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Review articles

Exploratory factor analysis of Kenny Music Performance Anxiety Inventory (K-MPAI) in a Brazilian musician sample

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Abstract

Background: The Kenny Music Performance Anxiety Inventory (K-MPAI) is very significant among the available instruments which measures Musical Performance Anxiety (MPA). **Objective:** The aim of this study is to find evidence of validity of the Kenny Music Performance Anxiety Inventory (K-MPAI), in its translated and adapted Brazilian version, through the study of its factor structure. **Methods:** A convenience sample of 230 amateur musicians completed the K-MPAI. **Results:** The initial factor analysis yielded eight factors, explaining 62.4% of variance. However, due to the factors' composition and internal consistency values lower than 0.50, the number of factors was later set at three, considering the internal consistency of those, the theoretical propositions and symptomatology aspects that supported the construction of scale. They were named "Worries and insecurity" (α = 0.82), "Depression and hopelessness" (α = 0.77) and "Early parental relationships" (α = 0.57). **Discussion/Conclusions:** These results point to the scale's construct validity, since they support the theoretical basis used for the development of the K-MPAI and the clinical manifestations of the MPA.

Barbar AEM et al. / Arch Clin Psychiatry. 2015;42(5):113-6

Keywords: Music, anxiety, scaling, test validity, factor analysis.

Introduction

Reading a text, dancing, singing a song, engaging in sports activities or even calculating in public can cause immense anxiety in some individuals. When this suffering represents a persistent and distressing apprehension towards public performance, it is characterized as an impairing disorder called Performance Anxiety. When anxiety is specifically related to musical performance of any nature, it is described as Musical Performance Anxiety (MPA), which may be, in some cases, considered a Social Anxiety Disorder subtype[1].

MPA is a multidimensional phenomenon that often affects professional musicians and music students during their music performances and that can have strongly impact not just on an isolated performance, but also on the career and mental health of the affected ones[2,3]. It has, until recently, been conceptualized as a unidimensional phenomenon with career stress at the low end and stage fright at the high end[1]. However, Kenny[1] has argued for a typology of MPA, with three relatively distinct forms of the condition. However, the field is in need of studies that can link assessment and diagnostic factors of MPA, using validated psychometrical instruments in clinical use.

Burgués[4] and Kenny[1] conducted literature reviews of the available instruments to assess MPA, as well as their instruments' published psychometrical parameters. Both authors observed that most of the instruments were either inadequate or not assessed for their psychometrical qualities. Their studies concluded that there is lack of adequate instruments to assess MPA disorder and it renders the meaningful conduct of epidemiological studies even more challenging. Further, such instruments do not provide robust reference parameters for clinical use and MPA treatment.

The Kenny Music Performance Anxiety Inventory (K-MPAI)[2] is very significant among the available instruments. This scale takes the anxiety model proposed by Barlow[5] as reference. According to this model three facets make individuals more or less susceptible to anxiety: a) vulnerability/biological inheritance; b) general psychological vulnerability, based on the development of primary experiences and; c) specific psychological vulnerability, associated with learning processes.

The K-MPAI is composed of 26 items and is used to evaluate symptoms of anxiety expression, tension, memory alterations and negative cognitions due to MPA. It also seeks to asses MPA through elements related to individual history, especially regarding the history of parent-child relationships and the attention received from parents during childhood (primary experiences during development, according to Barlow[5]).

In the original study presented by Kenny *et al.*[2], the K-MPAI was tested for its internal consistency and demonstrated 0.94 Cronbach's alpha. It also presented positive and significant correlations with the state and trait subscales of the STAI (State-Trait Anxiety Inventory) – which is a general anxiety assessment instrument – and with the Cox & Kenardy MPA Scale (CK-MPA) – which is a specific instrument to assess MPA. All these correlations were higher than 0.80 and it attests to the concurrent validity of the K-MPAI.

Kenny[6] subsequently suggested an expanded version of this instrument with 40 items: the K-MPAI-R. She conducted two exploratory factor analyses using this version: one with professional musicians and another with tertiary level music students. It has also been the object of research by Rocha *et al.* in Brazil[7]. Nevertheless, the current study aimed to conduct a cross-cultural validation in order to validate the initial version of the scale adapted to the Brazilian context[8]. This validation was based on version's adequate psychometric properties and on its smaller number of items. Both aspects were essential for screening. The current article presents evidence of K-MPAI validity by analyzing its internal structure.

Methods

Participants

The current study used a convenience sample composed of 230 adult musicians (mean age 39.17 years – SD = 16.48). The musicians had different school levels (graduates or undergraduates were the majority: 53.9%), most of them were women (58.3%) and most of them classified themselves as amateur musicians (61.3%). All of the participants signed the Free and Informed Consent Term adopted by the present study. The inclusion criterion was the participation in frequent public musical performances and the exclusion criterion was the incorrect filling of the instruments and psychotic disorders. Approximately 41.6% of the participants had voice as their main musical instrument, and it was followed by chords (18%) and keyboard instruments (10.8%).

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Instruments

The following instruments were used to achieve the current study aims:

- Kenny Music Performance Anxiety Inventory (K-MPAI) – instrument proposed by Kenny *et al.*[2], translated and adapted to Brazilian Portuguese by Barbar *et al.*[8]. She used bilingual independent translators and her version was evaluated by a specialist committee which analyzed the *back-translation* and the pilot study, according to the recommendations of Beaton *et al.*[9]. The instrument is composed of 26 items to be punctuated according to the *likert* scale, which ranges from "strongly disagree" (-3) to "strongly agree" (+3);
- Identification Form – was developed for the present study and composed of 12 items used to obtain a social-demographic description of the sample.

Procedure

Data collection: An initial inquiry was conducted to contact many of the musical groups and active schools in Ribeirão Preto County where potential participants could be found. The instruments were individually completed by musicians gathered in groups. There were always two previously trained researchers assisting the groups. They were in charge of conducting the procedure.

Data analysis: The sample's clinical and social-demographic data were analyzed by means of descriptive statistic. An exploratory factorial analysis was carried out to investigate data related to the K-MPAI construct validity using the components analysis by *varimax* rotation, after the *promax* rotation analysis showed that the factors were not correlated with each other (following parameters suggested by Fabrigar *et al.*[10]). The criteria used to compose the factors were: Kaiser-Meyer-Olkin (KMO) index above 0.60; significant Bartlett's test, self-values above 1; minimum variance accounted by factors of approximately 60%; and minimum load factor of approximately 0.40[11].

Ethical considerations: The current study was approved by the Local Ethics Committee, according to process 12206/2009.

Results

The KMO was calculated to test the habituation of the sample before the factorial analysis and the outcome was favorable (0.81). Bartlett's test was also significant ($\chi^2 = 1364.43$, $p < 0.001$). Kaiser's criteria – which considers all factors with self-values above 1 – were used to determine the number of factors: eight factors were found, as show in table 1.

All of the eight factors found on this analysis and presented on table 1 account for 62% of the variance, and Factor 1 contributes to more than 23% of the variance, whereas the other factors are responsible for less than 10% each. The same eight principal components were extracted by *varimax* rotation. Therefore, a new factorial matrix was created and it dealt with individual items of the scale that were related to the factors. However, the result seemed unsatisfactory, since some factors were composed of very few or even of only one item (Factor 7 had two, and Factors 6 and 8 had only one item). Besides, the *alpha* values were lower than 0.50 for some factors.

Hence, due to the theoretical structure on which this instrument was developed, other exploratory analyses were carried out by *a priori* fixing the factor number. Initially, different and random variable arrangements were tested. Finally, the models with three, four and five factors were preserved. After each model was qualitatively investigated, the content and the internal consistency indicators were analyzed. The present research team concluded that models 5 and 4 were inadequate due to the abovementioned with respect to the 8-factor model.

On the other hand, the same parameters showed that the 3-factor model was the most appropriate in view of the theoretical propositions and symptomatology used by the author by the time this assessment scale was developed. Table 2 shows the values of the rotated matrix of the K-MPAI components and it took a *varimax* rotation under consideration in the pre-fixed 3-factors model.

Table 1. Exploratory factor analysis of K-MPAI: self-values description and variance proportion explained by each factor (in percentage)

Factor	Self-value	% of variance
1	**6.003**	**23.090**
2	**2.212**	**8.510**
3	**1.783**	**6.856**
4	**1.487**	**5.721**
5	**1.376**	**5.292**
6	**1.187**	**4.565**
7	**1.146**	**4.409**
8	**1.027**	**3.950**
9	0.978	3.763
10	0.832	3.198
11	0.810	3.117
12	0.773	2.973
13	0.740	2.847
14	0.686	2.640
15	0.618	2.376
16	0.537	2.067
17	0.496	1.909
18	0.478	1.840
19	0.458	1.763
20	0.429	1.649
21	0.402	1.546
22	0.367	1.410
23	0.330	1.267
24	0.309	1.190
25	0.277	1.066
26	0.256	0.986

Table 2. Factor matrix to each K-MPAI item, considering a three-factor model and *varimax* rotation

Item	Factor		
	1	2	3
k20	**0.720**	0.152	-0.002
k12	**0.675**	0.182	0.133
k10	**0.661**	0.092	-0.055
k13	**0.624**	0.215	-0.212
k22	**0.624**	0.283	0.094
k18	**0.624**	0.133	-0.237
k15	**0.600**	0.168	0.025
k17	**0.544**	0.247	-0.113
k25	**0.544**	0.190	-0.197
k14	**0.448**	-0,022	0,324
k7	0.352	0.214	0.140
k11	0.192	**0.697**	0.015
k23	0.280	**0.678**	0.038
k4	0.195	**0.660**	-0.004
k1	0.110	**0.627**	0.077
k6	0.247	**0.604**	-0.030
k5	0.018	**0.545**	0.124
k3	0.139	**0.537**	0.067
k21	0.142	**0.477**	-0.076
k16	0.221	**0.458**	-0.247
k24	0.010	0.229	**0.718**
k19	-0.008	0.106	**0.687**
k9	-0.129	0.206	**0.544**
k26	0.322	-0.087	**0.428**
k2	-0.031	-0.207	0.265
k8	0.071	0.129	-0.215

As for the 3-factors model, it was observed that Factor 1 had ten items with loads ranging from 0.72 to 0.45. After the qualitative analysis, this factor was called "Worries and Insecurity", with 0.82 *alpha*. Factor 2 was composed by nine items, with 0.77 *alpha*. This factor was called "Depression and Hopelessness" due to the item content. Finally, Factor 3 was the one with the lowest number of items and it was composed of four items and 0.57 *alpha*. This factor was named "Early Parental Relationships", since these items mention the early experiences between musicians and their parents in childhood. Items 2, 7 and 8 were excluded from the factor arrangement because they didn't show significant load in any of the three factors. Table 3 presents the final factor composition suggested by the present analysis.

Discussion

The current article focused on the study of K-MPAI's construct validity, by means of an exploratory factor analysis of this scale. After testing different factor arrangements it was observed that the model with three factors ("Worries and Insecurity", "Depression and Hopelessness" and "Early Parental Relationships") was the most consistent one. These factors are closely bounded to some of the theoretical aspects pointed out in the literature as important etiological determinants of a clinical case in MPA. Some dimensions of the clinical framework in this disorder are also found on the following factors: the presence of strong negative cognition, feelings of insecurity and hopelessness.

The factors are associated not only with the theoretical principles used by the author when the scale was developed based on Barlow's theory[5], but also with the main expressions of the disorder. That being said, it can be observed that Factor 1 ("Worries and Insecurity") and Factor 2 ("Depression and Hopelessness") overlap with some of the symptoms of anxiety, depression and dysthymia within the MPA construct; especially when there is lack of trust in oneself and hopelessness regarding resources and cure likelihood. Such factors are closely related to biological inherited and learned vulnerability aspects[1], and it strengthens the multiaxial theories that describe MPA.

However, Factor 3 ("Early Parental Relationships") gathers items with weaker item-total correlation, as well as with internal consistency lower than that of the acceptable parameters. This factor maintains a direct association with the psychological vulnerability ideas based on early experiences, as it was highlighted by Barlow[5] and Kenny *et al.*[2]. An important discussion regarding the lower scores presented by this factor concerns the aspects related to parental relationships that are not seen as part of MPA development or maintenance processes. These aspects are not even mentioned in the theoretical framework proposed by Papageorgi *et al.*[12] as a relevant element to understand MPA. Therefore, the weak item-total correlation in Factor 3 and the consistency may pinpoint weaker correlations between the historical aspects of the individual and the MPA disorder development (and other possible comorbidities). It points towards the diminished importance of early experiences to MPA onset. It should be taken into account that Factor 3 had the smallest number of items and it has a negative effect on the *alpha* value.

The elements related to professional and environmental events associated with MPA and mentioned by Kenny *et al.*[13] and Papageorgi *et al.*[14], Lamont[15], Kenny[1], Ryan and Andrews[16], Yoshie *et al.*[17] and Taborsky[18], are not taken under consideration in the K-MPAI's items. This could be a limitation for the scale, since these variables are considered relevant in the literature and to the experience of MPA. On the other hand, responses to professional and environmental events such as solo *vs* ensemble performance, adjudicated *vs* non-adjudicated performances, or rehearsals *vs* performances show considerable uniformity of response among musicians, since most of them reported that auditions are the most stressful performance types, and rehearsals and private practice the least stressful ones. The K-MPAI is primarily focused on the psychological factors related to MPA, which are more poorly understood than these other factors.

The current study presents some guidelines to fulfill the absence of previous studies on the composition of the K-MPAI factors. However, the study used a convenience amateur musician sample from a specific Brazilian region.

Therefore, further studies must test this factor arrangement through confirmatory factor analysis to corroborate K-MPAI validity. The search for evidence of validity and reliability is also important in order to substantiate the psychometric properties of this scale and to stimulate its clinical use, as an assessment instrument for this impairing and underdiagnosed disorder[19,20]. Thus, it could open doors for the musicians seeking treatment to finally perform with success and reach the best of their musical careers.

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Table 3. Final result of the exploratory factor analysis of K-MPAI considering the three-factor model and *varimax* rotation

Factor	Alpha	Items in factor
1. Worries and Insecurity	0.82	10 – I never know before a concert whether I will perform well 12 – During a performance I find myself thinking about whether I'll even get through it 13 – Thinking about the evaluation I may get interferes with my performance 14 – Even in the most stressful performance situations, I am confident that I will perform well 15 – I am often concerned about a negative reaction from the audience 17 – From the beginning of my music studies, I remember being anxious about performing 18 – I worry that one bad performance will ruin my career 20 – I give up worthwhile performance opportunities due to anxiety 22 – I often prepare for a concert with a sense of dread and impending disaster 25 – I worry so much before a performance, I cannot sleep
2. Depression and Hopelessness	0.77	1 – Sometimes I feel depressed without knowing why 3 – I rarely feel in control of my life 4 – I often find it difficult to work up the energy to do things 5 – Excessive worrying is a characteristic of my family 6 – I often feel that life has not much to offer me 11 – I often feel that I am not worth much as a person 16 – Sometimes I feel anxious for no particular reason 21 – As a child, I often felt sad 23 – I often feel that I have nothing to look forward to
3. Early Parental Relationships	0.57	9 – My parents were mostly responsive to my needs 19 – My parents almost always listened to me 24 – My parents encouraged me to try new things 26 – My memory is usually very reliable

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Induction and comparison of craving for tobacco, marijuana and crack

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Abstract

Background: The literature findings report that use of multiple substances can produce adverse clinical and behavioral effects, which may affect craving and the results of drug treatment. Also, the understanding of craving construct and its interaction in the use of smoked substances is underexplored. **Objectives:** To induce and compare craving for tobacco, marijuana and crack-cocaine on hospitalized dependents whose drug of choice is crack-cocaine. **Methods:** Quasi-experimental study with a convenience sample consisting of 210 males divided into 3 equal groups (Group-1: craving induced by crack; Group-2: craving induced by tobacco; and Group-3: craving induced by marijuana). All participants met ICD-10 dependence criteria for cocaine/crack, marijuana and tobacco, were aged between 18 and 65 and had used these substances for at least one year. Photos were used to induce craving and self-report instruments to evaluate possible alterations. **Results:** This study showed that craving for tobacco was more intense than for marijuana and crack, when the groups were compared by VAS. Using specific scales, both craving for tobacco and craving for marijuana were more intense than craving for crack. **Discussion:** These results would imply interventions at the initial stages of abstinence with cognitive-behavioural techniques and pharmacotherapy in order to reduce craving.

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Keywords: Craving, tobacco, marijuana, crack cocaine, multiple dependence.

