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Can anxiety increase tremors in patients with Parkinson's disease? An experimental model

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Abstract

Background: Among non-motor symptoms of Parkinson's disease (PD), anxiety occurs in up to 67% of patients. Clinically, PD patients report worsening of tremors in anxiogenic situations. **Objective**: The aim of this study was to evaluate the association between motor symptoms and anxiety in PD patients and compare their performances with those of healthy volunteers. **Methods:** Fifteen volunteers with PD and 15 healthy volunteers without clinically significant psychiatric disorders were evaluated. Both groups were subjected to a simulated public speaking test (SPST). The following parameters were measured: visual analog mood scale (VAMS), items related to tremors of UPDRS, bradykinesia tests, blood pressure, and heart rate. **Results:** Results of repeated measures ANOVA indicated a significant effect on group × phase interaction ($F_{3.7,105.6} = 2.56$; $p = 0.046$) for VAMS anxiety factor. Regarding tremors, ANOVA indicated significant differences in group × phase interaction ($F_{4.5,121} = 2.88$; $p = 0.021$) and between the groups ($F_{1,27} = 45.88$, $p < 0.001$), with differences in the anticipatory phase, performance, and post-speech, compared with those in the baseline. There were no significant differences between the groups with regard to other factors of VAMS, physiological measurements, and bradykinesia. **Discussion:** Worsening of tremors occurred during SPST, particularly in phases with higher anxiety scores.

Chagas MHN et al. / Arch Clin Psychiatry. 2017;44(4):85-8

Keywords: Parkinson's disease, anxiety, simulated public speaking test.

Introduction

Parkinson's disease (PD) is one of the most common neurological syndromes and is the main cause of Parkinsonism among older people. In Brazil, approximately 3.3% of the population above age 64 has PD[1]. Although diagnosis is based on motor symptoms (rigidity, bradykinesia, resting tremor, and postural instability), the presence of non-motor symptoms is common; these symptoms potentiate the disability in PD and may have a major impact on the health and quality of life of patients[2].

Among the non-motor symptoms, anxiety affects up to 67% of patients with PD[3]. Notwithstanding, this topic is still little explored. Studies that have evaluated the prevalence of anxiety disorders in PD patients have reported a high prevalence of anxiety without other symptoms[4], which indicates the difficulty in characterizing anxiety in PD. Symptoms of anxiety are often related to motor symptoms[5] and the off period in patients with motor fluctuations[6], which suggests a close association between these symptoms.

Experimental tests used to induce anxiety in healthy volunteers are available. One of these tests is the simulated public speaking test (SPST), which was developed and validated by Mcnair *et al.*[7] and subsequently modified by Guimarães *et al.*[8] This clinical anxiety model involves making a speech in front of a video camera; this test has been used in several pharmacological studies in cases of normal anxiety and anxiety disorders, and its validity has been confirmed[9,10].

In the clinical setting, patients complain of worsening of tremors in anxiogenic situations; however, the association between these factors remains to be elucidated. Therefore, this study aimed to assess anxiety symptoms (subjective and physiological) and motor symptoms (tremor and bradykinesia) induced in patients with PD using SPST, and their performances were compared with those of healthy individuals without PD.

Methods

Local and participants

Fifteen subjects with PD were selected in the Movement Disorders Outpatient Clinic of the Clinics Hospital of the Medical School of Ribeirão Preto at the University of São Paulo (FMRP-USP), and 15 volunteers without PD were included in the control group. The inclusion criteria of the PD group were the following: idiopathic PD, Hoehn and Yahr score of 1–3, absence of marked cognitive impairment according to clinical evaluation, absence of treatment with benzodiazepines and antidepressants, use of stable doses of antiparkinsonian drugs for at least 30 days. The exclusion criteria were the following: atypical parkinsonism, presence of dementia, and/or current psychiatric diagnosis according to the DSM-IV criteria. For the control group, the inclusion criteria were absence of marked cognitive impairment according to clinical evaluation and Mini Mental State Exam[11], and absence of treatment with benzodiazepines and antidepressants. Elderly people with current psychiatric diagnosis were excluded. Experiments were performed in the psychopharmacology laboratory of FMRP-USP. This study was approved by the local ethics committee (process number – CAAE: 10082712.7.0000.5440) and the volunteers signed an informed consent to participate. Study performed according to the Declaration of Helsinki.

Measurements

The following parameters were measured:

Visual analog mood scale (VAMS)[12] translated and adapted to Portuguese[13]: this scale consisted of 16 pairs of adjectives with

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opposite meanings, and participants indicated how they felt about each of these adjectives at the time of the test. The scale items were divided into four groups: anxiety, sedation, cognitive impairment, and discomfort.

Tapping test (TT): bradykinesia test in which participants were asked to lightly touch two points that are 30 cm apart. Participants completed 10 cycles (one cycle corresponding to touching both sides of the segment) and the time to perform the task was measured on both sides[14].

Pronation–supination (PS): bradykinesia test was performed with the participants in a sitting position, in which they were asked to perform 20 cycles of alternately and lightly touching the back of their thighs with the back and palm of their hands[14].

Tremors: tremors were measured according to items 20 and 21 of the unified Parkinson's disease rating scale (UPDRS)[15]. A score was obtained from the sum of resting tremors and posture/movement in the upper limbs.

Procedures

STPS is an experimental model to induce anxiety. In this model, the participant is asked to prepare a speech on a neutral subject that is recorded and analyzed by a specialist. During the speech, the subject remains seated in front of a monitor that shows his/her image, which is captured by a camera positioned above the screen[7]. In this study, the volunteers were asked to perform a 4-min speech on the theme "the transport system in your city". During the procedure, physiological measurements (blood pressure and heart rate) were obtained at different phases of the experiment. Table 1 summarizes the procedure. All PD patients were evaluated in the on state.

Table 1. Timetable of the experimental session (SPST)

Time (min)	Phases	Procedure
- 0:30		
- 0:15	Baseline (B)	VAMS, TT, PS, HR, BP, Tremor
0	Pre-stress (P)	VAMS, TT, PS, HR, BP, Tremor
+ 0:10		Instrutions about the SPST
+ 0:12		Speech preparation
+ 0:14	Antecipatory speech (A)	VAMS, TT, PS, HR, BP, Tremor
+ 0:25		Start speech
+ 0:27	Speech performance (S)	VAMS, TT, PS, HR, BP, Tremor
+ 0:33		Continuation of speech
+ 0:35		End of speech
+ 0:40	Post-stress 1 (F0)	VAMS, TT, PS, HR, BP, Tremor
+ 0:55	Post-stress 2 (F1)	VAMS, TT, PS, HR, BP, Tremor

VAMS: visual analog mood scale; TT: tapping test; PS: pronation-supination; HR: heart rate; BP: blood pressure.

Statistical analysis

Clinical and demographic data related to sample pairing were statistically analyzed using Student's t-test for continuous data with normal distribution, non-parametric Mann–Whitney test for continuous data with non-normal distribution, and chi-square test for nominal data.

The differences between the scores of VAMS factors, physiological parameters (blood pressure and heart rate), tremor, and bradykinesia were evaluated using repeated measures analysis of variance (ANOVA) and the phases, groups, and group × phase interactions were evaluated. When sphericity was violated, the degrees of freedom were corrected using the Huynh–Feldt epsilon.

Statistical analysis was performed using the SPSS software version 21.0 at a significance level of $p < 0.05$.

Results

Participants

Table 2 describes the clinical and demographic data of the study sample, consisting of 15 PD patients and 15 control subjects without PD. There were no differences in sex, age, education, and cognition between the groups. The mean score on total UPDRS was 33.73 (SD: ±9.92). In relation to antiparkinsonian treatment of PD group, most of the patients were using levodopa (n = 14), either alone or in combination with other medications. Other medications prescribed for PD treatment were pramipexole (n = 9), amantadine (n = 3), and selegiline (n = 3).

Table 2. Clinical and demographic data stratified by the groups

	PD	Control	p
N	15	15	
Male/Female	10/5	9/6	0.705
Age in years (SD)	61.0 (±2.04)	63.2 (±2.04)	0.439
Years of education (SD)	7.8 (±4.24)	9.9 (±4.31)	0.190
MMSE (SD)	26.8 (±2.73)	27.9 (±1.75)	0.187
Levodopa equivalent dose (SD)	736.67 (±400.61)	-	-

SD: standard deviation; MMSE: Mini Mental State Exam.

Psychological and physiological anxiety measures

Repeated measures ANOVA indicated a significant effect on phase ($F_{3.7,105.6} = 7.77$; $p < 0.001$) and group × phase interaction ($F_{3.7,105.6} = 2.56$; $p = 0.046$) for VAMS anxiety factor (Figure 1). However, no difference was found between the groups ($F_{1.28} = 0.27$, $p = 0.608$). With regard to other VAMS factors, there was a significant effect of phase on mental sedation ($F_{4.1,114.9} = 3.32$; $p = 0.012$), physical sedation ($F_{4.1,114.3} = 4.70$; $p = 0.001$), and other feelings ($F_{4.1,115.4} = 2.55$; $p = 0.042$). However, there were no significant effects of these parameters on group × phase interaction and the groups.

Repeated measures ANOVA showed a significant effect of phase ($F_{5,140} = 4.59$, $p = 0.001$) on heart rate without differences between the groups or group × phase interaction. Moreover, there were no differences in systolic or diastolic blood pressure between the phases, groups, or group × phase interaction.

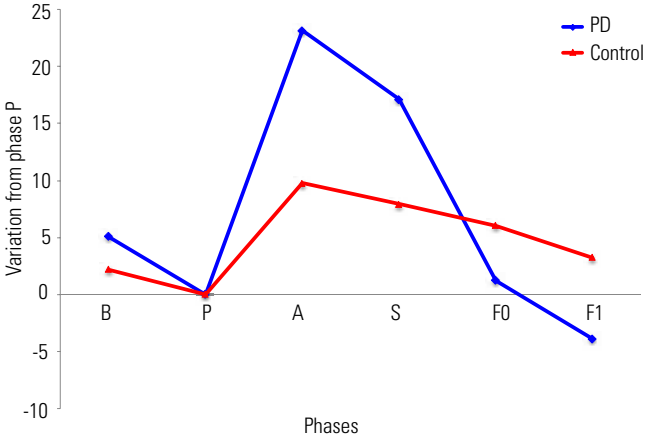

Figure 1. Changes in VAMS anxiety factor induced by SPST, measured in 15 PD patients and 15 healthy subjects. The phases of the experimental session are: B-basal; P-pretest; A-anticipation; S-speech performance; F1--post-speech measures 1; F2-post-speech measures.

Tremor and bradykinesia

Repeated measures ANOVA indicated a significant effect of phase on tremors ($F_{4.5,121} = 2.42$; $p = 0.046$), group × phase interaction ($F_{4.5,121} = 2.88$; $p = 0.021$) and group ($F_{1,27} = 45.88$; $p < 0.001$). The test of contrasts between the phases indicated significant differences between P and A phases ($F_{1,28} = 6.06$, $p = 0.020$). Results of the paired Student's t-test indicated differences between phases A ($t = -3.09$; $p = 0.008$), S ($t = -2.61$; $p = 0.018$), and F0 ($t = -2.35$; $p = 0.034$) and phase P (Figure 2).

In the bradykinesia tests, repeated measures ANOVA indicated a significant effect of phase for both PS ($F_{1.6,44.4} = 10.91$; $p < 0.001$) and TT ($F_{2,55.5} = 29.86$; $p < 0.001$) tests without a significant effect on group and group × phase interaction.

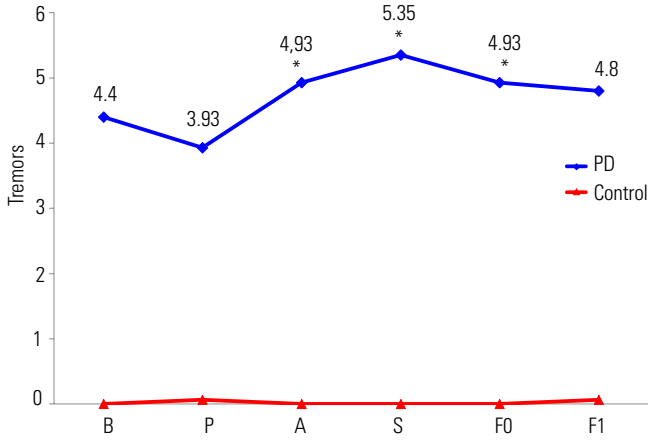

Figure 2. Changes in tremor score during SPST. * $p < 0.05$, Student's t test for paired samples (compared with fase P).

Discussion

Our findings indicate worsening of tremors in phases of higher anxiety scores (phases A and S) during STPS. This result confirms the hypothesis that tremors in PD patients worsen in anxiogenic situations. In addition, there was a statistically significant difference in the group × phase interaction between the study groups, which suggests anxiety behavior differences between patients with PD and healthy controls.

