0.25-0.84).

Frequencies of GNB3-C825T CC genotype in patients were higher compared with the frequencies in the controls. The individuals having GNB3-C825T CC genotype had 2 fold increased risk for schizophrenia (p: 0.011, $\chi^2$: 6.39, OR: 2.14, 95% CI: 1.18-3.90).

Individuals carrying GNB3-C825T TC genotype had decreased risk for schizophrenia (p: 0.011, $\chi^2$: 6.48, OR: 0.483, 95% CI: 0.27-0.84). Frequencies of TC genotype in controls were higher than the frequencies in patients.

However, we found no significant differences for GNAS1-T393C genotype and allele frequencies between schizophrenia patients, and controls (p > 0.05) (Table 2).

While GNB3-C825T CC genotype was associated with schizophrenia in univariate analysis, GNB3-C825T CC genotype was also associated with this disease in multivariate logistic regression analysis by adjusting sex, and age (Table 3).

**Table 1.** Characteristics of the schizophrenia patients and control groups

| | Controls | Patients | P | $X^2$ | OR | 95% CI |
|---|---|---|---|---|---|---|
| Age | 40.54 ± 12.83 | 41.25 ± 10.98 | 0.675 | – | – | – |
| Sex (male/female) | 49/51 | 48/52 | 0.887 | 0.02 | 1.04 | 0.59-1.82 |
| Smoking (%, yes/no) | 44.0/56.0 | 65.0/35.0 | 0.003 | 8.89 | 2.36 | 1.33-4.17 |
| Alcohol (%, yes/no) | 18.0/82.0 | 1.0/99.0 | 0.000 | 16.8 | 0.046 | 0.006-0.35 |

**Table 2.** The distribution of GNAS1-T393C and GNB3-C825T genotype frequencies in the patient and control groups

| GNAS1 -T393C Genotypes | Controls n: 100 | Patients n: 100 |
|---|---|---|
| TT | 40 (40%) | 38 (38%) |
| CC | 13 (13%) | 12 (12%) |
| TC | 47 (47%) | 50 (50%) |
| ALLELES | | |
| T | 127 (63.5%) | 126 (63%) |
| C | 73 (36.5%) | 74 (37%) |
| GNB3- C825T GENOTYPES | | |
| TT | 16 (16%) | 17 (17%) |
| CC | 26 (26%) | 43 (43%) |
| TC | 58 (58%) | 40 (40%) |
| ALLELES | | |
| T | 90 (45%) | 74 (37%) |
| C | 110 (55%) | 126 (63%) |

**Table 3.** The results of multivariate logistic regression analysis

| Variables in the Equation | B | S.E. | Wald | Sig. | Exp (B) | 95% CI for EXP(B) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Age | 0.007 | 0.012 | 0.322 | 0.571 | 1.007 | 0.983 | 1.031 |
| Sex | -0.056 | 0.290 | 0.037 | 0.847 | 0.946 | 0.535 | 1.671 |
| GNB3-C825T CC | -0.773 | 0.305 | 6.405 | 0.011 | 0.462 | 0.254 | 0.840 |

Variable(s) entered on step 1: Age, sex, GNB3-C825T CC genotype.

## Discussion

Imbalances of regulatory apoptotic proteins have associations with various diseases in addition to their association with cancer. Some researchers have reported a link between apoptosis and schizophrenia, which was based on the changes of some apoptotic protein levels in different brain areas of schizophrenic patients[23]. Due to this regulation, G-protein and its subunits become a question for schizophrenia by its transductional mechanisms and its critical role for the regulation of programmed cell death[24]. These findings logically might point out a link between G-proteins, and schizophrenia. Therefore, we hypothesized that the genes encoding for G-protein subunits might have a relation and be nominated as a candidate for schizophrenia.

In our research, our findings have showed the positive association of GNB3 gene variants as a risk factor for schizophrenia. In addition, the frequency of CC genotype in GNB3 was more prevalent in patients in contrast to controls. Moreover, we found that the frequencies of T+ and TC genotype of GNB3 gene were common in controls than the frequencies in patients. Researchers showed in a previous study that GNB3-C825T polymorphism was associated with treatment response in various antipsychotic drugs that support the aim of our study about the relation G protein and schizophrenia especially for the people receiving pharmacological treatment[25]. TT genotype or T allele carriers of C825T polymorphism were found to be associated with treatment response to serotonin selective reuptake inhibitors (SSRI) in the treatment of depression[25]. Supporting these data, we have found that T+ and TC genotype might have a protective role in schizophrenia with our patient scale. This results need to be improved and supported with further analyses by studying with larger scale.

Researchers reported that increased efficacy of GNAS1 signaling is observed in striatum and mononuclear leukocytes in schizophrenia patients[26]. In addition, the T393C polymorphism in GNAS1 was shown to be genetically linked to deficit schizophrenia in an Italian population sample, such that the 393TT genotype was observed significantly more in these patients (37.1%) than the controls (22.8%)[27]. Supporting this, the 393TT genotype appears to increase GNAS mRNA expression, as measured in bladder tumors and adipose tissue of patients suffering from transitional cell carcinoma[28]. On the other hand, we found no significant differences for GNAS1-T393C genotype and allele frequencies between schizophrenia patients, and controls[14]. We suggested that G-protein subunit Gαs (also known as GNAS1) may be one of the molecules for contributing to the pathophysiology of schizophrenia.

In conclusion, our findings suggested that GNB3-C825T polymorphism might be associated with schizophrenia and with its underlying mechanism. To understand the main impact and capacity for schizophrenia, further studies with larger sample groups are required to clarify the role of G protein genes for schizophrenia.

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## Disclosure

The authors report no conflicts of interest.

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# Parent-teacher report reliability on the fourth edition of the Swanson, Nolan and Pelham scale in a Brazilian clinical sample of children and adolescents with attention-deficit/hyperactivity disorder

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## Abstract

**Background:** Parents and teachers can be valuable sources of information for characterizing children's ADHD-related impairments in different environments. However, evidence indicated that those categories of informants often provide conflicting responses in formal assessment scales, which may challenge diagnostic decisions regarding the condition. **Objective:** We aimed to investigate reliability rates between parents and teachers of children and adolescents with and without ADHD using SNAP IV. **Methods:** 199 children and adolescents aged 6 to 17 years were evaluated for ADHD symptoms using parent-rated and teacher-rated SNAP IV scales. Intraclass correlation coefficients were analyzed for ADHD domains (inattention and hyperactivity/impulsivity), as well as for defiant-oppositional behavior. **Results:** Reports from parents and teachers showed low reliability for all ADHD domains. Parents' scores on the SNAP IV were higher than those of teachers. Parents and teachers provided highly discrepant responses concerning to the presence and severity of ADHD in children and adolescents, which might result from intrinsic aspects related to their daily functioning in different settings. **Discussion:** Clinicians should consider those trends in parental and teachers' responses when interpreting results from informant-based instruments for detecting ADHD.

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**Keywords:** Reproducibility of results, attention-deficit disorder with hyperactivity, Psychiatric Status Rating Scales, attention-deficit and disruptive behavior disorders.

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a life-long and potentially disabling neurodevelopmental disorder characterized by inattention and/or hyperactivity-impulsivity[1]. During the last decades, along with its establishment as a clinically relevant condition in the scientific and medical community, massive public interest for the disorder propelled large-scale pursuit for screening and parental guidance by millions of concerned individuals and their families[2]. Overall prevalence rates for ADHD have been estimated to be as high as 7% of children and adolescents and at least half of those individuals may present persistent symptoms into adulthood[3,4]. However, as awareness of ADHD increased, emerging allegations of overdiagnosis and overmedication, notably relative to school children, have been shifting public opinion towards skepticism for the importance of this clinical entity[5]. Controversies centered around ADHD assessment are abundant, especially regarding the validity of the diagnostic approaches[6,7].

Recommended practices for detecting ADHD, according to panel of experts, include a systematic investigation of the subjects' history of symptoms, including age of onset, psychiatric comorbidities and evidence of impairments in at least two areas (school, work, home and interpersonal contacts)[8]. Gathering information from multiple respondents, such as family members, teachers or coworkers has been recommended to allow identification of functional impairments in different environments[1,9,10]. In special, considering that self-reports of children about their own behavior can be inaccurate and that adolescents tend to underestimate their symptoms[10,11], collecting collateral impressions of the presence of ADHD clinical features in a variety of scenarios may be crucial for the assessment of this population. Among validated informant-based instruments for this purpose, the Swanson, Nolan and Pelham rating scale – 4th version (SNAP IV) is possibly the most widely used one in research settings[1,12,13]. It comprises twenty-six questions, corresponding to the list of ADHD symptoms, as depicted in the DSM-5[1]. Those include nine items aiming at detecting inattention, six assessing hyperactivity, and three measuring impulsive behavior.

Nonetheless, gaps in the knowledge regarding the best methods to assess ADHD are far from being filled. Several studies have suggested that reports from parents and teachers are often conflicting or weakly correlated, mainly regarding the presence and magnitude of clinical features. This shortcoming might challenge the interpretation of the results and raise serious doubts about the instruments' clinical utility,

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including for distinguishing the ADHD presentations (predominately inattentive type, predominately hyperactivity/impulsive presentation, and combined type)[14,15]. Detailed analyses of the responses suggested that teachers tended to be more benevolent in scoring symptom severity and that they might consistently report lower frequency of hyperactivity than parents[14,15]. Possible sources of divergences across informants may result from different cultural and environmental aspects, such as discrepancies between less structured home settings compared to typical schools and to varying amount of time spent with the children[15]. Moreover, it is known that raising a child with ADHD might demand more time and energy on caring that with non-ADHD children, which can lead to parental burnout[16].

Several strategies have been proposed in the literature to overcome those inconsistencies and to clarify whether informant-based tools are valid approaches to assess the disorder. Among them, mathematically-derived indices obtained from comparing responses from different sources for the same instrument have been largely used[17]. Inter-rater agreement, for example, measures the matching rates of the absolute scores across evaluators for one specific test[17]. However, as previously mentioned, results from parents and teachers in standardized scales are generally highly discordant, which corresponds to low inter-rater agreement. Alternatively, inter-rater reliability could be employed to investigate consistency of classification patterns across different raters for one particular instrument, regardless of the absolute scores[17]. Noteworthy, inter-rater agreement and reliability are often uncorrelated, which means that high scores for one measure do not necessarily predict changes in the other index[17].

In the present study, we aimed to investigate the reliability rate of responses of parents and teachers of children and adolescents aged 6 to 17 years in the SNAP IV. We hypothesized that despite low agreement, reliability might allow further information on the validity of the instrument as an assessment tool.

## Methods

### Participants

Participants were recruited at the *Centro de Neuropsicologia Aplicada*, D'Or Institute of Research and Education (IDOR) in Rio de Janeiro, Brazil. Most subjects were volunteers referred to the service by health professionals (physicians, psychologists and speech therapists), whereas others sought our institute due to recommendation from school personnel (9.5%) or upon spontaneous demand (20.3%).

Participants were included if the following criteria were fulfilled: (i) age between 6 to 18 years, corresponding to school-aged children and adolescents; (ii) regularly attending school, as informed by parents and teachers; (iii) living with one parent or both and (iv) all procedures were adequately completed. Exclusionary criteria were: (i) epilepsy, (ii) any psychotic disorder, (iii) current illicit drug use as reported by parents or self reported.

### Procedures

Patients and parents underwent an initial medical interview, followed by neuropsychological tests including WISC-IV[18] and all subtests (intelligence, attention, working memory, vocabulary, reasoning, abstraction, visual perception, constructional abilities, dexterity) and CPT – Continuous Performance Test (attention). The Swanson, Nolan, and Pelham, version IV (SNAP-IV) scale was completed by one of the parents and one school teacher[12]. This instrument contains 26 items which evaluate ADHD domains and comorbid oppositional-defiant behavior (ODD), distributed as follows: Inattention (9 items), Hyperactivity/impulsivity (9 items) and Opposition (8 items). Existence of more than one respondent for the scale (for example, when the two parents or more than one teacher completed it separately) was resolved by randomly withdrawing one of the repeated versions. All individuals from the sample had collateral reports from both parents and teachers.

### Diagnoses

Diagnoses of ADHD and other comorbid or concurrent mental disorders were based on results from the whole assessment protocol and were made according to the DSM-5 criteria by trained psychiatrists[1]. Upon this gold standard classification, sample was divided into groups with and without ADHD.

### Ethics

All parents provided a written informed consent prior to enrollment in this study. The research has been approved by the Ethics Committee of *Instituto D'Or de Pesquisa e Ensino* (IDOR), Rio de Janeiro, RJ, Brazil.

