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Review article

Letters to the editor

XRCC4 rs6869366 polymorphism is associated with susceptibility to both nicotine dependence and/or schizophrenia

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Abstract

Background: Oxidative stress induced DNA damage has been assumed to contribute to the etiopathogenesis of schizophrenia (Sch). Smoking prevalence was more common in patients with Sch. The X-ray repair cross-complementation group 4 (*XRCC4*) gene plays an important role in the repair of DNA double-strand breaks. **Objective:** The purpose of this study was to investigate whether *XRCC4* rs6869366 polymorphism has a relationship both in nicotine dependence (ND) and Sch+ND risk. **Methods:** One hundred and four patients with Sch+ND, 133 subjects with ND only and 70 healthy controls were enrolled in the study. *XRCC4* rs6869366 polymorphism was analyzed using PCR-RFLP assay. **Results:** The frequency of *XRCC4* rs6869366 GG genotype was more common in the ND and Sch+ND group than controls (p = 0.001 and p = 0.001, respectively). *XRCC4* rs6869366 TT genotype was lower in both ND and Sch+ND group compared to controls (p = 0.001 and p = 0.001, respectively). Also, *XRCC4* rs6869366 G allele was higher in Sch+ND group than controls (p = 0.001) while *XRCC4* rs6869366 T allele was lower in ND group than healthy controls (p=0.001). *XRCC4* rs6869366 GT genotype was lower in ND group than control group (p = 0.003). **Discussion:** These results suggested that the *XRCC4* rs6869366 polymorphism G related genotype/allele was associated with susceptibility to both ND and Sch+ND in a Turkish population.

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Keywords: DNA repair, Schizophrenia, nicotine dependence, *XRCC4*.

Introduction

Schizophrenia (Sch, OMIM181500), manifested by delusions, hallucinations, altered cognition, emotional reactivity, and disorganized behavior[1], is one of the most debilitating and heterogeneous neuropsychiatric diseases. It occurs in about 1% of the population worldwide. Scientific evidence suggests that environmental factors are not solely accused for the development of this disease, genetic factors also play crucial role in predisposition to Sch. Conventional twin studies and population based family trials have already implicated the heredity in Sch with a frequency exceeding 80% and 60% respectively, establishing genetic traits underlying Sch[2]. Smoking is an important public health problem all around the world, causing death of almost six million people annually. Evidence supports that patients with severe psychiatric disorders tend to suffer from nicotine dependence (ND)[3,4].

Oxidative stress occurs as a result of an abnormal redox regulation in which the intracellular concentrations of reactive oxygen species (ROS), exceed the antioxidant capacity[5]. It is generally assumed that a surplus of ROS is highly toxic and harms cellular elements, such as nucleic acids, proteins and lipids[6]. Oxidative damage leads to DNA base alterations, such as abasic sites, oxidized base modification, deamination, methylation, nucleotide deletion, nucleotide insertion, bulky abducts, single-strand breaks (SSBs), double-strand breaks (DSBs), inter- and intra-strand cross-links (ICLs), and DNA-protein cross-links[7].

In vivo studies have reported that chronic administration of nicotine leads to the instability of pro-oxidant/antioxidant equilibrium in blood cells, blood plasma and tissues of rats[8], while *in vitro* studies showed that nicotine heavily harms DNA and damages the prooxidant/antioxidant equilibrium in lymphocytes[9]. In addition, various experiments have also shown the relation between antioxidant status and symptom severity or psychosis ratings, that may associate the antioxidant defense system defects with Sch pathogenesis[10]. In mammalian cells, numerous predominant DNA repair mechanisms are well analyzed, such as direct repair, base excision repair (BER), nucleotide excision repair (NER), mismatch repair, homologous recombination repair (HR), and non-homologous end-joining repair (NHEJ)[11]. *XRCC4* gene is found on the chromosomal 5q14.2 and it is involved in precise end-joining of blunt DNA double strand breaks (DSBs)[12]. It was reported that genetic polymorphisms in DNA repair genes affect DNA repair ability and result in tendency to various disease types. Therefore, the purpose of this study was to investigate whether there is a relationship between *XRCC4* rs6869366 variant and ND and Sch+ND risk.

Methods

Subjects

The study population involved a total of 104 patients diagnosed with Sch+ND, 133 subjects with ND and age, gender matched 70 healthy individuals as controls. The subjects were selected among the individuals from Bakirkoy Research and Training Hospital for Psychiatry Hospital, Istanbul Turkey and Yedikule Hospital for Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul Turkey. Clinical diagnosis of Sch were made in strict accordance with DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders, the fourth edition) based on SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders) by two independent psychiatrists[13]. The average amount of tobacco consumed per day was recorded for each participant. The severity of ND was evaluated by the scores on Heaviness of Smoking Index (HSI) and the Fagerström Test for Nicotine Dependence (FTND). The healthy control subjects were randomly recruited from relatives of patients in the Medicine Department, outpatient clinic, in the

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same hospital. Control subjects had a negative family or past history of any psychiatric disorders and had no family relationship to the present study patients. Informed written consent was obtained from the patients. The patient's information was anonymized before submission. The work was approved by Local Ethics Committee. All the procedures performed in the study were in accordance with the Declaration of Helsinki.

Genotyping

DNA was isolated with high salt DNA extraction method from peripheral blood samples[14]. Genotyping of *XRCC4* rs6869366 variant was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay according to previous paper[15]. The *XRCC4* rs rs6869366 variant was determined using the following primers: 5′-GAT GCG AAC TCA AAG ATA CTG A-3′, 5′-TGT AAA GCC AGT ACT CAA ACT T-3′, 55°C annealing temperature for the PCR reaction. The PCR product was digested with *HincII* enzyme. The digested PCR products were separated on a 2% agarose gel and stained with ethidium bromide for visualization under ultraviolet light (Figure 1). For quality control, the genotyping analysis was done blind as regards participants.

Statistical analysis

The SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL; USA) was used for statistical analyses. The results were statistically analyzed by calculating the odds ratios (OR) and 95% confidence intervals (CI) using the χ^2 test. Differences in *XRCC4* rs6869366 genotype distribution between the patient and control groups were compared with chi-square test and, Fisher's exact test was used when needed. The Hardy-Weinberg Equilibrium (HWE) test was done to examine whether the allele and genotype frequencies in the studied groups remain constant from generation to generation in the absence of other evolutionary influences or not. All *p*-values were two sided, and a *p*-value was regarded as statistically significant when it less than 0.05.

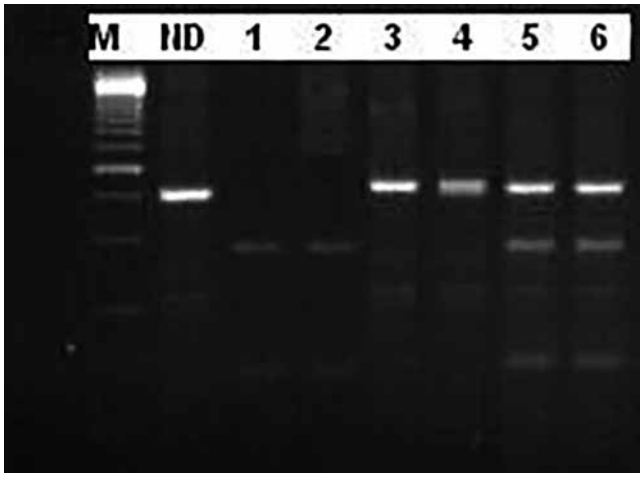

Figure 1. RFLP analysis of PCR products. Lane M: Marker; Lane ND: Non-digest PCR product; Lanes 1 and 2: homozygous TT; Lane 3 and 4: homozygous GG; Lanes 5 and 6: heterozygous GT.

Results

For *XRCC4* rs6869366 variant, 104 Sch+ND patients, 133 subjects with ND and 70 healthy controls were evaluated. The genotype and allele distributions of *XRCC4* rs6869366 among the groups are showed in Table 1. It was found that *XRCC4* rs6869366 TT genotype was significantly lower in Sch+ND and ND group compared to controls (p = 0.001, OR: 28.333, 95% Cl: 6.434–124.762; p = 0.001, OR: 82.884, 95% Cl: 10.936–628.176, respectively). The frequency of *XRCC4* rs6869366 GG genotype was more common in the Sch+ND and ND group than the control group (p = 0.001, OR: 0.112, 95% Cl: 0.056–0.227; p = 0.001, OR: 0.071, 95% Cl: 0.035–0.143, respectively). It was observed that the GT genotype was lower in ND group than the controls (p = 0.003, OR: 0.826, 95% Cl: 1.459–5.474).

Frequency of *XRCC4* rs6869366 G allele was higher in Sch+ND group than healthy control group (p = 0.001, OR: 0.173, 95% Cl: 0.107–0.281) while that of *XRCC4* rs6869366 T alelle was lower in ND group than controls (p = 0.001, OR:0.074, 95%Cl:0.043–0.127).

Discussion

Cigarette smoke contains more than 7000 chemical compounds, along with a high levels of oxidants[16]. Cigarette smoke holds 10^{17} oxidant molecules per puff[17]. Nicotine is the major alkaloid present in cigarettes. It was first obtained as a distillate from tobacco, is detected in the blood of smokers[18]. Nicotine is among the most addicting substances and can induce oxidative stress in quantities similar to those in cigarette smoke, as shown *in vitro* and *in vivo*[19,20]. Chemical carcinogens and ROS can play a role in the accumulation of bulky adducts, SSBs, and DSBs, and several forms of nucleotide base modification or loss which can result in genomic instability.

Sch is a chronic, severe mental illness. The pathogenesis of this disease is unknown, however one generally accepted hypothesis for the etiology is that variations in more than one risk genes, each with a modest additive consequence, interacting with environmental and developmental factors, are involved in appearance of disease phenotype[21]. Between 40 and 90% of schizophrenics smoke. This ratio is remarkably higher than a several comparison populations such as those with other serious mental diseases[22]. Numerous studies have reported various indices of oxidative stress (increased cellular levels of ROS, disturbed antioxidant balance and increased oxidative damage) in blood, cerebrospinal fluid, and post-mortem brains from Sch patients compared with matched normal controls[23]. Further findings supporting a role of redox imbalances and oxidative stress in the

Table 1. Genotypes and allelic frequencies for *XRCC4* rs6869366 polymorphism in Sch+ND, ND and control groups

XRCC4	Sch+ND	ND	Controls	OR*	%95 CI*	p
Genotypes	**n = 104 (%)**	**n = 133 (%)**	**n = 70 (%)**			
TT	2 (1.93)	1 (0.75)	27 (38.58)	28.333[a] 82.884[b]	6.434-124.762[a] 10.936-628.176[b]	0.001[a] 0.001[b]
GT	25 (24.04)	23 (17.29)	26 (37.14)	1.876[a] 2.826[b]	0.964-3.618[a] 1.459-5.474[b]	0.089[a] 0.003[b]
GG	77 (74.03)	109 (81.96)	17 (24.28)	0.112[a] 0.071[b]	0.056-0.227[a] 0.035-0.143[b]	0.001[a] 0.001[b]
Alleles						
T	29 (13.94)	25 (9.39)	80 (57.14)	0.074[b]	0.043-0.127[b]	0.001[b]
G	179 (86.06)	241 (90.61)	60 (42.86)	0.173[a]	0.107-0.281[a]	0.001[a]

Fisher's Exact Test, [a]:Sch + ND versus control group; [b]: ND versus control group.

The results that are statistically significant are shown in *boldface.

development of Sch arise from several animal models, which imply that increased oxidative stress during sensitive windows of brain development and maturation is related to the subsequent occurrence of Sch-linked brain and behavioral abnormalities[24,25]. Brain tissue is particularly vulnerable to oxidative stress because it has a high rate of oxidative metabolic activity, high oxygen consumption, relatively low concentrations of antioxidant enzymes, and a neural network that is vulnerable to damage[26].

The DNA repair system acts as a cellular defense mechanism against DNA damage due to mostly oxidative stress. Altered or deficient bases and SSBs are usually fixed through the BER. There are two major mechanisms for DSBs repair which are called homologous recombination and NHEJ. The NHEJ is the main pathway to repair DSBs in mammals[27]. To evaluate the cellular ability for DNA repair in Sch patients, DNA damage under basal conditions and due to cellular stressors was measured. Flow cytometric analysis of the DNA DSB marker γH2AX in immortalized lymphoblasts from Sch patients showed a significantly increased baseline levels of γH2AX in untreated cells, and a decreased γH2AX response upon irradiation with 5 Gray[28]. In the NHEJ pathway, a relatively small number of essential repair proteins regulate the DSB repair, such as *XRCC4*.

XRCC4 encodes a nuclear phosphoprotein that multimerizes and interacts with DNA Ligase 4 and DNA-dependent protein kinase, involving in the NHEJ pathway[29]. The *XRCC4* is expressed in brain. In mice, lack of *XRCC4* is lethal in embryos leading to a massive neuronal apoptosis, and *XRCC4* has been reported to act with p53 in the regulation of apoptosis, suggesting that *XRCC4* is important for genomic stability and for the inhibition of tumors[30]. In the gene-targeting mutation mice model, *XRCC4* gene inactivation results in late embryonic mortality along with defective lymphogenesis and defective neurogenesis characterized by broad apoptotic death of newly produced postmitotic neurons[31]. These results showed that differentiating lymphocytes and neurons rigorously necessitate the *XRCC4* end-joining proteins. Genome-wide scan showed that 5q14.1 is related with Sch risk, and the gene encoding *XRCC4* is found in this region. Several genetic variants in the *XRCC4* have been reported in humans. One of them is a variable number tandem repeat (VNTR) variant in intron 3 of the *XRCC4* gene. The other, the rs6869366 SNP is found at 1394 bp upstream of the *XRCC4* gene, and is involved in regulating gene expression[32].

It is generally believed that variations of the sequence of the promoter region are linked with a altered level of gene expression. Thus, this type of polymorphism may affect the expression level of the gene. Variants of these specific SNPs might result in an abnormal capacity for protein products, causing several deficiencies. When a DNA repair gene is incapable of normal expression, its downstream genes are directly influenced, leading to the dysfunction of the whole pathway. Therefore, these variants result in a decreased capacity of the repair system and increase the risk of cell pathogeneses.

Considering the higher smoking rates among Sch patients and the close association between nicotine and oxidative stress, and the crucial role of free radicals in the pathophysiology of Sch, we hypothesized that whether *XRCC4* rs6869366 variant is related with both ND group and ND+Sch group in a Turkish cohort. As far as we know, there has been no study conducted about the correlation between *XRCC4* rs6869366 variant and both ND and ND+Sch.

Previously, it was shown that frequencies of *XRCC4* rs6869366 TG+GG genotypes were higher in patients with autism spectrum disorder than the controls[33]. He *et al.* reported that patients who smoked and carried the *XRCC4* rs6869366 G allele had an increased risk for non small cell lung cancer (NSCLC)[34]. In a study conducted on the patients with lung cancer, Hsu *et al.* demonstrated that people with rs 6869366 GT genotype and smoking habit present the highest risk of lung cancer than other groups[35]. However in a study investigating urothelial bladder cancer, Mittal *et al.* found no association between *XRCC4* rs6869366 variant and smoking[36]. We have previously demonstrated that *XRCC4* intron 3 VNTR variant ID genotype was higher in ND group than in healthy control group[37]. In present study, we found that the frequency of *XRCC4* rs6869366 GG genotype and G allele were more common in the both ND group and Sch+ND group than the control group ($p = 0.001$ and $p = 0.001$, respectively). *XRCC4* rs6869366 TT genotype and T allele were significantly lower in ND and Sch+ND group compared to the controls ($p = 0.001$ and $p = 0.001$, respectively). Furthermore, we found that *XRCC4* rs6869366 GT genotype was lower in ND group than control group ($p = 0.003$). The absence of this significance in the Sch+ND group was attributed to heterozygous disadvantage.

In conclusion, for the first time, we showed that *XRCC4* functional rs6869366 variant plays a role in the risk of ND and ND+Sch in a Turkish population. Our results suggested that *XRCC4* rs6869366 GG genotype and G allele might be a susceptibility factor for both ND and Sch+ND. It stresses that this DNA repair mechanism has a role in the etiopathogenesis of Sch and ND, and that further studies in this issue should be done in different populations.