Several studies have reported an increase in anxiety symptoms in PD patients, even if these symptoms do not characterize a specific anxiety disorder[4]. These anxiety disorders include social anxiety disorder, which has a high prevalence in patients with PD[16,17], possibly by a two-way mechanism, because on the one hand, symptoms of anxiety potentially increase in social-interaction settings, thus leading to increased tremors, and on the other hand, motor symptoms result in negative self-evaluation and increased anxiety.

A recent study reported a correlation among increased levels of anxiety, impaired ability to perform activities of daily living, severity of motor symptoms, and presence of motor fluctuations[18]. Another study evaluated the correlation between virtual reality-induced anxiety and freezing of gait and concluded that anxiety had a strong influence on freezing of gait[19], thus strengthening the role of the limbic system in the motor symptoms of PD[19,20]. Most studies that have assessed the association between anxiety and motor symptoms primarily studied motor fluctuations that occurred throughout the day and their association with mood swings and anxiety[20-23]; however, their results were inconclusive, confirming the complexity of this topic.

In situations of anxiety, tremors may be one of the signs of anxiety, even in healthy individuals. Therefore, tremor in patients with PD could be potentiated in anxiogenic situations. Physiologic tremors primarily occur in cases of anxiety and stress, and the use of beta-blockers can be indicated in more severe cases and before important events[24].

With regard to pathophysiological mechanisms, the regions commonly involved in tremors are the thalamus, basal ganglia, and most of the cortical area via excitatory and inhibitory pathways. Furthermore, the cerebellum and locus coeruleus are a part of this complex mechanism of the motor system[24]. It is of note that these areas are also directly associated with mood symptoms[25] and anxiety in PD[26], thereby corroborating the influence of non-motor symptoms in tremors.

The limitations of this study include the use of UPDRS items alone as a measure to evaluate tremors. As this was an initial study, we sought to assess motor symptoms in general, and an increase in the number of assessments would greatly increase the duration of assessment at each stage of STPS. Moreover, a study is being conducted using accelerometry to evaluate tremors using more objective data. We would like to highlight STPS could be used in future studies as an experimental anxiety model to assess the effect of drugs on tremors induced or exacerbated by anxiogenic situations in patients with PD.

In conclusion, this study showed worsening of tremors during SPST, particularly in phases with higher anxiety scores.

Conflicts of interest

None.

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Severity and prevalence of behavioral and psychological symptoms among patients of different dementia stages in Taiwan

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Abstract

Background: To better understand the trends of behavioral and psychological symptoms of dementia (BPSD) over the disease progression is important to provide psychoeducation for dementia caregivers. **Objective:** This study examined the severity and occurrence of BPSD across the various degrees of the disease. **Methods:** This study was a cross-sectional design. Patients (N = 276) who had dementia from July 2001 to October 2008 were surveyed and assessed for dementia stage, using the clinical dementia rating scale (CDR). BPSD was evaluated using the Neuropsychiatric Inventory (NPI). We examined the differences between the severities and occurrence of the individual's BPSD among various CDR stages with the Kruskal-Wallis test and Chi-square test. **Results:** Delusion ($p = 0.01$), agitation/aggression ($p = 0.033$), apathy/indifference ($p = 0.009$), aberrant motor behavior ($p < 0.001$), nighttime behavior disturbances ($p < 0.001$), and eating abnormalities ($p = 0.001$) were significantly different among stages of dementia. The severity of BPSD became exacerbated over the course of the disease, and was highest in moderate (CDR = 2) or severe (CDR = 3) dementia. The occurrence of BPSD was highest when the CDR equaled 2 (97.5%). **Discussion:** The association of global (or certain) BPSD, across different stages of dementia, is a non-linear relationship. These findings suggest the importance of taking into account clinical dementia stage for managing BPSD.

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Keywords: Behavioral and psychological symptoms of dementia, dementia, prevalence, severity, Taiwan.

Introduction

The behavioral and psychological symptoms of dementia (BPSD) are common and serious problems that affect the quality of life for both patients with these symptoms, as well as their caregivers. BPSD present a major challenge in the medical management of patients, and are the major cause of institutionalization. After the onset of disease, more than 80% of demented patients exhibit at least one behavioral and psychological symptom, and no significant differences are observed in the prevalence between Alzheimer's disease (AD) and non-AD dementias[1]. Among the factors associated with caregiver distress, the patient's BPSD are most closely associated with caregiver burden[2]. Therefore, to better understand the trends of symptoms over the disease progression is important to provide psychoeducation for dementia caregivers in clinical practice.

The Neuropsychiatric Inventory (NPI)[3] was developed to assess psychopathology in dementia patients, and has been widely used in studies for dementia. It evaluates 12 BPSD, including delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behavioral disturbances, and appetite and eating abnormalities. Many studies have investigated the prevalence of various BPSD as the dementia disorder progresses, using NPI. Apathy has seemed to become increasingly common as the dementia worsens[4]. Aggressive behavior and aberrant motor behavior have also been found to correlate with an increase in cognitive impairment[5]. Conversely, some studies have found a reduction of such behavior in the most severe stages[6]. There is no general agreement concerning hallucinations about whether there is a relationship between the level of cognitive impairment and BPSD[4] or not[5,7]. The studies on depressive symptoms in dementia have shown heterogeneous results. Some studies have found a decreased prevalence in severe dementia, while other studies have not found a association[4,5,8]. Some studies have found almost no correlation at all between BPSD and the level of cognitive impairment[7,9].

In Taiwan, approximately 80% of the care for dementia patients is provided within the community by family members, and over half (56.6%) of main caregivers spend more than 8 hours per day caregiving[10]. Liu *et al.* reported a high prevalence of BPSD in Taiwanese patients with AD, and suggested that these symptoms were associated with cognitive deficits[11]. In a Taiwanese study, several clinical dementia stages[10] and more behavioral disturbances[12] were been reported to be the associative factors of caregiver burden. Huang *et al.*[13] found that caregiver burden was significantly negatively correlated with CDR stages, and it was presumed that a patient with dementia was more difficult to take care of during the early and middle stage of disease, in which they had more BPSD. However, the investigation of the severity and prevalence of BPSD along the progression of the disease was scarce in Taiwan.

Our aim was to examine the severity and occurrence of BPSD across the different stages of the disease in Taiwan.

Methods

Subjects

This study used a cross-sectional design. In total, 276 patients with dementia who visited the memory clinic of a medical center in central Taiwan, from July 2001 to October 2008, were recruited. For the reliability of the data, we defined the criteria for dementia caregivers were (1) a relative (older than 18 years) who caring for the individual at least 4 hours per day; (2) being the primary caregiver and having intimate information of the patient over time. Subjects who fit the diagnostic criteria for dementia of the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders[14] were recruited and assessed for their stage of dementia, using the clinical dementia rating scale (CDR)[15]. If the CDR revealed a score of 0.5, we further confirmed the clinical history, educational level, as well as the Mini-Mental State Examination (MMSE)[16] scores to validate the diagnosis of dementia. The diagnosis was made by two senior physicians (W.F.

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Wang and Y.C. Liao). The CDR, NPI, and cognitive functions test of all patients were assessed by well-trained and qualified psychologists. The hospital has a standardized objective, evidence-based procedure to authorize psychologists to provide clinical services consistent with their qualifications. The trained researchers verbally administered the instruments to the subjects and recorded the answers according to standardized procedure of each measurement. Caregivers' backgrounds were collected at a single visit to the memory clinic. This study was conducted according to the Declaration of Helsinki, the regulation of clinical research in the country and was approved by the institutional review board of the medical center. Written informed consent was obtained from all subjects.

Measures

The patients' BPSD were assessed using the NPI[3], which was developed to measure psychopathology in people with dementia. The NPI includes 12 symptoms. The caregiver rated the frequency and severity of each symptom, using scores from 0 to 4 for frequency, and scores from 0 to 3 for severity. The NPI score for each BPSD was the product of the frequency and severity subscores (frequency multiplied by the severity). The total NPI score ranged from 0 to 144. The Cronbach's alpha coefficient of the Chinese version of the NPI was 0.76. The test-retest reliabilities of frequency and severity were significantly correlated, with the overall correlations being 0.85 for frequency ($p < 0.001$), and 0.82 for severity ($p < 0.001$)[17]. The patients' clinical dementia stages were assessed with the CDR, and cognitive function with the Chinese version of the cognitive abilities screening instrument (CASI, C-2.0)[18]. The MMSE score in this study was derived from part of the CASI score.

Data analysis

We used descriptive statistics to characterize the study population. Statistical analysis was performed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). The assumption of a normal distribution of the variables was verified using the Kolmogorov–Smirnov test, which showed a violation. Therefore, we used the non-parametric test to evaluate the data. In addition to descriptive statistics, the differences of severity of BPSD (the product score of the frequency multiplied by the severity subscores of individual BPSD domain) among dementia stages (different CDR stages) were tested using the Kruskal Wallis test. Furthermore, we examined the differences on the occurrence rate of BPSD among different stages of dementia with a Chi-square test. For all analyses, the probability level used to indicate statistical significance was set at $p < 0.05$.

Results

A total of 276 patients were recruited. The mean age was 79.70 ± 7.20 years old. One hundred and eighty nine of 276 (68.5%) patients were female. The diagnosis of the patients comprised 167 cases of AD (60.5%), 70 cases of vascular dementia (25.4%), 25 cases of dementia due to multiple etiologies (9.0%), and 14 cases of dementia due to other general medical conditions (5.1%). Table 1 shows the characteristics of patients with dementia grouped by CDR in this study.

Table 2 lists the mean scores of the individual NPI domain, the product of the frequency and severity subscores (frequency multiplied by the severity), according to CDR stage in patients with dementia. The NPI total score resulted in a statistically significant difference among the different stages of dementia ($p < 0.001$), and scores were highest when the CDR equaled 3. By the individual NPI domain, delusion ($p = 0.01$), agitation/aggression ($p = 0.033$), apathy/indifference ($p = 0.009$), aberrant motor behavior ($p < 0.001$), nighttime behavior disturbances ($p < 0.001$), and appetite and eating abnormalities ($p = 0.001$) had statistically significant differences among the different stages of dementia. These BPSD became worse and worse over the disease course, and the product subscores were significantly higher in the moderate (CDR = 2) or severe (CDR = 3) stages, compared to the very mild (CDR = 0.5) stage of dementia.

Table 3 shows the percentage of the presence of each BPSD in different stages of dementia patients. The occurrence of BPSD (97.5%) was highest when the CDR equaled 2. There was a statistically significant difference in the occurrence rate among the stages of dementia. Considering each BPSD, the occurrence rate of delusion, apathy/indifference, aberrant motor behavior, nighttime behavior disturbances, and eating abnormalities was significantly different among the stages of dementia. The highest occurrence of delusion was 53.2% when the CDR equaled 2; apathy/indifference was 55.6%, when the CDR equaled 3; aberrant motor behavior was 48.1%, when the CDR equaled 3; nighttime behavior disturbances was 70.4%, when the CDR equaled 3; and appetite and eating abnormalities was 41.8%, when the CDR equaled 2. In group 1 (CDR = 0.5), the highest occurring symptom was depression (40.0 %); in group 2 (CDR = 1), the highest occurring symptom was depression (47.2%); in group 3 (CDR = 2), the highest occurring symptoms were delusion and nighttime behavior disturbances (53.2%); in group 4 (CDR = 3), the highest occurring symptom was nighttime behavior disturbances (70.4%).

Discussion

Although the number of subjects was small in the later stage group of dementia (CDR = 4), we included the sample in the analysis in an attempt to illustrate the trend of severity and prevalence of BPSD, from very early to later stages of dementia. The results of this study revealed that severity of BPSD was associated with different stages in dementia. The highest severity of global BPSD was seen in severe dementia (CDR = 3), and decreased in severity when CDR equaled 4. Considering individual BPSD, delusion, agitation/aggression, apathy/indifference, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities were significantly different among stages of dementia. The highest severity of the above symptoms was seen at the moderate (CDR = 2) or severe (CDR = 3) stage of dementia. The occurrence of BPSD was highest at the moderate stage of dementia (CDR = 2). By each BPSD, the occurrence rate of delusion, apathy/indifference, aberrant motor behavior, nighttime behavior disturbances, and eating abnormalities were significantly different among the stages of dementia. The occurrence rate of these BPSD was highest at the moderate (CDR = 2) or severe stage (CDR = 3) of dementia.

The severity of some BPSD has demonstrated that they are associated with the dementia stages. Hashimoto *et al.*[19] reported that seven of the 12 BPSD domains assessed by NPI revealed increased severity as dementia progressed. However, these results were only present for the patients in the very early stages (CDR = 0.5) to middle stages (CDR = 2) of dementia. The severity of seven BPSD domains included: delusion, hallucination, agitation, apathy, irritability, aberrant motor behavior, and sleep disturbance; and, all were highest at the moderate stage of dementia. These results did not find BPSD in later stages of dementia (CDR = 3 or 4). In the present study, the severity of delusion, agitation, apathy, aberrant motor behavior, nighttime behavior disturbances, and eating abnormalities were found to be statistically significantly different across the dementia stages. Indeed, as shown in Table 2, their NPI scores increased as the CDR progressed to the second stage. However, the severity of agitation and apathy continuously increased as the disease progressed to stage 4 of dementia. The severity of delusion was highest at stage 2 of dementia, and gradually lessened afterward; the severity of aberrant motor behavior and nighttime behavior disturbances was highest at stage 3, and attenuated afterward. The longitudinal changes in symptom severity did not always result in a positive correlation with dementia severity, according to present study.