### Data analyses

For the present study, reliability was defined as a measure of consistency among evaluators in the ordering or relative position of performance evaluations irrespective of the absolute value of each evaluator's rating[19]. In other words, it reflects the relative pattern similarity between two or more sets of ratings[19]. To evaluate the reliability between parents' and teachers' reports on the symptoms of inattention, hyperactivity/impulsivity and challenging/oppositional behavior, intraclass correlation coefficients (ICC) were calculated through one-way randomized analysis and selected measures mean of intraclass correlation. Values lower than 0.5, between 0.5 and 0.75, between 0.75 and 0.9 and greater than 0.90 were considered as representing poor, moderate, good and excellent reliabilities, respectively[20]. The Cronbach's α was used to investigate the internal consistency of the ADHD domains in the scale across responders[21]. To examine which of the respondents observed higher and lower levels of symptoms, mean scores given by categories of observers were compared, using t-test analyzes of repeated samples. Bootstrapping (1,000 re-sampling, with 99% confidence interval) was implemented, aiming at correcting for possible deviations from the normal distribution. Statistical analysis was performed using SPSS for Windows version 19.

## Results

### Classification and sociodemographic characteristics of the sample

From an initial sample of 225 children and adolescents, 199 attended the eligibility criteria and were included in the study. Age ranged from 6 to 17 years (M = 10.60; SD = 3.23) and schooling varied between 0 years and 11 years (M = 4.17; SD = 3.12). Diagnoses of the sample were as follows: ADHD (n = 77); Autism Spectrum Disorders (n = 15); Communication Disorders (n = 10); Learning Disorders (n = 39); Conduct Disorder and Oppositional Defiant Disorder – ODD (n = 3); Intellectual disability (n = 20) and other DSM-5 diagnoses (n = 9). 15 individuals presented no psychiatric disorder and 11 showed subthreshold attentional deficits, which did not meet the DSM-5 diagnostic criteria for ADHD or for any other conditions. Responses for ODD items were available for 189 participants, 73 of which had ADHD. Of note, individuals could score points in the ODD subscale without reaching diagnostic threshold. Subsequently, the sample was divided into two groups: (i) ADHD (n = 77) with ages ranging from 6 to 16 years (M = 10.06; SD = 3.03) and schooling between 0 and 10 years (M = 3.73; SD = 2.93) and (ii) non-ADHD (n = 122) with ages ranging from 6 to 17 years (M = 10.91; SD = 3.31) and schooling between 0 and 11 years (M = 4.42; SD = 3.21). Sociodemographic variables were not significantly different between the two groups.

### Differences between parents and teachers' responses

Parents' reports indicated higher mean rates for symptoms of inattention and hyperactivity than teachers in both ADHD

($p < 0.001$) and non-ADHD samples ($p < 0.001$). On the other hand, no group difference for the severity of ODD symptoms was detected across informants. Table 1 depicts those results.

### Assessment of internal consistency and inter-rater reliability

For most SNAP IV items, a good internal consistency was observed for both ADHD and non-ADHD groups. On the other hand, a Cronbach's α of 0.71 for parents' reports of Inattention in ADHD group indicated a lower, but acceptable, internal consistency. Moreover, for all SNAP IV subscales, inter-rater reliability was fair, as indicated by low ICC values. Those results are summarized on Table 2.

## Discussion

In line with previous reports[22,23], the current study showed that parent-rated and teacher-rated SNAP IV adequately measured ADHD domains, as well as ODD symptoms, as indicated by a satisfactory internal consistency for all the subscales. In contrast, inter-rater reliability was low for all the instrument's subscales, which demonstrated that perception of symptoms was largely divergent across parents and teachers. Precisely, parents rated symptoms of inattention and hyperactivity as significantly more frequent and severe compared to teachers in the instrument, whereas such discrepancy was not verified for the ODD items.

Evidence of lower perception of children's cognitive, emotional and behavioral problems among teachers in comparison to parents had been previously described in the literature[24,25]. Those heterogeneities could be associated with intrinsic differences in their roles with respect to the children. It would be plausible to admit that parents and teachers participate in the children's lives and routines in a complementary, but far from coincident way. Students spend predetermined limited time at schools and teachers must follow structured educational programs, which contrasts with a less formally regulated home environment[15]. Hence, it could be predicted that divergent expectations regarding the children's behavior and particular strategies to deal with potential problems in each setting would be identified[26]. Convergingly, studies have suggested that rating agreement was greater when informants had equivalent relationships with the child. For instance, scores were more correlated among parents than across parents and teachers, suggesting that the nature of the liaison and the setting may influence the awareness of the symptoms[27].

Other factors that might contribute for the disparity between responses ought to be discussed. Pervasive child difficulties and behavioral problems related to ADHD may result in considerable parental distress. Reports of feelings of irritation, isolation and exhaustion are common among those individuals, as well as experiencing marital conflicts, career setbacks and neglecting other children due to recurrent demands from the affected child[28]. In contrast, chronic occupational stress caused by students' misbehavior or low motivation tend to elicit a cynical attitude towards particular students or students in general on teachers[29]. Those results imply that dealing with ADHD children might evoke paradoxical effects on parents and teachers: whereas the former may respond with frustration and a trend for excessive complaining, the other group may react with less distress. Finally, parents often acknowledge that children are more attentive to activities related to leisure than to school tasks, which usually endorses their impressions of students' irresponsible attitude towards school and raises doubts about the ADHD diagnosis. Diversely, teachers' observations are restricted to a more structured classroom situation, and responses to ADHD scales were probably made simply through comparisons across peers of the same age and gender[30].

**Table 1.** Paired samples t test

| Symptoms | Respondents | All cases | | | | | ADHD | | | | | Non-ADHD | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean (SD) | N | *t* | gl | p-value | Mean (SD) | N | *t* | gl | p-value | Mean (SD) | N | *t* | gl | p-value |
| | Parents | 5,57 (2,63) | 199 | | | | 6,54 (2,07) | 77 | | | | 4,96 (2,76) | 122 | | | |
| Inattention | | | | 6,07 | 198 | 0,00 | | | 4,37 | 76 | 0,00 | | | 4,27 | 121 | 0,00 |
| | Teachers | 4,12 (2,94) | 199 | | | | 4,88 (2,79) | 77 | | | | 3,64 (2,94) | 122 | | | |
| | Parents | 3,37 (2,75) | 199 | | | | 4,28 (2,76) | 77 | | | | 2,79 (2,59) | 122 | | | |
| Hyperactivity | | | | 5,83 | 198 | 0,00 | | | 3,77 | 76 | 0,00 | | | 4,43 | 121 | 0,00 |
| | Teachers | 2,11 (2,59) | 199 | | | | 2,92 (2,71) | 77 | | | | 1,61 (2,40) | 122 | | | |
| | Parents | 1,63 (2,06) | 189* | | | | 1,65 (2,06) | 73** | | | | 1,57 (2,01) | 116*** | | | |
| | | | | 1,61 | 188 | 0,11 | | | 0,09 | 71 | 0,92 | | | 1,90 | 115 | 0,06 |
| | Teachers | 1,33 (2,18) | 189* | | | | 1,62 (2,20) | 73** | | | | 1,10 (2,11) | 116*** | | | |

N: number of participants; *t*: statistic of *t* of Student; gl: degrees of freedom.
* Specifically for the evaluation of ODD, the sample was composed of 189 participants.
** Specifically for the evaluation of ODD, the ADHD sample was composed of 73 participants.
*** Specifically for the evaluation of ODD, the non-ADHD sample was composed of 116 participants.

**Table 2.** Internal consistency and inter-rater reliability results of the reports of parents and teachers

| | | Raters | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Parents | | | | Teachers | | | | | |
| | | Non-ADHD | | ADHD | | Non-ADHD | | ADHD | | | |
| Symptoms | N of Items | N | α | N | α | N | α | N | α | ICC | 95% CI |
| Inattention | 9 | 122 | 0.83* | 77 | 0.71* | 122 | 0.86* | 77 | 0.83* | 0.27* | 0.14-0.39 |
| Hyperactivity | 9 | 122 | 0.83* | 77 | 0.82* | 122 | 0.87* | 77 | 0.84* | 0.36* | 0.23-0.47 |
| ODD | 8 | 116 | 0.80* | 73 | 0.82* | 122 | 0.90* | 77 | 0.84* | 0.26* | 0.12-0.39 |

N: number of participants; α: Cronbach's alpha; ICC: intraclass correlation; CI: confidence interval.
* Significant values $p < 0.05$.

The present study has its strengths, as it analyzed the reliability of SNAP IV across parents and teachers of ADHD subjects, for which the literature only provided agreement studies. However, some limitations should also be highlighted. Firstly, parental information may not be homogeneous between mothers and fathers. Mothers consistently report their children as having more problems of inattention and hyperactivity than fathers, therefore, the choice of the parental informant may impact considerably on the estimates of ADHD symptoms[31]. In addition, our sample has been drawn from one clinic, so data should be interpreted carefully when extrapolating to other situations. Finally, the presence of mood and stress-related disorders among collateral responders were not analyzed. Considering that informant-based scales could be highly influenced by the participant's mental health, validity of our findings could be undercut by this limitation.

## Conclusions

Diagnostic guidelines for ADHD in children, such as the DSM-5, strongly recommended that mental health practitioners collected reports from different informants, for the investigation of potential functional impairments at home and at school. For this purpose, formal validated instruments have been widely employed in both clinical and research practices. Our findings indicated that, for the SNAP IV, not only agreement, as previously demonstrated in the literature, but also reliability may be low regarding parents and teachers' impressions about the presence and severity of ADHD among children. A trend for overly perceiving the children's symptoms among parents and a much less emphatic report from teachers might be expected. With those results, we suggest that evaluators consider those traits of parental and teachers' responses when interpreting results from informant-based instruments for detecting ADHD.

## Limitations

Our findings should be interpreted in light of some limitations. Our sample was collected from a private outpatient clinic where clientele belongs to middle, upper-middle and upper classes. For this reason, findings cannot be generalized to other settings. On the other side, our sample mirrors what is seen in most private settings in the country. In addition, referred clinical samples may present different clinical profiles than non-clinical epidemiological ones.

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## Disclosure

The authors declare that there is no conflict of interests regarding the publication of this article.

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**Original article**

# Mediating role of childhood abuse for the relationship between schizotypal traits and obsessive-compulsive disorder

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## Abstract

**Background:** The mediating role of childhood trauma in the relationship between schizotypal symptoms and obsessive-compulsive disorder (OCD) was not sufficiently investigated to date. **Objectives:** In the present study, our major goal was to analyse the mediator role of childhood abuse (emotional, physical, and sexual), and neglect (emotional and physical) on the link between schizotypal symptoms and OCD, after controlling for duration of OCD, the mean number of comorbid Axis I disorders, and current anxiety. **Methods:** One hundred fifteen patients (aged 18-65 years) who had primary diagnosis of OCD and Yale-Brown Obsessive-Compulsive Scale score ≥16 were assessed using the short form of Childhood Trauma Questionnaire questionnaire (CTQ-SF), Schizotypal Personality Questionnaire (SPQ), and Beck Anxiety Inventory (BAI). **Results:** The all types of schizotypal symptoms were significantly correlated with the scores of childhood abuse and neglect, and BAI. The childhood abuse as a mediator significantly predicted the total YBOCS scores ($p = 0.02$) after when BAI scores were controlled. However, childhood neglect was not multivariately related to current OCD severity, and did not mediate the relationship between schizotypal traits and total YBOCS scores. **Discussion:** We suggested that childhood trauma mediated the schizotypal traits in relationship with current OCD severity independent from anxiety severity.

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**Keywords:** Obsessive-compulsive disorder, childhood trauma, schizotypal traits.

The obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by obsessions and/or compulsions, which affects 1%-3% of the population through the world[1]. There is growing evidence of differences in demographic and clinical characteristics of OCD patients with and without schizotypal traits, indicating a schizotypal subgroup of OCD[2-8]. Schizotypal traits emerged as a potent predictor of OCD symptoms relative to depression or general anxiety[2,4,9]. The term "schizotypal" describes psychopathological characteristics that are chronic, and stable over time and are assumed to represent an inherited general vulnerability to psychopathology that falls between healthy conditions and severe mental illness[9,10]. Cognitive-perceptual (positive), interpersonal (negative), and disorganization factors were described as prominent schizotypal traits[11]. Several studies demonstrated a link between positive symptoms of schizotypy (magical thinking, unusual perceptual experiences, ideas of reference, paranoid ideations) and OCS[6,8,12]. These patients with OCD and positive symptoms of schizotypy have been found to have more severe OCD symptoms[12-14], more prominent obsessions[14,15], a poorer prognosis[13] and an earlier age of onset of their disorder[2,16]. OCD and high-schizotypy has also been associated with specific OCD symptoms such as checking, counting, ordering/arranging, and hoarding[2,3,5]. Autogenous type of obsessions were suggested to be more highly associated with schizotypal features such as magical thinking, and anomalous perceptions[4]. However, little is known about how schizotypal traits contribute to OCD symptoms. One explanation is that the magical thinking of schizotypy may increase the risk for displaying the cognitive bias of likelihood thought-action fusion (TAF), which in turn may increase the risk for OCD[4]. Schizotypy traits may be linked to OCD symptoms through multiple pathways. In the present study, we supposed that childhood trauma may serve as a mediator on the link between schizotypal traits and OCD. In fact, childhood trauma may cause and contribute to the presence of personality disorders and emotional and behavioural deficits[17]. Some cross-sectional, prospective, and retrospective studies suggested an association between childhood trauma and increased schizotypal traits[18-20], which could not be accounted for genetic vulnerability alone[20,21]. Emotional abuse, neglect, and stressful childhood events were reported to be strong predictors of schizotypy[22,23], and may result in structural and functional brain differences that leads to schizotypal symptoms[24]. In general, traumatic experiences during childhood have been much more linked to reality distortion than to negative and disorganized traits[25-27]. A study reported that emotional abuse alone predicted the ideas of reference, excessive social anxiety, a lack of close friends, unusual perceptual experiences and eccentric behaviour or appearance[28].