References

1. Rao W, Zhou N, Zhang H, Liu R, Zhang S, Su Y, et al. A case-control study of the association between polymorphisms in the fibrinogen alpha chain gene and schizophrenia. Dis Markers. 2017;2017:3104180.
2. Feng Y, Cheng D, Zhang C, Li Y, Zhang Z, Wang J, et al. Association between ErbB4 single nucleotide polymorphisms and susceptibility to schizophrenia: A meta-analysis of case-control studies. Medicine (Baltimore). 2017;96(8):e5920.
3. de Leon J, Tracy J, McCann E, McGrory A, Diaz FJ. Schizophrenia and tobacco smoking: a replication study in another US psychiatric hospital. Schizophr Res. 2002;56(1-2):55-65.
4. Pawlina MMC, Rondina RC, Espinosa MM, Botelho C. Nicotine dependence and levels of depression and anxiety in smokers in the process. Rev Psiq Clín. 2014;41(4):101-5.
5. Mitra S, Natarajan R, Ziedonis D, Fan X. Antioxidant and anti-inflammatory nutrient status, supplementation, and mechanisms in patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2017;78:1-11.
6. Pizarro JG, Folch J, Vazquez De la Torre A, Verdaguer E, Junyent F, Jordán J, et al. Oxidative stress-induced DNA damage and cell cycle regulation in B65 dopaminergic cell line. Free Radic Res. 2009;43(10):985-94.
7. Yan J, Wang X, Tao H, Deng Z, Yang W, Lin F. Meta-Analysis of the Relationship between XRCC1-Arg399Gln and Arg280His Polymorphisms and the Risk of Prostate Cancer. Sci Rep. 2015;5:9905.
8. Suleyman H, Gumustekin K, Taysi S, Keles S, Oztasan N, Aktas O, et al. Beneficial effects of Hippophae rhamnoides L. on nicotine induced oxidative stress in rat blood compared with vitamin E. Biol Pharm Bull. 2002;25(9):1133-6.
9. Sudheer AR, Muthukumaran S, Devipriya N, Menon VP. Ellagic acid, a natural polyphenol protects rat peripheral blood lymphocytes against nicotine-induced cellular and DNA damage in vitro: with the comparison of N-acetylcysteine. Toxicology. 2007;230(1):11-21.
10. Wu JQ, Kosten TR, Zhang XY. Free radicals, antioxidant defense systems, and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2013;46:200-6.
11. Sancar A, Lindsey-Boltz LA, Unsal-Kaçmaz K, Linn S. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annu Rev Biochem. 2004;73:39-85.
12. Wang Y, Wang L, Li X, Liu B, Zhao Q, Chen P, et al. Polymorphisms of XRCC4 are involved in reduced colorectal cancer risk in Chinese schizophrenia patients. BMC Cancer. 2010;10:523.
13. American Psychiatric Association. Text Revision. 4th. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 2000.
14. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988;16(3):1215.
15. Cifci S, Yilmaz M, Pehlivan M, Sever T, Okan V, Pehlivan S. DNA repair genes polymorphisms in multiple myeloma: no association with XRCC1 (Arg399Gln) polymorphism, but the XRCC4 (VNTR in intron 3 and G-1394T) and XPD (Lys751Gln) polymorphisms is associated with the disease in Turkish patients. Hematology. 2011;16(6):361-7.
16. Faux SP, Tai T, Thorne D, Xu Y, Breheny D, Gaca M. The role of oxidative stress in the biological responses of lung epithelial cells to cigarette smoke. Biomarkers. 2009;14 Suppl 1:90-6.

17. Donohue JF. Ageing, smoking and oxidative stress. Thorax. 2006;61(6):461-2.
18. Hammond D, Collishaw NE, Callard C. Secret science: tobacco industry research on smoking behaviour and cigarette toxicity. Lancet. 2006;367:781-7.
19. Solak ZA, Kabaroglu C, Cok G, Parildar Z, Bayindir U, Ozmen D, et al. Effect of different levels of cigarette smoking on lipid peroxidation, glutathione enzymes and paraoxonase 1 activity in healthy people. Clin Exp Med. 2005;5(3):99-105.
20. Rytilä P, Rehn T, Ilumets H, Rouhos A, Sovijärvi A, Myllärniemi M, et al. Increased oxidative stress in asymptomatic current chronic smokers and GOLD stage 0 COPD. Respir Res. 2006;7(1):69.
21. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry. 2005;10(1):40-68.
22. Kelly C, McCreadie RG. Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. Am J Psychiatry. 1999;156(11):1751-7.
23. Mahadik SP, Pillai A, Joshi S, Foster A. Prevention of oxidative stress-mediated neuropathology and improved clinical outcome by adjunctive use of a combination of antioxidants and omega-3 fatty acids in schizophrenia. Int Rev Psychiatry. 2006;18(2):119-31.
24. Cabungcal JH, Counotte DS, Lewis E, Tejeda HA, Piantadosi P, Pollock C, et al. Juvenile antioxidant treatment prevents adult deficits in a developmental model of schizophrenia. Neuron. 2014;83(5):1073-84.
25. Cabungcal JH, Steullet P, Morishita H, Kraftsik R, Cuenod M, Hensch TK, et al. Perineuronal nets protect fast-spiking interneurons against oxidative stress.Proc Natl Acad Sci U S A. 2013;110(22):9130-5.
26. Bošković M, Vovk T, Kores Plesničar B, Grabnar I. Oxidative stress in schizophrenia. Curr Neuropharmacol. 2011;9(2):301-12.
27. Li Z, Otevrel T, Gao Y, Cheng HL, Seed B, Stamato TD, et al. The XRCC4 gene encodes a novel protein involved in DNA double-strand break repair and V(D)J recombination. Cell. 1995;83(7):1079-89.
28. Catts VS, Catts SV, Jablensky A, Chandler D, Weickert CS, Lavin MF. Evidence of aberrant DNA damage response signalling but normal rates of DNA repair in dividing lymphoblasts from patients with schizophrenia. World J Biol Psychiatry. 2012;13(2):114-25.
29. Hayden PJ, Tewari P, Morris DW, Staines A, Crowley D, Nieters A, et al. Variation in DNA repair genes XRCC3, XRCC4, XRCC5 and susceptibility to myeloma. Hum Mol Genet. 2007;16(24):3117-27.
30. Gao Y, Ferguson DO, Xie W, Manis JP, Sekiguchi J, Frank KM, et al. Interplay of p53 and DNA-repair protein XRCC4 in tumorigenesis, genomic stability and development. Nature. 2000;404(6780):897-900.
31. Chiu CF, Wang CH, Wang CL, Lin CC, Hsu NY, Weng JR, et al. A novel single nucleotide polymorphism in XRCC4 gene is associated with gastric cancer susceptibility in Taiwan. Ann Surg Oncol. 2008;15:514-8.
32. Wu KH, Wang CH, Yang YL, Peng CT, Lin WD, Tsai FJ, et al. Significant association of XRCC4 single nucleotide polymorphisms with childhood leukemia in Taiwan. Anticancer Res. 2010;30(2):529-33.
33. Dasdemir S, Guven M, Pekkoc KC, Ulucan H, Dogangun B, Kirtas E, et al. DNA repair gene XPD Asp312Asn and XRCC4 G-1394T polymorphisms and the risk of autism spectrum disorder. Cell Mol Biol (Noisy-le-grand). 2016;62(3):46-50.
34. He F, Chang SC, Wallar GM, Zhang ZF, Cai L. Association of XRCC3 and XRCC4 gene polymorphisms, family history of cancer and tobacco smoking with non-small-cell lung cancer in a Chinese population: a case-control study. J Hum Genet. 2013;58(10):679-85.
35. Hsu NY, Wang HC, Wang CH, Chang CL, Chiu CF, Lee HZ, et al. Lung cancer susceptibility and genetic polymorphism of DNA repair gene XRCC4 in Taiwan. Cancer Biomark. 2009;5(4):159-65.
36. Mittal RD, Gangwar R, Mandal RK, Srivastava P, Ahirwar DK. Gene variants of XRCC4 and XRCC3 and their association with risk for urothelial bladder cancer. Mol Biol Rep. 2012;39(2):1667-75.
37. Pehlivan S, Uysal MA, Aydin PC, Pehlivan M, Nursal AF, Yavuzlar H, et al. eNOS and XRCC4 VNTR variants contribute to formation of nicotine dependence and/or schizophrenia. Bratisl Lek Listy. 2017;118(8):467-71.

Development, applicability and effects of a pilot program of group cognitive-behavioral therapy in Brazilian adolescents with anorexia nervosa

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Abstract

Background: Most of the clinical trials involving cognitive-behavioral therapy (CBT) for the treatment of anorexia nervosa (AN) used the individual therapy format, and few have been dedicated to adapting and assessing the effects of the group format. **Objectives**: To assess the applicability and effects of a group CBT program for Brazilian adolescents with AN. **Methods:** Open clinical trial with 22 patients with AN divided into an intervention group – IG (n = 11; CBT, psychiatry, nutrition and family psychoeducation-6 months) and a control group – CG (n = 11; psychiatry, nutrition and family psychoeducation-6 months). Data collected at baseline, at the end of groups and six months after the completion were: weight, height, body mass index and Eating Disorder Examination Questionnaire (EDE-Q) used to assess the severity of AN symptoms. **Results:** Baseline homogeneous groups, with 91% adherence in the IG vs. 54% in the CG (p = 0.05). Participants in both groups regained weight and decreased symptoms of eating disorders at the end of groups. Comparing the EDE-Q scores IG presented a statistically significant difference in the restraint subscale of the EDE-Q between the end-of-group and the follow-up (p = 0.01). **Discussion:** Group CBT program produced positive effects and was applicable in Brazilian adolescents with AN as an adjuvant to multidisciplinary treatment.

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Keywords: Anorexia nervosa, cognitive therapy, adolescents, group therapy.

Introduction

Anorexia nervosa (AN) is a serious eating disorder, which stands out among psychiatric disorders because it has the highest mortality rate in the general population affected[1]. With typical onset in adolescence, it can affect up to 0.7% of girls at this phase, while being associated with family, sociocultural and biological risk factors[2]. Better prognoses are usually found in younger patients when treated early in the onset of symptoms[2].

A recent systematic review[3] indicated that the most tested model of treatment in childhood and adolescence is family-based therapy (FBT)[4], which is recommended by the international reference guidelines in mental health, such as those of the National Institute for Health and Clinical Excellence[5]. However, even this treatment modality may not be adequate for all families or patients[5] and the results are considered to be modest[3]. The authors of the study consider further studies to be needed due to the scarcity of clinical trials, the methodological weaknesses and the different designs tested.

CBT and CBT-E have also been studied as recommended alternatives for the treatment of these patients[5]. One of the basic assumptions of CBT is that individuals develop and maintain basic beliefs throughout their lives that interfere with and influence how they perceive themselves, as well as how they perceive the world around them[6]. In the case of AN patients, weight loss is perceived as an achievement, indicating self-discipline, whereas weight gain is understood as failure and loss of self-control, which seriously interferes with self-esteem[7]. These dysfunctional beliefs about physical shape, weight and eating, function as a risk factor for the establishment of eating pathology and also as maintainers of this condition[8].

Most of the randomized trials involving CBT and CBT-E for the treatment of AN used the individual therapy format based on the models of Garner *et al.*[8], Garner and Bemis[9], as well as the transdiagnostic model[10,11]. Despite it being possible to adapt these model to the group therapy format, few studies have been dedicated to adapting and assessing the effects of the treatment with this configuration.

In particular, in Brazil, where there is a shortage of specialized healthcare services for the treatment of eating disorders (ED) in the Public Healthcare System (SUS – *Sistema Único de Saúde*) and a waiting list to receive care[12], the group format could increase the capacity to absorb the existing demand. No study with this objective has been tested in Brazil. The objective of the study is to assess the applicability and effects of a group CBT program developed in a Brazilian teaching hospital for the treatment of AN.

Methods

Participants

This is an open clinical trial with AN patients under 18 years of age, that were diagnosed by way of a physician's assessment using the Development and Well-being Assessment (DAWBA), an instrument based on ICD-10 and DSM-IV criteria. Patients that had physical complications that required hospitalization, risk of suicide and/or psychiatric comorbidities prior to AN were excluded from the study.

Assessment instruments

Eating disorders examination questionnaire – EDE-Q[13,14]

Self-reporting questionnaire with 28 questions that aim to assess eating disorder symptoms associated with four subscales: restraint, concern with weight, concern with physical shape and concern with eating. The response options range from 0 to 6 according to the number of days or times in the last four weeks that the patient has

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experienced any of the eating disorder symptoms. The instrument was translated by the coordinators of Protad due to the lack of a version validated for use in Brazil.

Development and Well-Being Assessment – DAWBA

A set of questionnaires and interviews aimed at the diagnosis of psychiatric disorders in childhood and adolescence, based on ICD-10 and DSM-IV criteria[15].

Procedures

The sample was divided into two groups: IG, in which the patients received psychiatric, nutritional and family psychoeducational treatment and were submitted to group Cognitive-Behavioral treatment for 6 months; CG, in which the patients were submitted to psychiatric, nutritional, family psychoeducational treatment and to a control group for 6 months in which the patients maintained a food diary.

The study was developed in a teaching hospital and conducted in a Brazilian healthcare service specialized in the treatment of ED in childhood and adolescence. The study-design was approved by the Research Ethics Committee, under CAAE No.: 20524513.8.0000.0068.

The data collected at baseline, at the end and six months after the respective completion were: weight, height, body mass index (BMI) and the Eating Disorder Examination Questionnaire (EDE-Q) used to assess the severity of AN symptoms. The instruments were applied by the psychologists who were not directly involved in the patients' treatment.

CBT Program

The CBT program was developed based on a model used in the respective mental health department and the models of Garner *et al.*[8], as well as the Fairburn transdiagnostic model[11], used in randomized studies on CBT and AN, while respecting the adaptation for adolescents and for the group format. The initial model lasted three months, with 12 to 14 non-manualized sessions, with favorable clinical outcomes, despite not yet being tested in clinical trials.

The current program was structured in 24 manualized sessions held in a group setting, lasting 90 minutes, over a six-month period. The group was led by psychotherapists specialized in CBT. Hand-crafted glasses were developed to symbolize the main cognitive distortions present in AN patients, as well as a head band that the adolescents were to use when they identified with thoughts associated with AN.

Data analysis

Descriptive and inferential statistical analyses were performed using the Statistical Package for Social Science, version 24. The data were processed in the software platform Research Electronic Data Capture[16] (REDCap). Mean and standard deviation for weight, BMI and EDE-Q scores were calculated for the groups at baseline, at the end-of-groups and at six months of follow-up. The normality of the variables was verified by using the Shapiro-Wilk test.

For the calculation of the difference in the participants' adhesion in each group, the Z Test was used for the proportional difference in independent groups. The Mann-Whitney test (numerical variables) and the chi-square test (categorical variables) were used to assess, at baseline, possible sociodemographic and clinical differences between the IG and CG. Differences in baseline *vs.* end of group and end *vs.* follow-up, within each group, were assessed by the Wilcoxon test. Differences in performance between the groups at the end and in follow-up were assessed by using a nonparametric repeated-measures analysis of variance with two factors. A probability level of 95% ($p \leq 0.05$) was adopted for the rejection of null hypotheses.

Being adopted as a complete remission criterion was: zero score in the EDE-Q and weight recovery according to the percentile expected for gender and age, between 25 and 75 (or return to the percentile that the patient presented before the ED, except for the cases of prior obesity). Partial remission: patients who recovered weight but who still had eating psychopathology indicators, or patients weighing below the 25th percentile or reported to be underweight before the ED, while demonstrating improvement in eating psychopathology indicators.

Results

The IG and CG were compared at baseline, in order to assess the homogeneity of distribution of the participants. Regarding socio-demographic data in terms of socioeconomic status, family type and ethnicity, there were no statistically significant differences between the groups. No statistically significant differences were found in the clinical variables investigated. Table 1 shows the results for the comparisons between the groups.

Adherence to treatment

In the IG, of the initial 11 patients in the group, 10 (91%) remained until the end. In the CG, of the initial 11 patients, 6 (54%) patients remained until the end, with this difference being considered statistically significant ($Z = 1.91$, $p = 0.05$).

Remission at the end of groups

At the end, 2 (20%) IG patients presented complete remission of symptoms vs. 1 (16.7%) of the CG ($Z = 0.16$, $p = 0.86$). Partial remission occurred in 8 (80%) IG patients *vs.* 5 (83.3%) in the CG ($Z = -0.17$, $p = 0.86$). At the end in the IG, 10 (100%) patients were between the 25-50 percentiles or higher *vs.* 6 (100%) in the CG.

Remission at follow-up

In the follow-up of the IG, 3 (30%) presented complete remission vs. 1 (16.6%) of the CG ($Z = 0.59$, $p = 0.54$). At this stage, 7 (70%) from the IG presented partial remission *vs.* 5 (83.3%) from the CG ($Z = -0.60$, $p = 0.54$). At the follow-up stage, 7 (70%) participants were in the 25-50 percentiles *vs.* 6 (100%) from the CG ($Z = -1.48$, $p = 0.13$) (Table 2).

Table 1. Comparison of clinical characteristics of the IG and CG at baseline

	Intervention Group (IG) (N = 10)		Control Group (CG) (N = 06)		Mann-Whitney
Variables	Mean	SD	Mean	SD	p-value
Years of age	14.80	1.28	14.00	1.69	0.175
Duration of symptoms (months)	12.30	6.39	6.83	1.47	0.127
Initial weight (kg)	46.40	5.2	44.10	7.61	0.828
Initial height (cm)	162.1	5.6	157.8	4.8	0.158
Initial BMI (kg/m²)	17.62	1.51	17.56	2.22	0.745
Weight loss (kg)	9.10	6.47	10.10	3.46	0.581
EDE-q (Global)	3.25	1.83	4.56	0.75	0.159
EDE-q (Restraint)	3.20	1.94	4.60	0.82	0.230
EDE-q (Weight Concern)	3.48	1.95	4.73	1.00	0.210
EDE-q (Shape Concern)	3.76	1.81	5.12	0.81	0.127
EDE-q (Eating Concern)	2.56	1.92	3.80	1.33	0.276
	N (%)		N (%)		P value Chi-square
Depression	2 (20%)		2 (33.3%)		0.551
Anxiety	3 (30%)		3 (50%)		0.424
Amenorrhea	7 (70%)		5 (83.33%)		0.792

Source: study data.