Craving is an important concept in the area of drug dependence and has been discussed for more than a century; Merck's Manual of the Materia Medica[1,2] had, in 1899, already proposed that cocaine be used to relieve *craving* for alcohol, demonstrating one of the first attempts to "medicate" *craving*. In 1954, at a meeting of experts from the World Health Organization[3], Jellineck, among others, concluded that the term "*craving*" was scientifically inaccurate, as it referred only to an urgent and intense desire. The group therefore decided to replace "*craving*" for physical dependence – in cases of *craving* related to withdrawal symptoms – and pathological desire – in cases of desire occurring after a longer period of abstinence[4]. Isbell[5] emphasized that *craving* was very difficult to define as it could mean different things to different people.

Currently, different concepts of *craving* can be verified. These range from the best known "intense desire to consume a particular substance"[6] to one that encompasses not only the desire but also "the expectation of a positive effect, the relief of withdrawal symptoms and negative affect and the intention to use the drug"[7]. Rankin *et al.*[8] argued that *craving* is a multi-dimensional construction and must therefore involve physiological, psychological and behavioural aspects.

Despite the importance of this issue, there is little research analysing and comparing *craving* for psychoactive substances. Tiffany *et al.*[9] considered, for example, that *craving* for cocaine was related to a different area than that experienced by tobacco[7]: the lack of control; however no research was conducted to prove this difference. On the other hand some studies have demonstrated evidence that *craving* for tobacco and smoked cocaine (crack) are associated[10] and that exposure to nicotine can increase cocaine self-administration[11] as well as trigger its *craving*, especially among *crack* users[12].

Regarding *craving* for marijuana, on one hand, one study[13] verified that 93% of marijuana dependents reported only a mild *craving* for the substance whereas, another research[14] observed that dependents reported a more intense *craving* than cocaine dependents. Budney *et al.*[15] when comparing *craving* for marijuana and tobacco, found that *craving* for tobacco was slightly more intense.

The literature findings report that cocaine/crack dependents have a history of other psychoactive substances use[10] and that such use of multiple drugs can produce adverse clinical and behavioural effects, cumulative and synergistic, via interaction between the substances, which may affect *craving* and the results of drug treatment[16]. Because of the need to better understand the *craving* construct and its interaction in the use of smoked substances, the purpose of this article is to induce and compare *craving* for tobacco, marijuana and cocaine (crack) on hospitalized dependents whose drug of choice is crack.

Methods

Design

This is a quasi-experimental study.

Participants

The subjects were chosen "by convenience" which is defined[17] as a means of selecting data on which there is a no statistical randomness but a value judgment, for example, subjects' accessibility as a criterion. The sample consisted of 210 male subjects, admitted to the specialized chemical dependency unit of the São Pedro Psychiatric Hospital (Porto Alegre – RS), divided into 3 groups each comprising 70 subjects. Group 1 (induced *craving* for crack), group 2 (induced *craving* for tobacco) and group 3 (induced *craving* for marijuana).

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Inclusion criteria

Fulfil ICD-10[18] dependence criteria for cocaine/crack, marijuana and tobacco. Been using these substances for at least one year, with a minimum education level of fifth-grade elementary school and aged between 18 and 65 years old. Participants must have been abstinent for a period of 7-21 days. All were undergoing Nicotine Replacement Therapy (transdermal 21 mg) – which is part of the inpatient unit treatment protocol – and were using psychiatric medication. The inclusion of the subject in the study was only done if cocaine/crack was their "drug of choice" (favourite), since it is difficult to observe cocaine/crack dependents that do not use other substances. This criterion had already been used in previous studies[9,19].

Exclusion criteria

Presenting psychotic symptoms, acute symptoms of mood disorder (assessed by the SRQ-20; Mari & Williams, 1986), being dependent on other substances or having cognitive impairments that altered performance in the tests according to the Mini-Mental State Examination[20].

Instruments

Demographics and substance use

Form with socio-demographic data and information related to pattern of psychotropic substance consumption.

Cognitive level

Mini-Mental State Examination (MMSE)[20] – screening test to assess cognitive level at the time of the interview. 25/30 points suggests commitment, and < 20 points indicates, with certainty, that there is cognitive impairment[21]. For this research a cut-off point below 25 points was used to exclude patients with cognitive impairment from the sample group.

Presence of psychotic symptoms

SRQ-20 – A scale previously validated in Brazil[22], which screened the general population and classified adults either as neurotic (> 7), who could participate in the study, or psychotic (> 1), who were excluded.

Severity of dependence

Severity of Tobacco, Cocaine/Crack and Marijuana dependence – as there are no validated instruments to assess the severity of dependence on Cocaine/Crack and Marijuana, only on tobacco, in order to standardize the assessment of the severity in all groups, their weekly consumption was taken as a parameter.

Anxiety symptoms

Beck Anxiety Inventory (BAI)[23]: this is a scale that measures the severity of anxiety symptoms. It consists of 21 questions in which the subject must grade on a four point scale. The total score is obtained by summing the individual scores of each question. The cut-offs for psychiatric patients, according to the norms of the Portuguese version, are: 0-10 = minimal, 11-19 = mild, 20-30 = moderate and 31-63 = severe[24]. This will be administered to the three groups of participants.

Depression symptoms

Beck Depression Inventory (BDI)[25]: is designed for measuring the severity of depression, both in psychiatric patients and in the general population. It consists of 21 multiple-choice questions, each with four alternatives; the subject must choose the most applicable feeling at that moment. The total score is the sum of the points. The cut-offs for psychiatric patients were published in 2001 along with the Portuguese version by Cunha: 0-11 = minimal 12-19 = mild, 20-35 = moderate and 36-63 = severe[24].

Craving intensity

Visual Analogue Scale (VAS) – to assess *craving* this will be administered to all three groups, the individual will be asked to give their *craving* a grade, where 0 (zero) is the minimum grade (has no *craving*) and 10 the maximum (presents a very strong *craving*), this value is marked on a 10 cm scale. Several authors have used the Visual Analogue Scale to assess *craving* in their research[26-29].

Cocaine craving

Cocaine Craving Questionnaire Brief (CCQ-Brief)[19]: 10 scale statements compiled from the 45 statements Cocaine Craving Questionnaire – Now[9]. The CCQ-Brief is a Likert 7-point scale ranging from "strongly disagree" to "strongly agree". The CCQ-Brief and its version adapted for crack were validated in Brazil[30-31]. The score of the CCQ-Brief – Adapted Brazilian version for Crack is obtained from the total sum of the points (with the statements 4 and 7 reversed should be added to the other); from Factor 1 (points) – on the *craving* itself (the sum of all issues except 4 and 7) and Factor 2 – associated with lack of control of crack use (sum of questions 4 and 7 inverted). The cut-offs in the Brazilian version, for the total scale points, are: 0-11 points, minimum *craving*; 12 to 16, mild; 17-22, moderate; and 23 or more points, intense *craving*. This questionnaire will only be applied to Group 1.

Tobacco craving

Questionnaire of Smoking Urges Brief – Brazilian Version – QSU-B[32] – is an abbreviated scale developed by Cox *et al.*[33] from the Questionnaire of Smoking Urges (QSU)[7] used to assess *craving* for tobacco. It is comprised of 10 affirmative statements, to which the individual must state their position using a Likert 7-point scale ranging from "strongly disagree 'to' strongly agree". The QSU-B in its Brazilian validation[32] can be analysed by the sum total of points and by the points of factor 1 related to *craving* for the positive reinforcing properties of tobacco (statements 1, 3, 7 and 10) and by factor 2 related to *craving* of the negative reinforcing properties of this substance (statements 4, 8 and 9). The cut-offs in the Brazilian version for the scale points total are: 0-13 points, minimum *craving*; 14-26, light; 27-42, moderate; and 43 or more points, intense *craving*. This questionnaire will only be applied to Group 2.

Marijuana craving

Marijuana Craving Questionnaire – Short Form – MCQ-SF[34] – It is a self-reporting scale of 12 items, using Likert 7 points ranging from "strongly disagree" to "strongly agree". It is an abbreviated version of the MCQ[35], a multidimensional scale of 47 items. In Brazil, the semantic validation was made by Pedroso *et al.*[36]. In his psychometric[37] the MCQ-SF was divided into three factors: Emotionality (questions 1, 9 and 11), Intentionality (questions 3 and 10) and Compulsivity (questions 2 and 7) and may be analysed in addition to the method of the points in each factor by the sum of the total points (of 12 questions). The cut-off points in the Brazilian version for the total of the scale points are: 0-23 points, minimum *craving*; 24-38, light; 39-53, moderate; and 54 or more points, intense *craving*. This will only be applied to Group 3.

Materials to induce craving

¼ A4 size images of marijuana, crack cocaine and tobacco. Before being employed in this research the photos were considered faithful substance representations, with the potential to elicit *craving*, by a group of 20 hospitalized patients.

Ethical aspects

Data collection was only initiated after the research project had been approved by the Research Ethics Board of São Pedro Psychiatric Hospital. Before participants were accepted to be part of the research project its purpose was explained to them and they were provided with a written informed consent, which was read with the individual and any possible doubts clarified. The signing of this form was a precondition for the participant to be included in the sample. This research was also conducted in accordance with the Helsinki Declaration as revised 1989.

Procedures for data collection

Each participant who fulfilled the inclusion criteria was sent individually to a room where an assessment interview was conducted and a record containing socio-demographic data and pattern of psychoactive substance consumption was completed. The SRQ-20, on how they felt at that moment was administered its diagnosis evaluated using ICD-10. During the experimental study, we recorded the period of abstinence from the last crack, tobacco or marijuana consumption, which determined whether the participant would be part of Group 1, 2 or 3 (if evaluated to be part of the marijuana group they would go there, if possible, if not they would go to another group with priority given to the group with less participants).

After deciding into which group the participant would be placed, they were individually shown, for 3 minutes, a photo of the desired *craving* (crack, tobacco or marijuana) related to their group after which other evaluation instruments were administered in the following order: CCQ-Brief (only for patients in Group 1), QSU-B (only for patients in Group 2), MCQ-SF (only for patients in Group 3), VAS, BAI and BDI (for all groups).

Data analysis

The data collected was processed in the SPSS statistics software (v.20; SPSS Inc., Chicago, IL). Exploratory data analysis consisted of descriptive and frequency statistical tests. The inferential analysis employed the tests: Chi-squared and Analysis of Variance (ANOVA) with Tukey's test. As the QSU-B and CCQ-Brief scales have ten statements each but the MCQ-SF has twelve, the following calculation: "Total points MCQ-SF/12 x 10" was used to allow different substance *craving* results to be compared. The result of this calculation and the raw scores of the QSU-B and CCQ-Brief will be presented in table 1. The significance level used as a parameter was 5%.

Results

Each of the three groups was composed of 70 participants, regarding marital status, in accordance with the chi-squared test, there was no significant difference between groups ($\chi 2 = 8.217$; $p = 0.223$), with a prevalence of singles: 74.3% ($n = 52$) in the Crack Group, 80.0% ($n = 56$) in the Marijuana Group and 67.1% ($n = 47$) in the Tobacco Group. Group comparison regarding other socio-demographic variables, patterns of substance use and symptoms of depression and anxiety can be seen in table 2.

The comparison of *craving* in the three groups via the Visual Analogical Scale and other Scales to assess *craving* (CCQ-Brief, QSU-B and MCQ-SF), can be seen in table 1. In both tables, ANOVA with Tukey's test was used.

Table 3 shows the severity of *craving* according to the analysis of the total of points from the scales and according to the points of its factors considering its cut-offs, which were published in their respective psychometric validation.

Discussion

When analysing the results of this study, it was observed that the marijuana group was younger, had first begun by using alcohol (earlier than the tobacco group), had used crack and inhaled cocaine (earlier than the other two groups) and had spent less time without using inhaled cocaine (compared to the tobacco group) and without using marijuana (than either of the other two groups). In addition, they used an extreme amount of marijuana (about 30 joints per week), independent of this variable there didn't appear a significant difference in the three groups. Such findings may be due to the convenience sample since most patients stopped using marijuana for a period greater than 21 days and before hospital admission (an inclusion criteria). Those who remain using marijuana seem to have a more serious drug use profile, which may have interfered with the *craving*. This result associated with the interruption of marijuana use, well before hospitalization, had already been highlighted in previous studies[38,39] while researching crack addicts hospitalized for detoxification.

The Tobacco group was hospitalized for some time, but this difference did not affect the results, since the controlled variable was time in abstinence and not length of hospitalization and, the tendency of smokers to continue using tobacco. The Crack group used higher amounts of inhaled cocaine than the tobacco group, however, patients tended to be abstinent from this form of cocaine use during hospitalization, which cannot be taken as an intervening variable when comparing *craving* in the three groups. The interruption of inhaled cocaine when given crack was discussed by Balbinot and Araujo[38].

The abstinent period of marijuana, however, may have affected the intensity of *craving*, but this variable cannot be controlled because of the characteristic of the sample, who had – as observed in other studies[38,39] – a longer period abstinent from marijuana. However, the association between the length of abstinence of marijuana and *craving* was not found in a previous study[37].

There was no significant difference in the three groups for symptoms of depression and anxiety, mental states that could have interfered with *craving*, as already highlighted in other studies[7,31-32,40-42].

When comparing *craving* using the Visual Analogue Scale, the tobacco group demonstrated a more intense *craving* than the other groups; however when the specific assessing scales for *craving* were used, the tobacco and marijuana groups had a more intense *craving* than the crack group. That the *craving* result for marijuana is more intense than for crack resembles the one found by McRae *et al.*[14], however, with respect to inhaled cocaine it contrasts with another study[13] which didn't find an intense *craving* for marijuana.

The more intense tobacco *craving*, than that for other substances, might be associated with the fact that many patients – contrary to what occurs with crack – are not motivated to stop using this substance, this association had already been emphasized[43]. Haller *et al.*[44] also observed this phenomenon while researching the motivation for change in female smokers, however, it should be noted that other studies found no correlation between *craving* and motivation for change in smokers[32,40], which means this would be just one of the aspects to explain this finding, since dependence, abstinence and all corresponding phenomena with *craving* have multifactorial etiology.

Analysing *craving* for the three substances from their sub-factors, adding the rates of moderate and severe degrees, it can be observed that factor 2 of *craving* for crack (which refers to uncontrolled crack use), the emotionality factor *craving* for marijuana and factor 2 (negative reinforcing capacity) the *craving* for tobacco had higher scores. These results demonstrate that *craving* associated with the use of the substance for the relief of negative affect (such as anxiety and depression) or withdrawal symptoms was more intense than that for obtaining pleasure (positive reinforcement). The relevance, in this sample, of emotional aspects and negative reinforcing potential of substances to induce *craving* had already been verified in research concerning the *craving* for tobacco[7,43], and marijuana[37].

Limitations of this study are related to their possible interference with *craving*. They are: the large average amount of marijuana used by the three groups, the length of marijuana abstinence (which is higher in the marijuana group), the fact that psychiatric medication was not controlled[45] and the motivation to change addictive behaviour not being assessed; which mainly may have affected the tobacco *craving* values[43,44], which most patients did not intend to stop after hospitalization.

Table 1. Comparison of the averages in the three groups of scores on the craving scales

Variable	Total Sample			Group 1 – Crack			Group 2 – Marijuana			Group 3 – Tobacco			ANOVA	
	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	F	p-value
Craving according to Visual Analogic Scale	3.41 (3.39)	0	10	2.39 (2.82)[a]	0	10	3.15 (2.27)[a]	0	10	4.71 (3.64)[b]	0	10	9.287	< 0.001
Craving according to specifics scales for each group	28.60 (17.31)	10	70	19.68 (11.49)[a]	10	55	32.26 (15.86)[b]	10	64.17	33.70 (20.12)[b]	10	70	16.683	< 0.001

M: means; SD: standard deviation; Min: minimum; Max: maximum; [a, b]: means significant differences according to the Tukey's test; F: F-ratio test.