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Childhood trauma is known to predispose to several mood, anxiety, and personality disorders. Childhood traumatic experiences have also been proposed to play a role in causing or precipitating OCD through some specific personality traits. In OCD patients, neuroticism, extraversion, conscientiousness and agreeableness were reported to be related to childhood abuse, while openess was not[29,30]. However, the mediating role of childhood trauma in the relationship between schizotypal symptoms in OCD patients was not sufficiently investigated to date. Given the paucity of literature in this topic, we conducted a study to analyse the mediator role of childhood abuse (emotional, physical, and sexual), and neglect (emotional and physical) on the link between schizotypal symptoms and OCD. We hypothesized that if childhood trauma is related to schizotypal traits, then even would mediate their relationship with OCD even after controlling for duration of OCD, the mean number of comorbid Axis I disorders, and current anxiety.

## Materials and methods

### Subjects and assessment

A total of one hundred sixty patients (aged 18-65 years) who were OCD-diagnosed according to Structured Clinical Interviews for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I Disorders (SCID-I)[31] at the psychiatry department between June 2016 and December 2018 were included in the study. The severity of OCD symptoms were assessed using Yale Brown Obsessive-Compulsive Scale (Y-BOCS)[32,33]. The subjects with total scores ≥16 were required for study entry (n = 115). Patients with current and lifetime diagnoes of mental retardation, bipolar disorder, psychotic disorders, substance use disorders, and organic mental disorders were not included in this study. Institutional ethics committee approval was obtained prior to the study and all participants provided signed informed consent. The sociodemographic and clinical characteristics of participants, including age, sex, educational level, marital status, comorbid diagnoses of Axis I disorder, current severity of anxiety, and duration of OCD were recorded through a semi-structured interview form. The duration of OCD was determined from the age that the patient, or a family member, remembered as the beginning of the OC symptoms as used in previous studies[34].

To assess experienced maltreatment in childhood and adolescence, we used the short form of Childhood Trauma Questionnaire questionnaire (CTQ-SF) in which the 28 items are rated on a 5-point Likert scale35,36. This scale includes the subscales of emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. For the statistical analysis, we summed the first three subscale scores into a variable "childhood abuse". We obtained the variable "childhood neglect" by summing up emotional and physical neglect scores.

Schizotypal Personality Questionnaire (SPQ) was used to assess the severity of schizotypal traits[11,37]. This scale was designed to have one subscale for each of the nine symptoms of schizotypal personality disorder (ideas of reference, excessive social anxiety, odd beliefs and magical thinking, unusual perceptual experiences, odd or eccentric behaviour, no close friends, odd speech, constricted affect, suspiciousness). Items were rated for agreement on a dichotomous scale (Yes/No), with a subscale score computed as the total of all items. Cognitive-perceptual/positive (magical thinking, unusual perceptual experiences, ideas of reference, paranoid ideations), interpersonal/negative (lack of close friends, constricted affect), and disorganized (odd/eccentric behavior, odd speech) dimensions were used in this study.

The severity of current anxiety was measured by Beck Anxiety Inventory (BAI)[38]. The BAI is a 21-item self-report questionnaire designed specifically to distinguish symptoms of anxiety from those of depression over the past week. Each item is scored on a 4-point Likert scale, yielding a total score ranging from 0 to 63.

### Statistical analysis

All analyses were conducted using the SPSS (SPSS Science, Chicago, IL, USA) software, version 21.0. Descriptive analyses on sociodemographic, and clinical factors were conducted in terms of total number of subjects and percentage of sample. Bivariate correlations were used to determine the presence of significant associations between the schizotypal traits and several clinical variables.

The next step in our analysis was related to examine the role of childhood trauma as a mediator between schizotypal traits and the current OCD severity. The mediator is the factor through which a predictor impacts an outcome variable. To prove mediation, we followed a procedure described by Baron and Kenny[39]. We performed three regression equations for both childhood abuse and neglect in predicting their mediations on the relatinship between schizotypal traits and current YBOCS scores. According to this model, (a) the independent variable (schizotypal traits) should impact the mediator variable (childhood trauma) in the first equation (path a). (b) The independent variable should impact the dependent variable (YBOCS scores) in the second equation (path c). (c) The mediator should impact the dependent variable in the third equation (path b). (d) The effect of the independent variable on the dependent variable must be less in the third equation than in the second (path c'). Perfect mediation is revealed only if the independent variable has no effect when the mediator is added to the model. The mediator variable, then, serves to mediate the relationship between the independent and dependent variables. Otherwise, it is a partial mediation.

## Results

### Sample characteristics

Statistical analysis was executed on the basis of the data of the 115 subjects, 78 (67.8 %) of which were women. The mean age was 31.8 (SD = 10.3, range = 18-65) years. Fourty-nine of our participants (42.6 %) had at least one current Axis I comorbidity. The mean number of current Axis I diagnoses was 0.52 ± 0.65. Axis I comorbidity included the following current diagnoses: major depression (n = 30; 26.8%), generalized anxiety disorder (n = 8; 6.9%), panic disorder (n = 4; 3.4%), Tourette Disorder (n = 3; 2.6%), OCD spectrum disorders (n = 4; 3.4%). The mean age at onset of OCD symptoms was 20.3 years old (SD:6.9, range: 5-40). The mean YBOCS scores of the participants were 33.45 ± 4.47 (Table 1).

### Correlation analysis

As can be seen in Table 2, the all types of schizotypal symptoms were significantly correlated with the scores of childhood abuse and neglect, and BAI. There were no significant correlations between the schizotypal symptoms and the duration of OCD. Interpersonal subtype was not found to be correlated with total YBOCS scores.

### Mediated models for childhood abuse and neglect

We did not insert gender, and educational level into analyses, since they were categorical, or not normally distributed. The linear regression analyses showed that total SPQ scores had an unique effect on the childhood abuse ($B = 0.405$, 95% CI [0.243-0.565], $\beta = 0.428$, $t = 4.963$, $p < 0.0001$). Total SPQ scores were significantly associated with total YBOCS scores ($B = 0.084$, 95% CI [0.016-0.152], $\beta = 0.224$, $t = 2.438$, $p = 0.016$). A hierarchical regression analyses using total YBOCS scores as the outcome variable was performed using the scores of SPQ, childhood abuse, and BAI as predictors. After including childhood abuse, direct effect of schizotypal traits on OCD severity turned out to be nonsignificant ($B = 0.023$, 95% CI [-0.065-0.110], $\beta = 0.060$, $t = 0.513$, $p = 0.60$). BAI score was not a significant predictor in the model. The childhood abuse as a mediator significantly predicted the total YBOCS scores ($B = 0.093$,

**Table 1.** Demographic and clinical characteristics of the participants (n = 115)

| Variables | Participants | |
|---|---|---|
| | m | SD |
| Age | 31.80 | 10.36 |
| The at onset of OCD | 20.35 | 6.99 |
| Educational level (year) | 12.55 | 3.78 |
| The number of comorbid Axis I disorders | 0.52 | 0.65 |
| BAI | 22.07 | 14.85 |
| YBOCS Total | 24.63 | 5.86 |
| Obsession | 12.72 | 3.29 |
| Compulsion | 11.90 | 3.26 |
| CTQ-SF Total | 39.94 | 14.72 |
| Abuse | 22.10 | 9.47 |
| Neglect | 17.88 | 6.72 |
| SPQ Total | 32.13 | 15.74 |
| Cognitive-perceptual | 12.92 | 7.16 |
| Interpersonal | 13.15 | 6.52 |
| Disorganized | 6.05 | 4.49 |
| | n | % |
| Gender | | |
| Female | 78 | 67.8 |
| Male | 37 | 32.2 |
| Marital status | | |
| Single | 54 | 47.0 |
| Married | 54 | 47.0 |
| Separated/divorced | 7 | 6.1 |
| Comorbid Axis I Disorders | | |
| Present | 49 | 42.6 |

OCD: Obsessive-Compulsive Disorder; BAI: Beck Anxiety Inventory; YBOCS: Yale-Brown Obsessive-Compulsive Scale; CTQ-SF: Childhood Trauma Questionaire Short Form; SPQ: Schizotypal Personality Questionnaire.

**Table 2.** Pearson correlations between SPQ scores and clinical variables

| | CTQ-SF Abuse | CTQ-SF Neglect | Duration of OCD | The number of Axis I Dis | BAI | YBOCS |
|---|---|---|---|---|---|---|
| SPQ | | | | | | |
| Cognitive-perceptual | 0.36*** | 0.25** | 0.01 | 0.06 | 0.47*** | 0.19* |
| Interpersonal | 0.23** | 0.35*** | 0.07 | 0.18 | 0.49*** | 0.11 |
| Disorganized | 0.47*** | 0.34*** | 0.03 | 0.13 | 0.56*** | 0.32** |

* p < 0.05. ** p < 0.005. *** p < 0.0001.

95% CI [0.006-0.180], β = 0.232, $t$ = 2.115, $p$ = 0.03) (Table 3). We suggested that childhood trauma mediated the schizotypal traits in the relation of current OCD severity independent from anxiety severity (Figure 1).

In examining the mediating effects of childhood neglect on the relationship between schizotypal traits and OCD severity, the linear regression analyses showed that total SPQ scores predicted the childhood neglect ($B$ = 0.156, 95% CI [0.080-0.232], β = 0.362, $t$ = 4.070, $p$ < 0.0001). The hierarchical regression revealed that after including childhood neglect, and BAI scores, direct effect of schizotypal traits on OCD severity disappeared ($B$ = 0.095, 95% CI [-0.088-0.278], β = 0.087-0.110, $t$ = 0.513, $p$ = 0.60). Neither the mediator or independent variables were associated with the OCD severity. Therefore, we suggested that childhood neglect was not multivariately related to current OCD severity, and did not mediate the relationship between schizotypal traits and total YBOCS scores.

## Discussion

Research examining the factors which are supposed to contribute the relationship between schizotypy and OCD symptoms is limited. Dysfunctional and maladaptive beliefs are supposed to be causal in the development of a greater prevalance of OCD symptoms[40]. Lee *et al*.[4] suggested that the magical thinking characteristics of schizotypy may increase the risk for OCD through the increased likelihood of TAF. According to the authors, TAF is associated with a set of cognitive biases that involve faulty causal relationships between one's own thoughts and external reality. In the present study, we investigated whether childhood abuse and/or neglect would mediate the relationship between schizotypy traits and OCD. First of all, we explored the relationship of schizotypal traits with several variables including the duration and severity of OCD, anxiety levels, childhood abuse and neglect. In consistent with some previous studies[4-6,8,12,15], our results demonstrated that positive and disorganized schizotypal traits were signicifantly related to the current OCD severity. We have also found that current anxiety scores may interact between schizotypal symptoms and the current OCD severity.