Table 2. Results of assessments performed between the baseline, the end and follow-up for the intervention and control groups

Variables	Intervention Group (IG) (n = 10)			Control Group (CG) (n = 06)			IG	CG	IG	CG	Interaction IG vs. CG	Interaction IG vs. CG
	Baseline (T0)	End (T1)	Follow-up (T2)	Baseline (T0)	End (T1)	Follow-up (T2)	T0-T1		T1-T2		T0-T1	T1-T2
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	P*	P*	P*	P*	P**	P**
Weight (kg)	46.3 (5.2)	52.2 (5.7)	52.9 (7.5)	44.0 (7.6)	51.5 (9.2)	53.5 (10.8)	**0.005**	**0.028**	0.575	**0.028**	0.403	0.280
BMI (kg)	17.62 (1.51)	19.74 (1.27)	19.95 (2.00)	17.56 (2.22)	20.34 (2.59)	20.96 (3.27)	**0.005**	**0.028**	0.508	**0.028**	0.386	0.112
EDE Q Global	3.25 (1.83)	1.14 (1.53)	0.54 (1.38)	4.56 (0.75)	1.74 (1.57)	1.14 (1.67)	**0.007**	**0.046**	**0.012**	0.345	0.561	0.409
Subscales												
Restraint	3.20 (1.94)	0.56 (0.94)	0.30 (0.81)	4.60 (0.82)	0.70 (1.04)	0.93 (1.48)	**0.007**	**0.028**	**0.026**	0.414	0.234	**0.012**
Concern with weight	3.48 (1.95)	1.32 (1.94)	0.70 (1.80)	4.73 (1.00)	2.10 (1.64)	1.30 (1.97)	**0.014**	**0.028**	0.072	0.344	0.591	0.573
Concern with eating	2.56 (1.92)	0.86 (1.20)	0.44 (1.06)	3.8 (1.33)	1.46 (1.46)	0.73 (1.11)	**0.018**	0.074	**0.016**	0.131	0.585	0.952
Concern with shape	3.76 (1.81)	1.83 (2.21)	0.75 (1.86)	5.12 (0.81)	2.71 (2.60)	1.62 (2.22)	**0.036**	0.075	**0.018**	0.345	0.678	0.248

Intervention Group = (Cognitive Behavioral Therapy + psychiatry, nutrition and family psychoeducation), Control group = (psychiatry, nutrition and family psychoeducation). BMI = body mass index, EDE-Q = Eating Disorder Examination Questionnaire.

* Wilcoxon test used to compare the means of each variable between the baseline and the end of the IG and CG and between the end and the follow-up.

** Wald test for the effect of interaction, to assess the difference in performance between the intervention and control groups between the baseline and the end, and between the end-of-groups and the follow-up.

$P \leq 0.05$.

Source: study data.

Intragroup analysis

There was a statistically significant difference in all variables analyzed after the IG. Mean weight gain and change in BMI remained the same in the follow-up. With the exception of the weight concern subscale, all the variables investigated by the EDE-Q improved in the follow-up.

In the CG, at the end, significant differences in weight, BMI and in all variables assessed by EDE-Q were also found, with the exception of eating and shape concern subscales. In the follow-up, mean weight and BMI in the CG were statistically greater than those after the intervention. No significant difference was found in the variables of the EDE-Q.

Intergroup analysis

At the end of groups there was no statistically significant difference in any of the variables investigated. In the follow-up, despite the EDE-Q restraint subscale being the only subscale presenting a statistically significant difference in the comparison between IG and CG ($W = 6.19$, $p = 0.012$), the analysis of the means of all the EDE-Q scales were lower in the IG, which indicates a lower severity of ED symptoms.

Discussion

The results of this clinical trial demonstrated that the group CBT program is applicable, while having tools that were well accepted by the adolescents and is possibly responsible for the patients' improved treatment adherence in comparison with the CG. These results are in line with a recent systematic review that assessed the efficacy and adherence of CBT in 16 studies[17].

In the present study, complete remission was observed in 20% of patients at the end of the group therapy and in 30% at follow-up. Similar results were found in another study[18], which found complete remission in 19% at the end of treatment and 33% in the second year of follow-up. The clinical trial[19] found slightly higher complete remission rates: 30% at the end of treatment and 33% at three years of follow-up.

Partial remission was achieved by 80% of patients at the end-of-group in the IG and by 70% at follow-up. It was not possible to compare these results with those of other studies due to lack of data or methodological differences.

In this study, the IG patients presented a mean weight gain and improvement in the means for eating symptoms at the end of group and at follow-up. This result is in line with previous studies[18,20-22] and is a preliminary indicator of the positive effects of multidisciplinary treatment using CBT.

The majority of IG patients maintained their respective weight gain between the end-of-group and follow-up, except those who were discharged immediately following the end-of-group. Despite presenting worse results in comparison with those observed in the CG in terms of regained weight, the reduction of ED symptoms assessed by the EDE-Q was more expressive (in descriptive terms) in the IG, while showing a statistical difference in the comparison between the groups in the subscale which assesses restraint, in the follow-up. A similar result, with regard to the reduction of symptoms, was presented in a study[23] that compared CBT with Psychodynamic Therapy.

The CG did not present a significant statistical difference in the improvement of the eating symptoms between the end-of-group and the follow-up; whereby the intervention group continued to maintain improvement in three of the four subscales of the EDE-Q: restraint, eating concern and shape concern. The only subscale that did not present a significant statistical difference between the end-of-group and the follow-up in the intervention group was related to the weight concern.

As pointed out in a systematic review[17], CBT appears to be useful in preventing the risk of relapse in the future and the fact that IG demonstrated continued improvement in symptoms between the end-of-group and follow-up may support this observation, for example, the study by Carter *et al.*[24] who observed, in patients treated with CBT, the permanence without eating symptoms for a longer period of time.

Despite a weight gain being found in both groups, changes in dysfunctional beliefs regarding body, shape and eating were more visible in the IG, as assessed through the subscales of the EDE-Q. CBT in the treatment of EDs aims to modify the mechanisms that maintain the eating psychopathology[11]. Since dysfunctional beliefs are risk factors for engaging the diet and weight loss, which in turn are triggers for the reappearance of ED, it is therefore necessary to address these issues. This measure is indicative of better long-term prognostics[24].

This is the first Brazilian clinical trial with a control group to assess the effects of group CBT in the treatment of AN in adolescence. Therefore, this is a pioneering study, in that it presents a pilot program of group CBT adapted for adolescents with AN, while being manualized and capable of being replicated. The proposed objectives were achieved, however, some methodological weaknesses limit the significance of the findings. Although the number of sessions for each group was the same, the period of treatment offered to each patient varied between groups. In addition, because the CG did not receive psychotherapeutic intervention and because of the impossibility of blinding in the study, the professionals may have unintentionally offered more attention to these patients. In addition, there was no control for psychotropic medication for the symptoms of psychiatric comorbidities in the two groups, nor for the possible psychotherapeutic interventions that the patients of the CG may have undergone during the treatment, which translates into a threat to the internal validity of the study. As a threat to external validity, the reduced sample size is noted, which makes it difficult to generalize the results.

It is expected that the present study will stimulate additional scientific productions on the theme of ED in childhood and adolescence, in Brazil. For future studies we recommend replications with larger samples, a clinical trial in the Brazilian population with longer follow-up periods to better assess the effects of CBT in the treatment of adolescents with AN, and comparison between individual and group formats.

The results suggest that the group CBT program produced positive effects and was applicable in Brazilian adolescents with AN as an adjuvant to multidisciplinary treatment aimed at improving adherence and diminishing the risk of relapse.

Brazilian Clinical Trials Registry (ReBec)

RBR-4dpths.

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Conflict of interest

Nothing to declare.

References

1. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. Arch Gen Psychiatry. 2011;68(7):724-31.
2. Fitzpatrick KK, Lock J. Anorexia nervosa. BMJ Clin Evid. 2011;2011. pii: 1011.
3. Alckmin-Carvalho F, Bergamo JV, Cobelo AW, Fabbri A, Pinzon VD, Melo MHDS. Evidence-based psychotherapy for treatment of anorexia nervosa in children and adolescents: systematic review. Arch Clin Psychiatry. 2018;45(2):41-8.
4. Lock J, Le Grange D. Treatment manual for anorexia nervosa: A family-based approach. Guilford Publications; 2015.
5. National Institute for Health and Clinical Excellence. Eating disorders: recognition and treatment NICE guideline NG69. 2017. Available from: https://www.nice.org.uk/guidance/ng69/chapter/Recommendations. Acessed on: 8 Nov. 2017.
6. Beck JS. Teoria Cognitiva: Teoria e Prática. Porto Alegre: Artes Médicas; 1997.
7. American Psychiatric Association. DSM-5: Manual Diagnóstico e Estatístico de Transtornos Mentais. 5 ed. Porto Alegre: Artmed; 2014.
8. Garner DM, Vitousek KM, Pike KM. Cognitive-behavioral therapy for anorexia nervosa. In: Garner DM, Garfinkel PE, editors. Handbook for Treatment of Eating Disorders. New York: Guilford; 1997. p. 94-144.
9. Garner DM, Bemis KM. Cognitive therapy for anorexia nervosa. In: GD M, Garfinkel PE, editors. Handbook of Psychotherapy for Anorexia Nervosa and Bulimia. New York: Guilford; 1985. p. 107-46.
10. Fairburn CG, Cooper Z, Shafran R. Cognitive behaviour therapy for eating disorders: a "transdiagnostic" theory and treatment. Behav Res Ther. 2003;41(5):509-28.
11. Fairburn CG. Behavior Therapy and Eating Disorders. New York: The Guilford Press; 2008.
12. Moya T, Fleitlich-Bilyk B. Waiting lists for treatment of eating disorders in childhood and adolescence. Rev Bras Psiquiatr. 2003;25(4):259-60.
13. Fairburn CG, Beglin SJ. Assessment of eating disorders: interview or self-report questionnaire? Int J Eat Disord. 1994;16(4):363-70.
14. Fairburn, CG. Eating Disorder Examination Questionnaire (EDE-Q 6.0). In: Fairburn CG (ed). Cognitive Behavior Therapy and Eating Disorders. New York: Guilford Press; 2008. p. 309-13.
15. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry. 2000;41(5):645-55.
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
17. Galsworthy-Francis L, Allan S. Cognitive Behavioural Therapy for anorexia nervosa: a systematic review. Clin Psychol Rev. 2014;34(1):54-72.
18. Gowers SG, Clark A, Roberts C, Griffiths A, Edwards V, Bryan C, et al. Clinical effectiveness of treatments for anorexia nervosa in adolescents: randomised controlled trial. Br J Psychiatry. 2007;191:427-35.
19. Ricca V, Castellini G, Lo Sauro C, Mannucci E, Ravaldi C, Rotella F, et al. Cognitive-behavioral therapy for threshold and subthreshold anorexia nervosa: a three-year follow-up study. Psychother Psychosom. 2010;79(4):238-48.
20. McIntosh VV, Jordan J, Carter FA, Luty SE, McKenzie JM, Bulik CM, et al. Three psychotherapies for anorexia nervosa: a randomized, controlled trial. Am J Psychiatry. 2005;162(4):741-7.
21. Fairburn CG, Cooper Z, Doll HA, O'Connor ME, Palmer RL, Dalle Grave R. Enhanced cognitive behaviour therapy for adults with anorexia nervosa: a UK-Italy study. Behav Res Ther. 2013;51(1):R2-8.
22. Dalle Grave R, Calugi S, Doll HA, Fairburn CG. Enhanced cognitive behaviour therapy for adolescents with anorexia nervosa: an alternative to family therapy? Behav Res Ther. 2013;51(1):R9-12.
23. Zipfel LS, Wild B, Gross G, Friederich HC, Teufel M, Schellberg D, et al. Focal psychodynamic therapy, cognitive behaviour therapy, and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study): randomised controlled trial. Lancet 2014;383(9912):127-37.
24. Carter J, McFarlane T, Bewell C, Olmsted M, Woodside D, Kaplan A, Crosby R. Maintenance treatment for anorexia nervosa: a comparison of cognitive behavior therapy and treatment as usual. Int J Eat Disord. 2009;42(3):202-07.

The effect of obsessive compulsive symptoms on psychopathology in patients with schizophrenia

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Abstract

Background: There is a growing interest on the impact of comorbid obsessive-compulsive symptoms (OCS) on the course and severity of schizophrenia in recent years. **Objectives:** This study determined the prevalence of OCS in schizophrenia patients and the clinical outcomes of the comorbidity. **Methods:** A total of 220 schizophrenia patients were recruited. All the participants completed Structure Clinical Interview version, Yale Brown Obsessive Compulsive Scale, Calgary Depression Scale for Schizophrenia, Columbia Suicide Severity Rating Scale and World Health Organization Quality of Life – Brief Version (WHOQOL-BREF). **Results:** Significantly higher number of schizophrenia patients with OCS were taking Clozapine ($p = 0.023$) and antidepressants ($p = 0.013$). Schizophrenia patients with OCS showed more severe positive ($p < 0.001$) and general symptoms ($p < 0.001$) of schizophrenia, higher depressive symptoms ($p = 0.013$), higher suicidality ($p < 0.001$), more hospitalization ($p = 0.044$), poorer physical ($p = 0.034$) and psychological ($p = 0.032$) domain in WHOQOL-BREF. **Discussion:** Schizophrenia patients with OCS are associated with more severe psychopathology and depressive symptoms which subsequently suffered poorer physical and psychological health. Hence, recognition of OCS in schizophrenia and early initiation of effective treatment may be able to reduce the burden for people with chronic mental illness.

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Introduction

Schizophrenia is a long-term serious psychotic disorder characterized by main clinical features of hallucinations, delusions, disorganized thoughts, changes in behavior, and negative symptoms. Over the years, clinicians and researchers paid less attention to non-psychopathological manifestations among the schizophrenia patients, one of which is the obsessive-compulsive symptoms (OCS). Despite a wide variation of prevalence noted in many parts of the world, ranging from 1.1% to 50%[1], a more recent study observed that the pooled prevalence was 30.7%[2]. OCS in schizophrenia were once thought to be rare and benign in nature, however some recent studies have shown not only greater prevalence rate but poorer outcome among these patients[3]. Interestingly, many researchers were facing difficulties to generalize the findings as there were no standard criteria available to determine the presence of clinically significant OCS, as compared to obsessive compulsive disorder which can be clearly categorized in Diagnostic and Statistical Manual of Mental Disorder (DSM).

In the past, obsession had not only been postulated to protect against psychosis and thought disorganization[4] but also believed to prevent "personality disintegration" in schizophrenia[5]. However, these findings were not reproducible in subsequent studies, which found that schizophrenia with OCS had actually worse outcomes[6,7]. Two years ago, a group of researchers again proved that patients suffering from schizophrenia with OCS had significantly higher scores in both the Positive and Negative Syndrome Scale (PANSS) and Beck Depression Inventory (BDI) when compared to the non-OCS group[8]. Furthermore, higher rates of suicidal plans or attempts were also found among these patients[9,10]. There were findings from various studies to suggest that schizophrenia with OCS might be a distinct subtypes of schizophrenia[7,11,12]; and that OCS itself was considered as one of the core clinical features and symptom domains of schizophrenia rather than being an additional clinical condition[6].

There are growing evidence to suggest the existence of a schizo-obsessive compulsive disorder (Schizo-OCD) subtype of schizophrenia. This subtype is shown to manifest different neuropsychological and clinical outcomes among the schizophrenia patients. A proposed diagnostic criteria for Schizo-OCD was available since 2012[13]. In that proposed criteria, criterion A of OCD must be present at some point in time during the course of schizophrenia. In addition, the obsession/compulsion must be present in substantial amount of time and must not be related to the delusion or hallucination from schizophrenia. Neurological soft signs (NSS) were defined as "*minor neurological signs which reflect dysfunction in areas of motor coordination, integrative sensory function and ordering complex motor tasks, but the dysfunctions are not localizable to specific brain structure*"[14,15]. Studies showed that Schizo-OCD scored higher in the Neurological Evaluation Scale (NES) compared to healthy controls[16,17], but no difference when compared with schizophrenia alone. These findings have further suggested that Schizo-OCD may be a distinct subtype of schizophrenia, and not merely a more severe form of OCD. In addition, previous studies had consistently reported there were no significant differences between OCS in obsessive compulsive disorder (OCD) and Schizo-OCD in term of clinical characteristics[18,19]. Faragian *et al*. reported that the symptoms in Schizo-OCD were comparable to those revealed in "pure" OCD. The author concluded that the universal mechanisms were involved in the pathogenesis of OCD regardless of the presence of schizophrenia[18,19].

Contradictions on the effects of atypical anti-psychotic (AAPs) medications such as clozapine on schizophrenic patients still exist. The risk of AAPs-induced OCS has been reported in many studies[20-22]. AAPs with higher serotonergic activities has higher propensities in inducing OCS[23]. Clozapine stands out as the most frequently reported AAPs to induce OCS due to its highest propensity in serotonergic activities[24,25]. In contrary, existing literatures also showed

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that AAPs such as Aripiprazole and Risperidone to be effective in the augmentation of selective serotonin reuptake-inhibitor (SSRI)-resistant OCD[26,27]. In addition, AAPs with strong dopamine receptor 2 (D2) blockade were reported to be effective in treating Schizo-OCD.

Some studies, however, found no significant difference between schizophrenia with or without OCS in terms of their psychopathology and suicidality[28-30]. We believe that this finding could have been a result of different methodological approach. Studies which recruited inpatients tended to reflect a higher severity in psychopathological domains[6,7] as compared to those which studied on patients recruited from the outpatient settings[28,29]. During acute episodes of psychosis, it would also be very difficult to discern obsessions from delusions of schizophrenia[31]. In addition, some studies had used different definitions for clinically significant OCS resulted in a non-homogenous recruitment of study participants[8,32], while some researchers had shown that both obsessive-compulsive disorder (OCD) and schizophrenia with OCS were no different in terms of their obsessive and compulsive symptom structures[18].

Since the co-occurrence of OCS and schizophrenia had always been an interesting topic of discussion and a real challenge faced by the treating clinicians, but studies had mainly been done in the western countries, we decided to conduct this study in Malaysia to determine the prevalence of OCS among a group of stable schizophrenia patients attending a tertiary hospital outpatient clinic. In addition, our study also intended to resolve any conflicting evidence in literatures and examine the clinical variables of OCS in schizophrenia.