Some studies suggested that there was no difference in prevalence of BPSD among the stages of dementia[7,9]. Our study found that the prevalence of delusion, apathy/indifference, aberrant motor behavior,

Table 1. Demographic and clinical characteristics of patients with dementia according to disease severity

	CDR					All	P
	0.5	1	2	3	4		
N (%)	55 (19.9)	106 (38.4)	79 (28.6)	27 (9.8)	9 (3.3)	276 (100)	
Age (years)	75.84 ± 6.27	79.57 ± 7.33	82.06 ± 6.56	80.96 ± 7.40	80.44 ± 7.11	79.70 ± 7.20	< 0.001[a]
Gender (female, %)	36 (65.5)	70 (66.0)	56 (70.9)	21 (77.8)	6 (66.7)	189 (68.5)	0.766[b]
Education (years)	4.71 ± 4.84	3.63 ± 4.17	3.08 ± 4.37	2.52 ± 3.79	1.33 ± 2.65	3.50 ± 4.34	0.066[a]
Diagnosis (AD, %)	43 (78.2)	62 (58.5)	42 (53.2)	15 (55.6)	5 (55.6)	167 (60.5)	0.049[b]
MMSE	20.17 ± 4.17	15.28 ± 4.57	10.07 ± 4.90	3.91 ± 3.32	1.40 ± 2.61	13.56 ± 6.69	< 0.001[a]
CASI	66.53 ± 17.13	48.63 ± 17.93	29.07 ± 16.54	15.20 ± 17.32	3.60 ± 10.47	41.96 ± 24.33	< 0.001[a]

[a] Analysis of variance (ANOVA); [b] Chi-square test; Values are n (%) or the mean ± SD.
CDR: Clinical Dementia Rating Scale; AD: Alzheimer's Disease; MMSE: Mini-Mental State Examination; CASI: Cognitive Abilities Screening Instrument.

Table 2. Mean scores of individual NPI domains of the product subscores (frequency multiplied by the severity) according to dementia severity (CDR score), mean (SD)

	CDR					All	P[a]	Post hoc[b]
	0.5	1	2	3	4			
Delusion	1.15 (2.67)	1.84 (3.31)	3.32 (4.12)	3.00 (3.75)	1.33 (4.00)	2.22 (3.59)	0.01	0.5 < 2; 0.5 < 3; 1 < 2; 2 > 4
Hallucination	0.67 (1.70)	1.02 (2.57)	1.90 (3.53)	2.41 (3.66)	2.00 (4.24)	1.37 (2.96)	0.051	0.5 < 2; 0.5 < 3; 1 < 3
Agitation/aggression	0.78 (2.32)	1.33 (2.70)	2.38 (3.55)	2.41 (3.51)	3.33 (5.29)	1.69 (3.14)	0.033	0.5 < 2; 0.5 < 3
Dysphoria/depression	1.44 (2.80)	2.07 (3.41)	2.56 (3.82)	1.41 (2.85)	0.44 (0.73)	1.96 (3.34)	0.245	
Anxiety	1.05 (2.26)	1.63 (3.22)	2.42 (3.85)	2.59 (3.74)	1.44 (3.97)	1.83 (3.36)	0.455	
Euphoria/elation	0.04 (0.19)	0.03 (0.17)	0.47 (1.82)	0.44 (2.31)	0 (0)	0.20 (1.23)	0.175	1 < 2
Apathy/indifference	1.18 (2.66)	1.70 (3.20)	2.53 (3.52)	3.52 (4.02)	4.00 (6.00)	2.09 (3.46)	0.009	0.5 < 2; 0.5 < 3; 1 < 3
Disinhibition	0.67 (2.08)	0.66 (2.08)	1.10 (2.68)	1.19 (2.40)	0.11 (0.33)	0.82 (2.27)	0.464	
Irritability/Lability	1.22 (2.81)	1.80 (3.28)	2.32 (3.84)	2.89 (3.82)	2.67 (5.29)	1.97 (3.50)	0.361	
Aberrant motor behavior	0.33 (1.26)	1.47 (3.19)	3.08 (4.28)	3.04 (3.93)	1.33 (3.04)	1.85 (3.50)	< 0.001	0.5 < 1; 0.5 < 2; 0.5 < 3; 1 < 2; 1 < 3
Nighttime behavior disturbances	1.36 (2.51)	1.98 (3.30)	3.63 (4.33)	5.56 (5.01)	3.33 (5.29)	2.72 (3.94)	< 0.001	0.5 < 2; 0.5 < 3; 1 < 2; 1 < 3
Appetite and eating abnormalities	0.65 (1.80)	1.80 (3.43)	2.78 (4.00)	2.96 (4.09)	0 (0)	1.91 (3.47)	0.001	0.5 < 2; 0.5 < 3; 1 < 2; 2 > 3; 2 > 4; 3 > 4
NPI total score	10.55 (13.70)	17.33 (20.42)	28.48 (21.75)	31.41 (17.82)	20.00 (16.87)	20.63 (20.55)	< 0.001	0.5 < 1; 0.5 < 2; 0.5 < 3; 1 < 2; 1 < 3

[a] P values refer to the Kruskal-Wallis test; [b] Comparison of NPI symptoms between different dementia stages. The column lists the CDR stages that have significant differences in NPI scores.
NPI: Neuropsychiatric Inventory; CDR: Clinical Dementia Rating Scale.

Table 3. Occurrence of each behavioral and psychological symptoms of dementia according to the disease stage

Variables	CDR					All (n = 276)	P[a]	Post hoc[b]
	0.5 (n = 55)	1 (n = 106)	2 (n = 79)	3 (n = 27)	4 (n = 9)			
Delusion	15 (27.3)	37 (34.9)	42 (53.2)	14 (51.9)	1 (11.1)	109 (39.5)	0.004	0.5 < 2
Hallucination	11 (20.0)	26 (24.5)	28 (35.4)	12 (44.4)	2 (22.2)	79 (28.6)	0.086	
Agitation/Aggression	10 (18.2)	31 (29.2)	31 (39.2)	11 (40.7)	3 (33.3)	86 (31.2)	0.089	
Dysphoria/Depression	22 (40.0)	50 (47.2)	39 (49.4)	8 (29.6)	3 (33.3)	122 (44.2)	0.357	
Anxiety	16 (29.1)	37 (34.9)	29 (36.7)	11 (40.7)	2 (22.2)	95 (34.4)	0.744	
Euphoria/Elation	2 (3.6)	3 (2.8)	8 (10.1)	1 (3.7)	0 (0)	14 (5.2)	0.190	
Apathy/Indifference	11 (20.0)	33 (31.1)	34 (43.0)	15 (55.6)	3 (33.3)	96 (34.8)	0.009	0.5 < 3
Disinhibition	9 (16.4)	18 (17.0)	17 (21.5)	8 (29.6)	1 (11.1)	53 (19.2)	0.530	
Irritability/Lability	15 (27.3)	39 (36.8)	31 (39.2)	12 (44.4)	2 (22.2)	99 (35.9)	0.435	
Aberrant motor behavior	6 (10.9)	29 (27.4)	34 (43.0)	13 (48.1)	2 (22.2)	84 (30.4)	< 0.001	0.5 < 2; 0.5 < 3
Nighttime behavior disturbances	18 (32.7)	39 (36.8)	42 (53.2)	19 (70.4)	3 (33.3)	121 (43.8)	0.003	0.5 < 3; 1 < 3
Appetite and eating abnormalities	9 (16.4)	29 (27.4)	33 (41.8)	11 (40.7)	0 (0)	82 (29.7)	0.003	0.5 < 2
Any BPSD	41 (74.5)	90 (84.9)	77 (97.5)	26 (96.3)	7 (77.8)	234 (87.6)	0.001	0.5 < 2; 1 < 2

[a] P values refer to Chi-square test; [b] Post hoc analysis of comparison for each NPI symptoms between different dementia stage. The column lists the CDR stages that have significant differences; values are n (%).
CDR: Clinical Dementia Rating Scale.

nighttime behavior disturbances, and eating abnormalities was significantly different among the stages of dementia. Using 10 items of the NPI, Piccininni *et al.*[20] reported that only aberrant motor activity produced a statistically significant increase in NPI scores from a mild to severe degree of the disease; they also confirmed a clear trend of increased frequencies of disease severity in delusions and hallucinations. Symptoms of nighttime behavior disturbances and eating abnormalities were not mentioned in their study. These differing results, which may have been caused by both nighttime behavior disturbances and eating abnormalities, were not included in the 10-item NPI. Furthermore, in this study, hallucination symptoms occurred most frequently in those with severe dementia (CDR = 3); the p value equaled 0.086. Although the NPI is the most widely used measurement for BPSD, it still retains some shortcomings. For instance, the NPI is based on caregiver's observations that are obtained during a clinical interview, and does not allow for the clinician's judgment to be factored into the assessment. Non-professional caregivers may overlook some symptoms and signs of hallucinations or other BPSD. This may produce a bias in the study, and likely result in different findings between the current study and the others.

Our findings on the prevalence of BPSD showed a significant difference between the various stages of dementia. In general, the highest rate of occurrence was noted in stage 2 or 3 of dementia, and the lowest rate of occurrence was seen in more severe stages of dementia. We suggested that the association of global (or certain) BPSD (concerning severity and prevalence), across different stages of dementia, is a non-linear relationship. This finding is consistent with the study of Lövheim *et al.*[21], in which the correlation between some BPSD and the level of cognitive impairment was found to be significant and non-linear, and the highest prevalence rates occurred at the middle stages of dementia. Lövheim *et al.*[21] confirmed that the factor of passiveness had an almost linear correlation to the level of cognitive impairment. The aggressive behavior, wandering behavior, restless behavior, verbally disruptive/attention-seeking behavior, regressive/inappropriate behavior, hallucinatory symptoms, and depressive symptoms had the highest prevalence of middle-stage dementia and non-linear correlation. The use of a different scale (the Multi-Dimensional Dementia Assessment Scale, MDDAS[22]) in Lövheim *et al.*'s study may offer new information, although it has limited comparability. In comparing the MDDAS with the NPI, passiveness may partly correspond to apathy; aggressive behavior corresponds to delusion, wandering and restless behaviors correspond to aberrant motor behavior; verbally disruptive/attention-seeking behavior may partially correspond to nighttime behavior disturbances; and, some descriptions of restless behaviors may correspond to eating abnormalities in the NPI. In a similarity seen in both studies, some symptoms, like delusion, aberrant motor behavior, nighttime behavior disturbances, and eating abnormalities, showed the highest severity and occurrence when CDR was 2 or 3, and lessened at later stages of dementia. Divergently, and unlike Lövheim *et al.*'s results, we found that the prevalence of apathy was highest when CDR equaled 3, and it decreased at stage 4 of CDR. The occurrence rate of apathy did not show an increasing trend as dementia progressed. Because the subjects of the stage 4 group were few in number, statistical power may have been limited. The occurrence rates of depression and hallucinations were relatively stable and were not significantly different among the stages of dementia in our study. However, a slightly decreased occurrence rate was still noted for both symptoms at later stages of dementia. The relatively smaller sample size in stage 3 and 4 may have restricted the ability to generalize our results. Because of the patients' reduced speech, communication ability, and motor function, caregivers may have had difficulty interpreting symptoms (such as delusion) in later stages of dementia. Furthermore, motor functions were affected, and this may have contributed to the reduced prevalence of certain behavioral disturbances, such as aberrant motor behavior, nighttime behavior disturbances, and eating abnormalities at that stage.

Our study identified a high frequency and severity of depression in the very early stage (CDR = 0.5) of dementia patients, similar to previous findings[23]. It is possible that symptoms are associated with pathological changes in regions of the brain associated with its pathogenesis. There is evidence of increased neuropathological changes within the hippocampus in AD patients who suffer from depression[24]. An alternative explanation is that depression in dementia patients is an emotional reaction to the decline of cognitive function in the early stage of dementia. People with memory problems have a high risk of psychological distress and depressive symptoms as a result of the situation[25]. Compared with the relatively stable prevalence and severity of depression and anxiety, there was a progressive prevalence of apathy, delusion, aberrant motor behavior, nighttime behavior disturbances, and eating abnormalities symptoms, from the very early to middle stages of dementia. For example, structural atrophy and functional deficits in medial and frontal regions associated with motivation and reward mechanisms of the brain may account for the increased prevalence of apathy as the disease progresses[26]. This is supported by previous results, in which apathy increased with increased severity of memory deficits[27], or global cognitive impairment[9].