Table 2. Sample characteristics regarding sociodemographic variables, pattern of use of substances and symptoms of depression and anxiety

Variable	Total Sample (n = 210)			Group 1 – Crack (n = 70)			Group 2 – Marijuana (n = 70)			Group 3 – Tobacco (n = 70)			ANOVA	
	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	F	p-value
Age	28.02 (7.41)	18	50	29.35 (6.82)[a]	18	49	25.89 (7.26)[b]	18	50	28.89 (7.73)[a]	18	48	4.671	0.010
Years of Education	7.93 (2.37)	5	15	7.96 (2.28)	5	14	8.14 (2.61)	5	15	7.70 (2.37)	5	15	0.621	0.538
Days of hospitalization	8.68 (3.92)	2	30	8.04 (3.79)[a]	2	30	8.33 (3.74)[a]	2	20	9.64 (4.08)[b]	2	27	3.345	0.037
Age at first use of crack	21.39 (6.39)	10	48	22.94 (6.58)[a]	10	48	19.15 (5.31)[b]	12	35	22.09 (6.65)[a]	13	45	6.864	0.001
Amount of crack use (in rocks)/week	23.02 (27.37)	1	168	24.97 (30.66)	1	168	25.03 (28.10)	2	140	19.04 (22.67)	1	112	1.060	0.348
Last use of crack (days)	55.87 (303.96)	1	3600	9.54 (3.79)	7	21	38.58 (129.45)	1	780	138.54 (555.58)	4	3600	2.639	0.074
Age at first cocaine use	16.75 (3.08)	10	35	17.05 (2.41)[a]	13	25	15.73 (2.42)[b]	10	25	17.42 (3.94)[a]	11	35	5.236	0.006
Amount of cocaine grams/week	11.67 (20.12)	0	140	17.60 (24.97)[a]	0	100	9.74 (20.23)[ab]	0	140	7.80 (12.05)[b]	0	70	3.953	0.021
Last use of cocaine/ days	576.14 (1208.89)	2	7300	631.09 (1078.60)[ab]	2	5040	277 (759.21)[b]	6	5400	912.49 (1667.36)[a]	10	7300	3.400	0.036
Age at first use of marijuana	15.06 (3.05)	9	30	15.46 (3.51)	10	30	14.41 (2.54)	9	20	15.34 (2.98)	9	24	2.452	0.089
Amount of marijuana cigarette/week	24.35 (28.71)	1	160	22.59 (23.67)	1	140	30.07 (35.03)	2	160	19.86 (24.67)	1	140	2.365	0.097
Last use of marijuana (days)	357.21 (1040.44)	1	6480	506.32 (1121.44)[a]	2	5040	10 (3.89)[b]	7	21	732.27 (1508.07)[a]	1	6480	7.822	0.001
Age at first tobacco use	13.82 (3.43)	5	36	13.83 (3.04)	5	20	13.22 (2.80)	7	20	14.39 (4.19)	7	36	1.985	0.140
Amount of tobacco cigarettes/week	167.41 (103.11)	5	700	144.98 (70.65)	20	280	181.88 (127.07)	5	700	173.86 (100.10)	5	560	2.351	0.098
Last use of tobacco (days)	8.64 (3.49)	0	20	8.31 (3.20)	2	15	8.73 (4.01)	0	20	8.84 (3.12)	7	16	0.343	0.710
Age at first alcohol use	13.58 (3.24)	4	25	13.62 (2.98)[ab]	4	20	12.84 (3.52)[a]	5	25	14.26 (3.10)[b]	6	25	3.158	0.045
Units of alcohol* use/ week	63.66 (100.82)	0.80	560	63.17 (94.59)	1	373	61.82 (96.37)	1	560	65.89 (111.52)	0.80	560	0.026	0.974
Last use of alcohol (days)	89.22 (355.85)	1	4015	88.10 (241.96)	2	1440	40.03 (100.11)	1	540	155.67 (596.31)	5	4015	1.392	0.252
BDI total	15.93 (11.10)	0	55	14.23 (8.83)	0	37	17.82 (12.48)	0	55	15.69 (11.47)	0	52	1.898	0.152
BAI total	10.95 (10.43)	0	48	9.70 (9.79)	0	44	11.54 (10.96)	0	47	11.59 (10.51)	0	48	0.743	0.477

M: means; SD: standard deviation; Min: minimum; Max: maximum; * Unit of alcohol: 10 grams of alcohol; [a, b]: means significant differences according to the Tukey's test; F: F-ratio test.

Table 3. Levels of craving for crack, marijuana and tobacco

Variable	Craving levels							
	Minimum		Mild		Moderate		Severe	
	n	%	n	%	n	%	n	%
CCQ-Brief Total	23	32.9	14	20	15	21.4	18	25.7
Craving	0	0	38	54.3	6	8.6	26	37.1
Lack of control	27	38.6	5	7.1	4	5.7	34	48.6
MCQ-SF Total	22	31.4	13	18.6	21	30	14	20
Emotionality	15	21.4	19	27.1	18	25.7	18	25.7
Compulsivity	0	0	50	71.4	6	8.6	14	20
Intentionality	0	0	50	71.4	7	10	13	18.6
QSU-B Total	14	20	17	24.3	15	21.4	24	34.3
Craving positive reinforcing	16	22.9	18	25.7	12	17.1	24	34.3
Craving negative reinforcing	0	0	23	32.9	23	32.9	24	34.3

CCQ-Brief: Cocaine Craving Questionnaire-Brief; MCQ-SF: Marijuana Craving Questionnaire-Short Form; QSU-B: Questionnaire of Smoking Urges-Brief.

Crack, marijuana and tobacco dependent patients have proven to have a more intense *craving* for tobacco measured by generic scale (Visual Analogue Scale), and for tobacco and marijuana measured by specific scales. *Craving* has been associated with relief of negative emotional symptoms (such as anxiety and depression). Thus, taking into account the patient's suffering in the initial phase of treatment – acute period of abstinence – and the high rates of emotional episodes, it is important to link the cognitive-behavioural techniques with pharmacotherapy to relieve *craving*.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding this manuscript.

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Review article

A psychiatric perspective view of bariatric surgery patients

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Abstract

Background: Bariatric surgery is the only procedure that has significant results in weight loss and improvements in medical comorbidities in morbid obese patients. Severely obese patients are also associated with a higher prevalence of psychiatric disorders and poor quality of life. **Objective:** To evaluate specific areas of psychopathology in individuals undergoing bariatric surgery. **Methods:** A review of the literature was conducted from January 2002 to March 2014 by researching PubMed database using the following query: "morbid AND obesity AND bariatric AND surgery AND (psychiatry OR psychology)". **Results:** Overall improvements in eating behaviors, mood disorders and body image are reported after bariatric surgery, and the mechanism is not enlightened. Risk of suicide and consumption of substances of abuse, especially alcohol, after gastric bypass surgery are problems that clinicians must be aware. **Discussion:** Bariatric patients should be monitored after surgery to identify who did not show the expected benefits postoperatively and the ones who develop psychiatric symptoms after an initial positive response.

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Keywords: Morbid obesity, bariatric surgery, psychiatry, psychology.

Introduction

Obesity is associated with increased risk of medical complications[1]. Morbid obesity (MO) is defined as having a body mass index (BMI) ≥ 40 kg/m². In the United States, between 2000 and 2010, the prevalence of a BMI > 40 kg/m² increased by 70%, whereas the prevalence of BMI > 50 kg/m² increased even faster[2].

Pharmacological treatment, diet regimens and lifestyle alterations do not seem to be effective in morbidly obese patients[3]. Therefore, bariatric surgery is considered the most effective treatment in severe obesity, yielding more enduring weight loss[1]. Several surgical procedures are performed: Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, laparoscopic adjustable gastric banding (LAGB), vertical banded gastroplasty and biliopancreatic diversion[1,3,4].

Psychiatric problems are also common among morbidly obese patients and bariatric surgery may often contribute to improve it. The Swedish obese subjects (SOS) intervention study compared several psychosocial variables between a surgical group and a conventional group treated with diet and exercise counseling over ten years of follow-up. A significantly better outcome in depression, health perception, social interaction and psychosocial functioning was achieved by the surgical group whereas no significant differences were found in overall anxiety[5]. Furthermore, patients submitted to surgery lose significantly more weight than non-operated patients[6].

Several studies have reported a higher prevalence of psychiatric disorders in patients seeking bariatric surgery comparing to general population[7], as seen in other medical diseases, such as cancer[8,9]. Preoperative studies demonstrated that 20%-56% had a current psychiatric diagnosis[10]. Furthermore, at least one Axis I disorder was reported by 37%-43% of patients[11,12]. Recently, one study stated social phobia as the most prevalent Axis I disorder[11], in contrast to previous studies, where major depressive disorder was the most common[10,12,13]. In addition, studies reported preoperative prevalence rates of 15%-33% for mood disorders and of 24%-30% for anxiety disorders[10-12]. High incidences of somatization, hypochondria and obsessive compulsive disorder were also found in bariatric patients[14]. Moreover, the prevalence of binge eating behaviors and binge eating disorder (BED) is variable with a range from 4%-40%[11,15-18].

A large number of published studies have shown an overall improvement in mental health and psychosocial factors related to metabolic improvement and weight loss in most individuals undergoing weight loss surgery[19,20]. Additionally, a greater appreciation of life, greater sense of inner strength and improvement of interpersonal capabilities were experienced[21]. This alleviation of psychological, psychosocial and psychiatric status led to the suggestion that the negative psychological features result from the condition, the patient's severe obesity, and not the underlying character of the individual. On the other hand, improvements in psychological functioning were observed even though some patients remained obese after surgery when only a small amount of weight was lost. Therefore, greater optimism, higher self-esteem and taking an active role in life, leads to a better outcome[20].

However, not all studies have demonstrated a positive impact of bariatric surgery and a growing body of evidence has suggested that some of the stated benefits seem to be limited to the first years following weight loss surgery[22]. For instance, Scholtz *et al*. reported that nearly half of the sample developed a psychiatric disorder five years after bariatric surgery and those with a past of a psychiatric disturbance being significantly more at risk. Furthermore, postoperative psychiatric disorder predicted a lower probability of achieving a good outcome[23].

It has been reported that despite limited weight loss or side effects following bariatric surgery, most patients were satisfied with the results and did not regret the surgical option[19]. However, up to 20% appeared to be dissatisfied and the reasons pointed were psychosocial problems, surgical complications and not fulfilling their weight expectations[3,7].

Therefore, weight loss and improvement in medical comorbidities should be seen as successful factors after bariatric surgery, but the amelioration of psychiatric symptoms, eating behavior, psychosocial variables and quality of life are important outcomes to consider[3]. Thus, the aim of this review is to evaluate specific areas of psychopathology in individuals with morbid obesity underwent to bariatric surgery, such as, eating behaviors, mood disorders, body image, suicide and substances of abuse.

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This is relevant because psychological aspects potentially due to the postoperatively dramatic effects observed in weight loss, metabolic and behavior changes may be easily forgotten.

Methods

The relevant literature was identified by searching in PubMed database. Some limits were established prior to be searched, such as, publication date from January of 2002 to June of 2015, studies in humans and articles written in English.

The query used was: "morbid" AND "obesity" AND "bariatric" AND "surgery" AND ("psychiatry" OR "psychology"). A total of 422 articles were found. After eliminating the duplicates, 416 articles remained.

From the initial group of articles identified, 286 were excluded after abstract reading phase. The following exclusion criteria were used: studies in children or adolescents (n = 33); preoperative studies (n = 88); evaluating other aspects postoperatively that not psychiatric symptoms or disorders (n = 48); specific population studies (n = 7); non-morbid obese patients (n = 2); description of surgical procedures (n = 14); studies for analyze of psychological questionnaires (n = 15); studies related to medical comorbidities (n = 25); studies related to plastic surgery (n = 15); non-surgical studies (n = 13); studies with no available abstract (n = 12); clinical cases or opinion pieces (n = 14).

From the 130 articles of interest, the full-text of 20 articles remained inaccessible and 110 full-texts were read. The following inclusion criteria were used: studies which evaluated post-operative eating behaviors, post-operative weight loss, mood disorders, suicide, body image and substance use. Therefore, a total of 75 articles were included from the research. Further articles were included after inspection of references list from relevant articles.

Results

Eating behaviors

Eating patterns such as binge eating, night eating syndrome, "grazing" and excessive fluid intake are common in bariatric seeking population[24].

Assessing postsurgical data regarding eating behavior is considered difficult and one of the pointed drawbacks is the difference in definitions of binge eating employed by different studies[18]. Binge eating disorder (BED) is characterized by recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances, with episodes marked by feelings of lack of control. It is associated with marked distress, physical and psychological problems and occurs, on average, at least once a week every three months[25].

Despite the inconsistencies, the majority of studies report a decrease in binge eating and an improvement in eating behavior after bariatric surgery[4,26,27]. Moreover, most patients report a smaller amount of food eaten, a decrease in hunger, an earlier satiety, less inadequate eating behaviors and more control over their food intake[22,27]. When patients have binge eating behaviors postoperatively, it is being associated with reduced mental health and poor weight outcome[28-32].

Several studies have evaluated differences in weight and psychopathology between binge eaters (BE) and non-binge eaters (NBE) postoperatively. We need to be aware which surgery procedure was selected and we must account with that because we can have only a decrease of the stomach size or a reduction of the amount of calories absorbed by bypassing portions of the intestine also. A study compared psychopathological differences between BE and NBE after vertical banded gastroplasty in which the BE group reported higher scores for symptoms of eating disturbances, depression, alcohol dependence and personality disorders than NBE. Furthermore, the BE group lost less weight than the non-binge eating[33]. In other study in patients undergoing Roux-en-Y gastric bypass the authors found a less successful outcome for the BE patients compared with NBE in psychological wellbeing and quality of life[34].

Although the ingestion of large amounts of food becomes nearly impossible after gastrointestinal changes due to bariatric surgery, several maladaptive eating behaviors have been reported postoperatively. The frequency of these behaviors help to predict poorer weight loss, weight regain[28] and postoperative complications[35], such as inability to control food urges, decreased well-being, concerns over addictive behaviors (alcohol and substance abuse), lack of self-monitoring and fewer postoperative follow-up visits[36]. Several studies have demonstrated that a subgroup of patients after surgery will develop subjective binge or "loss of control" over eating[37,38]. "Grazing" is characterized by continual ingestion of small amounts of food over extended time with feelings of loss of control and some authors have suggested that it is a manifestation of binge eating behavior postoperatively[15,39]. According to Zunker *et al.*, bariatric surgery patients seem to interpret "grazing" as a healthy eating behavior characterized by mindful food choices that are consumed in small amounts frequently throughout the day[39]. However, the result is a greater intake of food which often ends in weight regain[20,40,41].

Emotional/stress eaters have difficulty in dealing with negative emotions and food may provide a transient shelter to avoid confronting difficult feelings[42]. The type of food usually consumed during these episodes, such as, candies or fast food have negative gastrointestinal symptoms, for example, nausea, vomiting or dumping syndrome. However, some patients persist in their attempts to eat in response to stress or emotional events. Instead of the large amount they used to ingest before surgery, patients consume high-fat and sugar content food in smaller amounts or drink sugar-sweetened beverages, so they will experience minimal gastrointestinal adverse symptoms[43]. Snacking post-surgery has been associated with poor weight loss[35,44].

Night eating syndrome (NES) is characterized by recurrent episodes of evening hyperphagia, poor sleep onset or maintenance, morning anorexia and a habit of getting up to eat during nocturnal awakenings. Additionally, the night eating has to be associated with significant distress[45]. A few studies have investigated this disorder after bariatric surgery. Latner *et al.* have reported that postoperative nocturnal eating is associated with greater postsurgical BMI and less treatment satisfaction[46]. On the other hand, Morrow *et al.* have shown no differences in weight loss after RYBG between the night eaters group and control group[47]. However, diagnostic criteria are inconsistent between studies which make it difficult to establish comparisons and draw conclusions. Therefore, NES definition should be revised and an agreement on the behavioral features and diagnostic criteria should be established. Furthermore, more studies evaluating this disorder in the severely obese population and the impact on bariatric surgery outcomes are required.

Symptoms such as vomiting, constipation and decreasing appetite are often seen after bariatric surgery. However, these symptoms may also be reported by patients with eating disorders. Therefore, it may be difficult for the clinician to distinguish if these symptoms are due to an eating problem or a surgical consequence[15]. Patients may vomit in response to intolerable food or non-compliance to the dietary regimen imposed by bariatric surgery[19]. However, De Zwaan *et al.* have interviewed 59 patients 2 years after RYGB about a range of eating behaviors. Vomiting was reported by over 60% of the participants and self-induced vomiting with the goal of influencing shape and weight was admitted by 12%[37]. An intense fear of regaining weight or dissatisfaction with body image secondary to hanging skin, excessive preoccupation with weight and the use of restricting and purging behaviors have been referred by bariatric patients[15,43]. Furthermore, it was suggested that other postoperative undesirable events, such as "plugging" (problems with the small opening of the stomach becoming plugged with food) and dumping syndrome (intense discomfort after sweet ingestions accompanied by nausea, vomiting, bloating, cramping, diarrhea, dizziness, fatigue, weakness and sweating), may lead patients to engage in compensatory or restrictive behaviors. The reasons for this are the uncomfortable feeling of having overeaten or having consumed food that is difficult to tolerate after surgery[15]. Therefore, when examining postoperative

eating patterns it is essential to investigate the motivation for them, especially because a postoperative eating disorder, such as bulimia nervosa can be easily confused with physical consequences of the surgical procedure.

All the postoperative inconsistent results make eating behavior a controversial area. Long-term research and standardized means of evaluation and diagnosis should be used in order to create clinical guidelines to ameliorate bariatric surgery follow-up and facilitate the early diagnosis of eating disorders after surgery.