Methods

Subjects

In this cross-sectional study, participants consisted of stable outpatients who were attending their follow up sessions in the psychiatric clinic in University Malaya Medical Center (UMMC) – a tertiary hospital situated in Kuala Lumpur, Malaysia – between August 2014 and July 2015. All recruited participants were diagnosed with schizophrenia based on Diagnostic and Statistical Manual for Mental Disorder, Fifth Edition (DSM-V), understood English or Malay language and were on the same antipsychotic treatment for at least six months. Patients were excluded if (1) they were having active psychotic symptoms, which would affect their capacity for informed consent; (2) they had intellectual disability and dementia, and (3) patients who refused to participate. The study was approved by the UMMC medical ethics committee. All participants were thoroughly briefed on the study protocol and their informed consent obtained. After participants' demographic data were obtained from the case files, all the participants were assessed by the author using Yale Brown Obsessive Compulsive Scale (YBOCS) Symptoms Checklist, Yale-Brown Obsessive Compulsive Scale (YBOCS), Positive and Negative Symptoms for Schizophrenia (PANSS), Calgary Depression Rating Scale (CDSS), Columbia Suicide Severity Rating Scale (C-SSRS) and World Health Organization Quality of Life Scale Brief Malay Version (WHOQOL-BREF).

Demographic variables

The socio-demographic questionnaire was used to record relevant information about the participants of this study which included age, gender, ethnic group, marital status, education level, religion, employment status, family mental history, duration of illness and type of medication. Participants were instructed to complete the questionnaire by filling in the blanks and selecting one response that best described them.

Obsessive compulsive symptomatology

Obsessive compulsive symptoms (OCS) were first screened with Yale Brown Obsessive Compulsive Scale (YBOCS) Symptoms Checklist. Subsequently, patients were assessed with YBOCS[33] to determine the severity of their OCS. It consists of 2 subscales; obsession and compulsion. Total YBOCS score was used to assess the severity of OCS. In this study, clinically significant OCS was defined as total YBOCS score of 8 and above. YBOCS was suitable in the assessment of OCS in Schizophrenia[34].

Schizophrenia psychopathology

Severity of schizophrenia symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS)[35] with the help of the Structure Clinical Interview version (SCI-PANSS). PANSS is a well-defined instrument to assess positive, negative as well as general symptoms in patients with schizophrenia. The higher the score, the more severe the psychopathologies. PANSS has 3 main sub-scales, namely *positive*, *negative* and *general psychopathology*. Overall, total PANSS score reflected the severity of schizophrenia.

Depressive symptomatology

In this study, we utilized the Calgary Depression Scale for Schizophrenia (CDSS)[36] to assess participants' depressive symptoms. CDSS contains nine items. Each item consists of 4 options – 0 for absent, 1 for mild, 2 for moderate and 3 for severe symptoms. Higher score represents worse depressive symptoms.

Suicidality assessment

Suicidality in the present study was assessed using the Columbia Suicide Severity Rating Scale (screening version) (CSSR-S)[37]. Suicidality is defined as any suicidal behavior or ideation during the period of assessment according to the scoring and data analysis guide for CSSR-S. In this study, dichotomous outcome was used to ascertain presence or absence of suicidality.

Quality of life assessment

Participants' quality of life was assessed by using the 26-item World Health Organization Quality of Life – Brief Version (WHOQOL-BREF). A validated Malay Version of WHOQOL-BREF[38] was used in this study. Four domains were assessed, namely physical, psychological, social and environmental which denotes individuals' perception of their quality of life in each domain. Higher score denotes higher quality of life. WHOQOL-BREF (M) score was transformed into domain score comparable with the score used in WHOQOL-100 for data analysis according to the provided guideline.

Statistical analysis

All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) Version 22.0. Normal distribution of quantitative data was assessed using the Shapiro-Wilk test. Chi Square Test and Fisher Exact Test were used when necessary to compare categorical variables between schizophrenia with OCS and without OCS. Mann Whitney's U test was used to compare non-normally distributed continuous variables. Analysis of Covariance (ANCOVA) was performed to control the effect of chronicity of illness which was assessed empirically using duration of illness and the use of clozapine mainly for treatment resistance schizophrenia. Spearman's correlation was performed to examine the possible correlation between obsessive compulsive symptoms and schizophrenia psychopathology. Finally, logistic regression was carried out to analyze independent variables which were associated with OCS in schizophrenia. Level of significance was set at $p < 0.05$.

Results

Demographic data

A total of 220 outpatients were recruited. There was equal gender distribution between males (48.6%) and females (51.4%). Mean age

for the participants was 43.7 years old (SD = 12.4). Majority of the participants were Chinese (57.7%), followed by Indian (23.6%), Malay (15.6%) and others (2.7%). More than two third of the study participants were single (70.0%) and their majority were unemployed (76.8%). Patients were divided into two groups; schizophrenia with OCS and without OCS. There was no significant difference in terms of age, gender, race, education level, employment status, duration of illness and family history of any psychiatric illness between the two groups. In addition, the use of antipsychotic drug classes (both first and second generations) were of no significant difference between the schizophrenia patients with OCS and those without. However, significantly higher number of schizophrenia patients with OCS were taking Clozapine at the time of recruitment (odds ratio = 2.267, $p = 0.023$) (Table 1).

Table 1. Comparison between Schizophrenia with and without OCS

	OCS		OR or U	95% CI or Z	*P* value
	Yes (n = 48) N (%)	No (n = 172) N (%)			
Age, median	38 (98.14)[c]	44 (113.95)[c]	3535.50[a]	-1.523[b]	0.128
Male	24 (50.0)	83 (48.3)	0.933	0.492 – 1.769	0.871
Female	24 (50.0)	89 (51.7)			
Chinese	24 (50.0)	103 (59.9)	0.670	0.352 – 1.274	0.249
Non-Chinese	24 (50.0)	69 (40.1)			
Malay	8 (17.0)	27 (15.7)	0.908	0.382 – 2.155	0.824
Non-Malay	39 (83.0)	145 (84.3)			
Indian	15 (31.3)	37 (21.5)	1.658	0.815 – 3.375	0.180
Non-Indian	33 (68.8)	135 (78.5)			
Single	35 (72.9)	119 (69.2)	0.834	0.408 – 1.703	0.723
Married	13 (27.1)	53 (30.8)			
Secondary and below education	30 (62.5)	129 (75.0)	1.800	0.913 – 3.548	0.102
Tertiary education	18 (37.5)	43 (25.0)			
Employed	10 (20.8)	41 (23.8)	0.841	0.385 – 1.834	0.847
Unemployed	38 (79.2)	131 (76.2)			
Family history of mental illness					
Yes	20 (41.7)	55 (32.0)	1.519	0.788 – 2.932	0.230
No	28 (58.3)	117 (68.0)			
Duration of illness					
Less than 5 years	8 (16.7)	24 (14.0)	0.811	0.339 – 1.941	0.646
5 years and above	40 (83.3)	148 (86.0)			
Antipsychotics					
Typical	6 (12.5)	42 (24.4)			0.171
Atypical	35 (72.9)	112 (65.1)			
Combination	7 (14.6)	18 (10.5)			
Clozapine	30 (62.5)	36 (20.9)	2.267	1.137 – 4.520	**0.023***
Olanzapine	8 (16.7)	30 (17.4)	0.947	0.403 – 2.226	1.000
Risperidone	9 (18.8)	50 (29.1)	0.563	0.254 – 1.248	0.197
Antidepressant	15 (31.3)	23 (13.4)	2.945	1.388 – 6.246	**0.008****
Clinical variables					
More than 5 admissions	29 (60.4)	133 (77.3)	2.234	1.132 – 4.409	0.026*
Antidepressant prescription	15 (31.3)	23 (13.4)	2.945	1.388 – 6.246	0.008**
Suicidality	27 (56.3)	45 (26.2)	3.629	1.868 – 7.048	< 0.001**
PANSS Positive	139.65[c]	102.37[c]	2729.00[a]	-3.603[b]	**< 0.001****
PANSS Negative	121.39[c]	107.46[c]	3605.50[a]	-1.343[b]	0.179
PANSS General	133.22[c]	104.16[c]	3038.00[a]	-2.801[b]	**0.005****
PANSS Total	133.22[c]	104.16[c]	3037.50[a]	-2.798[b]	**0.005****
CDSS	134.31[c]	103.85[c]	2985.00[a]	-3.183[b]	**0.001****
Physical QOL	93.34[c]	115.29[c]	3304.50[a]	-2.121[b]	**0.034***
Psychological QOL	93.13[c]	115.35[c]	3294.00[a]	-2.147[b]	**0.032***
Social QOL	105.22[c]	111.97[c]	3874.50[a]	-0.656[b]	0.512
Environmental QOL	104.97[c]	112.04[c]	3862.50[a]	-0.683[b]	0.494

[a] Median are compared with Mann Whitney's U test with b Z score.

[b] Median are compared with Mann Whitney's U test with b Z score.

[c] Non-normally distributed variables are expressed in mean rank.

Categorical variables with Fisher exact test.

* Significant level at $p < 0.05$.

** Significant level at $p < 0.01$.

Prevalence of OCS in Schizophrenia

In this study, we found that the prevalence of OCS in schizophrenia was 21.8% by using the total YBOCS score of 8 and above (N = 48). The most common obsessions were aggression (8.2%), contamination (8.2%) and miscellaneous (7.8%). For compulsion, the most commonly elicited compulsion was checking (8.2%) and cleaning/ washing (7.8%).

Clinical variables of schizophrenia with OCS

Spearman's correlation was performed and showed that obsession was significantly correlated with positive symptoms ($r = 0.292$, $p < 0.001$) and general symptoms ($r = 0.217$, $p = 0.001$) of schizophrenia. For compulsions, results showed they were significantly correlated with positive symptoms ($r = 0.195$, $p = 0.004$).

In this study, the group of schizophrenia patients with OCS documented significantly more hospitalizations (OR = 2.234, p = 0.026), higher number of prescription of antidepressants (odd ratio = 2.945, p = 0.008) and higher suicidality rate (OR = 3.629, p < 0.001). The same group of patients also scored higher in the PANSS positive subscale (n = 48, U = 2729.00, p < 0.001), general subscale (N = 48, U = 3038.00, p = 0.005), total PANSS (N = 48, U = 3037.50, p = 0.005), and CDSS total score (N = 48, U = 2985.00, p = 0.001). In addition, schizophrenia patients with OCS were also found to be associated with poorer physical quality of life (N = 48, U = 3304.50, p = 0.034) and poorer psychological quality of life (N = 48, U = 3294.00, p = 0.032) (Table 1).

We continued to observe statistically significant differences between schizophrenia patients with OCS and those without, as reflected in the PANSS positive subscale, PANSS general symptoms subscale, PANSS total score and CDSS score (Table 2) after all the confounders were adjusted. For categorical clinical variables, logistic regression was performed by using illness chronicity as the covariate. Results showed the number of hospitalization; presence of suicidality and the use of antidepressant were significantly higher in schizophrenia patients with OCS (Table 3).

Table 2. Comparison between Schizophrenia with or without OCS in clinical variables (PANSS, CDSS and WHOQOL-BREF) using analysis of covariance (ANCOVA), Generalized Linear Models after controlled for chronicity of illness in the study sample

	OCS		Mean difference	P value
	Yes (n = 48) (Mean)	No (n = 172) (Mean)		
PANSS				
Positive	14.98	12.56	2.42	**< 0.001****
General	25.78	22.95	2.82	**0.001****
Total	55.57	49.39	6.18	**< 0.001****
CDSS Total	3.79	2.10	1.69	**< 0.001****
WHOQOL-BREF				
Physical	62.35	57.12	5.23	0.145
Psychological	57.71	59.20	1.51	0.679

P value significant level at P < 0.01**.

Table 3. Logistic regression for clinical variables using chronicity of illness as covariate: hospitalization, suicidality and use of antidepressant

Variables	B	SE	Exp (B)	P value
Hospitalization	0.744	0.369	2.105	**0.044***
Suicidality	1.257	0.348	3.516	**< 0.001****
Use of antidepressant	0.974	0.392	2.650	**0.013***

P value significant level at p < 0.05*, p < 0.01**.

Discussion

From this study, we found that the prevalence of OCS among schizophrenia patients in our setting is 21.8%. This figure is very closed to the finding of a study done in another Asian country, Korea, which revealed a prevalence of 21.1%[21]. Nevertheless, our figure is lower when compared to the prevalence of 30.7% documented in a meta-analysis done in 2014[2]. Despite many studies conducted on this topic over the decades, there are still no universally accepted criteria for the diagnosis of OCS in schizophrenia. We believe that this shortcoming may have further complicated the estimation of prevalence of OCS in schizophrenia. In addition, studies which recruited inpatients[6,7,39] and outpatients[29,40,41] also showed a large difference in the prevalence of the comorbidity.

In terms of the socio-demographic factors between schizophrenia patients with OCS and those without, we observed that the duration of illness is not significantly associated with the presence of OCS in schizophrenia. This is in contrast with previous studies which reported that the longer the illness, the higher the prevalence of OCS in schizophrenia[2,8,42]. As expected, the usage of clozapine in schizophrenia was associated with high OCS, a finding consistent with previous studies[25,43-45]. It was postulated that high propensity of anti-serotonergic properties in clozapine could lead to or exacerbate serotonin deficiency, which subsequently trigger the onset of OCS and yield a full threshold OCD[22,24]. This iatrogenic mental disorder would pose additional challenge to the treatment. Clozapine is the only second generation antipsychotic that is effective in the treatment of resistant schizophrenia (TRS)[46]. Previous studies have identified few treatment options for clozapine induced OCS. One of the treatments is to combine Aripiprazole with Clozapine. Aripiprazole is a second-generation antipsychotic with few trials already carried out showing its effectiveness in treating Clozapine induced OCS in TRS. TRS patients who received the combination of Aripiprazole-Clozapine not only had reduced total YBOCS score at one month after treatment, but also showed better tolerability[47] and improvement in quality of life[48] as compared to Clozapine-placebo group[49]. In fact, by adding on a Selective Serotonin Reuptake Inhibitor (SSRI) it is more effective in treating induced OCS, in cases of treatment-resistant schizophrenia which normally only responds to clozapine. Escitalopram[50], fluvoxamine[51] and fluoxetine[52] had shown their effectiveness in treating induced OCS. However, more trials needed to be done to identify the most effective medication to be used in clozapine induced OCS in treating TRS.

In some of the previous studies, it was reported that schizophrenia patients with OCS were associated with more severe psychopathology[7,8] and depressive symptoms[9,10,40,53]. Our study findings are consistent with these previous studies, as our patients also had more psychotic symptoms and higher depressive symptom scores. These findings were not influenced by chronicity of illness in the participants, as well as the concurrent use of Clozapine. Furthermore, the presence of OCS had been associated with higher suicidality in patients with schizophrenia[12, 54] in which our study also revealed similar finding. This is clinically important as practicing clinicians ought to be aware of the impact of OCS, hence be more vigilant when assessing this group of patients for suicidality.

Our study also noted poorer physical and psychological quality of life among these schizophrenia patients with OCS. These findings are in line with a recent study conducted in Amsterdam which revealed that comorbid OCS in schizophrenia was associated with a lower mean across all domains, namely subjective wellbeing, social integration, emotional regulation, physical and mental health[41]. Similar findings were also reported by Tiryaki and Özkorumak in their study involving 62 patients with schizophrenia and OCS [6]. Thus, we need to create awareness among all practicing clinicians when they treat comorbid OCS, as this will contribute in the improvement of patients' quality of life[55].

Some limitations were present in our study. Firstly, by the nature of a cross-sectional design of our study, we were unable to explore the causal relationship between the presence of OCS and clinical

variables. Secondly, there was no universally accepted criteria to diagnose OCS in schizophrenia. Previous studies had used different criteria to diagnose OCS which produced variabilities in their study outcome. Thirdly, since this study was done at a local outpatient setting, the findings could not be generalized to other parts of the world. Thus, further systematic studies are needed in near future to explore the diagnostic criteria for OCS and a prospective study design to determine the causal relationship of OCS in schizophrenia.

Schizophrenia with OCS remains prevalent in many parts of the world. The awareness of this non-schizophrenia psychopathological comorbid among practicing clinicians is crucial as this is a different entity of psychiatric disorder needing special attention and treatment approach. Gross oversight of this comorbid will result in severe depressive symptoms and higher suicidality. In addition, clinicians need to also be aware of the pro-obsessive effect of Clozapine in the treatment of refractory schizophrenia. It is our hope that more attention will be given to this prevalent condition through rigorous research within this area in near future.

Competing interests

The author(s) declared that they have no competing interests.