This study had several limitations in terms of data generalization. First, because only the patients from community were recruited in this study, the difference between people accommodated from community and long-term institutions on the occurrence of BPSD[28] could not be compared in this study. Second, we included subjects with AD and non-AD. We were unable to differentiate the effects between different dementia subtypes, which may have produced differential effects on BPSD; although, there was no significant difference in severity and prevalence between AD and non-AD dementias in some studies[1,29]. Third, nighttime behavior disturbances and eating abnormalities were not included in the 10-item NPI. The evaluation instrument that assessed BPSD restricted the generalization of results among studies. Fourth, the symptoms present in the patients tended to fluctuate; the probability that a person's symptom occurred at certain time-point during the cognitive decline was probably higher. The prevalence rates were likely further affected by the fact that these BPSD may have been higher and more severe in a hospital-based study sample than a community population. Fifth, the relatively small sample size of the stage 4 dementia group may have limited the analysis and restricted the representativeness.

In summary, the severity and occurrence of BPSD are different in various stages of dementia. The highest severity of global BPSD occurred at the severe stage dementia (CDR = 3), and decreased at the later stage of dementia (CDR = 4). The severity and prevalence of delusion, apathy, aberrant motor behavior, nighttime behavior disturbances, and eating abnormalities were different among stages of dementia. The clinicians should take into account clinical dementia stage in managing BPSD and offering psychoeducation toward caregivers in clinical practice.

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Original article

Reduction of prefrontal thickness in military police officers with post-traumatic stress disorder

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Abstract

Background: Brain-imaging studies in post-traumatic stress disorder (PTSD) have consistently revealed alterations in brain structure and function and this is correlated to symptomatology. However, few studies have investigated the role of biomarkers in PTSD some specific groups, as police officers. **Objective:** To evaluate prefrontal and limbic volumes, and cortical thickness of police officers exposed to trauma during work who developed post-traumatic stress disorder, resilient matched controls (without PTSD), and compared to healthy civilians. **Methods:** Prefrontal and limbic volumes, and cortical thickness of 12 police officers with PTSD, 12 resilient police officers, and 12 healthy civilians who underwent brain MRI were analyzed. **Results:** Differences in limbic structures volume were not significative after Bonferroni correction. A significant reduction in cortical thickness on right rostral cingulate, right and left middle frontal gyrus, left superior frontal, left lingual, calcarine and cuneus were observed in PTSD group in comparison to controls was observed. **Discussion:** Although preliminary, our results suggested not only the association between cortical thickness and PTSD, but also indicated that patients and controls have anatomical differences.

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Keywords: Post-traumatic stress disorder, cortical thickness, limbic system, police officers, trauma.

Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric condition experienced by individuals after suffering psychological trauma. PTSD symptoms include avoidance of trauma-related stimuli, emotional numbing, re-experiencing the traumatic event, hyperarousal, and cognitive deficits[1-3]. Data from a large sample that the lifetime prevalence of PTSD in general population is approximately range from 1.3% to 9.2%[4], worldwide, and 11.1% to 14.7% in Brazil[5], with symptoms being triggered by many different types of events[4,5].

Brain-imaging studies in PTSD have consistently revealed alterations in brain structure and function and this is correlated to the PTSD symptomatology[6]. The most replicated findings are reduced volume in regions of the limbic system, such as amygdala[7,8], hippocampus[9], and anterior cingulate cortex (ACC)[1]. Other studies have found a thinner cortex in frontal and temporal areas[10,11], and in a longitudinal assessment conducted in a recovered group of PTSD showed a greater dorsolateral prefrontal cortex associated to improvement in PTSD symptoms[12].

Studies in adult PTSD have revealed altered function in several different areas of the prefrontal cortex including the dorsolateral prefrontal cortex, the ventrolateral prefrontal cortex, the medial prefrontal cortex, the anterior cingulate cortex, and the orbital frontal cortex compared to controls[13,14].

The medial prefrontal cortex (mPFC) seems to play a key role in fear extinction of neurocircuitry models in anxiety and PTSD[15] Studies in both humans and animals reinforce the involvement and interaction among amygdala, hippocampus and mPFC in fear contextual learning[15].

The presence of an adverse event is necessary but not sufficient for the development of PTSD. In fact, only one in 10 subjects will develop the disorder[16,17], stressing that there are genetic and environmental factors predisposing certain patients to PTSD. The study of biological markers associated with PTSD is an extensive research field with promising results for both basic and clinical knowledge[1,17]. Brazil has a unique environment to conduct translational research about psychological trauma and posttraumatic stress disorder, since urban violence became a Brazilian phenomenon, being particularly related to the rapid population growth of its cities[1,18].

The causes of posttraumatic stress disorder are many, including the different types of traumatic events each person can be exposed to. In turn, police officers are a group that is continually exposed to stressful and traumatic factors. At the same time, they are expensive to train and require quick return when they are ill, given their role in population safety. However, few studies have investigated the role of biomarkers in PTSD police officers[19,20]. Reduced amygdala, thalamus and globus pallidus volumes were observed in police officers with chronic PTSD that had higher re-experiencing scores associated to higher arousal ratings of negative pictures during trauma related paradigm[21].

Compared with other occupational groups, police officers face an increased and anticipated risk of exposure to life-threatening and potentially traumatic events in their work environments (for example, when intervening in violent situations or witnessing suffering and death of others[22]). It has been found that the organizational and psychosocial work environment of police officers may affect the degree and strength of PTSD symptoms[23]. The diagnosis of PTSD is intrinsically linked to the presence of a traumatic event, but the traumatic event per se is not sufficient for the disease development. In fact, only one in ten people will develop PTSD after experiencing trauma indicating that genetic and environmental factors contribute to the onset of PTSD[24].

In this study we hypothesized that the volumes of the cingulum and amygdala, and thickness of frontal cortex are lower in police officers exposed to traumatic situations who developed PTSD compared to those exposed to the same situation but did not develop PTSD and to healthy civilians. In this context, the goal of the present study was to investigate alterations in limbic structures and frontal cortex police officers exposed to traumatic events during work and compared to resilient military police and healthy civilians.

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Methods

Participants

Thirty-six subjects matched by gender (all males) and age (mean age: 35, standard deviation [SD] ± 4 years old) were divided into three groups: 12 police officers exposed to trauma with PTSD, 12 police officers exposed to trauma without PTSD (resilient officers), and 12 civilians without a history of trauma exposure. Police officers with at least 10 years of work experience were recruited from the General Command of the Military Police of Tocantins, Brazil. Healthy civilian subjects (controls) were recruited from the same community.

Traumatic experiences considered for the present study were defined as duty-related urban violence, and included the following experiences: being threatened, being shot, being beaten, witnessing a death, witnessing a beating, experiencing a car accident, witnessing the death a friend.

Patients were eligible for study participation if they met the following inclusion criteria: 1) DSM-IV criteria for a diagnosis of PTSD[25]; 2) aged between 18 and 60 years; 3) male gender; and 4) the experience of a traumatic event, as previously defined, during duty. Participant exclusion criteria included the following: 1) a history of bipolar, psychotic, or borderline personality disorder; 2) substance dependence or abuse (excluding nicotine and caffeine); 3) severe or unstable concurrent illness; 4) psychotropic medication use less than four weeks prior to MRI, 5) current suicidal ideation or the presence of psychotic symptoms; 6) use of psychoactive medications such as antidepressants, neuroleptics, anxiolytics or sedative hypnotics and mood stabilizers within the last eight weeks, 7) a Beck Depression Inventory (BDI) score of more than 11 points.

Participants were informed about the research procedures and risks of this study, and signed an informed consent form that was fully approved by the Ethical Committee of the Federal University of Tocantins (014/2012).

Measures

For the diagnosis of mental health disorders according to DSM-IV criteria, we used the Structured Clinical Interview for DSM-IV I[26,27].

To assess the presence of PTSD in patients, we used the Clinician-Administered PTSD Scale (CAPS)[28], a 30-item scale that investigates the frequency and intensity of PTSD symptoms and traumatic life experiences. Scores ranged from 0 to 136, with the following classifications: subclinical, 0 to 19; mild, 20 to 39; moderate, 40 to 59; severe, 60 to 79; and extreme, 80 and above. Symptoms were divided into the following clusters: re-experiencing symptoms, avoidance and numbing symptoms, and hyperarousal symptoms.

To assess depressive symptoms in clinical settings, we used the Beck Depression Inventory (BDI)[29], a self-administered 21-item questionnaire, which has been validated for the Brazilian population. Scores ranged from 0 to 63, with depression classified according to the following score categories: minimal, between 0 and 11; mild, between 12 and 19; moderate, between 20 and 35; and severe, between 36 and 63. Subjects with scores more than 11 points were excluded.

Image acquisition and analysis

Imaging data were acquired using a Philips 1.5T Sigma scanner. Structural MRI images were acquired using a sagittal T1 acquisition series (TR = 9.8 ms, TE = 3.1 ms, flip angle = 30°, NEX = 1, matrix size = 256 × 256, FOV = 24 cm, thickness = 1.0 mm), yielding 160 slices.

We used an automated, non-biased atlas-based Bayesian segmentation method, applied in Freesurfer v.5.0 (http://surfer.nmr.mgh.harvard.edu/). Too derive quantitative estimates of brain structure and to label cortical and subcortical tissue classes Freesurfer processing for volumetric T1-weighted images included: motion correction, brain extraction and removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated spatial transformation and white matter (WM) segmentation of subcortical volumetric structures, intensity normalization, tessellation of grey matter GM/WM boundary and automated topology correction and surface deformation, following intensity gradients to place optimally GM/WM and GM/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Image outputs from each stage of Freesurfer processing were visually inspected. Freesurfer automatically assigns a neuroanatomical place to each location on a cortical surface model based on probabilistic information estimated from a manually labeled training set (made using FreeSurfer). This method incorporates both geometric information derived from the cortical model, and neuroanatomical convention, as finding in the training set. The result is a complete labeling of cortical sulci and gyri. The resulting segmentation and parcellation was inspected by one of the authors and no adjustment or reprocessing was needed. No manual region of interest (ROI) was outlined in this study.

To account for inter-individual differences in head size, intracranial and cerebral volumes were corrected by dividing by each subject's intracranial volume and multiplying this ratio by 1000 (Figure 1).

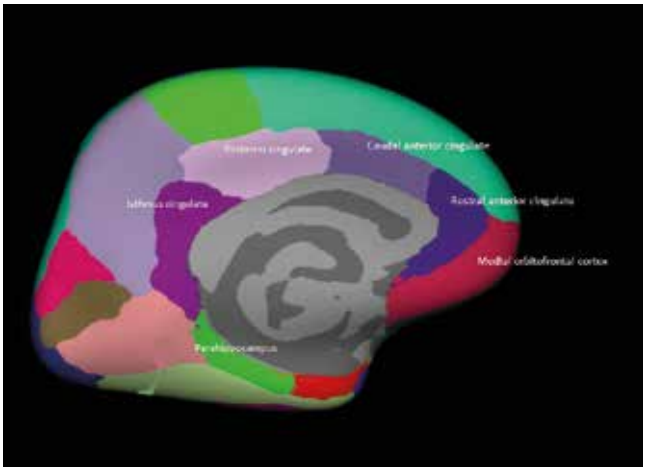

Figure 1. Regions analysed in the study.

Data analysis

Structural volume analysis

Data were codified and analyzed using the Statistical Package for the Social Sciences (IBM SPSS for Windows, version 15.0). Prior to analyses, measures were examined for normality using the Shapiro-Wilk test. Significance levels were set at $p < 0.05$, using a two-tailed test.

Group differences in volumes were investigated using the general linear model (Multivariate analysis of covariance – MANCOVA). Results were corrected for multiple comparisons using Dunnet's post-hoc test ($p \leq 0.05$), however to improve analysis all values were corrected by Bonferroni method ($p \leq 0.0028$). MANOVA effect sizes were calculated using eta partial squared (η^2), and compared between groups using Cohen's d method (d).

Cortical thickness analysis

The Query Design Estimate Contrast (QDEC) interface of FreeSurfer was used to carry out a general linear model (GLM) analysis at each vertex of the cortical surface.

Cortical thickness was considered as the dependent variable; group (patients vs healthy controls), age, and their interaction were explanatory variables, and intracranial volume was a nuisance variable. Results were corrected for multiple comparisons at the cluster level using the Monte Carlo approach for p-cluster < 0.05.

Results

PTSD subjects has total mean CAPS score of 64.9 (SD ± 28.5) and mean time to trauma of 2945 days (SD ± 2721). Mean time to trauma for resilient group was 3630 days (SD ± 2654).

Volume analysis

A significant reduction in cortical thickness on left rostral cingulate, left middle frontal gyrus, right middle frontal gyrus, right superior frontal, and right lingual were observed in PTSD group in comparison to controls survived Monte Carlo null-Z correction for multiple comparisons at $p < 0.05$. No differences between PTSD, healthy controls and resilient controls survived multiple comparison correction (Figures 2 and 3).

Cortical thickness

A significant reduction in cortical thickness on right rostral cingulate, right and left middle frontal gyrus, left superior frontal, left lingual were observed in PTSD group in comparison to controls survived Monte Carlo null-Z correction for multiple comparisons at $p < 0.05$. No differences between PTSD, healthy controls and resilient controls survived multiple comparison correction (Figures 2 and 3).