Childhood trauma can contribute to the development of bizarre and unusual perceptions and beliefs[14,19], and cognitive disorganisation[41]. In line with previous findings[18,19,21,42], our findings indicated that there was an association between two types of childhood trauma (abuse

**Table 3.** Examining mediator effects using multiple regression

| Testing steps in mediation model | β | S.E | B (95% CI) | $t$ | $p$ |
|---|---|---|---|---|---|
| Step 1 (Path a) | | | | | |
| Outcome: | | | | | |
| **Childhood abuse** | | | | | |
| Predictor: | | | | | |
| SPQ | 0.362 | 0.038 | 0.156 (0.080-0.232) | 4.070 | <0.0001 |
| Step 2: (Path c) | | | | | |
| Outcome: | | | | | |
| YBOCS | | | | | |
| Predictor: | | | | | |
| SPQ | 0.224 | 0.034 | 0.084 (0.016-0.152) | 2.438 | 0.01 |
| Step 3 (Path b and c') | | | | | |
| Outcome: | | | | | |
| YBOCS | | | | | |
| Mediator: | | | | | |
| Childhood abuse | 0.253 | 0.067 | 0.156 (0.024-0.289) | 2.348 | 0.02 |
| Predictors: | | | | | |
| SPQ | 0.062 | 0.044 | 0.062 (-0.063-0.110) | 0.538 | 0.59 |
| BAI | 0.107 | 0.048 | 0.107 (-0.053-0.138) | 0.883 | 0.13 |
| Step 1 (Path a) | | | | | |
| Outcome: | | | | | |
| **Childhood neglect** | | | | | |
| Predictor: | | | | | |
| SPQ | 0.362 | 0.038 | 0.156 (0.080-0.232) | 4.070 | <0.0001 |
| Step 2: (Path c) | | | | | |
| Outcome: | | | | | |
| YBOCS | | | | | |
| Predictor: | | | | | |
| SPQ | 0.224 | 0.034 | 0.084 (0.016-0.152) | 2.438 | 0.01 |
| Step 3 (Path b and c') | | | | | |
| Outcome: | | | | | |
| YBOCS | | | | | |
| Mediator: | | | | | |
| Childhood neglect | 0.106 | 0.092 | 0.033 (-0.055-0.122) | 1.026 | 0.30 |
| Predictors: | | | | | |
| SPQ | 0.087 | 0.045 | 0.095 (-0.088-0.278) | 0.745 | 0.45 |
| BAI | 0.176 | 0.047 | 0.070 (-0.024-0.164) | 1.480 | 0.14 |

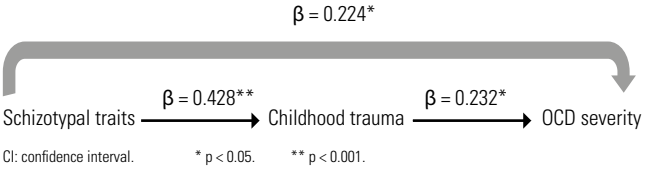


**Figure 1.** Statistical mediation model.

and neglect) and increased positive, negative, and disorganized schizotypal traits. Therefore, these results are not in line with previous hypothesis which proposed that negative/disorganized schizotypal symptoms are more associated with alterations in early brain development, whereas positive symptoms are influenced more by environmental risk factors such as childhood trauma[43,44]. There is some evidence of a differential effect of trauma on schizotypy, with especially strong predictors being emotional abuse[28] and neglect[18]. In fact, Johnson *et al*.[21], found that childhood verbal abuse was associated with increased levels of schizotypal symptoms even after taking into account physical abuse, sexual abuse, and neglect. A previous study found that the association of emotional abuse with schizotypy remained significant even after adjusting for different types of childhood trauma[45]. Emotional abuse alone also predicted ideas of reference, excessive social anxiety, a lack of close friends, unusual perceptual experiences and eccentric behaviour or appearance[28]. Another study reported that physical and sexual abuse were associated with higher levels of paranoia/suspiciousness and unusual perceptual experiences[46]. Our results seemed to be inconsistent with some of the previous studies which identified that neglect was associated with positive and negative schizotypy whereas childhood emotional and physical abuse were only associated with the positive schizotypy dimension[47]. In a similar study, the subjects who reported emotional abuse did not show higher scores within any of three measures of schizotypy[46].

Taking into account the strong correlations between two types of childhood trauma and three schiotypal dimensions, we supposed that childhood abuse and/or neglect may contribute to the influence of schizotypal traits on OCD. The mediation analysis revealed that childhood abuse mediated the relationship between schizotypal traits and OCD even after controlling for current anxiety scores. Similar to our results, a previous study[29] demonstrated that childhood trauma, particularly emotional abuse had significant association with OCS independent from comorbid anxiety. The authors also suggested that there was an indirect relationship between emotional abuse and OCS mediated through the personality traits of conscientiousness. We found that although childhood neglect was significantly correlated with all types of schizotypy, it did not mediate the relationship between schizotypal traits and OCD. Furthermore, we suggested that sychizotypal traits were not associated with OCD severity when childhood neglect and current anxiety were controlled. Some previous research reported that childhood neglect appeared to be central in the development of schizotypy[21,48]. Our findings may suggest that although childhood neglect seemed to be related with schizotypal symptoms, it did not have a mediator role in further establishing of a relationship between OCD and schizotypal traits.

## Conclusions

We believe that our study provides a substantial support to the primary hypothesis that childhood abuse experiences may mediate the relationship of schizotypal traits with OCD independent from higher levels of anxiety. The present findings may contribute to the literature by exploring the differential effects of specific trauma types in terms of mediators leading to schizotypal symptoms. Given that childhood emotional abuse may play a particularly important role in the development of psychopathology, longitudinal research examining the potential link between childhood emotional abuse, schizotypal traits and OCD is needed.

## Limitations

The most obvious limitation in this research was that the number of participants was relatively small to adequately address the research questions or to possibly generalize beyond the context of this study. The use of self-report scales may have led to over-reporting of some symptoms and psychopathology. Also, the self-report instruments about childhood adverse experiences may suffer from the bias of memory and the bias of attributing meaning to the events lived by the respondent. We did not assess the duration and frequency of traumatic experiences, or the age when trauma first occurred. The role of gender, and educational level in moderating the relationship between study variables were not measured, since these variables were categorical or not normally distributed. Additionally, the neglect of the content of lifetime obsessions and compulsions, and the current diagnosis of depression in analyses is another limitation of this study. Morever, the data on comorbid diagnoses may not be sufficient, since they were collected in an interview, and not be checked in medical records.

## Conflict of interests

The authors declare no conflict of interest.

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# Depression, PTSD and alexithymia in victims of intimate partner violence: a case-control study

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## Abstract

**Background:** Intimate partner violence (IPV) regards millions of women worldwide and can lead to serious psychopathological consequences. **Objective:** We aimed to evaluate differences between a group of abused women and controls, and potential predictors of depression and PTSD in the IPV group. **Methods:** We recruited 57 women who experienced IPV and 57 age-matched controls from the general population. After collecting socio-demographic characteristics, we administered the following scales: Hamilton Depression Rating Scale (HDRS), Davidson Trauma Scale (DTS), Toronto Alexithymia Scale (TAS-20) and Revised-Conflict Tactics Scale (CTS-2). **Results:** Our results showed differences between women who experienced IPV and controls in the socio-economic status, employment and educational levels, childhood abuse and early terminations of pregnancy. Notably, the rates of depression, PTSD, and alexithymia were significantly different between the two groups. Linear regression models revealed that sexual coercion was an independent positive predictor of depressive symptoms, while alexithymia played a role in the development of PTSD in the group of abused women. **Discussion:** Given the prevalence of depression and PTSD in victims of IPV, it is important to always investigate for IPV in women seeking for help in mental health services. Alexithymia in victims of IPV deserves to be further investigated by researchers.

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**Keywords:** Intimate partner violence, PTSD, depression, alexithymia, domestic violence, sexual coercion.

## Introduction

Intimate partner violence (IPV), defined by the World Health Organization (WHO) as "any behavior within an intimate relationship that causes physical, psychological or sexual harm to those in the relationship", is a major public issue which impacts millions of women worldwide[1]. It has been estimated that approximately one in three women around the world has suffered an episode of violence during their lives[2]. Although IPV regards people of various ages, ethnicities and socio-economic levels, prevalence of life-time IPV varies between 15% and 71% across countries. It has been hypothesized that the wide range may be related to different gender attitudes as well as to the presence of reinforcing factors for violence such as poverty[3]. Recently, a meta-analysis reported a significant association between childhood maltreatments and IPV victimization[4]. Moreover, it has been shown that women who experience IPV are more at risk of undesired pregnancies and premature gestation interruptions[5].

IPV is often characterized by an escalation of violence, which may become chronic with potentially dangerous consequences[6]. Women who have experienced IPV have multiple sequelae in the mental health sphere[7]. A meta-analysis reported that psychiatric disorders occur two to five times more frequently in survivors of IPV than in the general population. PTSD and depression were highly prevalent, with a weighted mean prevalence of 63.8% and 47.6%, respectively[8]. The link between IPV, depression and PTSD has been confirmed by several other studies[9,10].

Alexithymia, the inability of understanding, processing, or describing emotions[11], may play an important role in the context of domestic violence. Many studies have investigated the interplay between alexithymia and psychiatric diseases, such as depression[12,13] or PTSD[14], in several different contexts. Notably, it has been reported that people with higher levels of alexithymia are more at risk to develop PTSD after trauma exposure[15]. However, while research has thoroughly examined alexithymia in violent offenders[16], to our knowledge little is known about its prevalence in IPV victims and its role in the onset of psychiatric morbidities in this particular group of women. Recently, Craparo *et al.*[17] hypothesized that insecure attachment styles could contribute to difficulties in emotion regulation, typical of alexithymia, which in turn increased the vulnerability to IPV. In fact, in a group of abused women, these researchers found that alexithymia was negatively correlated with the ability to cope with stress[17].

Over recent decades the interest in IPV and its correlates, as well as the number of papers focusing on the topic, have rapidly increased. However, studies have been focused mainly on IPV in developing countries or in ethnic minorities, while less is known regarding the features of IPV in Western countries, particularly in Europe. Additionally, potential risk factors (i.e. alexithymia) for the onset of mental health problems in IPV population are not completely clear. Considering the paucity of relevant papers in the scientific literature, the aims of the present study were:

- To compare the characteristics of a group of women who experienced IPV to women from the general population, with a specific focus on depression, PTSD and alexithymia;

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- To investigate potential predictors of developing depressive or post-traumatic stress symptoms in women who suffered from IPV, such as age, alexithymia, and types of IPV.

## Methods

### Participants

We recruited 57 victims of IPV from three women's shelters (Catania, Enna, and Caltanissetta) in Sicily, Southern Italy. Fifty-seven age-matched controls were recruited from primary care centers or outpatient services of the Gynecology and Obstetrics Unit of Policlinico "G. Rodolico", Catania, Italy. Participants were recruited if they were between 18 and 65 years and had been involved in an intimate relationship for at least one year. Exclusion criteria were: illiteracy or non-comprehension of Italian language, psychotic disorders, intellectual disability or any clinical condition that could affect cognitive performance and comprehension.

The study was performed in accordance with the Declaration of Helsinki. All participants read and signed a written informed consent. Ethical approval was obtained by our internal review board.

### Procedures and measures

Women were invited to participate by a psychologist who fully explained the aims of the study, obtained written informed consent and collected socio-demographic data. A psychiatrist interviewed all participants to ascertain the presence of IPV, and then administered the assessment scales. Participants' partners were not present during the assessment.

All participants were asked to complete the following questionnaires or semi-structured interviews: Revised-Conflicts Tactics Scale (CTS-2), Davidson Trauma Scale (DTS), Hamilton Depression Rating Scale (HDRS) and Toronto Alexithymia Scale (TAS-20).

### Revised-Conflict Tactics Scale (CTS-2)[18,19]

The Revised-Conflict Tactics Scale (CTS-2) is a 78-item self-report scale, which measures psychological and physical attacks on a partner in a dating, cohabiting, or marital relationship, as well as the use of negotiation or reasoning to deal with conflicts. For the purposes of the present study, we considered only violence victimization, and not perpetration. The CTS-2 contains five subscales (negotiation, psychological aggression, physical assault, sexual coercion and physical injury). Each item is rated on an 8-point frequency scale ranging from never to more than 20 times[18]. The simplest way to calculate the score of each subscale is to sum the point assigned to each single item of the subscale to create a scale ranging from 0 to 8. Additionally, the CTS-2 provides rates of ever prevalence and annual frequency of spousal violence, as well as chronicity and severity for the aspects of spousal conflict.

### Davidson Trauma Scale (DTS)[20]

The Davidson Trauma Scale (DTS) is a 17-item self-rated measure that assesses DSM-IV symptoms of PTSD. Items are rated on 5-point scale. Respondents are asked to identify the trauma that is most disturbing to them and to rate, in the past week, how much trouble they have had with each symptom. DTS total score is computed by summing all item responses, with a possible range of 0 to 136. Consensus has not been reached regarding the cut-off score for a PTSD diagnosis. According to McDonald *et al.*[21], the original DTS has the best diagnostic efficiency (83%) when the cut-off score of 40 is used. Therefore, the cut-off of 40 was used in this study to determine whether PTSD was present. One major strength of the DTS is the possibility of administration a broad population of men and women exposed to different types of trauma.

### Hamilton Depression Rating Scale (HDRS)[22]

The Hamilton Depression Rating Scale (HDRS) is a clinician-rated measure of depressive symptoms in adults. Each item on the questionnaire is scored on a 3- or 5-point scale. Total score can range from 0 to 54 points, with scores from 7 to 17 indicating mild depression, from 18 to 24 indicating moderate depression, and above 24 indicating severe depression[23].

### Toronto Alexithymia Scale (TAS-20)[11]

The Toronto Alexithymia Scale (TAS-20) is a self-report measure of deficiency in understanding, processing, or describing emotions. The current version comprises 20 items rated on a 5-point Likert scale. Total score can range from 0 to 100. The TAS-20 uses the following cut-offs: scores equal to or less than 51 are indicative of non-alexithymia, scores of 52 to 60 indicate possible alexithymia, and scores above 61 are suggestive of alexithymia.