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References

1. Berman I, Merson A, Viegner B, Losonczy MF, Pappas D, Green AI. Obsessions and compulsions as a distinct cluster of symptoms in schizophrenia: a neuropsychological study. J Nerv Ment Dis. 1998;186(3):150-6.
2. Swets M, Dekker J, van Emmerik-van Oortmerssen K, Smid GE, Smit F, de Haan L, et al. The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates. Schizophr Res. 2014;152(2-3):458-68.
3. Mulky P, Raghavan DV, Maheshwari S, Kannan P, Jeyaprakash R. Obsessive-Compulsive symptoms in patients with Schizophrenia attending tertiary care centre in South India. Stanley Medical J. 2016;2(4):2-7.
4. Poyurovsky M, Fuchs C, Weizman A. Obsessive-compulsive disorder in patients with first-episode schizophrenia. Am J Psychiatry. 1999;156(12):1998-2000.
5. Bottas A, Cooke RG, Richter MA. Comorbidity and pathophysiology of obsessive-compulsive disorder in schizophrenia: is there evidence for a schizo-obsessive subtype of schizophrenia? J Psychiatry Neurosci. 2005;30(3):187-93.
6. Tiryaki A, Özkorumak E. Do the obsessive-compulsive symptoms have an effect in schizophrenia? Compr Psychiatry. 2010;51(4):357-62.
7. Owashi T, Ota A, Otsubo T, Susa Y, Kamijima K. Obsessive-compulsive disorder and obsessive-compulsive symptoms in Japanese inpatients with chronic schizophrenia - a possible schizophrenic subtype. Psychiatry Res. 2010;179(3):241-6.
8. Kim SW, Jeong BO1, Kim JM, Shin IS, Hwang MY, Paul Amminger G, et al. Associations of obsessive–compulsive symptoms with clinical and neurocognitive features in schizophrenia according to stage of illness. Psychiatry Res. 2015;226(1):368-75.
9. Hagen K, Hansen B, Joa I, Larsen TK. Prevalence and clinical characteristics of patients with obsessive-compulsive disorder in first-episode psychosis. BMC Psychiatry. 2013;13:156.
10. Niendam TA, Berzak J, Cannon TD, Bearden CE. Obsessive compulsive symptoms in the psychosis prodrome: Correlates of clinical and functional outcome. Schizophr Res. 2009;108(1-3):170-5.
11. Rajkumar RP, Reddy YCJ, Kandavel T. Clinical profile of "schizo-obsessive" disorder: a comparative study. Compr Psychiatry. 2008;49(3):262-8.
12. Sevincok L, Akoglu A, Kokcu F. Suicidality in schizophrenic patients with and without obsessive-compulsive disorder. Schizophr Res. 2007;90(1-3):198-202.
13. Poyurovsky M, Zohar J, Glick I, Koran LM, Weizman R, Tandon R, et al. Obsessive-compulsive symptoms in schizophrenia: implications for future psychiatric classifications. Compr Psychiatry. 2012;53(5):480-3.
14. Gupta S, Andreasen NC, Arndt S, Flaum M, Schultz SK, Hubbard WC, et al. Neurological soft signs in neuroleptic-naive and neuroleptic-treated schizophrenic patients and in normal comparison subjects. Am J Psychiatry. 1995;152(2):191-6.
15. Mohr F, Hubmann W, Albus M, Franz U, Hecht S, Scherer J, et al. Neurological soft signs and neuropsychological performance in patients with first episode schizophrenia. Psychiatry Res. 2003;121(1):21-30.
16. Sevincok L, Akoglu A, Topaloglu B, Arslantas H. Neurological soft signs in schizophrenic patients with obsessive-compulsive disorder. Psychiatry Clin Neurosci. 2004;58(3):274-9.
17. Sevincok L, Akoglu A, Arslantas H. Schizo-obsessive and obsessive--compulsive disorder: Comparison of clinical characteristics and neurological soft signs. Psychiatry Res. 2006;145(2-3):241-8.
18. Faragian S, Pashinian A, Fuchs C, Poyurovsky M. Obsessive–compulsive symptom dimensions in schizophrenia patients with comorbid obsessive–compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(6):1009-12.
19. Bloch MH, Landeros-Weisenberger A, Rosario MC, Pittenger C, Leckman JF. Meta-analysis of the symptom structure of obsessive-compulsive disorder. Am J Psychiatry. 2008;165(12):1532-42.
20. Lykouras L, Alevizos B, Michalopoulou P, Rabavilas A. Obsessive--compulsive symptoms induced by atypical antipsychotics. A review of the reported cases. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(3):333-46.
21. Lim M, Park DY, Kwon JS, Joo YH, Hong KS. Prevalence and clinical characteristics of obsessive-compulsive symptoms associated with atypical antipsychotics. J Clin Psychopharmacol. 2007;27(6):712-3.
22. Fonseka TM, Richter MA, Müller DJ. Second generation antipsychotic--induced obsessive-compulsive symptoms in schizophrenia: a review of the experimental literature. Curr Psychiatry Rep. 2014;16(11):510.
23. Schirmbeck F, Rausch F, Englisch S, et al. Differential effects of antipsychotic agents on obsessive - Compulsive symptoms in schizophrenia: A longitudinal study. J Psychopharmacol. 2013;27(4):349-57.
24. Baker RW, Chengappa KNR, Baird JW, Steingard S, Christ MAG, Schooler NR. Emergence of obsessive compulsive symptoms during treatment with clozapine. J Clin Psychiatry. 1992;53(12):439-42.
25. Doyle M, Chorcorain AN, Griffith E, Trimble T, O'Callaghan E. Obsessive compulsive symptoms in patients with Schizophrenia on Clozapine and with Obsessive Compulsive disorder: a comparison study. Compr Psychiatry. 2014;55(1):130-6.
26. Pampaloni I, Tyagi H, Drummond L. Augmentation in profound, SRI--refractory OCD: Is aripiprazole superior to other to other dopamine blockers? Eur Psychiatry. 2017;41:S322.
27. Masi G, Pfanner C, Brovedani P. Antipsychotic augmentation of selective serotonin reuptake inhibitors in resistant tic-related obsessive-compulsive disorder in children and adolescents: A naturalistic comparative study. J Psychiatr Res. 2013;47(8):1007-12.
28. Üçok A, Ceylan ME, Tihan AK, Lapçin S, Ger C, Tükel R. Obsessive compulsive disorder and symptoms may have different effects on schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(2): 429-33.
29. Frías A, Palma C, Farriols N, Becerra C, Álvarez A, Cañete J. Neuropsychological profile and treatment-related features among patients with comorbidity between schizophrenia spectrum disorder and obsessive–compulsive disorder: Is there evidence for a "schizo-obsessive" subtype? Psychiatry Res. 2014;220(3):846-54.
30. Poyurovsky M, Hramenkov S, Isakov V, Rauchverger B, Modai I, Schneidman M, et al. Obsessive–compulsive disorder in hospitalized patients with chronic schizophrenia. Psychiatry Res. 2001;102(1):49-57.
31. Bottas A, Cooke RG, Richter MA. Comorbidity and pathophysiology of obsessive-compulsive disorder in schizophrenia: is there evidence for a schizo-obsessive subtype of schizophrenia? J Psychiatry Neurosci. 2005;30(3):187-93.
32. Devi S, Rao NP, Badamath S, Chandrashekhar CR, Janardhan Reddy YC. Prevalence and clinical correlates of obsessive-compulsive disorder in schizophrenia. Compr Psychiatry. 2015;56:141-8.
33. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989;46(11):1006-11.

34. de Haan L, Hoogeboom B, Beuk N, Wouters L, Dingemans PM, Linszen DH. Reliability and validity of the Yale-Brown Obsessive-Compulsive Scale in schizophrenia patients. Psychopharmacol Bull. 2006;39(1):25-30.
35. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res. 1988;23(1):99-110.
36. Addington D, Addington J, Atkinson M. A psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. Schizophr Res. 1996;19(2-3):205-12.
37. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.
38. Hasanah CI, Naing L, Rahman AR. World Health Organization Quality of Life Assessment: brief version in Bahasa Malaysia. Med J Malaysia. 2003;58(1):79-88.
39. Poyurovsky M, Bergman J, Weizman R. Obsessive-compulsive disorder in elderly schizophrenia patients. J Psychiatr Res. 2006;40(3):189-91.
40. Ongur D, Goff DC. Obsessive-compulsive symptoms in schizophrenia: associated clinical features, cognitive function and medication status. Schizophr Res. 2005;75(2-3):349-62.
41. de Haan L, Sterk B, van der Valk R. Presence of obsessive compulsive symptoms in first-episode schizophrenia or related disorders is associated with subjective well-being and quality of life. Early Interv Psychiatry. 2013;7(3):285-90.
42. Tibbo P, Kroetsch M, Chue P, Warneke L. Obsessive-compulsive disorder in schizophrenia. J Psychiatr Res. 2000;34(2):139-46.
43. Goh KK, Chiu Y-H, Shen WW, Yeh E-K. Dilemma in Treating Clozapine--induced Obsessive-compulsive Symptoms in a Patient with Schizophrenia. J Exp Clin Med. 2013;3(5):118-19.
44. Scheltema BA, Swets M, Machielsen M, Korver N. Obsessive-compulsive symptoms in patients with schizophrenia: a naturalistic cross-sectional study comparing treatment with clozapine, olanzapine, risperidone, and no antipsychotics in 543 patients. J Clin Psychiatry. 2012;73(11):1395-402.
45. Galvez-Buccollini JA, Fiestas F, Herrera P, Vega-Dienstmaier JM, Guimas B, Mazzotti G. [Obsessive-compulsive symptoms in schizophrenia during treatment with clozapine and conventional antipsychotic drugs]. Actas Esp Psiquiatr. 2004;32(4):211-5.
46. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment--resistant schizophrenic: A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45(9):789-96.
47. Eryılmaz G, Hızlı Sayar G, Ozten E, Gögcegöz Gül I, Karamustafalıoğlu O. Aripirazole augmentation in clozapine-associated obsessive-compulsive symptoms in schizophrenia. Ann Gen Psychiatry. 2013;12(1):40.
48. Glick ID, Poyurovsky M, Ivanova O, Koran LM. Aripiprazole in schizophrenia patients with comorbid obsessive-compulsive symptoms: an open-label study of 15 patients. J Clin Psychiatry. 2008;69(12):1856-9.
49. Chang JS, Ahn YM, Park HJ, Lee KY, Kim SH, Kang UG, et al. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2008;69(5):720-31.
50. Stryjer R, Dambinsky Y, Timinsky I, Green T, Kotler M, Weizman A, et al. Escitalopram in the treatment of patients with schizophrenia and obsessive-compulsive disorder: An open-label, prospective study. Int Clin Psychopharmacol. 2013 Mar;28(2):96-8.
51. Poyurovsky M, Hermesh H, Weizman A. Fluvoxamine treatment in clozapine-induced obsessive-compulsive symptoms in schizophrenic patients. Clin Neuropharmacol. 1996;19(4):305-13.
52. Levy E, Margolese HC, Sultan S, Chouinard G. Obsessive-Compulsive Symptoms in Schizophrenia Induced by Risperidone and Responding to Fluoxetine. Can J Psychiatry. 2003;48(10):709-10.
53. DeVylder JE, Oh AJ, Ben-David S, Azimov N, Harkavy-Friedman JM, Corcoran CM. Obsessive compulsive symptoms in individuals at clinical risk for psychosis: association with depressive symptoms and suicidal ideation. Schizophr Res. 2012;140(1-3):110-3.
54. Ucok A, Tukel R, Ozgen G, Saylan M, Uzuner G. [Frequency of obsessive compulsive symptoms and disorder in patients with schizophrenia: importance for prognosis]. Encephale. 2006;32(1 Pt 1):41-4.
55. Ucok A, Kivrak Tihan A, Karadayi G, Tukel R. Obsessive compulsive symptoms are related to lower quality of life in patients with Schizophrenia. Int J Psychiatry Clin Pract. 2014;18(4):243-7.

Associations between competitive anxiety, athlete characteristics and sport context: evidence from a systematic review and meta-analysis

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Abstract

Background: There is a vast literature investigating the possible associations between competitive anxiety, athlete variables and sports context. As far as we are concerned, there is no study which has compiled such findings to produce more robust evidence on this topic. **Objectives:** The aim of the study was to conduct an exploratory systematic review of the literature followed by a meta-analysis in order to investigate possible associations between competitive anxiety, social-demographic characteristics, profile of the athlete and sports context. **Methods:** Systematic searches of PubMed, PsycInfo, Web of Science, Lilacs and SciELO electronic databases were performed to identify studies published between January 2006 and January 2018, including a manual search in the references of the selected studies. **Results:** A total of 59 studies were included for qualitative synthesis and 27 for meta-analysis. More robust associations were observed between competitive anxiety and female gender, lower age, and less experience time. **Discussion:** Knowing the variables which exert influence on competitive anxiety can be relevant to plan specific treatment and intervention programs, enabling the athlete´s development beyond technical and physical preparation.

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Keywords: Competitive anxiety, performance anxiety, athlete, sport, evaluation.

Introduction

Anxiety is an emotional response stimulated by the anticipation of a real or potential threat[1]. In sports, competition can be considered a source of threats as the athlete's image is usually associated with his or her performance, the final result is always uncertain, there is exposure to public opinion and judgement by third parties, among others[2,3].

Because this condition is potentially anxiogenic and usually experienced by athletes, studies show that high levels of anxiety are conversely associated with sport performance[4-6]. In addition, performance can be indirectly affected by different symptoms of anxiety, such as physiological (e.g. energetic expenditure and cardiovascular alterations), motor (e.g. impairment in co-ordination), cognitive (e.g. decrease in attention, concentration and decision-making capacity) and relational (e.g. increase in conflicts among staff members) changes[7,8].

Due to the peculiarities of this psychological phenomenon within the context of sports, the term "competitive anxiety" (CA) was coined to refer to the emotional reaction which regularly emerges before or during sports competitions[3]. This construct is shown to be partially correlated with general anxiety (r = 0.35 to 0.50), which justifies its assessment on a specific basis[9].

CA was initially understood one-dimensionally, but this approach was surpassed with the introduction of the Multidimensional Theory of Anxiety, which proposes the existence of somatic (SCA) and cognitive (CCA) dimensions correlating to each other positively despite being different[3,10,11].

SCA is characterised by symptoms such as muscle tension, tachycardia, facial reddening, tremors and sweating, whereas CCA involves preoccupations preoccupations with self-demand, poor performance, negative evaluations, social comparison, expectations and demands by technical commission, team, family and supporters. With regard to the impact on the athlete's performance, CCA tends to have a negative relationship and SCA, in turn, a U-inverted relationship[3].

In addition to the different CA dimensions from a symptomatic perspective, one should consider its state-trait type. State-CA is experienced transiently, whereas trait-CA is considered a relatively stable trend in individuals who perceive different situations to be threatening[12].

With regard to the factors influencing CA, a pioneer study by Martens *et al.*[3] found higher levels in female athletes as well as in solo athletes with little competition experience. Since then, researchers have been investigating the impact of these and other variables such as age, hormones and relationship with coach on the levels of CA because knowing these implications will contribute significantly to the design and guidance of prevention and intervention programs in the specific population.

Although extensive literature on this issue has been produced over the decades, as far as we know there is no study gathering findings to seek robust evidence. Therefore, we have aimed to conduct an exploratory systematic review followed by meta-analysis in order to investigate whether there are differences in the levels of CA between athletes in function of social-demographic characteristics, athlete's profile and sport context. The study of these variables was based on the fact that they were always present or already existing *a priori* in the athlete and in the context of competition.

Methods

Based on the Systematic Reviews and Meta-Analyses Guidelines[13], we have conducted systematic searches in the literature by using the electronic databases PubMed, PsycInfo, SciELO, Web of Science and Lilacs for the key-words "competitive anxiety" and "sports performance anxiety", including a manual search from the references cited in the selected studies.

The inclusion criteria for the studies were the following: a) written in English, Spanish or Portuguese; b) human samples with no age-group restrictions; c) quantitative methodology; d) published in the past 12 years (i.e. January 2006 to January 2018); e) objective of investigating the levels of CA in function of social-demographic characteristics, athlete's profile and sport context.

Exclusion criteria as well as selection flowchart for the studies are presented in Figure 1. This stage was conducted by two research

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psychologists in the field of mental healthcare, with any discrepancy being resolved through consensus.

The qualitative methodology used by the included studies was assessed by means of the using the Strengthening the Reporting of Observational Studies in Epidemiology – STROBE[14] and Consolidated Standarts of Reporting Trials – CONSORT[15], depending on their design. For each item of the checklist, the following scoring was applied: fully fulfilled (1 point), partially fulfilled (0.5 point) or not fulfilled (0 point). The index of methodological quality was obtained by adding the scores attributed to each item, with the total sum being divided by the total number of items applied to the study and then multiplied by 100.

The following information were extracted from the studies: sample size, age of the participants, sport modality, time of experience in the sport, recruitment source, study design, measurement instruments used, interest variables and outcomes. A global qualitative analysis of the outcomes of each study in function of the independent variables was conducted.

Then, meta-analyses were independently performed in function of the four most studied variables, namely: gender, age, experience and competitive level. We included the studies that described all the necessary gross data in the published material. The missing data were requested to the main authors of the studies. Of the 10 e-mail sent, only one returned with the information. The analyses were conducted according to the following parameters: a) SCA and CCA dimension, b) state-trait CA types.

Statistical analyses were performed using the Stats Direct software package. The heterogeneity was evaluated using Cochran's Q test. The studies were considered homogenous when the significance of the Cochran's Q test was > 0.05, in these cases, a fixed-effects method was used. In the case of heterogeneity among the studies (significance ≤ 0.05), a random-effects method was used[16]. Higgins and Thompson statistics were used for inconsistency (I^2), which was interpreted as follows: low (< 25%), moderate (26 to 75%) and high (> 75%)[17]. Egger's regression test was also used to assess the presence of publication bias. The test was rejected when the significance level was $p \geq 0.05$[18].