Discussion

Not all individuals exposed to traumatic events develop PTSD. Biological measures of PTSD should reflect predictive markers of risk/resilience (pre- or posttrauma exposure), or disease markers indicating diagnostic status or symptom severity. More refined applications include prognostic markers of therapy response that may inform treatment choice or monitor response[30]. Once the biological correlates of these constructs are identified, such biomarkers may help identify those at highest risk following trauma exposure, target prevention efforts, aid in diagnosis, treatment planning, and recovery assessment for patients, and ultimately inform the development of safe and effective pharmacological treatments for PTSD.

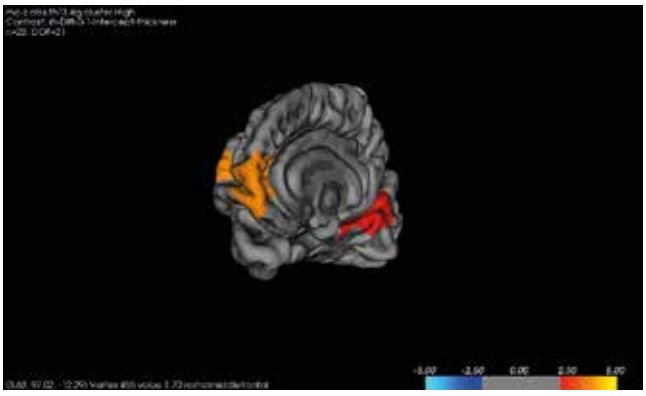

Figure 2. Reduced cortical thickness on right middle frontal gyrus, right superior frontal, and right lingual.

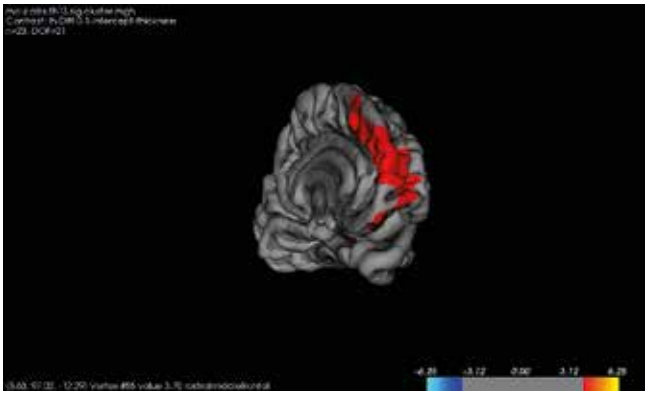

Figure 3. Reduced cortical thickness on left middle frontal gyrus and left rostral cingulate.

Table 1. Group differences in volumes of the Regions of Interest (cm^3)

Variables (volume in cm^3)	PTSD group Mean (CI)	Resilient group Mean (CI)	Control group Mean (CI)	F, df = 2	p	η^2
Intracranial volume	1637.53 (1558.62-1716.45)	1542.17 (1469.32-1615.01)	1578.77 (1489.27-1668.28)	1.721	0.195	0.094
Left hippocampus	2.56 (2.41-2.71)	2.64 (2.48-2.79)	2.66 (2.50-2.81)	0.435	0.651	0.026
Right hippocampus	2.65 (2.52-2.77)	2.60 (2.48-2.73)	2.59 (2.46-2.71)	0.239	0.789	0.014
Left parahippocampus	1.24 (1.10-1.38)	1.45 (1.32-1.59)	1.21 (1.07-1.35)	4.005	0.028*	0.195
Right parahippocampus	1.17 (1.07-1.27)	1.28 (1.19-1.38)	1.25 (1.16-1.35)	1.582	0.221	0.088
Left amygdala	0.94 (0.85-1.02)	0.94 (0.85-1.02)	0.93 (0.84-1.01)	0.011	0.989	0.001
Right amygdala	0.976 (0.91-1.04)	0.98 (0.92-1.05)	1.02 (0.96-1.09)	0.653	0.527	0.038
Left rostral anterior cingulate	1.62 (1.48-1.76)	1.87 (1.73-2.01)	1.88 (1.74-2.03)	4.389	0.020**	0.210
Right rostral anterior cingulate	1.32 (1.14-1.50)	1.36 (1.18-1.54)	1.48 (1.30-1.67)	0.876	0.426	0.050
Left dorsal anterior cingulate	1.20 (1.00-1.39)	1.30 (1.11-1.49)	1.22 (1.03-1.41)	0.350	0.707	0.021
Right dorsal anterior cingulate	1.39 (1.22-1.57)	1.34 (1.16-1.52)	1.43 (1.25-1.61)	0.271	0.765	0.016
Left isthmus cingulate	1.94 (1.77-2.12)	1.81 (1.64-1.99)	1.80 (1.62-1.97)	0.841	0.440	0.049
Right isthmus cingulate	1.75 (1.61-1.89)	1.65 (1.51-1.78)	1.67 (1.53-1.80)	0.692	0.508	0.040
Left posterior cingulate	2.05 (1.86-2.24)	2.15 (1.95-2.34)	2.12 (1.93-2.32)	0.273	0.763	0.016
Right posterior cingulate	2.12 (1.96-2.27)	2.07 (1.91-2.22)	2.17 (2.01-2.32)	0.450	0.642	0.027
Left lateral orbitofrontal	4.83 (4.57-5.10)	5.25 (5.00-5.52)	4.98 (4.72-5.24)	2.783	0.076	0.144
Right lateral orbitofrontal	4.73 (4.46-5.00)	5.06 (4.78-5.31)	4.88 (4.61-5.14)	1.461	0.247	0.081
Left medial orbitofrontal	3.52 (3.28-3.77)	3.73 (3.48-3.98)	3.88 (3.63-4.13)	2.150	0.133	0.115
Right medial orbitofrontal	3.25 (3.07-3.43)	3.55 (3.37-3.73)	3.50 (3.32-3.68)	3.226	0.053	0.164

cm^3: cubic centimeters. p threshold was set at $p < 0.05$

* Post-hoc control x PTSD left parahippocampus p = 0.929 (d = 0.127), resilient x PTSD left parahippocampus p = 0.054 (d = 0.933).

** Post-hoc control x PTSD left rostral anterior cingulate p = 0.024 (d = 1.04), resilient x PTSD left rostral anterior cingulate p = 0.032 (d = 1.15).

In this present study, we investigated possible alterations in brain volume and thickness of police officers with PTSD secondary to traumatic events during duty. Our results showed reduced cortical thickness in prefrontal area of PTSD group when compared to resilient police officers and healthy civilians.

Due to the cross-sectional nature of this study we can not state whether the changes were present before or after the disorder. For a while the results suggests involvement of the frontal region in individuals who develop PTSD.

On the other hand, the results also demonstrated lack of evidences of alterations in the frontal and limbic volumes in PTSD group compared to resilient police officers and controls.

Literature remains contradictory about neurobiological findings in PTSD. Previous studies have found reduced volume and gray matter of hippocampus and amygdala[31,32] related to PTSD. We previously observed that enlargement of hippocampus and amygdala was related to early trauma in subjects exposed to urban violence[1] which corroborates to the findings of Kuo *et al.*[33] that observed larger amygdala volumes among patients with PTSD with a positive correlation between early trauma and severity of adult trauma exposure. However, no volumetric differences in these structures were found in this study.

Despite our results regarding to the volume of brain structures did not reach statistical significance, others studies that investigated ACC volumes in patients with PTSD using MRI have yielded conflicting findings. For instance, one study using the conventional manual tracing method found significant volume reductions in the pregenual, but not dorsal, ACC[34]. A voxel-based analysis found gray matter volume reductions in the dorsal ACC among patients with PTSD[35]. Additionally, no differences were found in ACC volume between patients with acute PTSD and healthy subjects; however, structural dissimilarities were reported[35].

Few studies have assessed cortical thickness in PTSD. Corbo *et al.*[36] found a positive association between thickness of the left posterior cingulate/paracentral area and PTSD symptoms severity in veterans exposed to early trauma. On the other hand, this association was negative in the veterans without history of trauma in childhood[37]. Woodward (2009), also investigated the cortical thickness in adult combat-related PTSD and found thinner cortex in participants with PTSD at superior temporal cortex in comparison with healthy controls[37]. The study of Kuhn reported a reduction of cortical thickness of right medial orbitofrontal cortex negatively associated to trait anxiety in a healthy sample[38].

It has been suggested that the neurobiology of PTSD involves circuitry pathology, rather than implication of a single brain structure. In patients with PTSD, the default mode network, a set of structures including the medial prefrontal cortex and the posterior cingulate cortex (believed to be more "active" during the resting state) is believed to be affected by the pathology underlying the disorder[39]. Specifically, the resting-state functional connectivity of the posterior cingulate cortex, perigenual anterior cingulate cortex, and the right amygdala is associated with current PTSD symptoms, whereas functional correlation with the right amygdala is predictive of future PTSD symptoms[40]. There is also evidence using diffusion tensor imaging that white matter structural integrity in the cingulate bundle is compromised in PTSD patients compared with that of healthy individuals[41]. Therefore, in addition to functional impairment of the amygdala, mPFC and ACC, functional connectivity may be disrupted in PTSD[1].

Strengths and limitations

The primary strength of the current study is that the sample was well selected: we used paired groups, including only males, excluded those with alcohol abuse, and recruited subjects from the same site.

Secondly few studies have investigated morphometric brain alterations in police officers related PTSD and the result of this study may contribute to the understanding of PTSD in occupations with high stress levels.

This study has a few limitations that should be noted: first, the cross-sectional study design precludes determination whether the observed changes are cause or consequence of PTSD; secondly, the sample size in the present study was not sufficiently large to expand multivariate analysis.

Conclusions

Our results suggest that police officers with PTSD has reduce cortical thickness in prefrontal area compared to resilient police officers and healthy controls. This finding adds that the prefrontal region may be affected in police exposed to traumatic situations. Since this is an area involved in cognitive functions such impairment may have direct implications on the performance of this profession. Also, the results demonstrated lack of evidences of alterations in the frontal and limbic volumes in PTSD group compared to resilient police officers and controls.

However, these results need to be confirmed by studies with larger samples and different methods. Moreover, ours results compared to literature suggested that neuroimaging findings in PTSD is heterogeneous, and multiple factors (including individual factors) are related to this disorders.

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Contributors

There are no contributors to declare.

Conflict of interest

The authors report no financial or other relationship relevant to the subject of this article.

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Cognitive impact in children with "benign" childhood focal epilepsy with centrotemporal spikes

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Abstract

Background: Cognitive alterations are associated with benign childhood focal epilepsy with centrotemporal spikes (BCECTS) including aspects of executive functions. **Objectives:** This study presents the performance profile on attention and executive function tests of fifty-eight children (BCECTS, n = 30 and controls, n = 28) aged 8-13 years. **Methods:** The following tools were employed: Vocabulary and Block Design subtests from the Wechsler Intelligence Scale for Children III, Stroop Test, Modified Card Sorting Test, Controlled Oral Word Association – FAS and Tower of London. **Results:** Children with BCECTS presented average IQ measure, although their performance was statistically worse when compared to the control group. Children with BCECTS showed significantly lower performance compared to the control group in the following variables: total number of recollected words on the oral fluency test, total number of categories, categorization effect and total number of errors in MCST; and execution time for the Stroop Test Card 1. After controlling for the IQ effect, the total number of errors in the MCST did not show any significant difference between the groups. **Discussion:** Children with BCECTS showed lower performance in attention and executive functions when compared to healthy children. The results suggest that the concept of "benign" BCECTS should be reconsidered.

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Keywords: Childhood epilepsy, cognition, executive function, attention, child psychiatry.

Introduction

Benign focal childhood epilepsy with centrotemporal spikes (BCECTS) is one of the most frequent epileptic syndromes in childhood. Given its favorable prognosis, with seizures generally ceasing near puberty with normalization of electroencephalogram (EEG), neuropsychological evaluation was usually not considered. However, reports on cognitive disturbances presented by children with BCECTS have challenged the concept of favorable prognoses. Executive and attentional deficits[1], related to daily activities and proper social relationships have been previously described[1-11], including reading disabilities, sustained attention deficits, selective attention deficits, divided attention deficits, visuomotor and behavior difficulties.

The sustained attention deficits may be related to right-sided epileptiform activities in BCECTS, interfering in the right hemisphere function of sustaining attention. Attention is involved in cognitive functions and enables access to memory, sensory stimuli and motor responses.

These functions are acquired gradually during childhood and adolescence[12], progressively providing the child with the abilities to initiate, persist and accomplish tasks[13]. This study aims to investigate the performance profile of children with BCECTS by using neuropsychological tests that evaluate cognitive domains such as attention and executive functions and compare them to the performance of children with no neurological disturbances. We compared the differences in attention and executive functions between the performance of children with BCECTS and children without epilepsy.

Methods

Participants

Fifty-eight children aged between 8 to 13 took part of this study. Thirty children fulfilled the clinical and electroencephalographic criteria for BCECTS, according to the International League Against the Epilepsy (ILAE). All the children from the study group were assisted at the Child Neurology Clinic at the Hospital das Clínicas at the Universidade de São Paulo. The exclusion criteria were: estimated Intellectual Quotient (IQ) < 70; neuroimaging abnormalities; clinical disorders interfering with cognitive abilities; diagnosis of attention deficit hyperactivity disorder; and medical treatment for psychiatric and/or other central nervous system (CNS) disorders (except primary headache).