### Statistical analyses

Descriptive statistics for all collected variables were calculated. Data were presented as means and standard deviations, percentages or counts as appropriate. Data were tested for normal distribution and homogeneity of variance before statistical procedures were applied. Chi-square tests or t-tests were performed to detect differences between the two groups. To evaluate potential predictors of depression and PTSD in abused women, univariate linear regressions were performed with the HDRS and DTS total scores as dependent variables, and age, TAS-20 values, and CTS-2 subscales (negotiation, psychological aggression, physical assault, sexual coercion and physical injury) as independent predictors. Significant predictors were then inserted in a multivariate linear regression. A two-tailed p-value <0.05 was regarded as significant. All statistical analyses were performed using IBM SPSS 24.0 for Windows.

## Results

### Characteristics of women who experienced IPV and control group

IPV was evaluated by means of the CTS-2. All scales were significantly different between the two groups. Women in the IPV group used less negotiation tools ($M$ = 8.77, $SD$ = 6.76) compared to the control group ($M$ = 29.58, $SD$ = 8.92). Moreover, women in the IPV group reported experiencing more psychological aggression (IPV $M$ = 36.77, $SD$ = 10.07; controls $M$ = 6.23, $SD$ = 6.72), physical aggression (IPV $M$ = 36.79, $SD$ = 18.37; controls $M$ = 1.21, $SD$ = 5.78), injury (IPV $M$ = 11.68, $SD$ = 8.18; controls $M$ = 0.39, $SD$ = 2.06), and sexual coercion (IPV $M$ = 19.72, $SD$ = 15.71; controls $M$ = 2.26, $SD$ = 3.54) than non-abused women. All differences were regarded as statistically significant ($p < 0.001$). Figure 1 shows the differences between the two groups reported at each scale of the CTS-2.

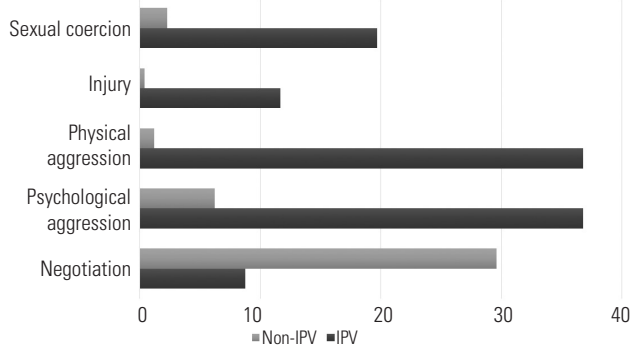


**Figure 1.** Differences at the CTS-2 between women who experienced IPV and women from the general population.

As reported in Table 1, the mean age of participants was 39.22 years (*SD* = 9.69), with no statistically significant differences between the two groups. No statistically significant differences were found also in the marital status or number of children. However, a larger number of women in the IPV group had voluntarily terminated a pregnancy during their lives (24.56% *vs.* 1.75%. of control group). Non-abused women had in average more years of education than abused women (*M* = 13.67, *SD* = 3.9 versus *M* = 11.74, *SD* = 3.68). Statistically significant differences were also present for employment status: 63% of controls had full-time or part-time employment, while only 44% of participants of IPV group were employed. About 37% was unemployed and about 20% were housewives. Also, socio-economic status significantly differed between the two groups: half of abused women were categorized as having a low socio-economic status, in comparison to only 8.77% of the control group. No statistically significant differences were found in history of drug or alcohol abuse. Of note, 25% of women in the IPV group was also victims of violence during childhood. Conversely, in the non-IPV group, only one person had suffered from childhood violence.

**Table 1.** Characteristics of participants

| | IPV (N = 57) | Controls (N = 57) | p-value | Total (N = 114) |
|---|---|---|---|---|
| Age | 39.21 ± 9.77 | 39.23 ± 9.68 | 0.992 | 39.22 ± 9.69 |
| Education (years) | 11.74 ± 3.68 | 13.67 ± 3.9 | 0.008* | 12.70 ± 3.90 |
| Marital status (%) | | | 0.34 | |
| In a relationship | 5 (8.77) | 9 (15.79) | | 14 (12.28) |
| In a domestic partnership/Married | 30 (52.63) | 32 (56.14) | | 62 (54.39) |
| Separated/Divorced | 22 (38.60) | 16 (28.07) | | 38 (33.33) |
| N of children (%) | | | 0.064 | |
| 0 | 10 (17.54) | 21 (36.84) | | 31 (27.19) |
| 1 | 6 (10.53) | 8 (14.03) | | 14 (12.28) |
| 2 | 32 (56.14) | 24 (42.10) | | 56 (49.12) |
| ≥3 | 9 (15.79) | 4 (7.02) | | 13 (11.40) |
| Voluntary termination of pregnancy (%) | 27 (47.37) | 1 (1.8) | <0.001* | 28 (24.56) |
| Employment (%) | | | <0.001* | |
| Full-time | 12 (21.05) | 23 (40.35) | | 35 (30.70) |
| Part-time | 13 (22.81) | 13 (22.81) | | 26 (22.81) |
| Unemployed | 21 (36.84) | 6 (10.53) | | 27 (23.68) |
| Housewife | 11 (19.30) | 15 (26.32) | | 26 (22.81) |
| Social status (%) | | | <0.001* | |
| High | 3 (5.26) | 15 (26.32) | | 18 (15.79) |
| Medium | 26 (45.61) | 37 (64.91) | | 63 (55.26) |
| Low | 28 (49.12) | 5 (8.77) | | 33 (28.95) |
| History of drug abuse (%) | 0 (0) | 1 (1.75) | 1 (Fisher) | 1 (0.88) |
| History of alcohol abuse (%) | 3 (5.26) | 0 (0) | 0.243 (Fisher) | 3 (2.63) |
| Violence during childhood (%) | 14 (24.56) | 1 (1.75) | <0.001* | 15 (13.16) |

* Statistically significant.

## Psychiatric characteristics of women who experienced IPV and control group

HDRS, DTS and TAS-20 scores of the two groups and corresponding classifications are reported in Table 2. Among IPV women, about 58% had moderate-to-severe depression according to HDRS. Moreover, according to the DTS, PTSD symptoms were significantly higher in the group of abused women, with a mean difference of 78.5 points between the IPV and control group. Using the cut-off score on the DTS of 40 proposed by McDonald *et al.*[21], the rate of PTSD was 87.7% in the group of victims of IPV, compared to only 3.5% in the control group. Finally, statistically significant differences were found in the TAS-20 scores, with IPV women having higher scores (*M* = 60.49, *SD* = 17.95) than non-abused women (*M* = 38.6, *SD* = 13.9). Figure 2 depicts the differences between the two groups at HDRS, DTS-2 and TAS-20.

**Table 2.** Scores reported by the two groups at the HDRS, DTS, and TAS-20

| Scale | IPV (*N* = 57) | Controls (*N* = 57) | p-value | Total (*N* = 114) |
|---|---|---|---|---|
| HDRS total score (depression) | 22.18 ± 10.75 | 8.32 ± 5.52 | <0.001* | 15.25 ± 10.99 |
| Normal (%) | 2 (3.5) | 29 (50.87) | <0.001* | 31 (27.19) |
| Mild depression (%) | 22 (38.6) | 24 (42.10) | | 46 (40.35) |
| Moderate depression (%) | 6 (10.5) | 2 (3.51) | | 8 (7.02) |
| Severe depression (%) | 27 (47.4) | 2 (3.51) | | 29 (25.44) |
| DTS total score (PTSD) | 81.58 ± 31.41 | 3.09 ± 12.9 | <0.001* | 42.33 ± 46.10 |
| PTSD (%) | 50 (87.7) | 2 (3.5) | <0.001* | 52 (45.61) |
| TAS-20 total score (alexithymia) | 60.49 ± 17.95 | 38.6 ± 13.9 | <0.001* | 49.54 ± 19.40 |
| Non-alexithymia (%) | 19 (33.33) | 40 (70.18) | <0.001* | 59 (51.75) |
| Possible alexithymia (%) | 13 (22.81) | 16 (28.07) | | 29 (25.44) |
| Alexithymia (%) | 25 (43.86) | 1 (1.75) | | 26 (22.81) |

* Statistically significant.

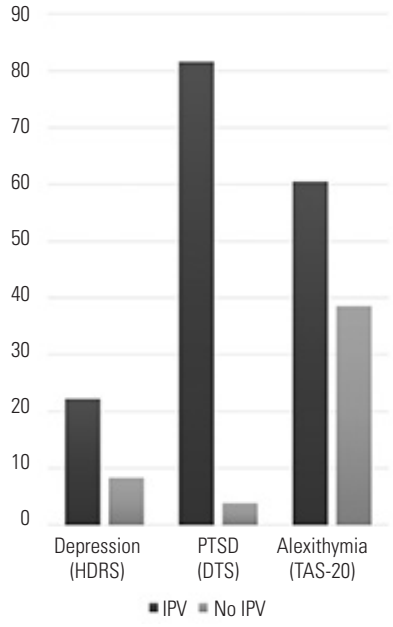


**Figure 2.** Differences at the HDRS, DTS and TAS-20 between women who experienced IPV and women from the general population.

## Predictors of depressive and post-traumatic stress symptoms in women who experienced IPV

We hypothesized that age, alexithymia and IPV factors, as measured by the scales of the CTS-2, could represent potential predictors of depression and PTSD in women who experienced IPV. Univariate linear regressions identified two independent predictors of HDRS scores, alexithymia and sexual coercion. The multivariate model was statistically significant ($p < 0.001$) and explained 26% of the variance. However, in the multivariate model only sexual coercion was confirmed as a significant predictor of depressive symptoms in the group of IPV women (Table 3).

**Table 3.** Univariate and multivariate linear regressions investigating predictors of HDRS scores (Model: R2 = 0.261; SE = 9.405; F = 9.56; p < 0.001).

| | Univariate linear regressions | | | | | Multivariate model | | |
|---|---|---|---|---|---|---|---|---|
| | $R^2$ | F | B | β | *p*-value | B | β | *p*-value |
| Age | 0.034 | 1.956 | -0.204 | -0.185 | 0.168 | | --- | |
| TAS-20 | 0.069 | 4.087 | 0.157 | 0.263 | 0.048* | 0.13 | 0.218 | 0.069 |
| Negotiation | 0.025 | 1.438 | -0.254 | -0.160 | 0.236 | | --- | |
| Psychological violence | 0.008 | 0.445 | 0.096 | 0.090 | 0.507 | | --- | |
| Physical violence | 0.005 | 0.265 | 0.040 | 0.069 | 0.609 | | --- | |
| Sexual coercion | 0.215 | 15.022 | 0.317 | 0.463 | <0.001* | 0.302 | 0.441 | <0.001* |
| Injury | 0.006 | 0.353 | -0.105 | -0.080 | 0.555 | | --- | |

* Statistically significant.

Univariate linear regressions were computed to evaluate potential predictors of post-traumatic stress symptoms, as measured by the DTS. Only alexithymia was regarded as a positive independent predictor of DTS scores (p = 0.008), explaining the 12% of the variance (Table 4).

**Table 4.** Univariate linear regressions investigating predictors of DTS scores

| | R2 | F | B | β | *p*-value |
|---|---|---|---|---|---|
| Age | 0.001 | 0.076 | -0.119 | -0.37 | 0.784 |
| TAS-20 | 0.120 | 7.507 | 0.606 | 0.347 | 0.008* |
| Negotiation | 0.008 | 1.462 | -0.747 | -0.161 | 0.232 |
| Psychological violence | 0.062 | 3.62 | 0.775 | 0.249 | 0.062 |
| Physical violence | 0.01 | 0.465 | 0.169 | 0.099 | 0.465 |
| Sexual coercion | 0.051 | 2.945 | 0.451 | 0.225 | 0.092 |
| Injury | 0.005 | 0.252 | 0.259 | 0.068 | 0.618 |

* Statistically significant.

## Discussion

### Main findings

IPV is a major public issue which affects about 25% of women in Europe. However, little is known about the characteristics of IPV victims in Italy and their correlates, including the type of violence they may experience. The present study compared a sample of victims of IPV to a group of women from the general population. Our results generally confirm findings in the existing literature: victims of IPV reported a lower socio-economic status, lower educational levels, and were less likely to be employed than controls[24]. These results suggest that poverty may play an important role in determining the perpetration of violence. Less education, in fact, may limit employment opportunities; unemployment could in turn cause isolation and limitation of resources. Therefore, given the poor financial and social resources, potential victims could be more exposed to IPV.

Our findings are consistent with other research reporting that adult victims of IPV have an increased likelihood of having experienced violence during childhood[4]. Several explanations could be hypothesized. First, maltreated children may perceive abusive interactions as normal and appropriate, thus justifying the presence of violence in intimate relationships[25]. Second, it might be difficult for them to develop adequate coping strategies, being more exposed to IPV victimization[26]. The poor quality of the parent-child relationship could represent another risk factor for victimization[27]: individuals who have been maltreated in childhood generally show the tendency to feel unlovable, helpless, and have a low self-esteem[28]. Given these characteristics, these individuals may appear weak and represent an easy target for IPV perpetrators[29].