Mood disorders

The majority of studies have reported a decrease in depression and depressive symptoms after bariatric surgery[24,27,48-56]. Women seem to show a more marked decline than men[57]. Some studies have stated significantly reduced levels of depression symptoms 1, 2, and 10 years after bariatric surgery in comparison with the preoperative period[5,58]. Other findings indicate an initial improvement in the first years postoperatively followed by the reappearance or worsening of depressive symptoms which seem to be associated with weight regain or weight stabilization[18]. Studies have reported increased levels of depression after 5 years when compared to the first year following bariatric surgery[59].

Considering anxiety symptoms, an overall improvement is observed after bariatric surgery[24,27,50-52], however, it is smaller when compared to depression symptomatology[58]. On the contrary, other studies reveal no significant changes in anxiety measurements postoperatively[48,49,56].

It has been suggested that a larger weight loss after surgery is associated with a more significant decrease in depressive and anxiety symptoms[5,16,60]. Additionally, a significant long-term relationship was found between depression and greater weight loss but the same did not happen for anxiety symptomology[5]. Moreover, some studies have demonstrated that bariatric patients may achieve normal scores of depression and anxiety following bariatric surgery[19,51].

De Zwaan *et al*. have examined the course and prognostic significance of anxiety and depressive disorders in a sample of 107 bariatric patients using face-to-face interviews conducted prior to surgery and two times postoperatively (6-12 months and 24-36 months). They have reported that preoperative depressive disorder predicted depressive disorder 24-36 months after surgery whereas preoperative anxiety significantly predicted postoperative anxiety disorders at both follow-up time points. In addition, postoperative depressive disorder was significantly associated with less weight loss whilst postoperative anxiety disorder was not associated with the degree of weight loss at any follow-up time-point[56].

Nevertheless, some studies do not report the expected improvement in depression and anxiety symptoms[19]. These inconsistent results may imply the presence of confounding factors. A prior trauma has been suggested as a possible candidate. Bariatric patients with traumatic background may present psychiatric complaints that are not fundamentally weight-related. Thus, traumatic histories might mediate the relationship between poorer postoperative weight loss and the maintenance of psychiatric symptoms[14]. Another implicated factor was the patient´s expectations after surgery that may have a negative impact if the expected results are not obtained[3]. Furthermore, it may be difficult to cope with the persistence of pre-surgical problems or new negative life events which were attributed to obesity in the past[18]. Regarding psychiatric medication, some studies showed a decrease in their overall usage following bariatric surgery[27]. Although, one study has reported no cases of symptomatic depression postoperatively, 32% of patients were taking antidepressant medication to maintain the level of symptomatic control[61]. Analyzing antidepressant medication specifically, a study has stated that the number of patients being treated for anxiety and depression did not change during the 2 years period of follow-up[58]. Moreover, in a retrospective study, Cunningham *et al*. have studied the changes in the use of antidepressants medication after RYGB in a sample of 439 patients. These authors have observed that 23% of patients had an increase in their antidepressant use, 40% continued to require the same dose of antidepressant, 18% had a change in antidepressant medication and only 16% of patients had a decrease or discontinued the antidepressant therapy[62]. In addition, in a sample of 67 bariatric patients with high level of depressive symptomology was found that 30% used antidepressants preoperatively and 24% were on antidepressants after bariatric surgery[55].

As the anatomy of the gastrointestinal tract is altered following bariatric surgery, drugs will not be absorbed as well. Beyond the absorption, distribution and elimination are pharmacokinetic processes we must consider. Each of these processes may be impacted by RYGB. With adjustable gastric banding the majority of these issues do not apply.

Roerig *et al*. have evaluated the changes in pharmacokinetics of the antidepressant sertraline after RYGB. There was a significantly smaller area under the plasma concentration/time curve in the postoperative group compared to the nonsurgical control group, which suggests an altered exposure to sertraline[63]. Despite the increasing numbers of bariatric surgeries performed, there is no accepted consensus regarding to antidepressant dosages after the different forms of bariatric surgery. Other aspect of concern is the choice of antidepressant taking into account the weight gain and the metabolic chances that may occur during the treatment with antidepressants[64]. Depressed patients are encouraged to receive pharmacologic treatment. Attempts should be made to place the patient on weight-neutral medications, avoiding medication such a tricyclic antidepressants or mirtazapine, which are known to cause weight gain[65]. For these reasons, postoperative monitoring of patients taking psychopharmacological medication is recommended. More knowledge needs to be acquired in the area of psychotropic medication pharmacokinetics in order to create clinical practice directives for the best care of bariatric patients[66].

Three studies were found analyzing bipolar disorder (BD) and bariatric surgery. BD is considered in some bariatric programs as a definite contradiction to surgery while others consider BD with controlled symptom a possible contraindication[67]. Nevertheless, not a large number of studies were found that can confirm or refute these assumptions. Interestingly, one study has reported that patients with a lifetime mood disorder diagnosis had a significant lower weight loss than patients without a psychiatric disorder, however, after removing the patients with BD no significant differences were found in weight loss. Some explanations were elaborated, for example the impulsivity, which is characteristic of this disorder, might make difficult to adhere to behavioral modification imposed by the surgery. Furthermore, lithium, a medication which can be used in the treatment of BD, has been shown to have a negative effect on memory and cognitive processing. Moreover, mood stabilizers are associated with an increased risk for several physical diseases, including obesity, dyslipidemia, *diabetes mellitus*[68,69]. On the contrary, another study has showed that patients with BD achieved positive weight loss outcomes at 12 months which were not significantly different from the patients with other psychiatric diagnosis or with no psychiatric disorder[70]. Additional research is needed regarding BD and bariatric surgery outcomes.

Body image

Body image dissatisfaction is more common in women and is associated with higher incidence of depression, low self-esteem and perfectionism[13,54]. A great psychological stress is observed due to stigmatization of obesity[3].

Several studies demonstrated that body image impairment, attractiveness and lack of familiarity with the body improved after bariatric surgery[16,19,71-73]. Additionally, less body shape and weight concerns were reported[74]. However, most studies have only investigated changes in the first and second year after surgery[54,72,75].

Although an overall improvement was found in body image after surgery, some studies have demonstrated poor results when

compared to general population samples[71] or non-obese populations[54]. Other authors have stated that body image-related concerns reached normal values postoperatively despite the fact that most patients continued to be overweight or obese[74].

Nevertheless, residual body image dissatisfaction due to increasing and/or sagging skin has been reported following weight loss surgery[16,19,52,75,76]. Recently, it has been established a correlation between the amount of excess skin and the degree of body image discomfort of bariatric patients[76]. Kinzl *et al.* have observed that 70% of obese patients who achieved a severe weight loss complained about flabby skin in their upper arms and thighs, abdominal flap and pendulous breasts. The authors have also stated that patients who were satisfied with their physical appearance lost less weight[77]. On the other hand, other studies have suggested that patients who had lost more weight were more satisfied with their image[19].

The skin excess resulting from bariatric surgery is a common cause of functional and esthetical impairment which increases the desire and search for cosmetic surgery[76,77]. Pecori *et al.* have demonstrated in a small sample that patients who underwent aesthetic surgery had similar results in body image improvements in a 2-year follow-up when compared to patients who were only submitted to bariatric surgery. In addition, the authors have reported that individuals who sought aesthetic surgery had similar values of body uneasiness and dissatisfaction to those of severely obese patients[72].

Therefore, bariatric surgeons must be advised to counsel their patients before surgery regarding body changes that they may experience postoperatively in order to prevent the psychological distress caused.

Inconsistent results were found relating body image and weight loss. Some studies have demonstrated that body image dissatisfaction did not correlate with weight loss[54] or marginally correlated[74], whereas, other authors have showed a more positive body image when the patient loses a greater amount of weight[53,71,78,79]. As a result, more studies are needed to elucidate the relationship between body image satisfaction and weight loss. Additionally, mediating variables that affect body image, such as self-esteem, appearance investment, social support and expectations of weight loss should be investigated.

Interestingly, one study was found in which body image satisfaction was compared between a night eaters group (NE) and control group (C) 5 months after RYBG. The two groups did not differ in weight loss or reductions in waist circumference. However, reported body image perceptions improved less in NE than C, the NE individuals saw themselves as heavier than they were[47].

Suicide

Severely obese people may have an increased mortality by suicide as stated Mirabelli *et al.*, in an Italian cohort study[80]. Other study which has evaluated the long-term mortality after bariatric surgery in a series of patient has reported a greater number of suicides in the surgical group comparing to the controls[81]. Tindle *et al.* have studied bariatric patients over a 10-years period and compared their suicide data to the U.S. and Pennsylvanian populations. They have reported an increase of suicides in the surgical group. The incidence of suicide in the surgical group was 6.6/10.000, which included 13.7/10.000 for men and 5.2/10.000 for women. These results were compared to the US population suicide rates (2.4/10.000 for men and 0.7/10.000 for women). The majority of the deceased were Caucasian women. The reported average time to death was about 3 years after surgery (10% in the first year, 29% in the second and 68% in the third). Furthermore, suicides were categorized by modes of death (drug overdose, gunshot wound, carbon monoxide poisoning and hanging)[82].

One study has been recently published comparing the reported suicide data after bariatric surgery with the Tindle *et al.* study and World Health Organization (WHO) data. Using 28 studies, they estimated a suicide rate after weight loss surgery of 4.1/10.000, which was significantly lower than the one reported by Tindle *et al.*[82]. Nevertheless, they report a four times higher probability of bariatric patients commit suicide when compared with WHO latest data (1.0/10.000). Regarding time frame, suicides occur between 18 months and 5 years after surgery[83].

In this important problem of the suicide we must account with the multiple factors like the disinhibition and potential impulsivity secondary to changes in the alcohol absorption, the recurrence of medical comorbidities after bariatric surgery, the effect of malnutrition on the brain, the metabolic or pharmacokinetic changes that may affect the absorption of psychiatric medications, all of these can happen after bariatric surgery. Furthermore, we can not to have a superficial look with the association between suicide and the fact of have been submitted to a bariatric surgery. Recently, in a review, possible risk factors for increased suicide following bariatric surgery were addressed which included disappointment with the amount of weight loss, unresolved or recurrent medical conditions, and continued or recurrent physical mobility restrictions[4]. Unrealistic expectations about the outcomes of surgery, the distress with the limitations in the diet and the diverse care applied postoperatively, are potential factors attached to suicide risk in post-surgery period[84]. Patients need more intensive postoperative care, particularly medical, nutritional or psychotherapeutic care. A special aim of a multidisciplinary program must be to identify those patients who need specific interventions. Postoperative follow-up in multidisciplinary regimen (surgeon, endocrinologist, psychiatrist or psychologist and nutritionist) is of great importance[85].

Although studies refer an increased rate of suicide, there is a significant variation in the characteristics of the studies and length of follow-up. Therefore, it is difficult to establish corrective comparisons between patients after bariatric surgery and the general population[18].

Substance use

A prospective investigation of alcohol use disorders (AUD) before and after bariatric surgery found a significantly higher prevalence of AUD in the second postoperative year, overall, and specifically post-RYGB, compared to the years immediately before and following surgery[86]. Ertelt *et al.* have reported that a small percentage of the sample developed an AUD after gastric bypass, despite not having a previous dependence[87]. Moreover, one study has reported a higher frequency of alcohol abuse after RYGB than LAGB[88].

Studies have reported that individuals submitted to bariatric surgery noticed that they become more intoxicated after consuming less alcohol and that there is a more rapid onset of intoxication effects comparing to the preoperative period[87]. Some studies showed that alcohol metabolism was significantly different between the postgastric bypass and control subjects[89,90]. Within minutes after consumption of a beverage containing a modest amount of alcohol, post-RYGB patients achieve disproportionately high blood alcohol concentrations[90]. Considering alcohol pharmacokinetics, ethanol is metabolized primarily in the stomach by the gastric alcohol dehydrogenase enzyme. RYGB limits the first step of metabolism and, consequently, higher serum levels of ethanol are obtained[36].

Conason *et al.* they have found a significant increase in alcohol use, recreational drug use and cigarette smoking 24 months after bariatric surgery[88]. In another study, 24 bariatric patients in an inpatient substance abuse treatment program were interviewed. Half of the sample stated that they had never experienced any alcohol or substance addiction prior to surgery[91].

In a study conducted to determine opioid use following bariatric surgery in patients using opioids chronically for pain control prior to their surgery, 77% of them continued chronic opioid use in the year following surgery and the amount of opioid substance was greater postoperatively than preoperatively[92]. One possible explanation is that some patients likely had pain unresponsive to weight loss but potentially responsive to opioids. Multiple factors likely contribute to increasing chronic opioid use over time. Obese individuals demonstrate more pain sensitivity and lower pain detection thresholds than those who are not obese and altered pain processing persists after

bariatric surgery. Contributing factors not unique to the bariatric surgery population include long-term opioid use possibly leading to tolerance, with need to take higher dosages to achieve equianalgesia and escalating dosages possibly increasing pain sensitivity, even when the initial cause has resolved[93].

According to Weingarten *et al.*, opioid consumption after bariatric surgery is greater among patients who are younger, men, and have been previously hospitalized because of psychiatric disorders. Additionally, they have reported that tobacco users tend to require more opioids and the current usage of psychotropic medications was not associated with greater opioid consumption or episodes of severe pain[93].

A small amount of published data address this issue but it seems that despite detailed preoperative screening individuals can develop unforeseen substance addiction. More studies evaluating substance abuse postoperatively are necessary to assist in the understanding of this area.

Conclusions

Psychiatric disorders such as depressive, anxiety and binge eating disorders are prevalent among bariatric surgery candidates and an overall improvement in this psychopathology is observed after bariatric surgery. Nevertheless, depending on the specificity of the problem, the kind of comorbidity, the metabolic evolution and the motivation and treatment compliance, patients may or may not present psychopathological benefits postoperatively.

In addition it is important for clinicians to be aware of vomiting and other maladaptive behaviors because an eating disorder may be misdiagnosed.

Regarding body image, one increasing concern is the excessive skin that appears after substantial weight loss. A growing concern indicates a possible increased risk of suicide and substances abuse, especially alcohol, after bariatric surgery. However, suicide and use of substances of abuse remain relatively undeveloped topics since a small number of studies were found and different methodologies were used.

Further research is warranted for a more complete understanding of psychopatological areas in bariatric surgery patients. Furthermore, long-term studies are needed to elucidate the decline in improvements with time that is reported in some studies. This knowledge will allow a better preoperative selection, but above all, a more efficient follow-up.

Conflict of interest

None of the authors has conflict of interest.

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Mediumship: review of quantitatives studies published in the 21st century

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Abstract

Background: Mediumship can be defined as the alleged ability to communicate with deceased persons. The last decade has been particularly productive for this field of research and the study of mediumship can help the understanding of the human mind-brain relationship and provide objective data to the scientific community and to the general population. **Objective:** The aim of this review is to summarize and discuss the results found on recent studies investigating mediumship. Furthermore, we aim to discuss the psychophysiology underlying mediumship and future perspectives for this study topic. **Methods:** A literature search for articles in English, Portuguese and Spanish published from January 2000 up to June 2015 was conducted using three electronic databases (PubMed, Lilacs and Web of Science). Review articles, qualitative studies and studies investigating altered states of consciousness caused by psychoactive substances were excluded. The original search returned 150 articles, but the application of exclusion criteria resulted in the inclusion of 19 articles for final analysis. **Results:** The general findings were: (1) an association of mediumship with good mental health, predominantly in experienced mediums, (2) heterogeneous findings regarding the ability of mediums to provide accurate information what may be due to different study methodologies and (3) incipient studies assessing physiological correlations during mediumistic communications (i.e. hypoactivation of brain regions responsible for cognitive processing and writing planning during psychography compared to a control task; electroencephalographic (EEG) changes and a slight predominance of the sympathetic nervous system). **Discussion:** There is a paucity of empirical data available in this controversial research field. New studies employing rigorous design (*e.g.* triple-blind protocols to test accuracy of mediumistic communications), and sensitive methods are required.

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Keywords: Mediumship, after-death communication, spiritual experiences, mental health, psychophysiology.

Introduction

Although there is no formal consensus on the definition of mediumship, it could be roughly defined as the alleged ability to communicate with deceased personalities on a regular basis[1], or as a set of experiences in which an individual, alleged "medium", maintains regular contact or stays under the control of someone else who has already died or of another immaterial being[2].

At different times and among different cultures in human History there were reports of experiences that could be interpreted as mediumistic phenomena, for example the reception of the Ten Commandments by Moses at the Mount Sinai (Christianity and Judaism) and the reception of information and advice from superior and protector beings (*dharmapalas*) by Tibetan Buddhist monks[3].