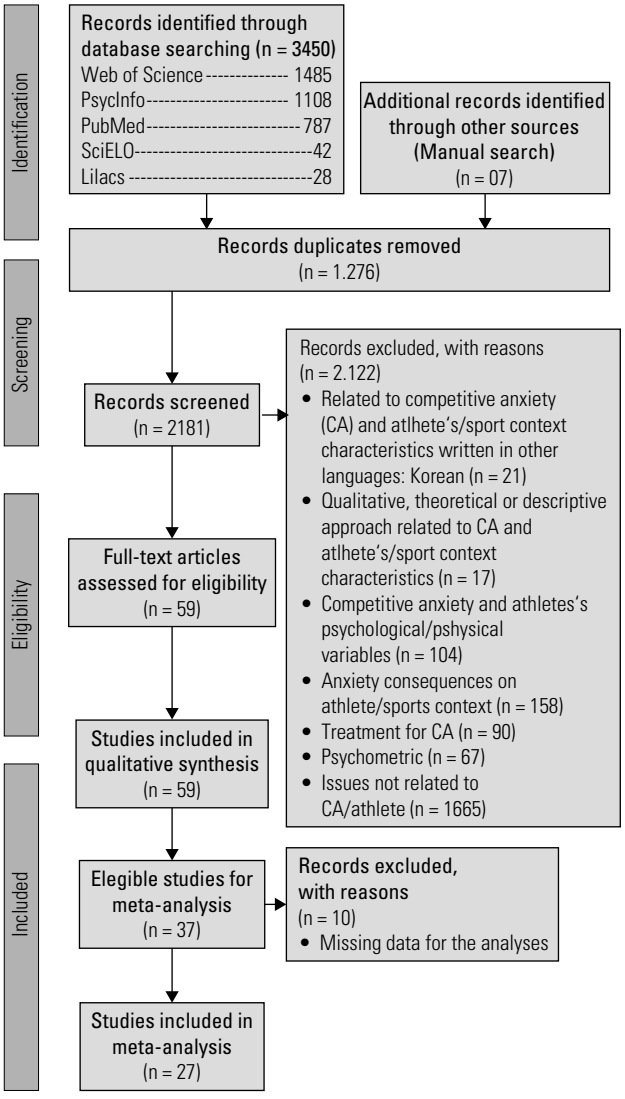

Figure 1. Inclusion and exclusion processes of studies based on PRISMA flowchart.

Results

A total of 3.457 studies have been identified. After application of exclusion criteria, 59 studies were included in the qualitative synthesis, and of these, 27 in the meta-analysis, as shown in Table 1.

With regard to the main characteristics of the studies, one can observe that sample size ranged from 9 to 1.038 athletes (totalizing = 8603 participants; mean = 145.8), the most used methodology was cross-sectional (n = 53; 89.8%), the main source of recruitment was local competition (n = 46; 78.0%), and the majority of the studies used multidimensional scales (n = 45; 76.3%) to evaluate the CA (for example, CSAI-2 and SAS-2).

With regard to methodological quality, the majority of the studies (n = 55; 93.2%) had indices equal or above 50% (mean = 58.9%). The most overlooked items in the studies were specification of measures aimed at preventing potential bias sources and calculation of sample size (Supplementary material available upon request to the author).

The independent variables assessed by the studies were distributed into three categories: a) socio-demographic characteristics (SG); b) athlete's profile (AT); and c) sport context (CO). Table 2 shows briefly the results of the qualitative synthesis regarding the influence of these variables on CA (Supplementary material available upon request to the author).

Qualitatively, higher levels of CA were observed in athletes who were female, younger and less competitively experienced as well as presenting previous poor experience, practicing individual sports, and competing in official events. These results were maintained even when studies using one-dimensional measurement or general anxiety assessment instruments were excluded.

The results of the meta-analysis are available in Table 3 (Supplementary material available upon request to the author).

Female athletes showed higher levels CA compared to males with small effect size in most of the analyses, however, this difference becomes more expressive in function of the trait-CA. There is evidence that younger athletes have higher levels of CA in the somatic dimension, and in the state condition, but the effect size effect is small. Although the difference was small, less experienced athletes have higher levels of CCA and state-CA compared to the more experienced. Finally, there were no differences between the athletes regarding the athlete's competitive level.

Discussion

The studies included in the present review have had, in general, moderate methodological quality. The weaknesses found are related to the lack of presentation of raw data, measures used to avoid potential bias sources and sample size calculation. Another negative point to be considered, despite the sound literature on the two-dimensionality of this psychological phenomenon[3,10,11], is the use of one-dimensional measurements of CA (SCAT) and others for measuring the general/global anxiety (STAI and BAI), suggesting that there may be an influence of other anxiety symptoms/characteristics other than competitive. This fact reinforces the importance of using specific anxiety scales in the sports context considering the multidimensionality of this phenomenon.

Table 1. Studies included in the systematic review and meta-analysis

Studies included		Sample					Methodological Aspects			
Ref.	Author (Year) Country	*n*	Age (Years) Mean (sd)/Range	Sport	Training (Years) Mean (sd)	Source of Recruitment	Design	Anxiety Instruments	Interest variables	Method Quality (%)
19	Bertuol & Valentini (2006) BRA	35♀ 33♂	12-16	A, V	< 1.0	CE	CS	SCAT	SG/AT/CO	50%
20	Carré *et al.* (2006) CAN	14♂	18.2 (1.48)	HK	NI	CE	CS	CSAI-2	CO	61%
21	Fernandes & Nunes (2006) BRA	9♂	27.8 (NI)	FT	> 5.0	CE	CS	STAI-S	CO	59%
22	Han *et al.* (2006) KOR	277♂	17.3 (2.99)	A, BB, CR, D, G, R, RG, J, JV, S, SW, TW, SW, WT	NI	NI	CS	STAI-ST	AT/CO	55%
23	Stavrou *et al.* (2006) GRC	52♀ 47♂	20.0 (4.5)	A, CC, ST, SW	> 7.9 (4.6)	CE	CS	CSAI-2D	CO	61%
24*	Gonçalves & Belo (2007) BRA	47♀ 58♂	15.2 (1.76)	F, H, SW, SSW, V	NI	LP	CS	SCAT	SG/AT/CO	61%
25	Haneishi *et al.* (2007) USA	18♀	18-24	S	NI	CE/LP	CS	SAS	AT	55%
26*	Vasconcelos-Raposo *et al.* (2007) BRA	529♂	23.0 (4.23)	S	11.21 (4.47)	LP	CS	CSAI-2	SG/AT/CO	55%
27*	Abrahamsen *et al.* (2008) NOR	89♀ 101♂	17.8 (5.7)	A, BD, G, O, SW, T	NI	CE	CS	SAS	SG	61%
28*	García *et al.* (2008) ESP	48♀ 49♂	14.7 (1.3)	J	NI	CE	CS	CSAI-2	SG	57%
29*	Géczi *et al.* (2008) HUN	52♂	U-18: 16.78 (NI) A-18: 27.21 (NI)	IHK	NI	LP	CS	CSAI-2	SG	50%
30*	Hanton *et al.* (2008) UK	97♀ 120♂	20.4 (2.92)	A, C, RG, T	NI	NI	CS	SAS-M CSAI-2M	AT	61%
31	Kaplan *et al.* (2008) TUR	22♂	22.6 (2.0)	S	10.8 (1.9)	CE	PL	STAI-S	CO	48%
32	Ramiro *et al.* (2008) ESP	18♀	24.0 (3.9)	HK	NI	CE	CS	STAI-S	AT	52%
33	Abenza *et al.* (2009) ESP	10♂	NI	B	NI	CE	CS	STAI-ST	CO	52%
34*	Filaire *et al.* (2009) FRA	8♀ 8♂	♀: 20.2 (1.0) ♂: 22.2 (2.8)	T	10.5 (3.2)	CE	CS	CSAI-2D	SG	55%
35*	Géczi *et al.* (2009) HUN	95♂	16-20	IHK	NI	CE	CS	CSAI-2	SG	57%
36*	Grossbard *et al.* (2009) USA	498♀ 540♂	11.5 (1.5)	BB, HK, S, V	NI	CE	CS	SAS-2	SG	64%
37	Guillén & Sánchez (2009) ESP	84♀	FD: 23.2 (4.0) NT: 24.9 (3.4)	B	> 5.3 (4.9)	CE	CS	STAI-ST	SG/CO	50%
38	Kim *et al.* (2009) KOR	12♂	EL: 16.2 (1.38) NEL: 15.8 (0.75)	G	NI	CE	CS	CSAI-2	AT	52%
39	Draper *et al.* (2010) NZL	9♂	20.3 (1.1)	CB	2.75 (1.75)	AS	E	CSAI-2R	CO	42%
40	Fernandes & Silva (2010) BRA	110♂ 151♂	JJ: 23.0 (5.06) SF: 18.1 (5.08)	JJ, SF	> 4.02 (4.08)	CE	CS	CSAI-2	SG/AT	57%
41	Ferreira *et al.* (2010) BRA	12♀	21.5 (2.9)	V	≥ 8.0	CE	CS	SCAT	SG/CO	34%
42	Interdonato *et al.* (2010) BRA	73♂	13.2 (1.88)	B, J, S, SW, V	3.43 (1.79)	LP	CS	SCAT	SG/AT/CO	57%
43*	Nicholls *et al.* (2010) UK	55♀ 252♂	21.3 (2.8)	VS	> 9.1 (5.2)	CE	CS	CSAI-2R	SG/AT/CO	52%
44	Aguirre-Loaiza & Bermúdez (2011) COL	93♂	17.4 (2.0)	S	7.7 (1.9)	CE	CS	STAI-S	SG/AT/CO	70%
45*	Kolayis & Sari (2011) TUR	44♀ 82♂	20.5 (2.93)	J	8.86 (3.84)	CE	CS	CSAI-2 STAI-S	SG/AT	50%
46*	León-Prados & García (2011) ESP	8♀ 8♂	♀: 10.6 (1.19) ♂: 20.6 (2.92)	AG	> 2.0	CE	CS	CSAI-2RD	SG/AT/CO	61%

Studies included			Sample					Methodological Aspects		
Ref.	Author (Year) Country	*n*	Age (Years) Mean (sd)/Range	Sport	Training (Years) Mean (sd)	Source of Recruitment	Design	Anxiety Instruments	Interest variables	Method Quality (%)
47*	Modroño & Guillén (2011) ESP	19♀ 60♂	24.7 (5.8)	W	NI	CE	CS	CSAI-2 SCAT	SG/AT	57%
48	Parry *et al.* (2011) AUT	3♀ 9♂	42.5 (3.6)	TH	> 5.0	CE	CS	CSAI-2	CO	50%
49	Radochonski *et al.* (2011) POL	132♀♂	20.5 (4.5)	A, K	NI	NI	CS	CSAI-2	CO	52%
50*	Vieira *et al.* (2011)BRA	28♀ 47♂	14-19	A	♀: 3.95 (2.45) ♂: 3.39 (2.12)	CE	CS	CSAI-2	SG	57%
51*	Borrego *et al.* (2012) PRT	44♀ 322♂	17.1 (1.6)	S	NI	CE	CS	CSAI-2	SG	57%
52	Singley *et al.* (2012) USA	8♀ 14♂	18-40	SD	NI	LP	CS	CSAI-2M	CO	64%
53*	Souza *et al.* (2012) BRA	18♀ 33♂	17.8 (2.85)	SW	> 4.11 (4.25)	CE	CS	CSAI-2 SCAT	SG/AT	64%
54	Villas Boas *et al.* (2012) BRA	48♂	12-13	F	NI	CE	CS	CSAI-2	AT/CO	45%
55	Asghar *et al.* (2013)	793♂	12-18	HK, S	NI	LP	CS	CSAI-2	SG	61%
56*	Fernandes *et al.* (2013) BRA	70♀ 233♂	24.2 (5.07)	B, F, H, J, JJ, K, R, S, SF, SW, T, V	9.03 (5.92)	NI	CS	CSAI-2R	SG/AT/CO	66%
57*	Ibarzábal (2013) ESP	40♀ 52♂	29.1 (5.61)	BB	11.02 (4.79)	CE	CS	CSAI-2	SG	57%
58	Jeong & Park (2013) KOR	9♀ 57♂	KR: 43.2 (NI) NKR: 33.5 (NI)	T	> 8.0	CE	CS	CSAI-2	SG	66%
59*	Morales *et al.* (2013) ESP	14♀ 10♂	NT: 22.3 (2.11) IT: 24.1 (1.78)	J	NI	CE	CS	CSAI-2R	AT/CO	57%
60	Parnabas & Mohamood (2013) MYS	147♀♂	NI	S	NI	CE	CS	CSAI-2	SG	57%
61	Ramis *et al.* (2013) ESP	422♀♀ 363♂	12.7 (2.20)	AG, B, H, SW, SSW, T, WP	NI	CE	CS	SAS-2	CO	55%
62*	Ruiz-Juan & Zarauz (2013) ESP	71♀ 330♂	♀: 45.7 (10.25) ♂: 47.9 (9.14)	A	NI	CE	CS	CSAI-2R	SG/AT/CO	52%
63	Arruda *et al.* (2014) BRA	24♂	17.8 (0.4)	B	NI	CE	CS	CSAI-2	CO	66%
64*	Fernandes *et al.* (2014) BRA	71♀ 196♂	24.3 (5.62)	B, H, F, FV, J, JJ, K, MC, R, S, SF, SW, V	10.03 (5.62)	CE	CS	CSAI-2R	AT	66%
65*	González & Fayos (2014) ESP	22♀ 90♂	27.4 (4.9)	SW, T, V	NI	LP	CS	STAI-ST	SG/AT/CO	68%
66	Han *et al.* (2014) KOR	33♀♂	NI	BS	NI	CE	CS	CSAI-2 STAI-T	AT	57%
67	Silva *et al.* (2014) BRA	13♀	16.3 (1.1)	V	4.7 (NI)	CE	PL	CSAI-2 BAI SSA	CO	59%
68*	Stenling *et al.* (2014) AUS	163♀ 152♂	♀: 19.4 (3.0) ♂: 20.6 (4.0)	FB, IHK	♀: > 10.1 ♂: > 12.1	CE	CS	CSAI-2R	SG	73%
69	Wolf *et al.* (2014) CAN	108♀ 144♂	20.32 (1.85)	B, IHK, V	> 10.03 (4.22)	CE	CS	CSAI-2D	SG/AT/CO	61%
70	Cunniffe *et al.* (2015) UK	24♂	26.2 (0.9)	RG	NI	CE	PL	CSAI-2R	AT/CO	55%
71	Fernandez-Fernandez *et al.* (2015) ESP	12♀	13.0 (0.3)	T	6.0 (2.8)	CE	PL	CSAI-2R	AT/CO	52%
72	Pesce *et al.* (2015) ITA	25♂	28.6 (5.34)	KB	NI	CE	PL	STAI-S	CO	59%
73*	Machado *et al.* (2016) BRA	24♀ 23♂	16.1 (0.34)	V	4.9 (1.99)	CE	CS	CSAI-2	SG/AT	84%
74*	Kurimay *et al.* (2017) USA	20♀ 80♂	10-60	TT	NI	CE	CS	CSAI-2R	SG	75%

Studies included			Sample				Methodological Aspects			
Ref.	Author (Year) Country	*n*	Age (Years) Mean (sd)/Range	Sport	Training (Years) Mean (sd)	Source of Recruitment	Design	Anxiety Instruments	Interest variables	Method Quality (%)
75*	Hagan *et al.* (2017)	E: 21♀ 26♂ SE: 14♀ 29♂	26.7 (5.29)	T	9.6 (5.12)	CE	CS	CSAI-2D	SG	89%
76*	Nikseresht *et al.* (2017)	14♂	11.7 (0.82)	SW	NI	CE	CS	SCAT	SG	77%
77	Arruda *et al.* (2017)	12♂	18.6 (0.50)	B	NI	CE	CS	CSAI-2	CO	77%

* = studies included in meta-analysis; ♀ = women; ♂ = men; A = Athletics; A-18 = above 18 years; AG = Artistic Gymnastics; AS = Artificial Situation; AT = Athlete's characteristics; AUS = Australia; AUT = Austria; B = Basketball; BAI = Beck Anxiety Inventory; BB = Bodybuilding; BD = Badminton; BRA = Brazil; BS = Baseball; C = Cricket; CAN = Canada; CB = Climbing; CC = Cycling; CE = Competitive Event; CO = Context characteristics; COL = Colombia; CR = Ci-reum; CS = Cross-sectional; CSAI-2 = Competitive State Anxiety Inventory-2(D = Direction; M = Modified by researchers; R = Revised); D = Discus; E = Experimental; EL = Elite; F = Futsal; FB = Floorball; FD = First Division; FRA = France; FT = Fistball; FV = Footvolley; G = Golf; GER = German; GRC = Greece; H = Handball; HK = Hockey; HUN = Hungary; IHK = Ice Hockey; IT = International; ITA = Italy; J = Judo; JJ = Jiu-Jitsu; JV = Javelin; K = Karate; KB = Kickboxing; KR = Korean; KOR = Republic of Korea (South Korea); LP = Local practice; MC = Motocross; MYS = Malaysia; *n* = Sample size; NEL = Non elite; NI = Not informed; NKR = Not Korean; NOR = Norway; NT = National; NZL = New Zealand; O = Orienteering; PL = Prospective longitudinal; POL = Poland; PRT = Portugal; R = Running; REF = Reference number; RG = Rugby; S = Soccer; SAS = Sport Anxiety Scale (-2: second version; M = Modified by researchers); SCAT = Sport Competition Anxiety Test; SD = Skydiving; SF = Surf; SG = Sociodemographic characteristic; SPA = Spain; SSA = Subjective Anxiety Scale; ST = Shooting; STAI = State-Trait Anxiety Inventory (S = only state subscale; T = only trait subscale; ST = both state and trait subscale); SW = Swimming; SSW = Synchronised Swimming; T = Tennis; TH = Triathlon; TUR = Turkey; TT = Table Tennis; TW = Taekwondo; UK = United Kingdom; USA = United States of America; U-18 = under 18 years; V = Volleyball; VS = Various sports; W = Windsurf; WP = Water Polo; WT = Wrestling.