Voluntary terminations of pregnancy were also significantly higher in the group of abused women. Our results are in line with previous reports[5]. We could hypothesize that abusive relationships, typically characterized by high levels of fear and control, and by sexual coercion, can result in women's inability to negotiate contraceptive methods, thus leading to unintended pregnancies and abortions.

Moving to mental health issues, our results confirmed that depression and PTSD symptoms represent significant psychiatric issues in abused women. However, retrieved prevalence rates are slightly higher than those previously reported[8]. According to the HDRS scores, almost 58% of women with IPV reported moderate-to-severe depression and based on the suggested cut-off score of 40 on the DTS, 87.7% of the IPV sample had PTSD. One possible explanation is that subjects included in the study had already been referred to shelters for help, which might reflect greater severity of violence and correspondingly a more severe symptomatology. It is also possible that using the suggested cut-off score of 40 as proposed by McDonald *et al.*[21] for a PTSD diagnosis on the DTS may have resulted in a high number of false positives. In fact, this cut-off has not been validated in different samples and while the specificity is excellent (0.95), the sensitivity is lower (0.69). Finally, we could hypothesize that the IPV subjects might have overestimated their symptoms, particularly while completing the DTS, which is a self-report tool. This interpretation is consistent with the findings of Brady *et al.*[30] who recently reported that alexithymia seemed to predict the over-reporting of PTSD symptoms in a group of veterans. Indeed, our data showed that levels of alexithymia were significantly higher for the IPV group than for controls. Notably, this is one of the first studies to specifically examine the role of alexithymia in abused women, cautiously supporting the hypothesis that alexithymia may be a risk factor for becoming an IPV victim[17].

### Predictors of depression and PTSD in the group of women who experienced IPV

The severity of depressive symptoms was predicted by alexithymia and the CTS-2 sexual coercion scale in the univariate regression. However, in the multivariate model, only sexual coercion was confirmed to be an independent predictor of depressive symptoms. Our results are in line with a paper examining IPV in Indian pregnant women[31], reporting that depressive and PTSD symptoms were higher in those with a history of abuse or sexual coercion. However, while the relationship between sexual abuse and peri- or post-natal depression have been examined by several studies, to our knowledge, no other authors have previously found a specific relationship between sexual coercion and depressive symptoms in the context of an abusive relationship. Sexual coercion is "unwanted sexual activity that happens when a person is pressured, tricked, threatened, or forced in a nonphysical way"[32]. However, since sex is an important aspect of intimate relationships, detecting or demonstrating sexual coercion in the context of an intimate partnership might be difficult or might not be identified by the victim as abuse. Additionally, given the widespread blaming attitude towards victims of IPV[33], women might be less likely to report the abuse, especially when physical signs of the violence such as bruises and abrasions are not. This may cause a vicious cycle in which women may develop depressive symptoms in response to feeling trapped in an abusive relationship where others may blame them for the abuse; this may in turn prevent them from reporting the domestic violence, even if they identify it as such. Of note, blaming attitudes towards victims, perceptions that the victim and not the perpetrator is responsible for the abuse and tolerance

towards perpetrators of violence may also explain the low rates of IPV reported at the CTS-2 by the control group[33]. In fact, it has been demonstrated that IPV is frequently unreported or underreported by victims[33].

Surprisingly, none of the CTS-2 subscales predicted PTSD symptoms in the group of abused women. This is in contrast with data reported by Basile *et al.*[9], who found that physical violence, psychological violence and stalking significantly predicted PTSD in a group of abused women. The differences with our findings might be related to the different sample sizes, as well as to the different types of measures used.

Of interest, we found that alexithymia was a positive independent predictor of PTSD. The interplay between alexithymia and post-traumatic stress symptoms has been thoroughly examined in literature. For instance, a meta-analysis by Frewen *et al.* has supported the hypothesis that individuals diagnosed with PTSD may experience symptoms of alexithymia[34]. More recently, a cross-sectional study found a significant relationship between alexithymia and number of traumatic experiences in a sample of healthy individuals, further bracing the association between multiple and complex traumatization and alexithymia[35]. Of note, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), PTSD may be characterized by negative changes in cognition and mood, such as loss of interest in activities, detachment from others, inability to experience positive emotions[36]. Similarly, the 11th revision of the World Health Organization's International Classification of Diseases (ICD-11) requires the presence of "severe and persistent problems in affect regulation" for the diagnosis of complex PTSD[37]. Nevertheless, mood changes and affective dysregulation may be related not only to PTSD, but also to alexithymia, which in fact consists in an impairment in emotional awareness. The overlapping symptomatology between the two conditions has led to discuss if alexithymia should be considered a facilitator of the development of PTSD in individuals who suffered traumatic experiences, such as IPV, or a component of PTSD itself, and therefore a consequence of the traumatic experience[35]. Our regression analysis was based on the hypothesis that alexithymia could represent a vulnerability factor for IPV[17], thus increasing the risk of developing PTSD[15]; however, given the cross-sectional design of the present study, we cannot exclude that alexithymic-like traits might be a component of the PTSD itself.

### Strengths and limitations

A strength of our study was that we investigated the characteristics of IPV in women in a European country, while heretofore the majority of literature has been focused on developing countries or ethnic minorities. Additionally, to the best of our knowledge, this is the first study to investigate potential predictors of comorbid psychopathology in abused women, and to explore the role of alexithymia. Nevertheless, several limitations should be acknowledged. First, given the case-control design, we did not consider the onset of mental health issues, such as depression or PTSD, longitudinally, and therefore we could not completely clarify the role of alexithymia in developing psychopathology after trauma-exposure. Also, we considered only two groups of symptoms (post-traumatic stress and depressive symptoms), which according to literature are the most frequently related to IPV. Future research should examine how IPV might be related to the onset of other psychiatric disease, such as anxiety or psychoses. Third, our population comprised only women living in a Southern Italy region. According to the literature, females are more likely to be at risk of IPV, but we are aware that this perspective could represent a bias and we encourage researchers to further explore the male perspective in IPV. Finally, our control group was representative of the general population: it might be interesting in future research to compare the mental health issues of women who suffered from IPV to those of women who suffered from other types of aggressive and intrusive behaviors (e.g. sexual harassment, sexual offences, bullying, cyberbullying, physical injuries). For all these reasons, we cannot extend the generalizability of our findings to other countries or populations.

### Implications for clinical practice and future research

Our findings confirmed that IPV is an important public health problem, with psychopathological consequences that might severely impact an individual's functioning. Sexual coercion seemed to predict the severity of depressive symptoms in women who experienced IPV, whereas alexithymia seemed to predict the severity of post-traumatic stress symptoms. Future research should further investigate the characteristics and mental health issues of women suffering from IPV. Of note, the role of alexithymia deserves additional investigation; more studies are needed to determine whether it is a causal factor of mental health issues in abused women or a consequence of the abuse, even if we are aware that longitudinal studies are extremely difficult to conduct. This could be important not only in terms of prevention and early detection, but also in terms of therapy: it has in fact been demonstrated that alexithymia may impact on the outcome of psychosocial interventions[38], which are fundamental for IPV victims.

Given the high prevalence of psychiatric conditions in victims of IPV, professionals (i.e. psychologists, psychiatrists) should always assess IPV while collecting personal and familiar history of women and men seeking for help in mental health services. Reported IPV, in fact, is only "the tip of the iceberg"[39]. Additionally, it is important to consider not only traditional types of IPV, but also new forms of IPV, such as stalking, which has dramatically increased over the last years[40,41].

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## Disclosure

All authors declare no conflict of interests.

## Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

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# An analytical study of iboga alkaloids contained in *Tabernanthe iboga*-derived products offered by ibogaine treatment providers

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## Abstract

**Background:** Therapeutic properties of ibogaine in the treatment of addiction are attracting both clinicians and patients to its use. Since ibogaine is not an authorized medicine, the quality of these products is not always known, increasing the probability of adverse reactions. **Objective:** This study collects different types of *iboga*-derived samples from treatment providers, vendors and online buyers to analyse their content. **Methods:** Analysis of *iboga* products (n = 16) was performed using gas chromatography and mass spectrometry methods (GC/MS). Products included *Iboga* root bark, Total Alkaloids (TA), Purified Total Alkaloids (PTA HCl), ibogaine hydrochloride (ibogaine HCl) and one *Voacanga africana* root bark. **Results:** The content of ibogaine was highly variable, ranging from 0.6% to 11.2% for products sold as iboga root bark, from 8.2% to 32.9% for products sold as TA, 73.7% for one sample sold as PTA and from 61.5% to 73.4% for products sold as ibogaine HCl. One sample did not show any *iboga* alkaloids. Other alkaloids and unknown substances were found in almost all samples. **Discussion:** The purity of iboga products is highly variable. These results should be taken into consideration by suppliers and users, especially regarding correct dosing to avoid overdose, as well as potential interactions with other substances.

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**Keywords:** *Tabernanthe iboga*, ibogaine, sample analysis, addiction treatment, harm reduction.

## Introduction

Ibogaine is a psychoactive alkaloid with hallucinogenic properties present in the root bark of *Tabernanthe iboga*, a tropical plant traditionally used in rites of passage and ethnomedicine in African countries such as Congo and Gabon[1]. Its anti-addictive properties were discovered serendipitously in the sixties by Howard Lotsof, who at that time was a heroin user and noticed that after using ibogaine his craving for heroin was significantly reduced. Since then, thousands of people have been treated with ibogaine to address drug dependence and/or for personal growth[2].

Pre-clinical research has demonstrated the anti-addictive properties of ibogaine in different animal species with reductions in self-administered morphine, cocaine, (meth)-amphetamines, alcohol and nicotine[3]. Ibogaine was also found to reduce or eliminate drug craving and withdrawal in humans in several case series and in clinical settings, but randomized trials are lacking[4-7].

Indeed, the number of ibogaine clinics and ibogaine treatment providers has been increasing during the last few years. In 2008 it was estimated that 3,414 people used ibogaine, approximately a fourfold increase relative to the estimation of 857 from five years before[8]. From those 3,414 subjects, 68% used ibogaine for the treatment of drug addiction. In New Zealand, Australia and South Africa, ibogaine can be prescribed for the treatment of drug addiction (the legal status of ibogaine around the world can be found at: https://www.ibogainealliance.org/ibogaine/law/). Most of the *iboga* that is

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used in ibogaine clinics comes from Gabon, where unlicensed *iboga* exportation is forbidden. The lack of a regulated market results in a lack of quality control and patients may therefore be consuming ibogaine with unknown concentrations of active ingredients.

While ibogaine clinics are spreading around the world, accidents and fatalities have been increasing. By 2015 22 ibogaine-related deaths were reported[9,10]. Although ibogaine is considered a safe treatment when conducted under medical supervision[11], many ibogaine providers offer ibogaine treatments outside of a medically controlled setting (for example, in hotel rooms). Furthermore, the purity of the ibogaine or *iboga* extracts used by treatment providers or self-administered by patients is frequently unknown, and. many clinics and private providers buy *iboga*/ibogaine from web-based suppliers without any quality control. This can increase the risks of adverse reactions and/or fatalities.

In one of the fatalities, the hypotensional substance reserpine[12] was found in the blood of a man who died after ingesting ibogaine in Slovenia in 2011[13]. Reserpine might potentiate the hypotensional effects of ibogaine, increasing the risks of cardiovascular toxicity. Furthermore, both reserpine and ibogaine are metabolized by CYP-2D6[14] and this specific drug interaction could increase the blood levels of ibogaine, increasing the risk of overdose. This is especially relevant when most of the time the concentration of *iboga* alkaloids in ibogaine samples is unknown. Because the ibogaine sample involved in the fatality was not analysed, it is unknown if it contained reserpine or if the person used any other herbal or pharmaceutical product containing it. In the same year, reserpine was found in ibogaine samples analysed in Slovenia[12]. Forensic analyses after ibogaine fatalities regularly show the presence of other drugs in the body[15].

Therefore, we performed this study to gain more insight into the purity and content of *iboga* samples available on the market, and to evaluate the claims made by the vendors about the characteristics of their products.

## Methods

### Sample collection

An advertisement was released through the website, newsletter and blog of the ICEERS Foundation (a non-profit organization that investigates the ethnobotany and therapeutic properties of iboga, ayahuasca, and cannabis) in July of 2013 (http://news.iceers.org/2013/07/scientific-study-analysis-of-iboga/) asking treatment providers, vendors and buyers to send samples for analysis. We requested information about (A) the type of material (root bark, *iboga* extract, ibogaine hydrochloride (HCl), etc.); (B) the source (company, vendor, country, etc.); (C) date of purchase; (D) the expected percentage of ibogaine; (E) any information about abnormal effects experienced, potency, etc.; and (F) any additional information considered relevant. Requested samples could include: (A) pulverized root bark; (B) total alkaloids (TA) (solid extracts containing the alkaloids present in the root bark); (C) purified total alkaloids (PTA) (solid extracts containing the semi-purified alkaloids in salt form); and (D) "pure" ibogaine HCl.