During the 19th century and in the early 20th century, many pioneers of modern Psychology and Psychiatry have studied cases of alleged mediums. This was the case of William James, who for many years studied the medium Leonora Piper[4]; Pierre Janet, who wrote a book about the "psychological automatism"[5]; Carl G. Jung, who received his doctorate degree after studying his cousin (S.W.), an alleged medium[6], among others. At that time, other renowned scientists also dedicated their time and effort to study mediumistic phenomena, such as William Crookes[7] and Charles Richet[8].

Talking to "spirits" or being possessed by "spirits" are cultural phenomena found in almost every society worldwide and their relationship with mental illness has been the topic of extensive investigations in the fields of cross-cultural psychiatry and anthropology[9,10]. Observational studies demonstrate a high prevalence (around 80 percent) of individuals who believe in the survival of the soul after death in general population[11,12], and this finding is congruent with the significant popularity that many cultural products covering this topic have (*e.g.:* books, films, novels, TV series)[13].

At present, mediumship is considered to be a form of dissociation[14,15]. Dissociation can be defined as "the occurrence of experiences and behaviors that are thought to exist apart from, or to have been disconnected from, the mainstream of one's conscious awareness, behavioral *repertoire*, and/or self-concept"[16]. The majority of culture-bound dissociation is considered normal, does not lead to distress or impairment, it often arises in willing individuals in appropriate (frequently religious) contexts, and is usually experienced as beneficial. In subjects with pathologic dissociation, the experiences occur in an unsolicited, unruly and socially nontolerated manner, causing considerable distress, with adverse effects on occupational activities and other impairments[17].

Many societies where culture-bound dissociation is observed are characterized by an authoritarian male hierarchy, being oppressive for women and children. Some scholars affirm that in many of these societies, the dissociative experiences are more common in women and they propose that dissociation would be a psychological mechanism with an emotion-regulatory role. This is seen as a socially sanctioned (and even valued) behavior that would allow cathartic expression of forbidden and disowned feelings by individuals living under characteristically oppressive conditions[14,17].

Self-hypnosis is one of the proposed psychophysiological mechanisms involved in dissociation. After carefully analyzing mediumship in the context of *Candomblé*, an Afro-Brazilian religion, Seligman (2005)[14] concluded that mediums would be individuals with a psychophysiological tendency to somatization and to dissociation that, submitted to emotional distress, find in the religion system (and in the assumption of a new social role as mediums) a way for a positive transformation of their identities, leading to a moderation of their somatic and emotional afflictions and to a global therapeutic effect[14,17].

Much of the controversy surrounding mediumship research derives from de fact that it stresses the "mind-brain problem"[18]. The explanation for how the human brain generates mind is one of the

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greatest philosophical and scientific challenges of the past, the present, and probably of the future[19]. The French seventeenth century philosopher René Descartes put forth the theory of Substance Dualism, supporting the idea that mind (subjective) and body (objective) are different natural substances and that it is the bond of mind to the brain that allows it to think. Mind and brain being independent entities, consciousness could continue to exist (and perhaps communicate) despite the death of the physical body. On the other hand, the dominant materialist perspective argues that consciousness is a byproduct of brain activity, being extinguished with the death of the physical body. A better understanding of mind could only be possible through an increase on the knowledge about brain functioning[20-22].

Contemporary dualist philosophers and scientists sustain that materialism has left a range of questions unanswered, as, for example, how human subjective and affective experiences exert such a decisive influence over body functions. For many dualist and post-materialist scientists the evidences stemming from high quality studies about near-death experiences and about mediumistic communication are strong indicators that consciousness has a non-local character and could survive the death of the physical body[19].

Currently, the three most common explanations for mediumship are: (1) fraud (conscious or unconscious), (2) after-death communication, and (3) telepathy. The first, the materialist model, excludes the possibility that any aspect of the personality can survive physical death and rejects extra-sensorial perceptions (ESP) in general. Thus, if a mediumistic information seems accurate this can only result of deliberate fraud, coincidence or "cold reading" (fishing of information) by the medium. The second explanation, the spiritualist model, argues that the mind (or soul) of the medium communicates with the mind (or soul) of the deceased person through some form of telepathy, obtaining information. From the third perspective, generally defended by investigators of ESP, when an alleged medium is asked to communicate with a deceased person, the medium's answers are given based on clairvoyant access to physical traits of the deceased personality and on telepathic access to the knowledge of the consultant (super-psi hypothesis). The supporters of this explanation, in general, also consider the survival as a plausible hypothesis requiring evidence-based proof[23]. This variety of possible explanations, hard to differentiate one from another, poses significant challenges and complexity for the studies aiming to prove the reality of mediumistic phenomena.

In fact, the last decade has been particularly productive for this field of research and the study of mediumship can help the understanding of the human mind-brain relationship and provide objective data to the scientific community and to the general population. Within this context, the aim of this review is to summarize and discuss the recent results found on studies investigating mediumship. Furthermore, we aim to discuss the psychophysiology underlying mediumship and future perspectives for this study topic.

Methods

Literature review and selection of studies

The Literature search strategy was carried out in three phases, as described below.

Phase 1 (primary Literature search): two researchers (MAVBJ and IHSO) independently screened the list of citations (full text were retrieved for further analysis whenever necessary) to exclude studies that did not address the issue at hand. Any disagreement between the researchers were discussed with a third reviewer (GL), and resolved by reaching a consensus.

Articles in English, Portuguese and Spanish dealing with quantitative investigation of mediumship, published within the time range from January 1st, 2000 up to June 10th, 2015, were selected – hence focusing only on the contemporary scientific aspects of the topic.

Review articles, qualitative studies (either anthropological, theological or ethnographic), studies investigating altered states of consciousness caused by psychoactive substances and letters to the editor were excluded. Regarding the studies testing accuracy of mediumistic information, works that have not applied rigorous designs aiming to eliminate information leakage (i.e. those not strictly adhering to protocols that minimize as much as possible the probability of the alleged medium having access to information about the deceased personality via other common means or via fishing of information) were also excluded. Regarding psychophysiologic correlates of alleged mediumship, due to extreme paucity of available data, case reports were not excluded. All articles not fulfilling the inclusion criteria and which met the exclusion criteria were omitted from the final analysis.

The following databases were evaluated: Web of Science, PubMed and Lilacs. For the Web of Science database, filters were used to limit the search to fields of Psychiatry, Psychology, Neurosciences/Neurology, Religion and General Internal Medicine, as this database also indexes citations in arts and humanities, which are beyond the scope of this review.

The keywords used were: "mediumship", "mediumistic" and "after-death communication". Although a few important concepts and theories accrued from anthropological and ethnographic studies about Possession Trance are cited, this is not the focus of this review.

Phase 2 (secondary Literature search): with the aim of identifying studies that could have been missed in the primary search, references lists of initially included articles were screened and the same three keywords were evaluated in Google Scholar. Only the first 100 references from Google Scholar were evaluated. The same inclusion and exclusion criteria were applied in both phase 1 and phase 2.

Phase 3 (critical review of studies): the included articles were evaluated regarding number of participants, methods applied, comparisons and main findings. The studies were grouped in the following three categories based on their methodology and type of outcomes evaluated: (1) mediumship and psychopathology, (2) testing the accuracy of information provided by mediums and (3) psychophysiological correlates of mediumship. These categories were adopted based on the classification proposed by Jinks (2013)[24] for quantitative research on mediumship.

Table 1 and figure 1 summarize the search and selection strategy.

The last section of this review consist of future perspectives for the study of alleged mediumship, especially in its psychophysiological aspects, and due to paucity of available empirical data on this field, it was based on authors' opinions and on recent reviews dealing with other dissociative and spiritual experiences.

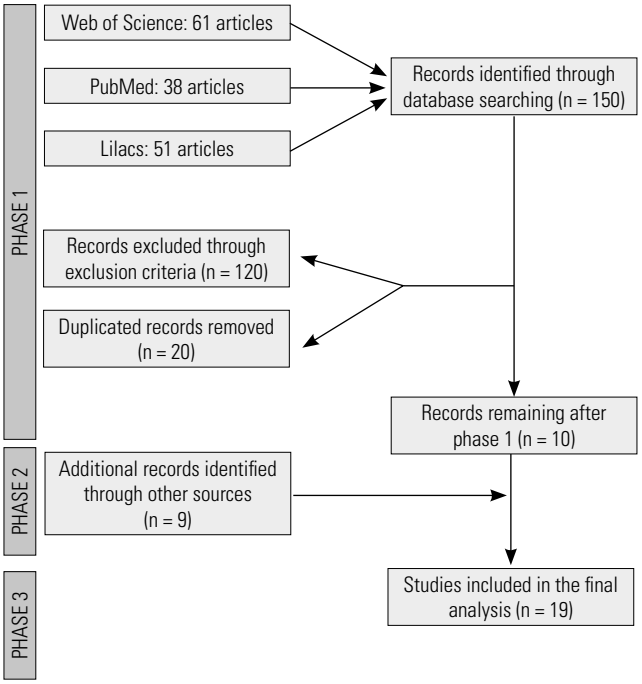

Figure 1. PRISMA (The Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram.

Table 1. Selection of studies – phase 1

Term	N° of articles found	N° of articles excluded	Reasons for exclusion	N° of articles included in final analysis
	Electronic database: Web of Science			
"Mediumship"	40	32	9 ethnographic studies 8 literature reviews 8 historical perspective articles 7 other reasons	8
"Mediumistic"	17	16	5 historical perspective articles 4 literature reviews 4 ethnographic studies 3 other reasons	1
"After-death communication"	4	4	2 qualitative studies 1 literature review 1 ethnographic study	0
	Electronic database: PubMed			
"Mediumship"	21	13	6 historical perspective articles 2 ethnographic studies 2 literature reviews 3 other reasons	8
"Mediumistic"	12	10	2 ethnographic studies 2 historical perspective articles 6 other reasons	2
"After-death communication"	5	5	3 qualitative studies 1 literature review 1 letter to editor	0
	Electronic database: Lilacs			
"Mediumship"	30	21	8 historical perspective articles 6 literature reviews 4 ethnographic studies 3 other reasons	9
"Mediumistic"	17	15	5 historical perspective articles 3 literature reviews 2 ethnographic studies 5 other reasons	2
"After-death communication"	4	4	2 qualitative studies 1 literature review 1 letter to editor	0
	All Databases			
		20	Duplicated articles among those included	
Total	150	140		10*

* The phase 2 of the search led to the inclusion of 9 additional articles totaling 19 articles for the final analysis.

Results and discussion

The phase 1 (primary Literature search) of the search led to the retrieval of a total of 150 articles. The application of the exclusion criteria resulted in the exclusion of 140 articles and the inclusion of 10 articles in this phase. As shown in table 1, the most frequent reasons for excluding articles, in descending order, were: historical perspective studies (34 articles), literature reviews (25 articles) and ethnographic studies (24 articles).

In phase 2 (secondary Literature search) of the search, screening of references lists and evaluating the keywords in Google Scholar led to the inclusion of 9 additional articles.

In phase 3 (critical review of studies), all 19 studies found were evaluated in terms of number of participants, methods applied, comparisons and main findings.

Tables 2, 3 and 4 briefly describe the 19 included studies. The main results are as follows:

(1) Mediumship and psychopathology (Table 2)

Most studies suggest that mediums have good mental health, are socially well adapted and occupationally active. However, one must notice that all but one study[25] took place in Brazil, so caution is necessary when trying to extrapolate these conclusions to other countries, since mediums have an established social role in Brazil[26], which may not be the case in other societies. It is known that a society's dominant ideas about questions like the dualism, the soul and paranormality influences the way dissociative experiences are viewed and whether they are tolerated or not[17].

Our findings corroborate with the theory proposed by Seligman[14] that affirms that mediumship has a therapeutic role to certain individuals under psychological distress, who find in the religious system a way for a positive transformation of their identities. The scores of mental health and control of the dissociative experiences are clearly different if the individuals are beginning to participate in the religion, as in the studies of Menezes Jr. *et al.*[2] and Alminhana *et al.*[27], or if they have many years of practice as socially sanctioned mediums, as it was the case in all the other studies, being significantly worse in the former case.

However, the psychosocial stressors theory may not fully explain the Brazilian Spiritist participants, since this group has one of the country's best socioeconomic status and best education level among all the other religious groups[28]. For instance, in the study of Moreira-Almeida (2004)[29], the financial situation of Spiritist mediums was not different from mentally healthy control participants, highlighting that other possible explanation for this phenomenon may be considered[14].

Table 2. Studies on mediumship and psychopathology

Study	Participants	Method	Comparisons	Findings
Negro *et al.* (2002)[73]	110 experienced Kardecists mediums (for 21 years on average)	Self-report questionnaires (SRQs) evaluating personality traits (happiness, sociability, religiosity, temper, mediumship) and dissociative experiences (Dissociative Experiences Scale – DES)	Correlation analysis between dissociation scores and sociability and adaptation scores. Correlation analysis between training in mediumship and control of dissociative experiences	Sociability and adaptation scores compatible with normality despite high dissociation scores. Majority (94%) considered to have control over the mediumistic experience. Positive correlation between formal training in mediumship and control of dissociative experiences
Moreira-Almeida (2004)[29]	115 Kardecist active mediums (for 16 years on average) and 34 subjects without previous or current mental disorder	Semi-structured interviews and self-report questionnaires assessing: socio-demographic data, mental health and phenomenology of dissociative experiences	Comparison of prevalence of hallucinatory experiences between groups. Correlation analysis between dissociative symptoms scores and intensity of mediumistic activity with mental health scores and social adequacy	Higher prevalence of hallucinatory experiences in mediums, with normal levels of social adequacy. There was no correlation between the intensity of mediumistic activity and mental health scores and social adequacy
Seligman (2005)[14]	Five groups: – 11 female *Candomblé* mediums – 10 non-medium initiates, – 20 uninitiated religious frequenters, – 20 control participants from outside the religion, matched for socio-economic status, – 10 control participants from outside the religion and from a higher socioeconomic status	– Instrument to screen for anxiety and depression (QMPA) – State Trait Anxiety Inventory (STAI) – Dissociative Experiences Scale (DES) – Semi-structured interviews	Comparison between mediums and nonmediums with varying degrees of proximity to *Candomblé* and the mediumship role	Group from higher socioeconomic status with significantly lower levels of anxiety and depression (QMPA). Significantly higher number of somatic symptoms reported by mediums. No difference between groups for STAI scores. DES scores higher in the 3 religious groups (none above clinical cut-off). No correlation between mediumship and DES score
Moreira-Almeida *et al.* (2008)[26]	24 Kardecist active mediums, being 12 mediums with (+) scores in the screening for mental disorders in primary care [SRQ +] and 12 mediums with (-) scores [SRQ -] 166 patients with Dissociative Identity Disorder – DID (data from this group was extracted from literature)	Self-report *questionnaire* assessing social adequacy, psychotic symptoms and structured interviews with mediums to evaluate diagnostic criteria for DID	Comparison between subgroups of mediums. Comparison between mediums and patients with DID	From the mediums, no one met criteria for DID. The only difference observed among the subgroups of mediums was social adaptation [slightly worse in SRQ (+)]. No difference between the group of mediums and DID group for psychotic symptoms, but better mental health and social adjustment in mediums
Roxburgh & Roe (2011)[25]	80 British spiritualist mediums and 79 control subjects (non-mediums, attended the same religion, without any diagnosed mental disorder)	Self-report *questionnaires* assessing personality traits and mental health indicators	Comparison between mediums and control group (healthy individuals from the same socio-cultural context)	Mediums scored significantly higher in well-being and lower in psychological stress. There were no significant differences among groups regarding dissociation or personality traits that could indicate psychopathology or proneness to fantazise
Menezes Jr. *et al.* (2012)[2]	115 individuals seeking help in spiritual centers due to their so-called mediumistic experiences	Semi-structured interview with a psychologist to evaluate socio-demographic data, mental health history and dissociative experiences	Qualitative exploration to assess the presence or not of nine criteria considered suggestive of non-pathological anomalous experiences (AEs)	The most frequent AEs were visual (63%) and hearing (54%) hallucinations and "perception of spirit" (53%) For most of mediums, AE did not bring socio-occupational losses, were brief, episodic and benefic; but 59.2% related them with emotional distress and 54.8% did not present control over experiences
Alminhana *et al.* (2013)[27]	115 individuals seeking help in spiritual centers due to their so-called mediumistic experiences	Self-report questionnaires to assess personality traits, quality of life and religiosity	Comparison between experimental group, general population and individuals with mental disorders (data of control groups extracted from literature)	Individuals with AE presented intermediate scores on personality traits, religiosity and quality of life when compared with general population and individuals with mental disorders. Authors hypothesized that mediums may be a population at higher risk for mental disorders

(2) Accuracy of information provided by mediums (Table 3)

Quantitative research on alleged mediums has been done for more than a hundred years, and meanwhile the designs of studies have been progressively improved as to eliminate information leakage and telepathy as explanations for the reception of accurate information by mediums[23]. Research protocols reproduce the habitual situation of a friend or relative (the named "sitters") of a deceased person consulting a claimed medium looking for postmortem information about this person, but they apply a "triple blind" design[30]. That is, mediums are blind to the identities of the consultant ("sitter") and of his/her related-deceased person; the researcher interacting with the mediums (acting as a proxy for the consultant) also remains blind to the identities of the consultants and his/her related-deceased person; and consultants who score the accuracy of the "readings" remain blind about the information source (reading really intended for him/her *vs* decoy reading)[18].