Table 2. Qualitative synthesis of the results

Qualitative variables	n	At least one evidence of influence in competitive anxiety#	
Sociodemographic		**No**	**Yes***
Gender (Female x Male)	21	7 [19,45,46,47,50,69,73]	♀ >: 12 [24,27,34,36,43,51,53,56,62,65,68,74] | ♂ >: 2 [57,75]
Age (Younger x Older)	18	7 [24,35,42,44,46,58,76]	Younger >: 9 [26,28,29,40,41,45,47,53,62] | Older >: 2[19,36]
Nationality/Ethnics**	3	0	3 [55,58,60]
Educational Level (Higher x Lower)	2	1 [44]	Higher >: 1 [45]
Income (Higher x Lower)	1	0	Higher >: 1 [44]
Place of Birth (Interior x Capital)	1	1 [44]	0
Athletes' Profile		**No**	**Yes***
Experience (Less x More)	13	5 [40,56,64,69,73]	Less >: 7 [26,30,40,44,45,53,62] | More >: 1 [19]
Competition Level (Lower x Higher)	11	4 [24,32,46,47]	Lower >: 6 [26,30,38,53,59,65] | Higher >: 1 [43]
Previous Performance (Worse x Better)	4	0	Worse >: 3 [22,66,71] | Better >: 1 [69]
Status (Nonstarter x Starter)	5	5 [25,54,69,70,73]	0
Team Position**	4	3 [26,37,54]	1 [44]
Sport Context		**No**	**Yes***
Temporal Pattern (Pre x Post Competition)	8	2 [23,25]	Pre >: 5 [31,41,48,52,71] | Post >: 3 [31,71,72]
Type of Sport (Individual x Team)	6	1 [24]	Individual >: 4 [19,22,42,43] | Team >: 1 [56]
Sport Modality**	7	2 [39,42]	5 [22,49,61,62,65]
Place of Competition (Away x Home)	6	3 [63,67,70]	Away >: 3 [20,23,69]
Type of Competition (Official x Unofficial)	5	0	Official >: 5 [25,59,71,72,77]
Opponent´s Level (Higher x Lower)	3	1 [69]	Higher >: 2 [33,77]

* = Non exclusive category; ** = It was not possible to draw up categories for comparisons due to data's heterogeneity; # = number of the study as mentioned in Table 1; ♀ = Female; ♂ = Male; _ = studies that used one-dimensional or general scales to assess CA.

From a qualitative point of view, it was observed the influence of some variables on the CA levels: female, younger and less competitively experienced as well as presenting previous poor experience, individual sports, and official events.

Meta-analyses have been conducted to seek more robust results by using SCA/CCA dimensions and type of trait-state anxiety as moderating variables. With regard to gender, it was found that female athletes had a higher level of anxiety compared to male counterparts. This fact was corroborated by the meta-analysis, showing significant differences in all dimensions, mainly in the trait-CA. In the neurological perspective of the psychopathology, these findings are supported by the literature showing a higher prevalence of anxiety symptoms and disorders in females due to the fact that the oscillating levels of gonadal hormones occur more often clinically in women than in men, which increases the susceptibility of the former to stress and anxiety[78-81].

However, sports specialists argue that female athletes are more anxious than male ones due to the influence of other factors, such as honesty to speak about feelings/emotions[27], susceptibility to external stimuli[53], commitment to the sports practicing[62], susceptibility to pressures from sports environment[82] and greater focus on the risk of failure rather than on achieving success[83].

With regard to age, the levels of CA tend to be higher in groups of young athletes. Quantitative analysis indicated a small effect size between the groups in the SCA and state-CA. Previous studies associated these findings to the fact that young age is directly related to factors such as feelings of insecurity, emotional dependency and use of less elaborated strategies for coping with physiological responses[28,36,41,47,53].

Similarly, qualitative analyses indicated that less experienced athletes were those with higher levels of CA, but in meta-analysis, differences with small effect size were found in the CCA and state-CA. Martens *et al.*[3] believe that experienced athletes have more capacity to control their concerns, whereas other authors support the hypothesis that experienced athletes tend to perceive the competition from a more positive perspective[30] as they are more exposed to competitions and reflect

positively on self-effectiveness, which in turn increases self-confidence during the contests[53] and favours the development of more effective coping strategies to deal with criticism from oneself and others[26,84].

Qualitative analysis has shown that the levels of CA tend to be higher in athletes with low competitive level, but these results were not confirmed in the quantitative analysis as no significant differences were found between the groups assessed. This leads to the questioning of the hypothesis that less competitive athletes tend to use less coping strategies and consequently they are more likely to experience anxiety symptoms[26,30].

The findings of the qualitative analysis indicate higher levels of CA in athletes who practice individual sports compared to those who practice team sports. Studies reporting that athletes who practice individual sports are more anxious during competitions because of the responsibility for achieving results which depend exclusively on one person only, whereas those practicing team sports would share this responsibility with other members of the team[19].

With regard to competition, qualitative analysis has shown that the levels of CA tend to increase before and during official competitions and in contests played away from home. The proximity of competition increases the athlete's level of anxiety because of a threatening competitive environment, since important values and goals are at stake[79]. In addition, away contests would be influenced by travel, poor familiarity with venue, away supporters, referee bias and absence of family and social support[20,70].

Other evidence found has to do with the athlete's previous performance. Qualitative analysis has shown the 75% of the studies reported that poor performance tends to increase the levels of CA, a fact which may be attributed to the low level of self-confidence among athletes following a defeat. Unfortunately, this finding cannot be quantitatively analysed as the selected studies using this variable did not list all raw data needed.

With regard to team status, quantitative analysis has shown no difference in the levels of CA between starting and reserve athletes. However, there are a few studies focusing on this issue, which limits robust conclusions to be drawn. It is believed that the absence of difference may be associated with the fact that starting and reserve athletes are usually submitted to the same routine, level of demand and sports results, which would have a similar impact on their experience of CA.

Despite the reduced number of studies and heterogeneity of the groups studied, the qualitative results indicate influence of nationality/ethnics on the levels of CA. The role of sports and the preference for a specific modality can reveal important characteristics of a country's culture, norms and customs. Experience and manifestation of anxiety may be influenced by ethnical and cultural factors due to beliefs on mental diseases, including social context and norms to which an individual is exposed[85].

With regard to team position, despite the specificities of each sports modality, the qualitative analysis has shown no differences in the levels of CA in football, futsal and basketball athletes. As for country of birth, education level, income level and opponent's status, one can highlight the presence of exploratory data with heterogeneous and inconclusive results, thus requiring further investigations on their impact on CA.

Despite the efforts made to cover all the scientific studies on the theme available in the past twelve years, we also have to emphasise that there are limitations in the present work: 1) low number of studies included in the quantitative analyses, despite the effort to contact the authors; 2) exclusion of studies written in Korean due to lack of domain of the language, warning that possible specificities of this population should be explored.

For a better understanding of the construct CA, it is suggested that new systematic reviews should be performed in order to seek evidence of associations with other psychological (i.e. personality traits, coping skills, motivation, self-esteem, self-confidence), physiological (i.e. injuries, hormonal changes) and relational (i.e. relationship with coach, family, teammates) variables. Knowing these aspects and those addressed by our study will contribute to the development of a more integrative view of athletes and better management of their symptoms of CA.

In view of the results obtained, one can conclude that CA is a phenomenon occurring in the sports context which deserves attention as it is closely related to the athlete's quality of life and performance, being more significantly associated with female, younger and less experienced athletes.

Table 3. Gross results of the meta-analysis

Independent Variables	Moderator Analysis	Effect Size (95% CI)	Cochran Q	I2 (95% CI)	Egger (95% CI)
	Somatic dimension (SCA)	0.24 (0.02 to 0.45)	84.43 (df = 15); p < 0.0001	82.2% (71.6% to 87.7%)	1.60 (-0.74 to 3.95); p = 0.17
GENDER	Cognitive dimension (CCA)	0.26 (0.10 to 0.43)	119.09 (df = 19); p < 0.0001	84.0% (76.5% to 88.3%)	1.04 (-1.18 to 3.26); p = 0.34
♀ x ♂ (Ref.)	State-CA	0.25 (0.10 to 0.41)	141.41 (df = 30); p < 0.0001	78.8% (70.0% to 84.1%)	-0.78 (2.89 to 1.33); p = 0.46
	Trait-CA	0.78 (0.35 to 1.21)	217.91 (df = 6); p < 0.0001	97.2% (96.3% to 97.8%)	10.38 (3.77 to 16.99); p = 0.01
	Somatic dimension (SCA)	0.29 (0.02 to 0.55)	24.14 (df = 7); p = 0.0011	71.0% (24.0% to 84.3%)	1.55 (-0.64 to 3.73); p = 0.13
AGE	Cognitive dimension (CCA)	0.11 (-0.13 to 0.36)	44.71 (df = 8); p < 0.0001	82.1% (64.6% to 88.9%)	1.85 (-0.77 to 4.50); p = 0.14
Younger x Older (Ref.)	State-CA	0.38 (0.16 to 0.60)	28.78 (df = 11); p = 0.0025	61.8% (13.1% to 78.1%)	1.31 (-0.57 to 3.18); p = 0.15
	Trait-CA	-0.08 (-0.25 to 0.10)	20.30 (df = 6); p = 0.0024	70.4% (13.0% to 84.7%)	0.86 (-2.09 to 3.82); p = 0.48
	Somatic dimension (SCA)	0.23 (-0.05 to 0.50)	18.32 (df = 4); p = 0.0011	78.2% (26.6% to 89.1%)	3.14 (-5.16 to 11.45); p = 0.32
EXPERIENCE	Cognitive dimension (CCA)	0.25 (0.03 to 0.47)	7.20 (df = 3); p = 0.0659	58.3% (0% to 84.1%)	3.55 (3.17 to 3.90); p = 0.001
Less x More (Ref.)	State-CA	0.21 (0.03 to 0.40)	24.07 (df = 7); p = 0.0011	70.9% (23.6% to 84.2%)	3.19 (-0.10 to 6.47); p = 0.05
	Trait-CA*	--	--	--	--
	Somatic dimension (SCA)	0.29 (-0.37 to 0.94)	19.01 (df = 4); p = 0.0008	79.0% (31.2% to 89.4%)	5.13 (-3.87 to 14.12); p = 0.17
COMPETITIVE LEVEL	Cognitive dimension (CCA)	0.21 (-0.31 to 0.73)	57.30 (df = 6); p < 0.0001	89.5% (80.8% to 93.2%)	-0.32 (-6.11 to 5.50); p = 0.90
Lower x Higher (Ref.)	State-CA	0.22 (-0.23 to 0.67)	73.27 (df = 10); p < 0.0001	86.4% (77.2% to 90.8%)	0.17 (-3.21 to 3.55); p = 0.91
	Trait-CA*	--	--	--	--

* Unrealized analysis due to small number of avaliable studies; CA = Competitive Anxiety; CI = Confidence Interval; I^2 = Inconsistency; MQI = Methodological quality index.

Although the effect size has been small, our findings contribute to the relevance of considering these vulnerabilities in the prevention and intervention programs aimed at managing environmental stimuli, arousal and negative thoughts by means of visualisation, relaxing, breathing and self-dialogue techniques, thus stimulating the athlete's development beyond technical and physical preparation[86].

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Author contributions statement

Both authors contributed equally to this work.

Conflict of interest statement

There is no conflict of interest.

References

1. Gross C, Hen R. The developmental origins of Anxiety. Nat Rev Neurosci. 2004;5(7):545-52.
2. Frischnecht P. A influência da ansiedade no desempenho do atleta e do treinador. Treino Desportivo. Lisboa: II série. 1990;15:21-8.
3. Martens R, Vealey RS, Burton D. Competitive Anxiety in Sport. Champaign, IL: Human Kinetics; 1990.
4. Judge LW, Urbina LJ, Hoover DL, Craig BW, Judge LM, Leitzelar BM, et al. The impact of competitive trait anxiety on collegiate powerlifting performance. J Strength Cond Res. 2016;30(9):2399-405.
5. Milavić B, Jurko D, Grgantov Z. Relations of competitive state anxiety and efficacy of young volleyball players. Coll Antropol. 2013;37(suppl 2):83-92.
6. Mottaghi M, Atarodi A, Rohani Z. The relationship between coaches' and athlete's competitive anxiety, and their performance. Iran J Psychiatry Behav Sci. 2013;7(2):68-76.
7. Mesquita RM, Todt NS. A especialização esportiva precoce e a maturação biológica: investigando a base do Olimpismo. Rev Perfil. 2000;4(4):83-7.
8. Weinberg RS, Gould D. Fundamentos da Psicologia do Esporte e do Exercício. Porto Alegre: Artmed; 2001.
9. Fernandes MG, Vasconcelos-Raposo J, Fernandes HM. Propriedades psicométricas do CSAI-2 em atletas brasileiros. Psicologia: Reflexão e Crítica. 2012;25(4):679-87.
10. Burton D. Measuring competitive state anxiety. In: Duda JL (Ed.). Advances in sport and exercise psychology measurement. Morgantown, WV: Fitness Information Technology; 1998.
11. Smith RE, Smoll FL, Cumming SP, Grossbard JR. Measurement of Multidimensional Sport Performance Anxiety in Children and Adults: The Sport Anxiety Scale-2. J Sport Exerc Psychol. 2006;28:479-501.
12. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. Paolo Alto, California, Consulting Psychologists Press; 1970.
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. BMJ. 2009;339:b2700.
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9.
15. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. BMJ. 2010;340:c332.
16. Lau J, Ioannids JP, Schmid CH. Summing up evidence: one answer is not always enough. Lancet. 1998;351(9096):123-7.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
18. Egger M, Smith GD, Schneider M, Christoph M. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.
19. Bertuol L, Valentini C. Ansiedade competitiva de adolescentes: gênero, maturação, nível de experiência e modalidades esportivas. Rev Educ Fís Maringá. 2006;17(1):65-74.
20. Carré J, Muir C, Belanger J, Putnam SK. Pre-competition hormonal and psychological levels of elite hockey players: relationship to the "home advantage". Physiol Behav. 2006;89(3):392-8.
21. Fernandes MG, Nunes SAN. Ansiedade pré-competitiva e home advantage. Rev Saúde. 2006;2(1):21-9.
22. Han DH, Kim JH, Lee YS, Bae SJ, Bae SJ, Kim HJ, et al. Influence of temperament and anxiety on athletic performance. J Sports Sci Med. 2006;5(3):381-9.
23. Stavrou NA, Psychountaki M, Zervas Y. Intensity and direction dimensions of competitive state anxiety: a time-to-event approach. Percept Mot Skills. 2006;103(1):91-8.
24. Gonçalves MP, Belo RP. Ansiedade-traço competitiva: diferenças quanto ao gênero, faixa etária, experiência em competições e modalidade esportiva em jovens atletas. Psico-USF. 2007;12(2):301-7.
25. Haneishi K, Fry AC, Moore CA, Schilling BK, Li Y, Fry MD. Cortisol and stress responses during a game and practice in female collegiate soccer players. J Strength Cond Res. 2007;21(2):583-8.
26. Vasconcelos-Raposo J, Coelho EM, Mahl AC, Fernandes HM. Intensidade do Negativismo e Autoconfiança em Jogadores de Futebol Profissionais Brasileiros. Motricidade. 2007;3(3):7-15.
27. Abrahamsen FE, Roberts GC, Pensgaard AM. Achievement goals and gender effects on multidimensional anxiety in national elite sport. Psychol Sport Exerc. 2008;9(4):449-64.
28. García RH, Zafra AO, Toro EO. Ansiedad y autoconfianza de jóvenes judokas en situaciones competitivas de alta presión. Análise Psicológica. 2008;26(4):689-96.
29. Géczi G, Bognár J, Tóth L, Sipos K, Fügedi B. Anxiety and Coping of Hungarian National Ice Hockey Players. Int J Sports Sci Coach. 2008;3(2):277-85.
30. Hanton S, Neil R, Mellalieu SD, Fletcher D. Competitive experience and performance status: an investigation into multidimensional anxiety and coping. Eur J Sport Sci. 2008;8(3):143-52.
31. Kaplan T, Taskin H, Altin M, Erkmen N. Examination of the level of state anxiety points of the soccer player during the tournament. Selcuk Universitesi Sosyal Bilimler Enstitusu Dergisi. 2008;20:447-57.
32. Ramiro EMD, Valdehita RS, García JM, Moreno LL. Rendimiento deportivo en jugadoras de élite de hockey hierba: diferencias en ansiedad y estrategias cognitivas. eduPsykhé. 2008;7(1):23-41.
33. Abenza L, Piñar MI, Ureña N, López FA. Relationship between the anxiety and performance of a basketball team during competition. Rev Psicología del Deporte. 2009;18(Suppl):409-13.
34. Filaire E, Alix D, Ferrand C, Verger M. Psychophysiological stress in tennis players during the first single match of a tournament. Psychoneuroendocrinology. 2009;34(1):150-7.
35. Géczi G, Tóth L, Sipos K. Psychological profile of Hungarian national young ice hockey players. Kinesiology. 2009;41(1):88-96.
36. Grossbard JR, Smith RE, Smoll FL, Cumming SP. Competitive anxiety in young athletes: differentiating somatic anxiety, worry, and concentration disruption. Anxiety Stress Coping. 2009;22(2):153-66.
37. Guillén F, Sánchez R. Competitive anxiety in expert female athletes: sources and intensity of anxiety in National Team and First Division Spanish basketball player. Percept Mot Skills. 2009;109(2):407-19.
38. Kim KJ, Chung JW, Park S, Shin JT. Psychophysiological stress response during competition between elite and non-elite Korean junior golfers. Int J Sports Med. 2009;30(7):503-8.
39. Draper N, Jones GA, Fryer S, Hodgson C, Blackwell G. Physiological and psychological responses to lead and top rope climbing for intermediate rock climbers. Eur J Sport Sci. 2010;10(1):13-20.
40. Fernandes MG, Silva LH. Relação entre ansiedade competitiva e experiência em atletas de jui-jitsu e surfe. Rev Digital-Efdeportes.com. 2010;15(145):1-7.
41. Ferreira JS, Leite LPR, Nascimento CMC. Relação entre níveis de ansiedade-traço competitiva e idade de atletas de voleibol e análise destes níveis pré e pós-competição. Motriz: Rev Educ Fís. 2010;16(4):853-7.
42. Interdonato GC, Oliveira AR, Luiz Júnior CC, Greguol M. Análise da ansiedade traço competitiva em jovens atletas. Conexões: Revista da Faculdade de Educação Física da Unicamp. 2010;8(3):1-9.
43. Nicholls AR, Polman R, Levy AR. Coping self-efficacy, pre-competitive anxiety, and subjective performance among athletes. Eur J Sport Sci. 2010;10(2):97-102.