The control-group was represented by twenty-eight children according to demographic variables: age, gender, schooling and socio-economic levels, and selected among students in São Paulo city public schools. The exclusion criteria were the same employed for BCECTS children, in addition to the lack of complaints regarding learning difficulties. The groups were similar according to gender, age, schooling and socio-economic status.

Procedure

All children with BCECTS were submitted to a neurological evaluation and complementary exams, neuroimaging, cranial tomography (CT) or cranial magnetic resonance (MR) and EEG. Both study and control groups were submitted to the same neuropsychological evaluation.

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A questionnaire assessing the socio-demographic data was applied to the responsible informants. In order to check for hand preference, the child was given a pencil and a sheet of paper and asked to write his/her name. The hand spontaneously chosen to accomplish the task was recorded. The study was approved by the Ethics Committee of the University of São Paulo Medical School and written informed consent was obtained from respective responsible persons.

Measures (neuropsychological evaluation) and instruments

Intellectual efficiency: short form of the Wechsler Intelligence Scale for Children Third Edition[14,15], i.e., Vocabulary and Block Design subtests sum of the scaled scores for the calculation of estimated IQ[16].

Attention and executive functions: *Modified Card Sorting Test*[17], to evaluate the executive functions of cognitive flexibility, categorization ability and attention errors in the strategy for action; *Controlled Oral Word Association* – FAS[18] used as a measurement of phonemic verbal fluency; *Victoria Stroop Test*[19,20], to evaluate selective attention and mental flexibility; Tower of London[21] as a measurement of the executive planning function.

Statistical analysis

The results were analyzed with the statistical package STATA/SE version 11 for Windows. The chi-squared test for categorical variables and the T-test for numerical variables analysis were performed to verify the differences between control and study groups concerning the socio-demographic variables and the tests scores. When the groups presented different variances, the unequal variance t-test was used and if the groups presented equivalent variances, the t-test for equal variances was chosen. The differences between the control and study groups concerning the estimated IQ were also evaluated by the t-test. Further analyses were made controlling for the IQ measure to verify the significance of the cognitive variables. In order to test the influence of the estimated IQ in each test score presenting difference (dependent variables) between the groups (independent variable), the covariance analysis (ANCOVA) was used, isolating the IQ interference (covariable) and checking if the difference between the groups persisted. Furthermore, the relationship between the estimated IQ and the scores of the tests for attention and executive function was verified by Pearson correlation. The significance level established was $P \leq 0.05$.

Results

Fifty-eight children were evaluated (32 boys and 26 girls) between the ages of 8 and 13 (average age = 10.3 SD = 1.7), all of them from public schools in the city of São Paulo. Among these, thirty children (18 boys and 12 girls) with an average age of 10.5 (SD = 1.7) and diagnosed with BCECTS, represent the study-group and twenty eight healthy children (14 boys and 14 girls) with an average age of 10.11 (SD = 1.7) represented the control-group.

Regarding the laterality of the epileptiform activity in the EEG, ten children (70% male) presented left-sided discharges, 9 children (78% male) right-sided discharges and eight children (75% female) presented bilateral discharges. Regarding the use of anticonvulsants, fourteen children (71% male) were not taking medication while thirteen (62% female) were under medication, of which twelve were under monotherapy and only one under polytherapy. Of the 30 children, three showed no epileptiform activity on EEG.

The comparative statistical analysis between the study and the control groups showed that the groups were homogeneous regarding socio-demographic variables.

Intellectual efficiency

The comparison between the estimated IQ in both groups showed a significant difference between the means (p = 0.013) and a better efficiency in the control group (mean = 112.28; SD = 2.20) in contrast to the study group (mean = 103.13; SD = 2.76) as shown in Table 1. The analysis of the relationship between the estimated IQ and the efficiency in the tests showed significant associations only for some of the test scores. Also, despite presenting a weak correlation, the IQ results were positively correlated with the total number of words in FAS (rho = 0.392).

Attention and executive functions

Modified Card Sorting Test

The groups were statistically different when comparing the number of categories score (p = 0.007), categorization efficiency (p = 0.007) and total errors (p = 0.019) revealing a better performance of the control-group, as shown in Table 1. There were no significant difference in the number of perseverative errors and failure to maintain set.

Controlled Oral Word Association – FAS

The analysis of the results revealed significant difference (p = 0.0004) between the groups for the Verbal Fluency test with a better performance of the control group as shown in Table 1.

Victoria Stroop Test

The analysis of the execution time in boards 1 and 3 and errors in board 3 as well as time of board 2 in the Stroop test – Victoria version showed significant differences only for the time of board 1 of the test (p = 0.029).

Due to the fact that one subject of the study group could not read, therefore could not run the Cards 1 and 2, a separate analysis was conducted for this test. It is presented in Table 1.

Table 1. Mean (SD) neuropsychological test results for the study group and control group

Measure	BCECTS	Control Group	*p*
*IQ	103.13 (15.12)	112.28 (11.68)	0.013
*MCST – No. of categories	3.8 (1.64)	4.85 (1.17)	***0.007***
*MCST – Categorization efficiency	23.86 (11.33)	31.75 (10.20)	***0.007***
*MCST – Total errors	16.36 (7.58)	11.5 (7.79)	***0.019***
*MCST – Perseverative errors	4.16 (3.21)	2.82 (3.25)	0.119
*MCST – Set loss	0.67 (0.08)	0.67 (0.94)	0.510
*F.A.S.	16.93 (6.54)	23.5 (6.77)	***0.0004***
**Stroop Test I	20.17 (6.93)	16.82 (3.92)	***0.029***
*Stroop Test II	25.56 (7.59)	24.35 (7.73)	0.461
**Stroop Test III	36.89 (2.73)	34.71 (1.92)	0.519
**Stroop Test III errors	0.62 (1.11)	0.32 (0.47)	0.193
*Tower of London – total score	28.46 (4.00)	20.03 (3.31)	0.111
*Tower of London – extra attempts	6.6 (3.05)	5.57 (2.94)	0.198
*Tower of London – planning time	6.79 (5.13)	5.09 (3.68)	0.156
*Tower of London – mean execution time	24.52 (12.44)	19.65 (8.65)	0.091

* T-test for equalvariances. ** T-test for unequalvariances.

Tower of London

There were no significant differences for the total score, number of extra attempts, mean time of planning and execution between both groups. The values are described in Table 1.

Differences between groups in attention and executive function tests after isolating of the IQ interference

ANCOVAs of the group effect for the scores in Stroop Test, MCST and FAS setting estimated IQ as a covariant revealed significant

differences for most of the considered tests, except for the Total errors score in the MCST, as shown in Table 2.

Table 2. Result of ANCOVAs on the group effect over the scores in Stroop, MCST and FAS tests setting estimated QI as covariant

Test	Variable	F	*p*
Stroop	Execution time for board	4.48	***0.039***
MCST	No. of categories	5.09	***0.028***
	Categorization efficiency	4.98	***0.030***
	Total errors	3.70	0.060
FAS	Recollected words with the letters F, A and S	8.66	***0.005***

Discussion

This study aimed to verify the performance obtained by children with benign focal epilepsy in childhood and children without epilepsy in neuropsychological tests of attention and executive functions. Studies have shown an association between neurological disorders and cognitive deficits[1-10].

Although children with BCECTS presented average levels of estimated IQ, their performance was significantly lower in specific attention and executive functions tasks compared to that obtained by the control group. This result is similar to the ones presented by other studies[2,5,10,22-25]. It is noteworthy that most of these studies used all or at least eight of the Wechsler Intelligence scale subtests for the calculation of the total IQ, while we used only two subtests (Block Design and Vocabulary) for the estimated IQ calculation. The choice for the short form to estimate intellectual efficiency did not compromise the analysis of results because it took into account the reliability of both subtests as well as its correlation to the Global Scale of the WISC-III. Both Vocabulary and Block Design subtests present a high correlation with the global scale and provide good measurements to evaluate general intelligence[14,16]. On the other hand, some authors did not show any differences between the IQ of BCECTS children and children in the control groups[1,2,6,9,23,26-28].

This study showed that children with BCECTS presented significantly worse performance than the control group in executive functions of cognitive flexibility, categorization ability and attention errors in the strategy for action, in phonemic verbal fluency and selective attention and mental flexibility. Notwithstanding, the performance in executive planning function did not present discrepancy in comparison with the control group.

The results from the Victoria Stroop evaluating selective attention and mental flexibility suggests that children with BCECTS present an adequate ability for selective attention and mental flexibility. However, slower performance in naming colors, which correlates with previous studies finding that children with BCECTS perform with reduced speed in attention tasks, was also observed[29]. However, studies using other versions of the Stroop test showed different results. Chevalier *et al.*[4] found a significantly higher number of errors made by children with BCECTS with the Incongruous card and no difference between the groups concerning the performance with the Control card. Baglietto *et al.*[5] showed execution time significantly higher in the study group compared to the control group, in addition to a higher number of errors in the first two cards. In a more recent study, the discrepancy among the results can be explained by the use of different modalities of the Stroop test. However, these results suggest that the deficient performance of children with BCECTS is more likely related to the precision (measured by the total of errors) than to the response speed.

Difficulties in planning and problem solving as assessed by the Tower of London were not found in our study, contrary to previous data showing worse performances for the children with BCECTS compared to the control-group[1].

The Phonemic Fluency Test (*Controlled Oral Word Association*) seems to be sensitive to the presence of BCECTS. Studies showed that children with BCECTS present worse performances in phonemic verbal fluency tasks[1,22] even after total remission of seizures and EEG normalization[5,9,10]. Such results agree with the results obtained in this study and seem to confirm the presence of alterations in the verbal fluency in children with BCECTS.

Finally, although we used the Modified WCST, differences in performance in the MCST for executive functions of cognitive flexibility, categorization ability and attention errors in the strategy for action were verified. The comparison between groups revealed worse performance in number of categories, categorization efficiency and total number of errors scores for children with BCECTS, however no significant difference related to perseverative errors and inability to maintain the set. Our results partially agree with the results presented by Hoie *et al.*[22], which showed lower performance of children with BCECTS in all WCST scores compared to the control-group.

Although our study has showed worse performance of children with BCECTS in executive functions of cognitive flexibility, categorization ability and attention errors in the strategy for action, in phonemic verbal fluency and selective attention and mental flexibility, the impact of the intellectual functions in the performance of these tests must be considered, since there were differences in the estimated IQ between the groups. The analysis of correlations between the tests and the estimated IQ showed weak or null correlations between some of the tests' scores. However, studies with healthy children showed that the estimated IQ influences the performance on executive functions tests such as WCST and the Phonemic Fluency Test[30]. This issue is usually neglected in studies[5,9,23,25,27] or is approached as an attempt to match the study and control groups according to the participants IQ[8,10,11,22,29].

This study has some limitations. One of them is that we did not assess the possible influence of the frequency of epileptiform activity on cognitive functioning, as many studies have linked the higher frequency of discharges with an increased cognitive loss[2,22,25]. The fact that previous studies used different instruments for the assessment of cognitive functioning, and that only a few of them included executive functions instruments, do not allow further comparisons. In addition, a possible limitation is that psychiatric symptoms were not actively asked.

Conclusion

Our findings show that children with BCECTS present impaired categorization ability, worse performance in color naming and deficits in verbal fluency. These cognitive abnormalities are not influenced by the intellectual capacity. Another important aspect is that, despite evidence that BCECTS do impact on cognition, we must consider that nearly half of the sample was taking antiepileptic drugs, which probably plays an influence the cognition of children.

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Ayahuasca: what mental health professionals need to know

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Abstract

Background: Ayahuasca is a psychoactive ethnobotanical concoction that has been used for decades by indigenous groups of the Northwestern Amazon and by syncretic religious organizations for ritual and therapeutic purposes. In the last two decades, it is being used worldwide in evolving practices. Ayahuasca seem to therapeutic effects, but controlled studies are lacking. Moreover, its safety and toxicity are not completely understood. **Objectives:** To present an overview of the effects of ayahuasca based on the most recent human studies. **Methods:** Narrative review. **Results:** Ayahuasca administration in controlled settings appears to be safe from a subjective and physiological perspective, with few adverse reactions being reported. More frequent adverse reactions occur in non-controlled settings. Prolonged psychotic reactions are rare and seem to occur especially in susceptible individuals. Ayahuasca showed antidepressive, anxiolytic, and antiaddictive effects in animal models, observational studies, and in open-label and controlled studies. **Discussion:** Ayahuasca administration in controlled settings appear to be safe. Moreover, ayahuasca seem to have therapeutic effects for treatment-resistant psychiatric disorders that should be further investigated in randomized controlled clinical trials. However, medical complications and cases of prolonged psychotic reactions have been reported, and people with personal or family history of psychotic disorders should avoid ayahuasca intake.

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Keywords: hallucinogens, ayahuasca, dimethyltryptamine, psychopharmacology, mental health.