In the present review, only studies considered to have sufficient control against information leakage (i.e. which strictly adhered to triple-blind protocols) were included. Hence the works of Roy & Robertson[31] and Schwartz *et al.*[32], although consist of important contributions as exploratory methods, were excluded (they applied methods where mediums had direct contact and talked to the consultants, among other shortcomings). Data from experiment 2 of the study of Kelly & Arcangel[33] was also excluded from this review because of lack of strict adherence to triple-blind protocol (mediums received pictures from the deceased individuals, many of the sitters were colleagues or friends of one of the investigators, and this investigator knew some of the deceased individuals). Altogether the results of the well-controlled studies included in this review show: (a) in two studies[30,34] (totaling 28 mediums and 102 readings) the sitters' accuracy ratings of specific information from target readings were statistically higher than for decoy readings; and (b) in three[33,35,36] studies (totaling 10 mediums and 44 readings) there was no statistical difference in the fit scores assigned by sitters for the target or decoy readings.

Interestingly, the "triple-blind" design was used in all these studies, but there were slight methodological differences between them that can have influenced the outcomes. For example, in the studies with positive results, the sitters were asked to decide which was the fittest between only two readings, while in "negative studies" the sitters needed to decide among three to seven readings. Moreover, "positive" but not "negative" studies have used a pairing procedure of the deceased persons to optimize differences (in categories like age at passing, hobbies, physical description, cause of death). Hence, it seems that, for methodological reasons, choosing the target reading was less difficult for sitters of the "positive" than for "negative" studies.

Different from the others, the study of Rocha *et al.*[37] did not use a controlled design, choosing a retrospective approach. Authors screened published and unpublished letters that were psychographed (allegedly written under the influence of a spirit) by a Brazilian medium, Chico Xavier, who died in 2002. Then, a set of 13 letters was selected because these letters contained much specific and objective information about a deceased person, and living relatives and friends of this person agreed to participate in interviews with the investigators to verify the fit and accuracy of the mediumistic information conveyed. Among 71 items of specific information extracted from the letters, a high percentage (97,2%) was scored as having a "clear and precise fit". As authors acknowledge, one significant limitation of this type of study is that the scoring may have been subject to memory bias, as letters were written more than forty years before. However, three "drop-in" communications ("situations where allegedly a deceased personality communicates via the medium without the request of relatives or friends"[37]) were identified in the letters. Pieces of specific information from these communications were objectively verified, and they proved to be true.

(3) Psychophysiological correlates of mediumship (Table 4)

The most common findings concerning psychophysiological correlates of mediumship were: increased noradrenalin levels during possession trance in a controlled study[38], increased muscle tone in a case report[39], increased heart rate[38,39] and increased spectral power in various EEG frequency bands during mediumistic communication and possession trance[40,41]. None of the studies included in this review has demonstrated an ictal pattern on EEG during the experience. These results could point to a state of mental and physical arousal during the phenomena[42,43].

On the other hand, the only study using functional neuroimaging, in this case a Single Positron Emission Tomography (SPECT), showed a reduction of cerebral blood flow (CBF) in left culmen, left hippocampus, left inferior occipital gyrus, left anterior cingulated cortex, right superior temporal gyrus and right pre-central gyrus (brain areas associated with memory, language and writing planning) during mediumistic communication (psychography) as compared to a control task. There was also a surprising negative correlation between the CBF in these areas and the linguistic complexity of the written text produced during psychography[15]. Taken together with the case series report of a slowing of background EEG activity in some mediums during psychophony (allegedly speaking under the influence of a spirit) and psychography[44] these data could suggest the activation of fewer neuronal populations during the dissociative experience.

Considering the dominant current psychobiological explanation for the possession trance and mediumship, there is a number of authors, which propose the role of self-hypnosis[14,17]. Hypnosis is seen as a state of focused attention and concentration, inner absorption and a relative suspension of external awareness. There is evidence for a correlation between hypnotizability and number of dissociative symptoms and that patients with dissociative disorders have higher rate of hypnotizability. Although differences occur according to the phase of hypnotic procedure (relaxation – induction – suggestion – waking up) and to which actions are suggested to the individual, many studies show increased theta power during hypnosis, indicating an intensification of attention processes. Regarding functional neuroimaging, the most characteristic finding of the hypnotic state is the hypoactivity of the "extrinsic brain network", which encompasses lateral fronto-parietal regions and which has been linked to cognitive processes of external sensory input. The reduced activity of this network can reflect a blocking of the sensorial systems to receive stimulus. A structural Magnetic Ressonance study has shown neuro-anatomical differences between high and low hypnotizable individuals: larger (32%) rostrum of the corpus callosum in highs than in lows. This area is involved in the information transfer between pre-frontal cortices and in attention allocation. The authors suggest that high hypnotizable subjects would have more efficient frontal attentional systems, with greater ability to monitor performance and to inhibit undesirable stimulus for conscious awareness[45].

Although it is not possible to say that spontaneous dissociative symptoms, like mediumship, share strictly the same neurophysiological processes of hypnosis, evidence suggest that many parallels can be drawn between them[45]. There are already some reports of research groups using hypnosis on healthy individuals to "model" dissociative symptoms (*e.g.* "automatic writing") and more easily study them in the neurophysiology and neuroimaging lab[46,47]. This strategy might bring valuable complementary data for the understanding of the neurobiology of alleged mediumship.

Future perspectives

Mediumship is a controversial research topic with ongoing experiments. Regarding its relation to psychopathology, in practical terms, it is important to avoid the risk of a "category fallacy". In other words, here both risks exist and should be avoided: pathologizing normal religious experiences and considering potentially dangerous clinical conditions as a common religious/spiritual experience. Thus, if such cases of mediumship and possession come to medical attention, besides a comprehensive assessment of the sociocultural implications and of the possible secondary gains for the individual, a standard psychiatric evaluation should not be neglected. In this evaluation, not only the patient but also family and community

members should be interviewed, so that the extent of impairment of daily life by the dissociative experiences can be inferred. Possible psychiatric comorbidities should also be sought. The most commonly used type of therapy for possession disorders is psychotherapy, and some scholars advise it should focus on the stressing factors that can initiate the dissociative phenomena[48,49].

Concerning studies on the accuracy of information provided by mediums, their design must reach a balance between control against information leakage and the provision of a research environment that optimizes the phenomenon for both the medium and for the alleged communicating deceased person[36,50-52]. Apparently, among the reviewed studies, the protocol proposed by Beischel is the most successful in meeting these conditions, and it requires replication by other research groups to broaden the database and to eventually demonstrate or not the scientific evidence of mediumship. Notwithstanding, some investigators affirm that even accurate results of mediumship studies do not prove the postmortem survival hypothesis and that the best explanation would still be some form of telepathy between the medium and other "living agent psi"[53].

Studies evaluating physiological correlations during mediumistic communications are still very incipient. Here, as for other types of psychophysiologic studies, the employment of a process-based approach is recommended[54]. Before initiating any data collection, a detailed definition of the phenomenon, based on systematic observation, is necessary. This should include a definition, as precise as possible, of when the mediumistic communication begins and when it ends. Proper initial definitions about the process under investigation are necessary if one aims to obtain valid physiological research data about it[55].

Table 3. Studies on the accuracy of mediumistic information

Study	Participants	Method	Comparison	Findings
O'Keefe & Wiseman (2005)[35]	5 professional mediums and 5 consultants ("sitters")	Triple-blind study, properly executed. Five "readings" were itemized, grouped and sent to consultants for "blind" scoring of items for accuracy and applicability	Comparison between scores of "readings" really intended for the consulent with the scores of readings made for other consultants	There was no significant difference between scores. In only one occasion the consultant assigned higher scores to the "reading" that was directed to him.
Beischel & Schwartz (2007)[30]	8 mediums (who had previously demonstrated ability to provide mediumistic information with accuracy, according to the authors) and 8 consultants (highly motivated to receive information from deceased relatives)	Triple-blind study, properly executed. Each "blind" consultant received two "readings" to score accuracy and choose which of them better applied to his/her deceased family member	Comparison between "reading" scores that supposedly came from the deceased family member and "reading" scores that were directed to other consultants	The consultants chose the correct "reading" (directed to them) in 81% of cases (13/16). The "reading" scores from messages directed to them were significantly higher than control "reading" scores
Jensen & Cardeña (2009)[36]	1 professional experienced medium and 7 consultants ("sitters")	Triple-blind study, properly executed. Seven "readings" were itemized, grouped and sent to consultants for "blind" scoring of items for accuracy and applicability	Comparison between scores of 7 "readings" (one reading really intended for the consultant and 6 other decoy readings")	Scores assigned by the consultants for neither global nor specific information from "target readings" were significantly better than expected by chance. No sitter chose his target reading as the most applicable. Measures of paranormal belief of sitters positively correlated with rating of reading
Kelly & Arcangel (2011)[33]	Experiment 1: 4 mediums and 12 consultants Experiment 2: 9 mediums and 40 consultants	Triple-blind study adequately performed only in experiment 1 In experiment 2: methodological weaknesses substantially increased the likelihood of "fishing" or information leakage	Comparison between "reading" scores that supposedly came from the deceased family member and "reading" scores that were directed to other consultants Note: consultants chose one reading among three in experiment 1 and chose one reading among 6 in experiment 2	Experiment 1: only 2 of 12 consultants were able to identify the "reading" directed to them (3 hits would be expected to occur by chance) Experiment 2: 14 of 38 consultants chose the correct "reading" and 30 consultants positioned the "reading" directed to them among the three first places s in the accuracy rank
Rocha *et al.* (2014)[37]	5 relatives and friends of a deceased personality (JP), who is the alleged spiritual author of 13 *psychographed* letters (by the spiritist medium Chico Xavier)	Verifiable items were extracted from the letters. Interviews with participants to assess items' fit and accuracy and probability of information leakage. Based on the interviews, three researchers scored each item	Comparison of types of verifiable information. Comparison of scores of fit and of information leakage probability between the items from the first letter and the subsequent letters	The percentage of "clear and precise fit" among the 71 verified items was 97.2%. Considering the first letter (written 40 days after JP´s death), 100% of the items were scored as "very unlikely leakage". For subsequent letters, 63% of the items were scored as "unlikely leakage"
Beischel *et al.* (2015)[34]	Experiment 1: 14 mediums and 28 consultants Experiment 2: 20 mediums and 40 consultants (total of 20 mediums, 18 of them female, with same characteristics as from study of Beischel & Schwartz, 2007) (total of 86 readings)	Experiment 1 & 2: Triple-blind study, properly executed. Each "blind" consultant received two "readings" to score accuracy and choose which of them better applied to his/her deceased family member Experiment 2: 12 of the readings took place during an examination of EEG of 6 mediums	Comparison between "reading" scores that supposedly came from the deceased family member and "reading" scores that were directed to other consultants	The scores assigned by the consultants for both global and specific information from "target readings" were significantly higher than for "decoy readings". Significantly higher percentage accuracy of "target reading" items

Table 4. Studies involving psychophysiological correlates of mediumship

Study	Participants	Method	Comparison	Findings
Kawai *et al.* (2001)[38]	15 subjects presenting an alleged possession trance while participating in a religious ritual and 9 subjects participating in the same religious ritual but not presenting a possession trance	Analysis of norepinephrine, dopamine and beta-endorphin levels in blood samples. Assessment of heart rate and blood pressure	Comparison of plasma levels of the analytes and of its variation (Δ) at baseline and immediately after the possession trance. Comparison of the trance and control groups	The increase in plasma levels of norepinephrine, dopamine and beta-endorphin was significantly higher in the group presenting a possession trance. There was no significant difference among the groups regarding blood pressure and heart rate
Oohashi *et al.* (2002)[40]	One subject during an alleged possession trance while participating in a religious ritual and two subjects participating in the same religious ritual but not presenting a possession trance	Electroencephalography (EEG)	Spectral power analysis for each EEG frequency band comparing baseline *vs* trance *vs* recovery in the subject who went into a trance compared with the other two	An ictal EEG pattern was not observed. In the individual who went into a trance, it was observed an intense and significant increase of theta and alpha power during the trance state, when compared with the pre-trance. These changes persisted in the post-trance period. In the 2 control subjects, no significant changes in spectral power were observed among the periods
Krippner *et al.* (2008)[39] Data colleted in 1999	2 mediums (1 spiritist presenting psychography and 1 from *Camdomblé* presenting psychophony) and 1 control (no mediumship, same socio-cultural environment)	Electroencephalography (EEG) Assessment of heart rate, muscle tone and skin conductance	Comparison of the percent time in which each EEG frequency band was observed during: baseline *vs* mediumistic communication (MC) *vs* recovery Comparison of measurements obtained during: baseline *vs* mediumistic communication (MC) *vs* recovery	Spiritist medium: increase in the percentage of alpha and beta waves during MC when compared with baseline. This pattern persisted during recovery *Camdomblé* medium: increase in the percentage of theta waves during MC when compared with baseline Control subject: increase in the percentage of alpha waves during control task In mediums, there was an increase in muscle tone and slight increase in heart rate during MC when compared with baseline. In recovery phase, there was a decrease in muscle tone and heart rate. There was a reduction of the mean skin conductance during the MC in one medium and an increase in the other medium. In the control subject there was no significant change in any of these parameters at the different periods
Hageman *et al.* (2010)[44]	9 mediums (6 presenting psychophony and 3 presenting psychography)	Electroencephalography (EEG) Note: insufficient description of methodology	Analysis of EEG record looking for the presence of epileptic discharge during baseline *vs* mediumistic communication (MC) *vs* recovery	Ictal EEG pattern was not observed. A slowing of background activity on the EEG during MC was observed in 6 participants
Peres *et al.* (2012)[15]	10 spiritist mediums (allocated in 2 groups: 5more experienced and 5 less experienced)	Functional neuroimaging (SPECT). Evaluation of linguistic complexity of texts written under controlled conditions	Comparison of regional cerebral blood flow (CBF) during automatic writing (psychography) and during control task (writing a text in the usual state of consciousness). Correlation analysis between neuroimaging findings and linguistic complexity of the texts	Hypoactivation of brain regions responsible for cognitive processing and writing planning during psychography Inverse correlation trend: increasing levels of linguistic complexity of the texts produced during psychography associated with gradual reduction in CBF in brain regions responsible for cognitive processing and writing planning
Delorme *et al.* (2013)[41]	6 professional mental mediums	Experiment 1: triple-blind design to investigate accuracy of the information provided by mediums + Electroencephalography (EEG) Experiment 2: analysis of EEG records of mediums while performing 4 different mental tasks: perception, memory, imagination and mediumistic communication (MC)	Experiment 1: correlational analysis between the accuracy of mediumistic information provided and the EEG spectral power on each frequency band during MC Experiment 2: Comparison of EEG spectral power on each frequency band during the 4 different mental tasks	Experiment 1: significant correlation was observed in 2 mediums (in one medium theta power was negatively correlated with accuracy and in the other alpha power was positively correlated with accuracy) Experiment 2: The most significant difference occurred between mediumistic communication and the mental task of perception Gamma and beta were the frequency bands in which there were more electrodes revealing significant differences during the diverse mental tasks

Moreover, because spiritual and religious experiences are complex and multidimensional, and because mediums usually describe them in terms of changes in perception, cognition and affect[52], the measurement of the subjective elements of the phenomena is highly advisable. Posteriorly, a possible correlation among these psychological, affective and cognitive elements with specific brain regions and brain functions can be explored[56,57]. Some examples of instruments that can be used for this purpose are: the Phenomenology of Consciousness Inventory (PCI)[58], the Assessment Schedule for Altered States of Consciousness (ASASC)[59] and Hartmann's Boundary Questionnaire[60], among many others. These *questionnaires* quantify different phenomenological elements of consciousness and can be useful for helping to distinguish qualitatively different ASC[57]. Likewise, considering that mediumistic phenomena usually involve dissociative experiences, it is also advisable to conduct a baseline assessment of the personality trait absorption. For this purpose, questionnaires such as the Tellegen Absorption Scale[61] or the Harvard Group Scale of Hypnotic Susceptibility[62] could be used. Evidence suggests that individual differences in these characteristics are associated with significant differences in neurological findings[63,64].