### Samples preparation for GC/MS

GC/MS qualitative and quantitative analysis was carried by Energy Control, a Spanish non-governmental organization with extensive experience in drug analysis. Their methodology for the GC/MS analysis has been previously reported[16].

The samples were prepared by dissolving 5.0 mg of each sample in 5.0 mL of methanol in glass vials. All vials were vortexed for 1 minute and then sonicated for 15 minutes.

The substances were determined with gas chromatography coupled with mass spectrometry (Agilent 7890B gas chromatograph coupled to a 5977A quadrupole mass spectrometer detector; (Agilent; Santa Clara, CA, USA) at the Municipal Institute for Medical Research in Barcelona (IMIM – Hospital del Mar). The gas chromatograph was fitted with a G4513A auto-sampler injector. Samples were injected in split mode into a 30 meter, 0.25 mm i.d., 0.25 mm film thickness 5% phenylmethylsilicone column (HP-5MS, Agilent Technologies). The oven temperature was initially maintained at 90 ºC for 2 min and programmed to reach 320 ºC at 20 ºC per min. It was finally maintained at 320 ºC for 9.5 min. The total run time was 21.5 min. Insert liners packed with silanized glass wool were used. The injector and the interface were operated at 280 ºC. Helium was used as carrier gas at a flow rate of 1 mL/min. The mass spectrometer was operated in electron impact ionization mode at 70 eV. To confirm the mass spectra, two libraries were used: the Searchable Mass Spectral Library NIST/EPA/NIH Mass Spectral Library, Data Version: NIST 14 and the Searchable Mass Spectral Library Version 2.3 (http://www.swgdrug.org/ms.htm). A GC/MS comparison of the samples with the analytical standards of ibogaine, ibogamine, and voacangine was also performed. Ibogaine and voacangine were provided by Phytostan Inc., Montreal, Quebec. Analysis certificates of Phytostan Inc. alkaloids have been performed by the laboratory of Martin Kuehne, Department of Chemistru, University of Vermont, Burlington, Vermont, verifying the high purities of those alkaloids[15]. Ibogamine was provided by REFORM Italia srd.

### Data analysis

The moles of ibogaine HCl in the Phytostan reference sample per unit of signal intensity for the ibogaine peak were calculated based on the injected mass. The moles of each detected component in a sample were then calculated based on its signal intensity relative to that of the Phytostan sample times the moles in the Phytostan sample. The mass of each component was calculated using its molecular weight, accounting for salt form. The mass percent of each component was then obtained by dividing the mass of each component by the mass injected for the sample.

## Results

Table 1 shows all the information gathered from the received samples.

### Source

We received 17 samples from five different known vendors during 2013. Samples were submitted from nine different countries with date purchases from 2006 to 2013. One of the 17 samples was excluded due to suspected contamination during handling.

### Samples

The 16 remaining samples used were: iboga root bark (n = 6), iboga TA extract (n = 5), iboga PTA HCl (n = 1), ibogaine HCl (n = 3), and *Voacanga africana* root bark (n = 1). Of the six samples of iboga root bark, one was sold as coming from a supplier in Cameroon.

### Alkaloid content

We were able to identify and quantify up to five different alkaloids from the samples (see Table 1).

Table 2 shows means and ranges of iboga alkaloids found in the analysed samples.

The alkaloid identification profile of the samples was similar for all products, except for one sample which did not contain any iboga alkaloid. The quantity of ibogaine was highly variable among the samples of each type of product and also among different types of products. High variability was especially worrying for the case of samples labelled as TA, which had the largest ibogaine variation. High variation in the content of ibogaine HCl samples was also found, possibly because some were actually PTA HCl based on all

**Table 1.** Description of the samples

| Material | Date of Purchase | Country | Form | Color | Expected ibogaine concentration | Quantitative analysis (GC/MS) |
|---|---|---|---|---|---|---|
| Iboga Root bark | Unknown | Australia | Powder | Light brown | -- | A: 0,6% |
| Iboga Root bark | 2006 | Netherlands | Fine chopped bark | Brown | -- | All unknown substances |
| Iboga Root bark | 17/10/2012 | New Zealand | Powder | Light brown | 2-4% | A: 11.2%<br>C: 0.7% |
| Iboga Root bark | 11/04/2012 | Canada | Powder | Brown | -- | A: 2.1%<br>C: 0,3% |
| Iboga Root bark | 11/04/2012 | Mexico | Powder | Light brown | -- | A: 9.9%<br>B: 0.1%<br>C: 0.6% |
| Iboga Root bark | 03/04/2013 | Germany | Chopped bark | Brown | -- | A: 7.1%<br>B: 1.5%<br>C: 2.3%<br>D: 0.2% |
| Iboga extract-PTA | 11/04/2012 | South Africa | Powder | Light brown | 80% | A: 73.7%<br>B: 4.7%<br>C: 6.1% |
| Iboga extract-TA | Unknown | Australia | Powder | Brown | -- | A: 9.1%<br>B: 2.3%<br>C: 0.6%<br>D: 0.2%<br>E: 0.1% |
| Iboga extract-TA | 07/04/2010 | South Africa | Powder | Brown | 40% | A: 32.9%<br>B: 0.2%<br>C: 2.1%<br>D: 0.4%<br>E: 0.3% |
| Iboga extract-TA | 16/05/2012 | New Zealand | Sticky raisin | Dark brown | 35% (sold as 35% of ibogaine) | A: 25.4%<br>B: 0.5%<br>C: 16.4%<br>D: 0.6%<br>E: 0.6% |
| Iboga extract-TA | 16/08/2012 | New Zealand | Pressed Powder | Dark brown | Less than 5% (sold as 35% of ibogaine) | A: 13.3%<br>B: 0.2%<br>C: 1.6%<br>D: 0.1%<br>E: 0.1% |
| Iboga extract-TA | 11/10/2012 | New Zealand | Powder | Dark brown | Less than 10% (sold as 35% of ibogaine) | A: 8.2%<br>B: 0.2%<br>C: 0.8%<br>D: 0.1%<br>E: 0.1% |
| Iboga extract-TA | 07/05/2013 | Hawai USA | Powder | Light brown | -- | A: 61.6%<br>B: 7.2%<br>C: 7.1% |
| Voacanga africana Root bark | 03/04/2013 | Spain | Pieces of bark | Brown | 5-10% carbometoxi-ibogaina (voacangine) | A: 0.6%<br>D: 2.1% |
| Ibogaine HCL | Unknown | Australia | Powder | White | -- | A: 73.4%<br>C: 2.1% |
| Ibogaine HCL | 07/05/2013 | Hawai USA | Powder | White | -- | A: 65.9%<br>C: 8.7% |

Note. A: ibogaine; B: ibogaline; C: ibogamine; D: iboleutine; E: voacangine.

**Table 2.** Alkaloid summary

| | Iboga Root Bark (n = 6) | | | TA (n = 5) | | | Ibogaine HCl (n = 3) | | | PTA HCl (n = 1) | | | *V. africana* (n = 1) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Ave. | Range | N | Ave. | Range | N | Ave. | Range | N | Ave. | Range | N | Ave. | Range |
| Ibogaine | 5 | 6.2% | 0.6%-11.2% | 5 | 17.8% | 8.2%-32.9% | 3 | 67.0% | 61.6%-73.4% | 1 | 73.7% | -- | 1 | 0.6% | -- |
| Ibogaline | 2 | 0.8% | 0.1%-1.5% | 5 | 0.69%% | 0.2%-2.3% | 1 | 7.2% | -- | 1 | 4.7% | -- | 0 | -- | -- |
| Ibogamine | 4 | 0.98% | 0.3%-2.3% | 5 | 4.3% | 0.6%-16.4% | 3 | 5.9% | 2.1%-8.7% | 1 | 6.1% | -- | 0 | -- | -- |
| Voacangine | 1 | 0.2% | -- | 5 | 0.25% | 0.1%-0.6% | 0 | -- | -- | 0 | -- | -- | 1 | 2.1% | -- |
| Iboleutine | 0 | -- | -- | 5 | 0.27% | 0.1%-0.6% | 0 | -- | -- | 0 | -- | -- | 0 | -- | -- |

of them containing ibogamine and/or ibogaline in amounts similar to those for PTA HCl.

The expected concentrations of ibogaine in the samples (which were rated by the senders) were below our results in two cases, with a large difference in iboga root bark from Cameroon, which had almost three times more ibogaine than expected. The remaining samples rated by the senders were above our results, with the largest discrepancy observed in the *V. africana* sample, which was expected to have a concentration of 5%-10% of voacangine but showed less than 2.1%.

We also found unknown substances in several samples which we were unable to identify.

## Discussion and conclusions

This is the first report analysing iboga products from on-line suppliers. Results show a large diversity of iboga alkaloid content in all the different products (iboga root bark, iboga extracts and ibogaine HCl). This is especially meaningful for the ibogaine HCl samples, which are supposed to be purified. However, some ibogaine samples that have been used for scientific purposes in the past showed traces of ibogamine or ibogaline, even when the concentration of ibogaine was between 95% and 99.6%[17]. Traces of ibogamine or ibogaline are to be expected in ibogaine isolated from the Tabernanthe iboga plant. During the analysis we also found substances other than iboga alkaloids in three of the samples, although we could not identify them. As noted above, we also found one sample that did not contain any iboga alkaloid. Also, two other samples contained less than 1% ibogaine. Low or zero concentrations of ibogaine should be of high concern. A recent report of a product sold as iboga bark was found to be Rauvolfia powder, which did not contain any iboga alkaloids and caused the death of the subject who used it thinking it was iboga root bark[18].

The most relevant implication from these results is that ibogaine users are often not able to know the quality and purity of the purchased products when they come from on-line suppliers. Since many users and treatment providers obtain iboga/ibogaine for the treatment of addiction, they increase the potential risk of suffering side effects or adverse situations when they buy material of unknown quality from on-line suppliers. These adverse situations can include overdoses and fatalities[15,19].

The contents of alkaloids in the iboga plant have a large variation and depend on many variables such as subspecies, growing environment, harvesting time, conservation of the samples, etc. Our results could be a reflection of the variability of alkaloid concentrations in iboga-derived products and its relationship with dosing difficulties. Important cardiovascular effects are observed at doses often used in drug-detoxification. Ibogaine needs to be provided in low doses to ensure safety[20] and because the variability within iboga products can be a source of serious adverse reactions, this is an issue that should be taken into account by practitioners.

Given the high variability of ibogaine concentrations in iboga-derived products, both users and providers should be careful during dose calculations. At the same time, harm reduction programs should include qualitative and quantitative drug analysis to avoid overdosing and related fatalities. Since this 2013 analysis, the manufacture of high-purity ibogaine HCl from *Voacanga africana* bark has increased, offering treatment providers with a another way to avoid the quality issues inherent in using bark or crude alkaloids for treatment.

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Contributors: JCB and BDL conceived of the study and collected the samples. JCB wrote the first draft of the manuscript. IF and MMV performed the analysis of the products. IF, MMV and CWJ interpreted the chemical analysis. BDL, ASC, DFG, RGD, JECH, MAAC and CWJ contributed to data interpretation and literature review. All authors contributed to and have approved the final manuscript.

## Conflict of interest

No conflict declared.

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# Neutrophil-lymphocyte ratio in catatonia

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## Abstract

**Background:** There is growing evidence of subclinical inflammation in mental disorders. **Objective:** The aim of this study was to investigate frequency of symptoms of catatonia and the newly diagnosed subclinical inflammatory markers which are neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), monocyte/lymphocyte (MLR) ratios in catatonia patients due to mental disorders. **Methods:** Patients who were admitted to psychiatry clinic with the diagnosis of catatonia according to DSM 5 in the last two years and equal number of control group were included in this retrospective study. Univariate analysis of covariance controlled for possible confounders was used to compare NLR, PLR, MLR ratios between patients and the control group. **Results:** A total of 34 catatonia patients and 34 healthy controls were included in the study. Patients' mean age was 30.88 + 13.4. NLR value was significantly higher in the patient group than control group. There was no significant difference between the patients and control group according to PLR, MLR values. **Discussion:** The presence of subclinical inflammation in catatonic syndrome due to mental disorders should be considered. Subclinical inflammation that was observed in numerous mental disorders continues in catatonia due to mental disorders. Large-scale studies are needed to determine the role of inflammation in catatonia.

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**Keywords:** Catatonia, inflammation, neutrophil-lymphocyte ratio, platelet lymphocyte ratio, monocyte/lymphocyte ratio, symptom frequency.