Introduction

Ayahuasca (from the Quechua *Aya* – "soul", "dead spirit"; and *Waska* – "rope", "vine") is a natural psychoactive concoction used for centuries by indigenous groups from Northwestern Amazonian countries such as Brazil, Peru, Colombia and Ecuador for ritual, religious, and therapeutic purposes[1]. Ayahuasca has dozens of indigenous names, such as *Yajé*, *Kamarampi* and *Huni*, and is also used by the nonindigenous *mestizo* populations of these countries. Syncretic religious organizations that originated in Brazil in the 1930-1960's such as the *Santo Daime*, *Barquinha*, and *União do Vegetal* (UDV) use ayahuasca as a sacrament, where is known as *daime*, *vegetal* or *hoasca*. In the last 25 years, these groups spread from Brazil to Europe, the United States, Asia and Africa[2,3].

Botany, chemistry and mechanism of action

The main ingredient of ayahuasca is the vine *Banisteriopsis caapi* (Figure 1), which contains β-carbolines alkaloids such as harmine, tetrahydroharmine (THH) and harmaline (Figure 2)[4]. The vine is commonly used in combination with lots of different plants depending on the purpose of the ceremony[1,2,4]. In the Western world, ayahuasca is known to be the mixture of the vine *B. caapi* with the leaves of *Psychotria viridis* (Figure 1) or from the vine *Diplopterys cabrerana*, that contain the tryptamine hallucinogen dimethyltryptamine (DMT) (Figure 2). This probably happened because of the international expansion of ayahuasca by the Brazilian ayahuasca churches and also by South American shamans[4]. The beverage is usually prepared by the prolonged decoction of these plants and has a brownish color (Figure 1).

DMT is not active when ingested alone because it is metabolized in the gastrointestinal tract and in the liver by monoamine oxidase A (MAO-A). However, the β-carbolines in the vine reversibly inhibit MAO-A and allow DMT to reach the Central Nervous System[4-6]. The main mechanism of action of DMT appears to partial agonism on serotonergic 2A (5-HT_{2A}) receptors expressed on layer V cortical neurons, a process that also seems to involve metabotropic glutamate receptors (mGluR)[7,8]. DMT is an endogenous compound, although its physiological functions are not known[9,10]. There is some evidence that endogenous DMT could act as a neurotransmitter on sigma receptors[11,12], but human studies suggest that the psychoactive effects of classic/serotonergic hallucinogens such as lysergic acid diethylamide (LSD), psilocybin and DMT are mainly mediated by the 5-HT_{2A} receptor[8,13-15].

Figure 1. Ayahuasca preparation (*from right to left*): Banisteriopsis caapi; Psychotria viridis; ayahuasca decoction; ayahuasca prepared and bottled. Photographs by Rafael G. dos Santos.

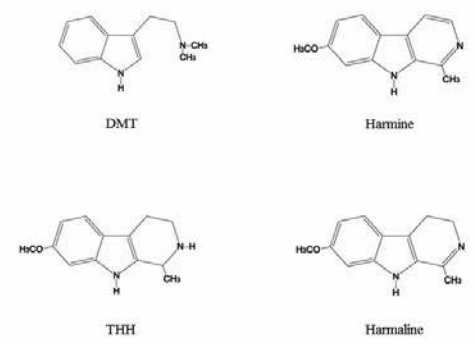

Figure 2. Chemical structures of the ayahuasca alkaloids: dimethyltryptamine (DMT); harmine; tetrahydroharmine (THH); and harmaline.

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Subjective effects

The subjective effects of ayahuasca (and other hallucinogens) are difficult to describe and measure[16,17]. Experimental studies with healthy volunteers and longitudinal studies with experienced ayahuasca users show that these subjective effects include increases in introspection, serenity, and in experiencing memories with autobiographical content, positive mood, affect, and wellbeing, altered perception of colors and sounds often accompanied by synesthesia, and also mystical-like and religious experiences (Table 1)[16,18-21]. In the clinical studies, the variable that measure volition (or the capacity to interact with the environment) is only slightly affected and subjects usually rate the experience as "good effects" and "liking", while the ratings on "drunken" and "bad effects" are the variables with the lower scores[5,19]. Administration of two consecutive doses of ayahuasca four hours apart does not seem to induce tolerance or sensitization to the psychological effects[19]. Dysphoric reaction are less frequent and my include anxiety, fear, and psychotomimetic symptoms, but these effects are generally transient and usually do not need medical intervention[16,18,20,21]. Prolonged dysphoric or psychotic reactions in controlled contexts (experimental or ritual) are rare and seem to occur mostly among individuals with a personal or family psychiatric history, although cases where there was no personal of family antecedent have also been reported (Table 1)[22,23].

Table 1. Subjective and physiological effects of ayahuasca

Positive subjective effects (acute)[16,18-21]
Introspection
Serenity
Memories with autobiographical content
Positive mood, affect and wellbeing
Altered perception of colors and sounds (synesthesia)
Mystical/religious experiences
Negative subjective effects (acute/subacute)[16,18,20-22]
Anxiety, panic, and fear
Psychotic symptoms (less common)
Negative subjective effects (prolonged)[23,59]
Psychotic reactions (rare)
Physiological effects (acute)[5,14,18,19,21,24]
Moderate increases in blood pressure and heart rate
Mydriasis
Increases in body temperature
Increases in prolactin, cortisol, and growth hormone secretion
Increases in natural killer cells levels
Decreases on CD3 and CD4 lymphocyte levels

Physiological effects

Experimental studies with healthy volunteers showed that administration of a single ayahuasca dose induced moderate and transient (less than 24 hours) increases in blood pressure and heart rate, on prolactin, cortisol, and growth hormone (GH) levels, on pupil size and body temperature, and in natural killer (NK) cells levels. Ayahuasca administration also induced transitory decreases on lymphocyte (CD3 and CD4) levels (Table 1)[5,14,18,19,21,24]. Two consecutive doses of ayahuasca did not induce tolerance or sensitization for most physiological variables, but a trend to lower cardiovascular activation was observed, and tolerance was reported to GH secretion[19].

Neurophysiological and neuroimaging studies

The effects of ayahuasca on brain dynamics were assessed in healthy volunteers using electroencephalography (EEG), single-photon emission computed tomography (SPECT), and structural and functional magnetic resonance imaging (MRI and fMRI, respectively).[21,25,26] Results from EEG studies are inconsistent and sometimes conflicting (Table 2)[26]. For instance, although reduced power in the alpha, delta and theta bands was observed in some studies[14,27-29], it was not reported in others[19,24]. Likewise, increased power in the beta band was reported in some studies[19,24,27] but not in others[14,28,29]. Increased gamma power was not reported in most studies[26,29]. Regarding other serotonergic hallucinogens, reductions in alpha power were also observed in studies with psilocybin and LSD, an effect that seem to underlie the visual effects of these compounds through their agonism at cortical 5-HT_{2A} receptors[14,26,30,31].

In the last 10 years, the neural basis of the effects of ayahuasca have been investigated using SPECT, MRI and fMRI (Table 2)[21,25,26]. A SPECT study of acute administration with healthy volunteers showed that ayahuasca increased bilateral activation of the anterior insula/inferior frontal gyrus, right hemisphere activation of the anterior cingulate cortex (ACC) and frontomedial cortex, and left hemisphere activation of the amygdala and parahippocampal gyrus[32]. These brain areas are involved in the modulation of emotions, internal feelings and sensations, perception and self-awareness. An fMRI study using an imagery task showed that ayahuasca not only increased activation of the parahippocampal and frontopolar cortices, but also of the cuneus and lingual gyrus and retrosplenial cortex[20]. Interestingly, during the imagery task ayahuasca increased activation of the primary visual area in a manner similar to the activation levels of seeing a natural image with the eyes open. This effect may be one explanation to the so vivid and "real" effects of the ayahuasca experience. Moreover, a significant correlation was observed between cortical area BA17 activation and BPRS (Brief Psychiatric Ratings Scale) data. Finally, ayahuasca reversed fronto-occipital connectivity, what seems to mean that the visions induced by ayahuasca may be initiated in the primary visual cortex. The difference between this study and the SPECT study, where visual areas were not activated, may be determined by the task since in the fMRI study subjects were instructed to do tasks related with visual stimulation and/or imagery.

Table 2. Effects of ayahuasca on the human brain

EEG (acute)[14,19,24,26-29]
Reduced power in the alpha, delta and theta bands
Increased power in the beta and gamma bands
Neuroimaging (acute)[20,32,33]
Increased activation of frontal and limbic areas (parahippocampal gyrus, insula, amygdala, visual and frontal cortices, ACC) (SPECT, fMRI)
Increased activation of the primary visual area during an imagery task (fMRI)
Decreased activation of key hubs of the DMN (PCC, mPFC, precuneus) (fMRI)
Decreased functional connectivity within the PCC/precuneus (fMRI)
Neuroimaging (long-term)[34]
Cortical thickening in precentral gyrus and ACC (CT)
Cortical thinning in the mesotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, PCC, and superior occipital gyrus (CT)

ACC: anterior cingulate cortex; CT: cortical thickness; DMN: default mode network; EEG: electroencephalography; fMRI: functional magnetic resonance imaging; mPFC: medial prefrontal cortex; PCC: posterior cingulate cortex; SPECT: single-photon emission computed tomography.

A resting-state fMRI study showed that ayahuasca decreased activation of key hubs of the default mode network (DMN), including the posterior cingulate (PCC) and the medial prefrontal cortices and the precuneus[33]. Furthermore, ayahuasca decreased functional connectivity within the PCC/precuneus. Studies with psilocybin and LSD also show that these drugs produce their effects by modulating brain structures involved in emotional processing and in memory and self-awareness, such as the parahippocampal gyrus, visual and frontal cortices, ACC and PCC, insula and amygdala[15,21,25,26,30,31].

An MRI study assessing cortical thickness in long-term ritual ayahuasca users showed that regular use (average 5.3 years, range

2-13 years) was associated with cortical thinning in the mesotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, PCC and superior occipital gyrus. On the other hand, increased cortical thickening was observed in precentral gyrus and ACC[34]. Importantly, these structural characteristics were not associated with increased psychopathology among ayahuasca users. Moreover, cortical thinning in the PCC was inversely correlated to age of onset and intensity of prior ayahuasca use and to core on a "self-transcendence" scale. Ayahuasca users also scored better in some neuropsychological tasks related with executive functions compared to controls that were were matched in fluid and verbal IQ, age and gender, among others variables.

Therapeutic potentials

Ayahuasca has been traditionally used by indigenous groups and *mestizo* populations for getting in contact with the sacred or supernatural world, for political and artistic purposes, and also for healing[1,2,35]. Nevertheless, the worldview and culture of these populations, and the way they understand and use ayahuasca, are often different from those of nonindigenous populations. Thus, it is not always possible to translate a therapeutic effect described in a traditional context to the concepts of diseases that are shared in the nonindigenous culture. However, over the last 30 years, an increasing number of anecdotal reports and experimental evidence has accumulated suggesting that ayahuasca may have therapeutic potentials in the treatment of difficult-to-treat psychiatric disorders such as drug dependence and anxiety and mood disorders[21,25,36].

Preclinical studies and observational studies of ayahuasca users suggest that ayahuasca has anxiolytic, antidepressive and antiaddictive effects (Table 3)[21,34,37-40]. Regarding anxiolytic and antidepressive effects in humans, a double-blind, placebo-controlled studies with nine experienced ayahuasca users showed that a single ayahuasca dose was associated with less panic symptoms and reduced hopelessness[41]. An open-label study by our group showed that a single ayahuasca dose was associated with rapid and sustained reductions in anxiety and depressive symptoms in 17 patients with treatment-resistant major depressive disorder[42]. The anxiolytic and antidepressive effects were observed already in the first hours after ayahuasca intake and remained significant for 21 days. Moreover, SPECT imaging showed that ayahuasca administration was associated with increased blood perfusion in the left nucleus accumbens, right insula, and left subgenual area, brain regions associated with emotional processing and the therapeutic effects of traditional antidepressants. These results were partially replicated by our group in a recent parallel arm, double-blind, randomized, placebo-controlled trial in which 35 patients with treatment-resistant major depression received a single dose of ayahuasca or placebo[43]. Compared with patients that received placebo, patients that received ayahuasca had lower depressive symptoms seven days after drug administration. These results are in agreement with recent studies showing anxiolytic and antidepressive effects of serotonergic hallucinogens such as psilocybin and LSD[36,44-47]. Regarding antiaddictive effects in humans, although there are no controlled trials, non-controlled studies in therapeutic and ritual settings suggest that ayahuasca use may have antiaddictive effects[48,49]. Moreover, studies with psilocybin and LSD also suggest that hallucinogenic compounds that act as 5-HT_{2A} agonists have antiaddictive effects[36,50,51].