Concerning the possibility of studying mediumship through functional neuroimaging technique, one important aspect is the selection of the control task. Usually the participant acts as his/her own control, being asked to perform two similar tasks, one with and another without spiritual (mediumistic in this case) connotation. This allows the control task to be comparable to mediumistic practice with respect to a range of elements (open or closed eyes, talking or not talking, listening or not listening) and potentially optimizes de identification of characteristic neurophysiological correlates of the mediumistic experience[56]. The decision of which specific method to use depends on availability and financial possibilities[52] but SPECT (Single-Photon Emission Computed Tomography) and PET (Positron Emission Tomography) techniques are usually preferred because images can be captured after the completion of the event under investigation (not simultaneously as it is necessary for functional Magnetic Resonance Imaging [MRI]). In addition, the noise during MRI may disturb mediums, interfering with the phenomenon[56].

The electroencephalography (EEG) can also offer important information about the degree of brain activation during the mediumistic practice, particularly of cortical regions. Unlike neuroimaging techniques, which provide excellent spatial location of cerebral functioning but less precise timing information, the EEG provides greater time precision (accuracy of milliseconds, in real time) with much lesser spatial accuracy[65]. However, because EEG recording requires stillness to avoid muscle artifacts, and as mediumship usually involves talking and moving, there might be some technical difficulties.

The objective measurement of physiological parameters that may vary according to the emotions experienced (*e.g.* heart rate variability – HRV)[66,67] could also bring relevant contributions to this research field. These parameters can be correlated with subjective self-reports and with neuroimaging findings, bringing to sight a more global physiological picture of the mediumistic phenomenon[56]. Measurements related to the immune and endocrine systems may also contribute to broaden this understanding[68,69].

Finally, it should be taken into account that different mediumistic modalities may require different study designs. Psychography and psychopictography (allegedly painting under the influence of a spirit) may adapt more easily to an experimental protocol employing functional neuroimaging. In regard of psychophony, although it may represent a larger universe of potential research participants (great prevalence of "spirit release therapy" sessions employing psychophonic mediums in countries such as Brazil[70,71] and Puerto Rico[72]), it offers obstacles to neuroimaging studies as it usually requires team work. In these cases, protocols involving EEG and ECG may be preferred as they allow researchers to record the event "in loco" using portable equipment.

Limitations

The present study has some limitations, which should be highlighted. First, the searches were limited to English, Spanish and Portuguese; therefore potentially relevant articles published in other languages were not included. Second, although the terms searched are the most frequently used ones, and although three databases were used, potentially relevant articles not indexed in these databases or described with other terms may have been missed.

Conclusions

The evidence analyzed in this review suggests: (1) mediumship seems to be associated with good mental health, mainly when individuals have many years of work as socially sanctioned mediums (2) there was heterogeneous evidence regarding the accuracy of information provided by alleged mediums, what may be due to different study methodologies, and (3) there is a paucity of studies investigating the physiologic correlates of mediumship. These results emphasize the need for more studies in this field to further elucidate mediumistic experiences, what could broaden the understanding of the mind-brain relationship.

Conflicts of interest

None of the authors have any conflicts of interest related to writing this review.

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An updated review on the neuropsychological profile of subjects with bipolar disorder

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Abstract

Background: In recent years, growing interest in the neuropsychology of bipolar disorder has emerged, giving rise to the accumulation of a robust body of evidence on this topic and to several related questions. **Objective:** To provide a state-of-the-art overview of the neuropsychological profile of bipolar disorder. **Method:** A thorough literature search was performed. Published research evidence was summarized and organized along three key pathways: findings from cross-sectional studies of cognition in bipolar patients, cognitive heterogeneity among affected subjects, and trajectory of neuropsychological deficits. **Results:** At least two thirds of bipolar patients display neuropsychological deficits, even in euthymia. Although bipolar disorder was found to be associated with an increased risk of dementia, data from elderly subjects and longitudinal research do not support a worsening of cognitive performance over time. **Discussion:** Cognitive dysfunctions are part of the clinical conceptualization of bipolar illness. However, they may not be present in all affected subjects and their course appears to be stable in most cases. Available evidence may be highlighting the fact that bipolar disorder is characterized by remarkable heterogeneity regarding cognitive outcomes. Different variables may be related to such heterogeneity and should be the focus of therapeutic approaches and further research.

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Keywords: Bipolar disorder, neuropsychological functioning, heterogeneity, evolution.

Introduction

Bipolar disorder (BD) is a complex chronic illness that affects mood and biological rhythms, causing subtle to severe distortions of normal behavior. BD is associated with significant functional impairment, even when appropriately treated and after symptomatic recovery is achieved[1,2].

Poor functional outcomes have been shown to be strongly associated with persistent neuropsychological deficits[3-5], which are currently acknowledged as an important feature of BD. Indeed, during the last decade, the long-held assumption of cognitive indemnity of BD was debunked as a result of compelling evidence for conspicuous cognitive deficits in a significant percentage of affected subjects, even during periods of euthymia[6]. Notwithstanding the release of copious amounts of research reports on this topic, the neuropsychological profile of the disorder remains unclear, and several related questions have arisen in the last few years.

The aim of this study was to integrate the pieces of evidence gathered at present in order to provide an updated review on cognitive functioning in BD. The most controversial issues related to this subject were discussed, and targets for forthcoming research were highlighted.

Methods

First, an extensive computerized literature search was performed. Articles available with an abstract in English were retrieved from electronic databases (PubMed, PsychINFO, SciELO, and Lilacs), covering the period from January 1990 to August 2015. Afterwards, a narrative review was conducted, giving special consideration to large studies, systematic reviews, and, particularly, to meta-analyses, as the last allow for more precise estimates of effect magnitude than data derived from primary studies. In order to provide a comprehensive framework, the currently available evidence on neuropsychological functioning in BD was summarized and organized around three key topics: 1) neuropsychological profile of BD patients; 2) cognitive heterogeneity among bipolar subjects; and 3) longitudinal trajectory of cognitive deficits in BD.

Results

Neuropsychological profile of BD

In order to characterize a BD profile of neuropsychological performance, findings from both subjects in the premorbid phase of the disorder and patients with established illness are exhibited (Table 1). Among the latter, the findings of studies on subjects belonging to different age groups are reviewed.

Findings in the premorbid phase of BD

Neurocognitive functioning in the premorbid phase of the illness has been appraised by means of three methodologies: prospective conscript studies, evidence from birth cohorts and at-risk subjects followed longitudinally. Martino *et al.*[7] reviewed the findings from these approaches and reported that with the exception of one study[8], which showed that poor performance on visuospatial reasoning and increased performance on the arithmetic subtest were associated with BD, studies failed to find any differences between people who were subsequently diagnosed with BD and healthy controls on measures of general intelligence[9-11]. In keeping, Trotta *et al.*[12], in a meta-analysis of four prospective cohort studies, yielded a nonsignificant overall effect size for premorbid IQ in BD.

However, these studies assessed general intellectual function and not specific cognitive domains. Findings regarding the latter are scant so far. Meyer *et al.*[13] used data from a 23-year longitudinal prospective study of offspring of mothers with BD, unipolar depression or no history of BD (n = 74). They were evaluated from 8 to 15 years with general intelligence tests, from 11 to 19 years with executive functions measures and as young adults with psychopathology measures (SCID-I). Offspring who were later diagnosed with BD during adulthood (n = 9) had lower performance than healthy controls on

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measures of executive functions with moderate-large effect sizes (d = 0.58-1.34) at age 11-19, although they had comparable IQ when they were 8-15 years old. Ratheesh *et al.*[14] followed a cohort of 413 children who were at ultra-high risk for psychosis for a mean period of 8.2 years. Children who were later diagnosed with BD showed lower performance than healthy controls on measures of global intelligence, visuospatial ability and executive function with large effect sizes (d = 1.35-1.56). In keeping, Klimes-Dougan *et al.*[15] conducted an extensive neuropsychological assessment of adolescent children of mothers with a history of BD (n = 43) or major depressive disorder (n = 72). They found that offspring of mothers with BD had poorer performance on the Wisconsin Card Sorting Test, which remained significant after adjusting for IQ and depressive/manic symptoms.

Findings in pediatric and adolescent patients

A systematic review on cognitive performance in pediatric BD patients[16] reported that significant deficits in verbal/visual-spatial memory, processing speed, working memory and social cognition were found quite consistently across the primary studies included. Furthermore, two previous meta-analyses showed moderate deficits (d = 0.5-0.8) in verbal memory, attention, processing speed and executive domains among pediatric and adolescent patients[17,18].

However, most of the primary studies included in these reviews were performed during affective episodes. Data on euthymic BD pediatric patients are very scant so far. At the primary study level, the largest study evaluating cognitive impairments in pediatric bipolar patients included 28 unmedicated patients during manic episode, medicated euthymic patients (n = 28) and healthy individuals (n = 28)[19]. Both patient groups (mean age = 11.74, SD = 2.99) showed large ($d \geq 0.8$) impairments in domains of attention, executive functions, working memory and verbal memory compared to healthy controls. However, half of the patients in each group had comorbid ADHD, which made it difficult to identify deficits specific to pediatric BD.

Findings in young and middle-aged adults

Aggregate data meta-analyses of neurocognitive functioning in young and middle-aged adults[20-26] have reported moderate (d = 0.5-0.8) and large ($d \geq 0.8$) deficits across executive functions, verbal memory, attention and processing speed. However, the only individual patient data meta-analysis of cognition in BD (n = 2876) conducted at present[27] showed small-to-moderate deficits (d = 0.26-0.63) in most neurocognitive domains after controlling for age, premorbid IQ and gender. Furthermore, this study reported a large degree of heterogeneity across studies, which may explain some differences observed in the effect sizes yielded by previous meta-analyses.

Kurtz and Gerraty[25] performed a meta-analysis evaluating the profile of neurocognitive impairment of BD patients and the impact of clinical episodes on those measures. The study combined results from 42 studies conducted in euthymic patients, 13 studies in manic/mixed phase and 5 studies of patients in a depressed state, suggesting that, although present during euthymia, a subset of these neurocognitive impairments would worsen during periods of acute affective episodes.

With regard to social cognitive domains, evidence for impaired emotion recognition and theory of mind in the three phases of BD is rather consistent across studies[28]. A recent meta-analysis of social cognition in euthymic bipolar patients[29] showed no significant patient-control differences for the recognition of three basic emotions (happiness, sadness, and anger) whereas small but significant effect sizes favoring healthy controls (d < 0.5) were noted for emotional intelligence, the Hinting Task, the Eyes Test, and the recognition of fear, disgust, and surprise. Furthermore, this study showed a medium effect size of impairment (d = 0.58) for the Faux Pas Test. However, it is not yet clear whether these social cognitive flaws are epiphenomena of neurocognitive deficits. Finally, the only meta-analysis of studies assessing decision-making in samples composed exclusively of euthymic subjects[30] reported no significant differences between controls and patients in the total net score of the Iowa Gambling Task. In contrast, primary studies of subjects during acute episodes revealed suboptimal task performance[31,32] particularly during mania, suggesting that decision-making impairments are state-dependent in BD patients.

Findings in elderly adults

The only meta-analysis of neurocognition in late-life BD[33] revealed moderate impairments for the cognitive variables analyzed, except for phonemic fluency (d = 0.80) and cognitive flexibility (d = 0.88). This report took into account the fact that older adults with BD constitute a heterogeneous population composed by both people with early-onset BD (EOBD), who developed their illness during adolescence/young adulthood, and people with late-onset BD (LOBD), who experienced their first affective episode at the age of 40 or over. These two subgroups may have different features. Typically, patients with LOBD show a weaker family history of affective disorders, higher frequency of neurological comorbidities, higher cardiovascular risk burden[34-36] and worst neuropsychological performance on almost all measures[37], suggesting a high influence of non-genetic etiological factors on this subgroup of patients. So, when meta-analysis was performed after removing the data from LOBD subjects and overall effect sizes were recalculated, estimates became much smaller[33]. A subsequent study[38] showed that euthymic, non-demented elderly patients with BD performed worse than healthy controls on a verbal fluency test (semantic fluency-animal naming) with a large magnitude of impairment (d = 0.86). Furthermore, this study revealed that demented BD subjects had a significantly worse performance on the Clock Drawing Test as compared with patients with dementia due to Alzheimer's disease.

Cognitive heterogeneity among subjects with BD

A recent study by Martino *et al.*[39] showed that 30% of a sample of 100 BD patients was indistinguishable from healthy subjects in terms of cognitive functioning, whereas another 30% displayed more severe cognitive deficits than usually reported in the literature (d = 1.13). These findings are in keeping with other studies indicating that the prevalence of patients without clinically significant cognitive impairment fluctuates between 43% and 70%[40-44]. Such results may be suggesting that primary studies and meta-analyses reporting mean values of neurocognitive functioning in BD patients might be failing to recognize that a subgroup of patients is demonstrating most of the impairment: while some patients might have a neurocognitive functioning within normal limits, others might show poorer performance than usually reported.

Longitudinal course of cognitive deficits in BD

In order to evaluate longitudinal trajectories of cognitive deficits in patients with BD, four strategies were considered: studies of cognitive performance after first affective episode, longitudinal follow-up studies of cognitive functioning, data from patients with long illness duration, and evolution to dementia in subjects with BD (Table 2).

Cognitive functioning in the first episode of BD

Martino *et al.*[7] reviewed 14 studies of cognitive performance in first-episode patients, and reported that impairments in verbal memory, attention, and executive functions tended to be present during and after the first episode of the disorder. Considering only studies that evaluated patients during euthymia, after recovery of their first manic episode, Nehra *et al.*[45] found impairments in IQ, executive functions, verbal memory and attention with large effect sizes for all measures. Torres *et al.*[46] reported that patients with BD did not differ from controls with regard to premorbid IQ and attention, while moderate effect size impairments in executive functions, working

Table 1. Meta-analyses of cognitive functioning in BD

Meta- analysis	Study population	Mood state	Results[a]
Arts *et al.* (2008)[22]	Adult patients and FDR	Euthymia	BD: Large effect sizes for executive functions and verbal memory Medium effect sizes for processing speed and sustained attention Small effect sizes for visuoperception FDR: small, but significant, effect sizes across cognitive domains
Bora *et al.* (2009)[23]	Adult patients and FDR	Euthymia	BD: Moderate-to-large effect sizes for executive functions, sustained attention and verbal memory FDR: small, but significant, effect sizes across cognitive domains
Bora *et al.* (2011)[24]	Adult patients	Euthymia and depression (mixed sample)	Small-to-moderate effect sizes across all domains (BD II-only *vs.* controls) BD II less impaired than BD I on memory measures
Bora and Pantelis (2015)[49]	FEBD	Euthymia and mood episodes (mixed sample)	Moderate effect sizes for attention, processing speed, verbal and visual memory. Small effect sizes for most executive domains
Bourne *et al.* (2013)[27]	Adult patients	Euthymia	Small-to-moderate effect sizes for verbal memory, executive functions and sustained attention
Garcia Nieto and Castellanos (2011)[18]	Pediatric patients	Euthymia and mood episodes (mixed sample)	Moderate effect sizes for verbal memory, attention, processing speed and executive domains
Joseph *et al.* (2008)[17]	Pediatric patients	Euthymia and mood episodes (mixed sample)	Moderate-to-large effects for verbal memory, attention, executive functions, working memory and verbal fluency. Small effects for IQ and motor speed
Kurtz and Gerraty (2009)[25]	Adult patients	Euthymia Manic episode Depressive episode	Euthymia: moderate effect sizes for attention, delayed memory and executive functions. Large effect sizes for verbal learning Depressive and manic episodes: more severe impairment in verbal learning and phonemic fluency
Lee *et al.* (2014)[48]	FEBD	Euthymia and manic episode	Medium-to-large deficits for psychomotor speed, attention, working memory and cognitive flexibility Small deficits for verbal learning and memory, attentional switching, and verbal fluency. Medium-to-large deficit for response inhibition only detected in non-euthymic cases
Mann-Wrobel *et al.* (2011)[26]	Adult patients	Euthymia	Moderate-to-large effect sizes across all domains
Robinson *et al.* (2006)[20]	Adult patients	Euthymia	Large effect sizes for executive function and verbal learning. Medium effect sizes for delayed recall, set-shifting, processing speed, sustained attention and response inhibition. Small effect sizes for verbal fluency
Torres *et al.* (2007)[21]	Adult patients	Euthymia	Medium-to-large impairment for executive functions, attention, processing speed and episodic memory
Trotta *et al* (2015)[12]	Subjects in the premorbid stage of illness	Euthymia	Non-significant overall effect size for IQ between subjects who subsequently developed BD and those who did not develop any disorder
Samamé *et al.* (2012)[30]	Adult patients	Euthymia	Non-significant overall effect size for decision-making (Iowa Gambling Task). Small effect size for facial emotion recognition. Moderate effect sizes for mentalizing domains
Samamé *et al.* (2013)[33]	Elderly patients	Euthymia	Non-significant differences for the MMSE and CDT. Moderate effect sizes for sustained attention, digit span, delayed recall, verbal fluency and cognitive flexibility
Samamé *et al.* (2015)[29]	Adult patients	Euthymia	Medium effect size for the Faux-Pas test. Non-significant differences for the recognition of three emotions (happiness, anger and sadness). Small effect size for the recognition of surprise, fear and disgust, emotional intelligence and the Hinting task

[a] All effect sizes favor healthy controls.
BD: bipolar disorder; FDR: first degree relatives; FEBD: first episode bipolar disorder; MMSE: Mini-Mental State Examination; CDT: Clock Drawing Test.

memory and visual reasoning were found. Finally, López-Jaramillo *et al.*[47] showed that patients with BD performed worse than healthy controls on a measure of working memory with moderate effect size, without between-group differences for IQ, verbal memory, attention, processing speed and executive functions. These results are in line with two recent meta-analyses of cognitive functioning in BD patients after their first affective episode[48,49], which showed widespread impairment. According to these quantitative reviews, the severity of impairment was generally comparable to that found in studies with patients after recurring episodes, with medium effect sizes for most neuropsychological variables.