## Introduction

Catatonia, first described by Karl Kahlbaum, is a neuropsychiatric disorder characterized by the presence of motor, behavioral, emotional and vegetative symptoms[1]. DSM-IV included the schizophrenia catatonic subtype. Catatonic type: a type of schizophrenia in which the clinical picture is dominated by at least two of the following: 1) motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor; 2) excessive motor activity (that is apparently purposeless and not influenced by external stimuli); 3) extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism; 4) peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing; 5) echolalia or echopraxia. In DSM-5 catatonia is defined by the presence of three or more of the following symptoms; stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypes, agitation, grimacing, echolalia, echopraxia[2]. The most common catatonic symptoms are staring, mutism, negativism, stupor, withdrawal, rigidity, posturing and catalepsy[3,4]. It can be seen as neurological disorders, endocrine, metabolic disorders, acute onset due to systemic infections and also psychiatric conditions[5] and it is increasingly becoming one of the main psychopathological areas within the spectrum of schizophrenia and other psychotic disorders and mood disorders[6].

It has been thought that there is central GABAergic, dopaminergic and glutamatergic dysfunction in physiopathology of catatonia[7]. Its pathophysiology is not clearly understood[7]. Medical catatonia is related to inflammation, neural damage, neurodevelopmental disorders, structural brain pathologies that affect central nervous system[8]. Researches on etiological basis of catatonia due to psychiatric disorders are still insufficient. Various evidence has been put forward regarding familial-genetic factors[9].

Subclinical inflammation is defined as a low grade inflammatory which may continue in symptom free periods of inflamatuar diseases[10-12]. High-sensitive C-reactive protein (hs-CRP), interleukin 6 (IL-6), IL-1 receptor antagonist are some of the subclinical inflammatory markers which were used in clinical studies[13-15]. Subclinical inflammation has been described in also mental disorders like major depressive disorder, bipolar disorder, schizophrenia and schizoaffective disorder which can be presented with catatonia[15-17]. Recent studies support this inflammation hypothesis in severe mental disorders[18]. In fact, the evidence of subclinical inflammation presence in mental disorders that do not exhibit catatonic features is also prominent[19-21]. However, the role of inflammation in mental disorders is not clearly understood. Also there are studies suggest that auto-immune diseases increase the risk of schizophrenia and bipolar disorders[21,22]. It has been reported that systemic lupus erythematous which is a chronic inflammatory auto-immune disease presented with catatonia symptoms and was improved with lupus treatment[23].

One of the determinants of chronic inflammation is the white blood cell count and its subtypes. Neutrophil/lymphocyte ratio (NLR) is a new parameter indicating the subclinical inflammation[24,25]. Recently, platelet/lymphocyte (PLR), monocyte/lymphocyte (MLR) ratio has been used to determine inflammation[26,27].

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In this study, we aimed to explore the frequency of symptoms of catatonia in primary outcome and investigate whether there is an increase in NLR, PLR, and MLR in catatonia patients as part of mental disorders that have been implicated with subclinical inflammation as secondary outcome.

## Methods

Patients diagnosed with catatonia according to the DSM-5 criteria and treated in the psychiatry clinic were included in this retrospective study between November 2016 and November 2018. The approval for the study was obtained from the Ethics Committee before collection of data. Totally 43 patients were detected in this review of inpatients records. Patients with severe neurological disease, diabetes mellitus and other endocrinopathies, patients with liver disease, malignant disease, mental retardation, obesity (BMI ≥ 30), pregnancy, using anti-inflammatory drugs (NSAIDs, corticosteroids) and alcohol/substance use disorder or addiction history were excluded from the study. Rest of the patients (34) were included the study. Symptoms of the patients according to DSM 5 criteria were examined. Magnetic resonance imaging without contrast had been performed in all patients and no organic brain damage had been observed. Patients' hemoglobin values had been within normal range. Preliminary evaluation of all patients had been completed and patients had not had any active infections. Patients' thyroid stimulant hormone values had been within normal range. No substance had been detected in the urine. The control group was chosen as the last 34 healthy individuals without any disabilities who applied to the health board in the last 6 months.

Sociodemographic and clinical variables as age, gender, education, smoking status, weight and length had been recorded. Weight/length$^2$ (kg/m$^2$) formula was used to calculate BMI.

NLR, PLR, MLR which are subclinical inflammatory markers were compared between 34 patients and 34 control groups. Descriptive statistics were used for the demographic characteristics of 34 patients with catatonia. $\chi^2$ test was used to compare categorical variables. t-test was used for comparison of normally distributed variables between the two groups. Mann-Whitney U test was used for comparison of abnormal distributed variables. Finally, the effects of factors such as age, sex, smoking and BMI on NLR, PLR, MLR levels of patients were analyzed using univariate analysis of covariance (ANCOVA). SPSS 22.0 (IBM Corporation, Armonk, New York, United States) software was used in the analysis of variables.

## Results

A total of 68 cases (34 catatonia and 34 healthy controls) were included in our study. Eighteen patients (53%) were female, 16 were male (47%). Mean age was 30.88 + 13.4; mean education years were 6.08 + 3.2. Seven of the catatonia patients had no psychiatric diagnosis in the past. Of these 7 patients who were admitted for catatonia for the first time, 3 were diagnosed with bipolar manic episode and 4 with major depression at the end of the treatment in psychiatry clinic. Of the 27 patients who had psychiatric follow-up in the past, 5 had schizophrenia, 14 had bipolar disorder (9 had manic episodes before catatonia, 5 had depressive episodes) and 8 had major depression (4 with psychotic features). There were no significant differences between the groups in terms of age, sex, smoking and marital status (Table 1).

The most common symptoms in patients were mutism 70.5% and negativism 64.7%. The symptoms and frequencies according to DSM 5 are shown in Table 2.

NLR ratio was significantly higher in patients with catatonia compared to controls (p = 0.004). No difference was found between the patient and the control group in terms of MLR, PLR (Table 3).

Covariance analysis revealed that NLR levels were significantly higher in patients compared to control group (Table 4).

**Table 1.** Sociodemographic data

| | | Case control | | P |
|---|---|---|---|---|
| | | Catatonia | Control | |
| Sex | Male | 16 (47%) | 13 (38.2%) | 0.469 |
| | Female | 18 (53%) | 21(61.8%) | |
| Age | | 30.88 ± 13.4 | 36,4 ± 12,2 | 0.084 |
| Education (year) | | 6.08 ± 3.2 | 7,58 ± 3,7 | 0.086 |
| Body mass index | | 23.5 ± 7.5 | 22.9 ± 1.26 | 0.054 |
| Smoke | Yes | 14 | 11 | 0.458 |
| | No | 20 | 23 | |
| Marital Status | Married | 20 | 26 | 0.097 |
| | Single | 14 | 8 | |

**Table 2.** Frequency of catatonia symptoms according to DSM 5 criteria

| Catatonia symptoms | Symptom frequency |
|---|---|
| Mutism | 24 (70.5%) |
| Negativism | 22 (64.7%) |
| Waxy Flexibility | 18 (51.4%) |
| Posturing | 14 (41.7%) |
| Stupor | 12 (35.2%) |
| Catalepsy | 9 (26.4%) |
| Stereotypes | 8 (22.8%) |
| Agitation | 8 (22.8%) |
| Grimacing | 6 (17.6%) |
| Mannerism | 3 (8.8%) |
| Echolalia | 1 (2.9%) |
| Echopraxia | 0 |

**Table 3.** Comparison of NLR, PLR, MLR of patients and control group

| | Mean ± standard deviation | | P |
|---|---|---|---|
| | Catatonia | Control | |
| NLR | 2.81 ± 1.5 | 1.95 ± 0.70 | 0.004* |
| MLR | 0.33 ± 0.1 | 0.27 ± 0.1 | 0.080 |
| PLR | 134.0 ± 47.2 | 147.1 ± 52.6 | 0.287 |

*p<0.05

**Table 4.** Results of NLR, PLR, MLR levels between patients and control group with ANCOVA

| | Mean ± standard error | | P |
|---|---|---|---|
| | Catatonia | Control | |
| NLR | 2.85 ± 0.20 | 2.09 ± 0.21 | 0.010* |
| MLR | 0.33 ± 0.02 | 0.29 ± 0.02 | 0.298 |
| PLR | 133.8 ± 8.6 | 154.7 ± 8.9 | 0.100 |

*p<0.05

## Discussion

In this study, we investigated NLR, PLR, and MLR in catatonia patients as part of mental disorders that have been implicated with subclinical inflammation. The results of our study put forth that there is a subclinical inflammation (higher NLR) in catatonia patients due to mental disorders. Additionally, frequency of clinical features related with catatonia will be discussed.

The first finding of our study is the frequency of mood disorders in catatonia patients. Catatonia is associated with many pathophysiological processes and is most commonly associated with mood disorders[28]. In our study, 29/34 (85%) of the patients were followed up with mood disorder and 17/34 (50%) with bipolar disorder.

Excitation (72.7%), immobility/stupor (21.4%) and mutism (15.6%) were reported as the most common symptoms in catatonia due to medical conditions[28]. We found that mutism (70.5%) and

negativism (64.7%) were the most common symptoms in catatonia due to mental disorders compatible with previous studies[3,4].

Considering the dysfunction associated with GABAergic, dopaminergic, and glutamatergic neurotransmitter[7] in the mechanism of catatonia, the link between neurotransmitters and inflammation is noteworthy. Pro-inflammatory cytokines interact with the cytokine network in the central nervous system; neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and related motor activity so these inflammatory cytokines can affect almost every aspect of brain function related to motivational behavior[29,30]. These effects of the immune system in the brain can cause behavioral consequences and neuropsychiatric disorders[29,30]. Large-scale studies are needed to determine the role of inflammation in catatonic patients and to evaluate NLR separately bipolar disorder, major depression and psychosis with catatonia.

According to our literature review, this study is the first study investigating systemic low grade inflammation in catatonia syndrome due to psychiatric disorders. There are evidence that proinflammatory cytokines, CRP, oxidative parameters increase in psychiatric disorders. These are findings that support subclinical inflammation[16,17,31,32]. Recent studies have explored the subclinical inflammation in severe mental disorders using NLR, MLR, and PLR. A study found that NLR was higher in patients with drug naïve major depressive disorder patients[33] and NLR and PLR were found to be higher in bipolar disorder both depressive and euthymic phase[33,34]. A study compared bipolar disorder and schizophrenia in terms of subclinical inflammation and found that NLR, PLR, MLR higher in patients with bipolar disorder or schizophrenia than in control group, NLR, MLR but not PLR were higher in patients with schizophrenia than in patients with bipolar disorder[27]. Another study was found that NLR, MLR but not PLR were higher in patients with bipolar disorder in manic state. A recent meta-analysis identified 11 studies exploring the NLR, PLR, MLR in mood disorders has shown that NLR and PLR higher in patients with bipolar disorders than healthy controls while the differences were not significant in subgroup analysis among studies including only patients with bipolar disorder euthymic phase[35]. Another recent meta-analysis identified 11 studies exploring NLR, PLR, MLR in non-affective psychosis has shown that NLR an d MLR higher in patients than control group[36]. So predominantly NLR seems to be more reliable inflammatory markers in severe mental disorders[18].

PLR was not shown significant differences between patients and controls in this study. But, NLR was found to be more reliable marker for subclinical inflammation than PLR[37]. So these results support the presence of subclinical inflammation in catatonia.

NLR is low cost and reproducible tests that can be easily determined, calculated in simple laboratory conditions. NLR has been shown to predict poor prognosis and major inflammation in chronic medical disorders[38,39]. The result of our study supports the presence of subclinical inflammation in catatonia. In our literature review, we could not find a study of systemic inflammation in catatonia patients. However, myelin abnormalities have been described to cause low grade neuroinflammation and catatonic behavior[38]. Probably myelin abnormalities and systemic low grade inflammation are interrelated. The underlying mechanism of neuroinflammation caused catatonic behavior is not fully understood[38].

The retrospective design of the study and the low number of patients are limitations of this study. The drug use duration of the patients was unknown. Patient group was not a homogenous group in terms of mental disorders. Seven of them had no psychiatric diagnosis in the past and they were newly diagnosed. Comparisons are needed in the same mental diagnostic groups. Also NLR, MLR, PLR rates may be a weak parameter in the determination of inflammation and it is recommended that they should be supported through studies using other inflammatory markers together. There was a statistical trend for age and education between groups. The diagnosis of catatonia was made according to the DSM-5, and a clinical examination was performed by two psychiatrists. But, structured psychiatric assessments, such as the SCID II were not performed.

As a result, the presence of a subclinical inflammation in the catatonic syndrome due to mental disorder should be considered in addition to medical and neurological conditions. NLR as a subclinical inflammatory marker is higher in catatonia. Subclinical inflammation that was observed in numerous mental disorders continues in catatonia due to mental disorders. NLR may be a more reliable marker for subclinical inflammation in severe mental disorders. This study will guide the future studies in the evaluation of the etiology of catatonia and evaluation of treatment options.

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## Disclosure

The authors report no conflict of interests.

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