44. Aguirre-Loaiza HH, Bermúdez SR. Ansiedad-estado y variables sociodemográficas en futbolistas juveniles colombianos durante competencia. Diversitas: Perspectivas en Psicología. 2011;7(1):239-51.
45. Kolayis H, Sari I. Anxiety, self-esteem and competition ranking of judokas. Arch Budo. 2011;7(1):11-5.
46. León-Prados JA, García IF, Lluch AC. Ansiedad estado y autoconfianza precompetitiva en gimnastas. Rev Int Cienc Deporte. 2011;7(23):76-91.
47. Modroño C, Guillén F. Anxiety Characteristics of Competitive Windsurfers: Relationships with Age, Gender, and Performance Outcomes. J Sport Behav. 2011;34(3):281-94.
48. Parry D, Chinnasamy C, Papadopoulou E, Noakes T, Micklewright D. Cognition and performance: anxiety, mood and perceived exertion among Ironman triathletes. Br J Sports Med. 2011;45(14):1088-94.
49. Radochonski M, Cynarski WJ, Perenc L, et al. Competitive Anxiety and Coping Strategies in Young Martial Arts and Track and Field Athletes. J Hum Kinet. 2011;27:181-90.
50. Vieira L, Teixeira C, Vieira J, Oliveira Filho A. Autoeficácia e nível de ansiedade em atletas jovens do atletismo paranaense. Rev Bras Cineantropom Desempenho Hum. 2011;13(3):183-8.
51. Borrego CC, Cid L, Silva C. Relationship between group cohesion and anxiety in soccer. J Hum Kinet. 2012;34:119-27.
52. Singley KI, Hale BD, Russell DM. Heart rate, anxiety, and hardiness in novice (tandem) and experienced (solo) skydivers. J Sport Behav. 2012;35(4):453-69.
53. Souza MAP, Teixeira RB, Lobato PL. Manifestação da ansiedade pré-competitiva em nadadores amadores. Rev Educação Física UEM. 2012;23(2):195-203.
54. Villas Boas MS, Coelho RW, Vieira LF, Fonseca PHS, Kuczynski KM. Análise do nível de ansiedade de jovens atletas da modalidade de futsal. Conexões: Revista da Faculdade de Educação Física da Unicamp. 2012;10(3):77-86.
55. Asghar E, Wang X, Linde K, et al. Comparisons between Asian and German male adolescent athletes on goal orientation, physical self-concept, and competitive anxiety. J Sport Exerc Psychol. 2013;11(3):229-43.
56. Fernandes MG, Nunes SAN, Vasconcelos-Raposo J, Fernandes HM. Factors influencing competitive anxiety in Brazilian athletes. Rev Bras Cineantropom Desempenho Hum. 2013;15(6):705-14.
57. Ibarzábal FA. Fisicoculturismo: diferencias de sexo en el estado de ánimo y la ansiedad precompetitive. Rev Psicología del Deporte. 2013;22(2):353-60.
58. Jeong I, Park S. Participation motivation and competition anxiety among Korean and non-Korean wheelchair tennis players. J Exerc Rehabil. 2013;9(6):520-5.
59. Morales J, Garcia V, García-Massó X, Salvá P, Escobar R, Buscà B. The use of heart rate variability in assessing precompetitive stress in high-standard judo athletes. Int J Sports Med. 2013;34(2):144-51.
60. Parnabas VA, Mahamood Y. Cognitive and Somatic Anxiety among Football Players of Different Ethnics Groups in Malaysia. Procedia Soc Behav Sci. 2013;85:258-66.
61. Ramis Y, Torregrosa M, Cruz J. Revisitando a Simon & Martens: La ansiedad competitiva en deportes de iniciación. Revista de Psicología del Deporte. 2013;22(1):77-83.
62. Ruiz-Juan F, Zarauz A. Análisis de la ansiedad en el atlestismo; un estudio con veteranos. Rev Int Cienc Deporte. 2013;33(9):222-35.
63. Arruda AF, Aoki MS, Freitas CG, Drago G, Oliveira R, Crewther BT, et al. Influence of competition playing venue on the hormonal responses, state anxiety and perception of effort in elite basketball athletes. Physiol Behav. 2014;130:1-5.
64. Fernandes MG, Nunes SAN, Vasconcelos-Raposo J, Fernandes HM. Efeitos da experiência nas dimensões de intensidade, direção e frequência da ansiedade e autoconfiança competitiva: Um estudo em atletas de desportos individuais e coletivos. Motricidade. 2014;10(2):81-9.
65. González J, Fayos EJG. Diferencias individuales e indicadores de ansiedad como estrategias adaptativas de autoeficacia en el desportista. Ansiedad y Estrés. 2014;20(1):51-9.
66. Han DH, Kim BN, Cheong JH, Kang KD, Renshaw PF. Anxiety and attention shifting in professional baseball players. Int J Sports Med. 2014;35(8):708-13.
67. Silva MMF, Vidual BP, Afonso RO, Yoshida HM, Borin JP, Fernandes PT. Ansiedade e desempenho de jogadoras de voleibol em partidas realizadas dentro e fora de casa. Rev Educação Física UEM. 2014;25(4):585-96.
68. Stenling A, Hassmén P, Holmström S. Implicit beliefs of ability, approach-avoidance goals and cognitive anxiety among team sport athletes. Eur J Sport Sci. 2014;14(7):720-9.
69. Wolf SA, Eys MA, Kleinert J. Predictors of the precompetitive anxiety response: Relative impact and prospects for anxiety regulation. J Sport Exerc Psychol. 2015;13(4):344-58.
70. Cunniffe B, Morgan KA, Baker JS, Cardinale M, Davies B. Home Versus Away Competition: Effect on Psychophysiological Variables in Elite Rugby Union. Int J Sports Physiol Perform. 2015;10(6):687-94.
71. Fernandez-Fernandez J, Boullosa DA, Sanz-Rivas D, Abreu L, Filaire E, Mendez-Villanueva A. Psychophysiological stress responses during training and competition in young female competitive tennis players. Int J Sports Med. 2015;36(1):22-8.
72. Pesce M, Fratta IL, Ialenti V, Patruno A, Ferrone A, Franceschelli S, et al. Emotions, immunity and sport: Winner and loser athlete's profile of fighting sport. Brain Behav Immun. 2015;46:261-9.
73. Machado TA, Paes MJ, Alquiere SM, Osiecki ACV, Lirani LS, Stefanello JMF. Ansiedade estado pré-competitiva em atletas de voleibol infanto-juvenis. Rev Bras Educ Fis Esporte (São Paulo). 2016;30(4):1061-67.
74. Kurimay D, Pope-Rhodius A, Kondric M. The relationship between stress and coping in table tennis. J Hum Kinetics. 2017;55:75-81.
75. Hagan Jr JE, Pollmann D, Schack T. Interaction between gender and skill on competitive state anxiety using the time-to-event paradigm: what roles do intensity, direction, and frequency dimensions play? Front Psychol. 2017;8:692.
76. Nikseresht A, Yabande AA, Rahmanian K, Jahromi AS. Pre-competition anxiety score among elite boy swimmers in Iran. MEJFM. 2017;15(6):65-70.
77. Arruda AFS, Aoki MS, Paludo AC, Moreira A. Salivary steroid response and competitive anxiety in elite basketball players: effect of opponent level. Physiol Behav. 2017;177:291-6.
78. American Psychiatric Association – APA. Manual diagnóstico e estatístico de transtornos mentais: DSM-V. Porto Alegre: Artmed; 2014.
79. Altemus M, Sarvaiya N, Epperson CN. Sex differences in anxiety and depression clinical perspectives. Front Neuroendocrinol. 2014;35(3):320-30.
80. Maeng LY, Milad MR. Sex differences in anxiety disorders: interactions between fear, stress, and gonadal hormones. Horm Behav. 2015;76:106-17.
81. Marques AA, Bevilaqua MCN, Fonseca AMP, Nardi AE, Thuret S, Dias GP. Gender differences in the neurobiology of anxiety: focus on hippocampal neurogenesis. Neural Plast. 2016;2016:1-14.
82. Stefanello JMF. Ansiedade competitiva e os fatores de personalidade de adolescentes que praticam voleibol: um estudo casual–comparativo. Rev Kinesis. 1990;6(2):202-24.
83. Morris RL, Kavussanu M. Antecedents of approach-avoidance versus task and ego goals in enjoyment and cognitive anxiety in youth sport. Int J Sport Exerc Psychol. 2009;7:185-202.
84. Lazarus RS, Folkman S. Stress, appraisal and, coping. New York: Erlbaum; 1984.
85. Hofmann SG, Asnaani A. Cultural aspects in social anxiety and social anxiety disorder. Depress Anxiety. 2010;27(12):1117-27.
86. Tobar BU. Evaluación de la efectividad del entrenamiento de estrategias de afrontamiento en el nivel de ansiedad precompetitiva en tenimesistas. Rev Psicol Deport. 2014;23(1):67-74.

Convergent validity of the Brazilian version of the Theory of Mind Task Battery for the assessment of social cognition in older adults

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Dear Editor,

Social cognition is an individual's ability to differentiate his/her own mental state from the mental state of another person and recognize the desires, beliefs and feelings of this person[1]. The 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) recommends the use of facial emotion recognition tasks and theory of mind to evaluate social cognition[2]. The interest in appropriate Theory of Mind (ToM) tasks for use on older adults increased with the inclusion of social cognition among the criteria for the diagnosis of dementia in the DSM-5[2].

Our research group recently published the translation and cross-cultural adaptation of the Brazilian version of the Theory of Mind Task Battery (ToM TB) in this journal[3]. Thus, the objective of this study was to investigate the convergent validation of the ToM TB in a sample of community-dwelling older adults in the community.

The study was conducted in the city of São Carlos, which is located in the state of São Paulo, Brazil. Data collection was performed by a psychologist and gerontologist, who had undergone training exercises for the administration of the instruments. All participants signed a statement of informed consent. The ToM TB is composed of nine different situations arranged in order of increasing difficulty, with the total score ranging from 0 to 15[4]. For convergent validation, the Brazilian version of Reading the Mind in the Eyes Test (RMET) was applied and the correlation between it and the ToM TB was calculated. The RMET consists of 36 figures of eyes and the participant must choose the word that best describes the feeling shown in the figure among four options[5].

The sample was composed of 20 participants (8 men and 12 women) selected randomly from the list of adults older than 60 years registered at a family health unit. The exclusion criteria were severe cognitive decline, and auditory or visual deficits that could interfere with performance tasks. Mean age was 68.6 years (SD: ±7.61), mean schooling was 3.55 years (SD: ±2.63) and the majority (55%) was married. The score on the Mini Mental State Examination[6] was 22.65 (SD: ±5.38).

On the RMET, mean number of correct guesses was 14.95 (SD: ±4.62), with a minimum score of 6 and maximum of 22. For the ToM TB, the total score was 8.85 (SD: ±3.56), with a minimum score of 1 and maximum of 14. With regard to convergent validity, Pearson's correlation coefficient between the ToM TB and RMET was 0.715 ($p < 0.001$), indicating a strong correlation between the instruments. There was no significant correlation between schooling and the ToM TB (rho = 0.200; p = 0.399) as well as between schooling and RMET (rho = 0.337; p = 0.146) (Figure 1).

The existence of an instrument for the assessment of theory of mind validated for older adults may contribute to future studies and assist in the clinical evaluation of older adults with neurocognitive disorders, as impaired social cognition is currently one of the criteria for the diagnosis of dementia.

The small sample may be considered a limitation of the study. However, the minimum sample calculated for a strong correlation coefficient of 0.7, with two-tailed test and 80% test power was 13 individuals, demonstrating that the present sample was suitable for the purposes of the study. Other limitation of the study is that despite the RMET be used by several studies for ToM assessment, a recent study suggested that the RMET measures emotion recognition rather than ToM ability[7].

Considering the aim and the results of the study, we conclude that the Brazilian version of the ToM TB is a valid instrument for evaluating theory of mind in the older adults.

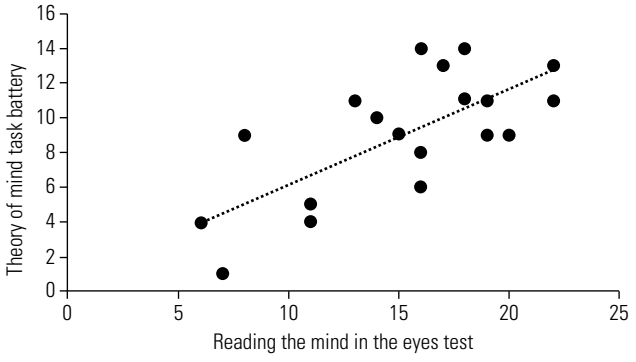

Figure 1. Scatter plot of correlation between Theory of Mind Task Battery and Reading the Mind in the Eyes test.

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References

1. Frith CD, Frith U. Social cognition in humans. Curr Biol. 2007;17(16):R724-32.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington DC: American Psychiatric Press; 2013.

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3. Chagas MHNC, Chagas NMS, Osorio FL. Translation and transcultural adaptation to Brazilian Portuguese of the Theory of Mind Task Battery for assessment of social cognition in the elderly. Arch Clin Psychiatry. 2017;44(1):30-1.
4. Hutchins TL, Prelock PA, Chace W. Test-retest reliability of a theory of mind task battery for children with Autism Spectrum Disorders. Focus Autism Other Dev Disabl. 2008;23(4):195-206.
5. Sanvicente-Vieira B, Kluwe-Schiavon B, Wearick-Silva LE, Piccoli GL, Scherer L, Tonelli HA, et al. Revised Reading the Mind in the Eyes Test (RMET) – Brazilian version. Rev Bras Psiquiatr. 2014;36(1):60-7.
6. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.
7. Oakley BF, Brewer R, Bird G, Catmur C. Theory of mind is not theory of emotion: A cautionary note on the Reading the Mind in the Eyes Test. J Abnorm Psychol. 2016;125(6):818-23.

Capgras syndrome in a first-episode, late-onset and super-refractory schizophrenia case

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Dear Editor,

Capgras syndrome (CS), late-onset schizophrenia (LOS) and refractory schizophrenia are relatively common conditions in psychiatric practice. However, the combination of these three conditions in a single case is a very rare event and so far seldom reported[1]. We report a case of a patient with LOS presenting with of CS and super-refractoriness since its first crisis.

A 53-year-old woman was admitted to a psychiatric hospital in an acute psychotic episode. On admission, she was convicted that her family had been enrolled in a plot in which they were replaced by lookalikes. This was the first time she presented psychotic symptoms and no treatment had yet been instituted. Physical examination, laboratory tests and brain MRI presented no abnormalities. She was diagnosed with late-onset schizophrenia (LOS) and Capgras Syndrome (CS). Haloperidol, risperidone and olanzapine, all in monotherapy, were tried at optimal doses for a period of four weeks each, with unsatisfactory response. Then, clozapine was started in a dose up to 425 mg daily leading to serum levels of 587 ng/mL (reference value: 50 to 700 ng/mL), with no clinical signs of response after 33 weeks. Subsequently, electroconvulsive therapy was prescribed as adjuvant therapy to clozapine. After 17 bitemporal sessions, psychosis with Capgras delusion persisted, maintaining high risk of aggression against her family and the need to remain hospitalized.

Schizophrenia is a relatively common disorder in clinical practice. Predominantly, it onsets in adolescence or early adult years, however 23,5% of these patients have this condition triggered after 40 years and are classified as LOS[2]. This subtype schizophrenia have a preponderance of cases among women and the presence of schizoid and paranoid personality traits are frequent[2].

Several hypotheses have been proposed to understand schizophrenia, especially cases that occur with CS, a condition characterized by delusions that a close subject, usually parents or spouse, has been replaced by a lookalike. In CS, some studies indicate the affection lack when in their relatives' presence. Delusion development would be an attempt to explain it[3].

No complementary test is necessary for the schizophrenia diagnosis. In LOS, laboratory exams and brain images are advisable, especially in the elderly. Particularly, in this population, there is a higher incidence of potentially serious neurological conditions, such as stroke or dementia, which could also present with psychotic symptoms and be misdiagnosed as schizophrenia at first sight[4].

Given the unsatisfactory response to two different antipsychotics, clozapine is an important option to be considered, despite its potential side effects. Nonresponders patients are classified as super-refractory. However, the literature lacks well-designed studies with large enough samples to draw subsequent guidelines. Also of note, electroconvulsive therapy proved to be effective in association to clozapine[5].

This case highlights the unusual combination of three different conditions that is rarely reported in the literature[1], the occurrence of CS in a case of LOS and super-refractory schizophrenia since its first crisis. In addition, it is important to emphasize the need for more well-designed studies to shed light on the treatment of refractory schizophrenia.

References

1. Ain MK, Rosdinom R, Raynuha M. Capgras syndrome in a very late onset, treatment resistant schizophrenia. Int Psychogeriatr. 2015;27(9):1573-5.
2. Harris MJ, Jeste DV. Late-onset schizophrenia: an overview. Schizophr Bull. 1988;14(1):39-55.
3. Corlett PR, Taylor JR, Wang XJ, Fletcher PC, Krystal JH. Toward a neurobiology of delusions. Prog Neurobiol. 2010;92(3):345-69.
4. Reinhardt MM, Cohen CI. Late-life psychosis: diagnosis and treatment. Curr Psychiatry Rep. 2015;17(2):1.
5. Elkis H, Buckley PF. Treatment-Resistant Schizophrenia. Psychiatr Clin North Am. 2016;39(2):239-65.

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