However, another systematic review[50] reported that BD patients in remission immediately after first manic episode did not display deficits in non-verbal memory and verbal fluency, whereas evidence for impairments in other neurocognitive domains was inconsistent across reports, with most studies revealing negative findings, except for working memory.

Longitudinal studies

The only meta-analysis summarizing the results of longitudinal studies of euthymic adults with BD did not show any significant differences between BD patients' performance at baseline and healthy controls after a mean follow-up period of 4.62 years for 14 cognitive variables[51]. In this line, a recent study analyzed the one-year trajectory of cognitive deficits in recently diagnosed BD and reported an improvement in processing speed and executive functions[52]. Similarly, Santos *et al.*[53] found no differences in neuropsychological trajectory

between patients and healthy controls after 5 years follow-up of a large sample of BD subjects. Another recent study followed prospectively a cohort of 71 major depressive disorder, 61 BD and 35 schizophrenia patients, evaluated at baseline and after a mean of 20.6 months. The authors reported that, as a group, BD displayed stable cognitive functioning and even improved on a measure of verbal memory[54]. However, there are a number of limitations to be considered when analyzing these data. First, follow-up periods were relatively short in most studies and it should not be assumed that no cognitive decline occurred after this period. Another important limitation was that not all studies controlled for mood symptomatology at baseline and during follow-up. Therefore, changes in mood state could have influenced the results. Finally, longitudinal studies available at present only explored the trajectory of cognitive functioning in full-blown BD, whereas the course of cognition in the period comprised between the premorbid stage of the disorder and the onset of mood symptoms remains unexplored.

Patients with long illness duration

Studies of cognitive performance in elderly patients with BD tended to find the same pattern of cognitive deficits both in terms of domain affected and magnitude reported in younger patients, suggesting indirectly no neurocognitive progression of the illness[33]. In order to assess the potential effect of illness progression on neurocognition, a study compared neurocognitive functioning between patients aged 40 years or younger (Y-BD) and patients aged 60 years or older (E-BD). Despite E-BD patients having illness duration almost four times longer than Y-BD patients, no significant differences in neurocognitive functioning were found between these two groups[55].

A possible limitation of these studies is selection bias in samples of elderly BD patients, since those who developed dementia or severe cognitive impairment, might have been institutionalized or dead and therefore under-represented.

Evolution to dementia

Some small pioneering studies of non-euthymic bipolar elders found that a high percentage of them scored positively on screening tests for dementia[56,57]. In accordance with these findings, evidence from population-based studies showed that the diagnosis of BD was significantly associated with an increased risk of dementia[58,59].

These results indicate that overall, there seems to be a percentage of people with BD that will develop dementia. However, this outcome may be present in around 6-9% of BD patients included. Taking this into account, dementia might be an infrequent outcome rather than the average evolution of BD[6].

Discussion

In this study, the available evidence on the neuropsychological profile of BD was reviewed in order to address some of the controversies regarding this matter. Our findings indicate that cognitive deficits are present in a significant percentage of affected subjects, even during euthymia periods and that they seem to exacerbate during acute mood episodes. Such impairments could be present prior to illness onset, and are evident in BD patients belonging to different age groups. Furthermore, some findings suggest that the magnitude of these deficits would be similar in young and elderly patients. These results are in line with preliminary findings from longitudinal studies, which do not reveal any changes in the neuropsychological performance of BD subjects over time.

At present, there appears to be a certain degree of agreement in the fact that neuropsychological performance is a major determinant of functional outcomes in BD patients. As shown in this review, although it is widely acknowledged that bipolar subjects exhibit neurocognitive impairments in domains of verbal memory, attention and executive functions, among others, the notion of cognitive impairment may not be applicable to all patients[40,60]. This cognitive heterogeneity might be explained by a number of environmental and genetic causes reported in the literature to alter normal cognitive functioning in BD patients such as obstetric complications[61], genetic polymorphisms[62], childhood trauma[63], infection with Herpes Simplex virus type 1[64,65], comorbidity with anxiety disorder[66] or alcohol abuse[67-69], age at onset[37,70], subclinical hypothyroidism[71] and exposure to antipsychotics[72,73].

Beyond the well-documented relationship between cognitive and functional outcomes in BD, another variable that has been traditionally associated with cognitive performance is the number of previous episodes, especially manic ones[74,75]. This finding has led some authors to suggest a progressively deteriorating nature of cognitive deficits in BD. However, these data derive from cross-sectional studies, and therefore, the direction of causality cannot be ascertained. In fact, a recent prospective study[76] found that patients with clinically significant cognitive deficits had an increased risk of suffering any recurrence and suggested that severe cognitive impairment may be the cause, rather than the consequence, of a poorer course of illness, thus providing an alternative explanation to this relationship. This result may also be suggesting that the subgroups of patients with better clinical outcomes and with preserved cognitive function might overlap. Hence, the importance of this finding lies in the fact that cognitive heterogeneity might be a clue to explain the variability seen in areas like global functioning and course of illness, although the mechanisms underlying these associations are a matter of speculation nowadays. For example, patients with poor cognitive functioning might have poorer treatment adherence[77], poorer response to

Table 2. Main approaches to the study of the longitudinal course of cognitive deficits in BD

Methodological approach	Results	Main limitations
Cognitive functioning in first-episode BD	Inconsistent findings. Both impaired and preserved cognitive outcomes have been reported[48-50]	Small sample sizes Results potentially confounded by mood symptomatology
Longitudinal research	Longitudinal meta-analysis does not show any test-retest differences for neurocognitive variables[51]	Short follow-up periods Few data on healthy controls Dropout bias Results potentially confounded by mood symptomatology Results only account for the course of cognitive deficits after illness onset
Cognitive functioning in long-standing BD	Meta-analysis of cognition in E-BD subjects shows a pattern and magnitude of impairment similar to those reported for young adult patients[33] Comparison between Y-BD and E-BD reveals no significant differences in cognitive performance[55]	Small sample sizes Few studies performed on E-BD BD patients with poor outcomes (dementia, institutionalized) probably not included in E-BD samples
Population-based studies	An association between BD and an increased risk of dementia is supported by available data[58,59]	These studies reflect the outcome of a minority of BD patients (6%-9%)

BD: bipolar disorder; E-BD: elderly BD patients (aged 60 years or above); Y-BD: young BD patients (aged 40 years or under).

psychoeducation programs and psychotherapeutic interventions leading to poorer disease evolution and global functioning. Indeed, a previous study noted that cognition was probably a major source of uncontrolled variance regarding response to treatment[41].

Despite these considerations, the aforementioned relationship between number of episodes and cognitive functioning[47,78], together with several recent reports showing a tendency towards episode acceleration and the evidence of an increased risk of suffering dementia in bipolar subjects, has given rise to the notion of BD as a progressively deteriorating condition and the application of staging models to this group of disorders. In the context of the utilization of staging conceptualizations for the appraisal of severe psychiatric conditions, the term 'neuroprogression' has been coined to refer to a pathological reorganization of the central nervous system that would occur along the course of these illnesses[79]. Applied to BDs, the hypothesis of neuroprogression suggests that different characteristics of the disorder follow a progressive path from prodromic to more severe and refractory presentations[80]. However, it has not been adequately validated so far and several artifacts must be considered when interpreting the evidence often thought of as being 'in support' of this notion[81]. What is more, recent reports have emphatically stated that cognitive deficits are progressive in BD on the basis of the findings of cross-sectional studies[82,83]. According to these investigations, patients in later stages have worse functional outcome/higher number of episodes than subjects in early stages, who display better outcomes. Given the strong correlation between functional outcomes and cognitive functioning[84-86], the finding of a worse neuropsychological performance in late-stage patients as defined on the basis of poor global functioning is predictable. However, it is not possible to infer neuroprogression from this, given that no longitudinal study at present has proved that the different presentations of BD are moments in the development of the disorder as the utilization of the word "stage" would necessarily imply. In fact, taken together, findings evaluating long-term evolution of cognitive deficits in BD do not support the hypothesis that cognitive deficits tend to worsen over the course of illness. Rather, it would be more sensible to conclude in the light of the currently available evidence that there are different subgroups within the disorder that may have different cognitive trajectories. Indeed, a meta-analysis by our group[33], revealed that elderly BD subjects, with about three decades of illness duration and the longstanding exposure to variables which may negatively impact cognition, displayed a magnitude of impairment similar to that observed in young adult subjects with BD. Such finding may be indicating that the time being ill does not allow for any prediction on the cognitive outcomes nor the assumption of an evolving nature of the disorder. Instead, evidence available so far may be indicating the existence of different clinical subgroups within BD, each having distinct features and cognitive trajectories. For example, data regarding evolution to dementia in BD suggests that only 6%-9% might have a poorer evolution and this malignant outcome.

Nevertheless, it is not yet possible to conclude from these findings that cognitive deficits are static over the course of BD. On the one hand, because the approaches utilized to the study of this issue have several methodological limitations. On the other hand, because cognitive decline could occur after the emergence of mood symptoms or at a preclinical stage and there are no studies assessing cognitive function in the same subjects both before and after the onset of the disorder. However, as shown in this review, neuropsychological studies using specific domain tasks, though scant, have not supported the hypothesis of preserved cognition in the premorbid stage. In spite of this, it could be hypothesized that whereas some patients present with cognitive impairment at the moment of their first affective episode, some patients do not, resulting in subgroups in terms of cognitive performance at the time of illness onset. Indeed, Mac Cabe *et al.*[87] reported that both low and high grades in high school predicted future manic episodes, underscoring heterogeneity in cognitive functioning in adolescents prior to receiving a BD diagnosis. Thus, the evidence available at present shows that patients in the premorbid phase of BD, as a whole, may not present with preserved cognitive functioning. However, cognitive outcomes may be heterogeneous among these patiens. Such preliminary findings do not support the hypothesis of progressive deterioration of cognition either and highlight the heterogeneous nature of BD.

In view of the existing evidence on cognitive functioning in BD, targets for future research are proposed. First, further studies of euthymic patients and subjects at risk for the disorder are needed in order to better clarify the neuropsychological profile of BD. For example, it is currently a matter of debate whether BD patients display an intermediate performance between subjects with schizophrenia and healthy controls or if the neuropsychological profiles of these disorders are qualitatively different. Recent preliminary findings support the latter notion[39,88]. Second, large longitudinal studies, with long follow-up periods, assessing specific cognitive domains in BD patients are clearly needed as well as studies of cognitive performance in the same subjects both after and before the onset of mood episodes in order to ascertain whether neuropsychological deficits worsen over time, and if so, to determine the moment in which cognitive decline would occur. Third, a number of variables found to be related to poorer cognitive outcomes should be studied more deeply. In addition, the relationship between mood episodes and cognitive dysfunction (i.e., as inductors of cognitive impairments or exacerbating existing cognitive dysfunctions) should be further assessed. Insights into cognitive subgroups in BD might also be useful. For example, prospective studies evaluating clinical course/functional outcomes in newly diagnosed patients (i.e. after recovery of their first manic episode) or high-risk BD, divided by their cognitive performance might be useful in determining whether cognitive performance determines poor clinical outcomes or vice versa.

Therapeutic implications of cognitive impairment in BD

As neuropsychological impairment is currently acknowledged as an important target for therapeutic efforts, it is important that clinicians are aware of a number of variables that may affect cognitive outcomes.

At present, preclinical findings have suggested that lithium might have beneficial effect on cognition[89-92]. Although no direct evidence for a beneficial effect of this drug on cognitive impairment exists, preliminary findings report an association between the use of lithium and more preserved cognitive functioning. For instance, Nunes *et al.*[93] compared the prevalence of Alzheimer's disease between a group of BD subjects treated chronically with lithium therapy and another group of patients without recent lithium therapy. They found that lithium-treated BD patients had lower prevalence of Alzheimer's disease and suggested that lithium treatment reduced the prevalence of Alzheimer's disease (AD) in BD patients to levels found in general elderly population. In keeping, a recent population-based cohort study evaluated dementia risk among BD adults on lithium therapy[94]. Compared with non-use, a year of lithium treatment was associated with significantly reduced dementia risk. Moreover, there is preliminary evidence of improved white matter integrity in BD patients[95]. However, contradictory results exist when evaluating literature on cognitive performance in specific domains in subjects under treatment with lithium. Recent studies compared the neuropsychological performance of patients treated with and without lithium and found significant differences favoring the former[96,97]. On the other hand, prolonged administration of lithium has also been associated with discrete negative effects in learning, surveillance, alert and short-term memory[98]. In keeping, a meta-analysis comparing healthy volunteers and affective disorder patients reported that lithium had a small, but significant, deleterious effect on immediate verbal learning, memory and creativity, with no significant effect on other measures[99]). Taken together, this findings point towards a modest, if any, effect of lithium on traditional neurocognitive measures.

On the other hand, there is evidence from healthy subjects, BD and other clinical populations suggesting that exposure to different psychotropic agents commonly prescribed to bipolar patients is

associated with impaired cognition[73,100-104]. In the same line, obesity and metabolic syndrome induced by atypical antipsychotics may further influence cognitive functioning[105,106]. Thus, it is also possible that patients responding to lithium treatment are less exposed to antipsychotics and better cognitive outcomes are a reflection of that.

To further support this, studies comparing cognitive performance between drug-free BD patients during euthymia and healthy controls show less impairment than reported in studies that included treated patients. Joffe *et al.*[107] found no differences between drug-free BD patients and healthy controls in measures of attention and verbal memory. Also, no differences were found when comparing drug-free patients with lithium-treated patients. López-Jaramillo *et al.*[108] found differences only in measures of verbal, logical and working memory while non-medicated patients performed as well as healthy controls on other traditional neurocognitive measures. The subgroup of BD patients under treatment with lithium performed equally as those without pharmacological treatment on all measures. Finally, Torrent *et al.*[73] found no differences in neurocognitive performance between drug-free BD patients and healthy controls except for one test, the TMT-B, which evaluates executive functions. Despite some limitations, like small sample sizes and a possible selection bias of highly selected sample of patients with good outcomes, these results point towards some sort of iatrogenic-pharmacologic effect of medication on cognitive performance affecting treated BD patients usually included in studies[73].

Taking together findings from drug-free patients and cognitive heterogeneity in BD, initially, it should not be assumed that cognitive deficits are necessarily present in the course of the disorder. Clinicians should rule out potentially treatable causes of these deficits such as clinical (i.e., hypothyroidism or metabolic syndrome) or psychiatric (i.e., anxiety disorders or abuse/dependence of alcohol) comorbidities among patients with clinically significant cognitive impairments. Likewise, this subgroup of patients may not be candidate for receiving drugs such as benzodiazepines, anticholinergic agents or antipsychotics with a negative impact on cognition[72,102,109]. On the other hand, the efficacy of psychosocial interventions may be influenced by cognitive status, although this has not been formally studied so far.

In conclusion, cognitive deficits in BD are of paramount importance as they may represent a bridge between symptomatic remission and functional recovery that could be targeted by therapeutic interventions. They may also constitute a useful tool for predicting clinical and functional outcomes to individual patients, a great difficulty that many clinicians acknowledge when treating subjects with BD. Finally, as stated above, cognitive performance and related variables should be taken into account at the time of selecting proper pharmacological treatment to an individual patient.

Conflict of interest

None.

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