Table 3. Main therapeutic potentials of ayahuasca

Evidence from uncontrolled studies[42,48,49]
Anxiolytic
Antidepressive
Antiaddictive
Evidence from controlled studies[41,43]
Anxiolytic
Antidepressive

Safety and toxicity

Classic or serotonergic hallucinogens including LSD, psilocybin, mescaline and DMT are considered drugs with low physiological toxicity that can be safely administered in controlled settings, including both ritual and experimental/clinical contexts[8,17,25,26,36,52,53]. Recent human studies involving acute administration of LSD and psilocybin to healthy volunteers and to patients with drug dependence or anxiety and mood disorders show that these drugs induce significant subjective and physiological effects that are transient, well tolerated, and apparently associated with therapeutic effects[13,15,30,31,44,47,50,51,53].

In the specific case of ayahuasca, in the last 30 years a few observational studies of long-term ayahuasca users were conducted, and their results suggest that ritual use of this substance is not associated with increased psychopathology or cognitive deficits[21,34,37,38,54-57]. Moreover, a clinical evaluation of long-term (at least 10 years) ritual ayahuasca users, including blood analysis and assessments of cardiovascular, endocrine, immunological, hepatic and renal function, did not show any clinically relevant findings compared to a control groups without ayahuasca use[58]. However, in these studies the samples are mostly composed of experienced users well adapted to the effects of ayahuasca and that are long-term members of organized religious groups. Thus, these participants may have specific characteristics that could limit the generalization of the results. Moreover, although psychiatric complications such as anxiety and psychotic reactions associated with ritual ayahuasca are rare, they may occur, especially among vulnerable individuals[21-23]. In the ritual contexts of ayahuasca use, individuals with a personal or family history of psychotic illness or that are currently with psychotic symptoms are generally not allowed to use ayahuasca or are advised that they should avoid it[23,59]. This could explain at least in part the low incidence of psychotic reactions among ritual ayahuasca users, and show that individuals with a personal or family history of psychotic illness or nonpsychotic mania should avoid ayahuasca use[23,59].

Regarding experimental and clinical studies of acute ayahuasca administration, several studies performed in the last 15 years with both healthy volunteers and clinical populations consistently show that ayahuasca can be safely administered in the laboratory[5,14,18-21,24,27-29,32,33,36,41-43]. The most common adverse reactions to ayahuasca are nausea and vomiting, which is often accompanied by other somatic-dysphoric effects such as feeling heat and/or cold and gastrointestinal discomfort (Table 4)[18,19,24,42,43]. In ritual contexts, vomiting is not interpreted as negative, being understood as a cleansing process[2,16,35]. In early laboratory studies using freeze-dried ayahuasca, vomiting was observed in four of 53 ayahuasca administrations (7.5%)[5,18,60]. In a subsequent study by the same group involving the administration of two consecutive ayahuasca doses four hours apart, only nine of the 17 enrolled volunteers completed the trial, and five of them were excluded from the trial due to vomiting (self-induced in one case), since it was a pharmacokinetic study[19]. In our open-label study involving the administration of a single ayahuasca dose to 17 patients with treatment-resistant major depressive disorder, vomiting was the only adverse effect reported and occurred in 47% of the volunteers[42]. In our subsequent randomized controlled trial, the most common adverse reaction were nausea (71%), vomiting (57%), transient anxiety (50%), transient headache (42%), and restlessness (50%)[43].

As discussed above in the topic on the physiological effects of ayahuasca, acute administration of this substance may induce transient and moderate increases in blood pressure and heart rate, in both healthy volunteers and depressed patients[5,18,19,42,60]. However, since the cardiovascular effects of ayahuasca were only assessed in studies of acute administration to young volunteers without cardiovascular complications, the long-term effects of continuous ayahuasca intake and its use by older individuals or by people with hypertension or other cardiac disorders are not known. Although the above-mentioned study among experienced ayahuasca user did not find evidence of increased incidence of cardiovascular diseases in

this group compared to the control group, seven electrocardiographic alterations were found in the ayahuasca group (one case of right branch bundle block, one of left branch bundle block, one of diffuse ventricular repolarization disturbance, and four of sinusal bradycardia), while among the controls there was only a single case of sinusal bradycardia[58]. Moreover, although these alterations were not clinically relevant, this is only a single study, and a recent study by our group showed that ayahuasca altered some structural parameters of the rat aorta[61]. Thus, more studies are needed to better clarify the cardiovascular effects of ayahuasca, especially the long-term effects.

Although ayahuasca administration in the experimental or clinical setting may induce anxiety and psychotic/psychotomimetic or dissociative symptoms, these effects are usually mild and short-lived, and most participants consider the experience pleasant[18,20,21,42,43,60]. Its important to highlight that individuals with a personal or family history of psychotic illness or nonpsychotic mania are usually not enrolled in these studies, which could explain the absence of reports of prolonged dysphoric or psychotic reaction in the experimental and clinical settings[5,14,18-21,23,24,27-29,32,33,36,41-43,60]. These results are in line with experimental and clinical studies with other serotonergic hallucinogens such as LSD and psilocybin[13,15,30,31,36,44-47,50-53].

Limitations of the studies

Although the number of observational studies of long-term ayahuasca users and of studies involving ayahuasca administration to both healthy volunteers and clinical populations has increased over the last years, most of them share similar limitations that render their results preliminary and inconsistent. For instance, most studies of acute and subacute effects, both uncontrolled and controlled, had small sample sizes. Long-term studies usually had bigger samples, but some studies also had small samples. Moreover, several studies were open-label, observational, or had no control groups. Thus, it is difficult to affirm that ayahuasca had a causal role in the observed effects. In several studies where multiple comparisons were performed, there was no statistical correction for this, which could inflate false positive results by reporting variables that show positive results even when a large number of variables exist for small sample sizes. Another important limitation is that some of the subjective effects of ayahuasca were measured with questionnaires that did not have their psychometric qualities validated, which basically means that maybe they were not measuring what they say they were[62].

Despite these important limitations, many of the results seem to be consistent among different studies[21,25,26,36], and recent studies with other hallucinogenic compounds that also act as serotonin 5-HT_{2A} receptor agonists, such as psilocybin and LSD, further support these findings[8,25,26,36,53]. Nevertheless, it is important to highlight the fact that some of these studies share the same limitations as those observed in ayahuasca studies, especially regarding small sample sizes and lack of a double-blind design[31,45,50,51]. Therefore, future studies should be well designed. What we are observing in psychedelic research in general and in ayahuasca research in particular is that in the one hand, there are several studies that have published only preliminary results but that do not mention their most important limitations and that are even popularizing these results in the media, leading both the general public and the scientific community to conclusions that cannot be achieved from the original research. On the other hand, almost none of the findings obtained were replicated until the present moment. Thus, in many review papers assertions appear citing papers with preliminary research as if those assertions were already confirmed. Studies methodically well designed, data analysis performed with proper statistical analysis, and the limitations completely described are urgent needs to improve this research field, so that we can avoid falling into the criticism and lack of trust from the scientific community regarding the psychedelic research performed in the 1950-1970's[63].

Suggestions for future research

Besides the methodological issues commented above, there are other areas of ayahuasca research that could be explored. For instance, the antidepressive and anxiolytic effects of ayahuasca in patients with treatment-resistant major depressive disorder should be further explored in other clinical populations in randomized controlled trials with bigger samples and using different dosage schemes (multiple or repeated doses) to assess safety, tolerability, efficacy, and to compare to the results of single doses. Moreover, the antidepressive and anxiolytic effects of ayahuasca should be evaluated in other anxiety and mood disorders. For instance, recent studies with LSD and psilocybin for depression and anxiety in patients with life-threatening cancer reported promising results, and ayahuasca could also be evaluated in this clinical population[44,46,47]. Regarding drug dependence, although there is evidence from animal studies and from anecdotal reports and uncontrolled studies suggesting that ayahuasca has antiaddictive properties[21,38,40,48,49,54,57], no controlled trials were ever performed and they are urgent needed.

Another area that should be better investigated is related to the possible chemical interactions between ayahuasca and other compounds such as certain foods, recreational drugs, psychoactive plants, or medications in general. Some studies suggest that there is a risk of serotonin syndrome with the concomitant ingestion of ayahuasca and antidepressants or other pro-serotonergic drugs, but more studies are needed in this area[64,65]. Other area of research focus should be the health contraindications to ayahuasca use. For instance, there is no information regarding the possible effects of ayahuasca in people with cardiovascular disease, and more research is needed on the cardiovascular effects of chronic ayahuasca intake.

There is also a lack of information regarding the possible effects of ayahuasca (harmful or beneficial) on people suffering neuropsychiatric diseases such as epilepsy, Parkinson's disease and Alzheimer's disease, or in those with autoimmune and neuroinflammatory diseases[11,12]. In the specific case of Parkinson's disease, early evidence shows that harmine was used to treat symptoms of this disease in the late 1920s and early 1930s[66]. Evidence supporting this use has been recently reported in preclinical studies using *B. caapi* extract[67] and also in a double-blind, randomized, placebo-controlled trial in which *B. caapi* extracts improved motor function in these patients[68]. The benefits obtained by the use of *B. caapi* were more significant than the results showed by harmine alone, which may suggest and "entourage" effect that should also be considered in ayahuasca research. Probably, the different alkaloids present in the vine "cooperate" to produce a final effect more effective than the different compounds in their pure form and separately. Therefore, more research in this area is needed.

Recent reports suggest the possible role of harmine in neurogenesis[69]. Furthermore, it is known that DMT act as an agonist at 5-HT_{1A} receptors[8,70]. The activation of 5-H_{1A} receptors may be in the basis of neurogenesis in the hippocampus and in the prefrontal cortex and its activation seems to be in the basis of the antidepressant effects of antidepressive drugs[71].

Regarding adverse effects, a recent study from the United States showed that 538 calls related to ayahuasca use were reported between

Table 4. Main adverse reactions associated with ayahuasca intake

Physical symptoms (acute)[16,18-21]
Moderate increases in blood pressure and heart rate
Gastrointestinal discomfort
Nausea
Vomiting
Diarrhea (less common)
Restlessness
Headache
Psychological symptoms (acute/subacute)[16,18,20-22]
Anxiety, panic, and fear
Psychotic symptoms (less common)
Psychological symptoms (prolonged)[23,59]
Psychotic reactions (rare)

September 1, 2005 to September 1, 2015 to the American Association of Poison Controls Centers' (AAPCC) National Poison Data System (NPDS)[72]. Most cases involved acute intoxication in young male adults and were considered of major or moderate clinical significance, and included symptoms such as hallucinations, tachycardia, agitation, hypertension, mydriasis and vomiting. Importantly, 28 cases required endotracheal intubation, and there were four cases of cardiac arrest, seven of respiratory arrest, 12 of seizures, and three fatalities. Unfortunately, there is no detailed description of the cases, which makes it difficult to affirm that all of them were directly caused only by ayahuasca. Indeed, some of the mediatic and scientific descriptions of severe intoxications supposedly caused by ayahuasca could possibly be referring to the result of a combination of several factors, including the addition of more toxic plants to the ayahuasca preparation (such as some *Brugmansia* species) and the previous physical and mental health of the person drinking ayahuasca, including the medications being used by this person[73]. Moreover, it appears that such cases seem to be more common on countries where ayahuasca is not part of the local religious traditions (such as the United States), and seem to be less common in countries where ayahuasca is part of the culture (such as Brazil, Peru and Colombia)[72,73]. Furthermore, several of the incidents reported in South American countries involved North Americans or Europeans[72,73]. Maybe the tourism around ayahuasca is bringing to Amazonian countries foreigners with health problems that are not always screened by all people organizing ayahuasca rituals, and maybe some people organizing these rituals outside South America are serving ayahuasca to people that they do not know their previous health condition.

Regarding the incidence of prolonged dysphoric reactions to ayahuasca use, characterized by anxiety, panic, or psychotic symptoms, the research conducted so far in this area is limited to anecdotal evidence, case reports and case series, and should be further developed[22,23,59]. It seems that only a minority of individuals suffer such reactions, and in many of those cases these individuals had personal or family histories of psychiatric disorders[22,23,59]. This kind of reaction have not been reported in experimental and clinical studies with ayahuasca[21,23,36] and are also rare in the case of controlled administration of other hallucinogens[36,52,53]. It seems that carefully screening the volunteers to exclude individuals with some predisposition to psychotic disorders is an important measure to reduce the possibility of the occurrence of such cases[23,52,53]. Future research should focus on trying to better identity who are those individuals more prone to suffer a prolonged dysphoric or psychotic reaction to ayahuasca.

In the last 20 years, an increasing number of neuroimaging studies involving the administration of classic hallucinogens to humans has been conducted, and this area is still in full development[25,26]. Compared to other hallucinogens such as psilocybin, neuroimaging studies with ayahuasca are still small in number, but this picture should change in the near future since there is an increasing number of studies with ayahuasca[20,25,26,32-34,42]. Areas that are currently being investigated and that should be further explored include the study of the neural basis of the antidepressant and anxiolytic effects of ayahuasca and its effects on the default mode network (DMN), a network whose alteration may be related to diseases that go from autism to schizophrenia or depression, and on brain areas that regulate emotions, memory, and higher cognition including self-awareness and introspection[20,25,26,32-34,42]. Moreover, recent uncontrolled studies suggest that ayahuasca may increase mindfulness capacities and creativity[74-76] Thus, studies with improved methodologies that include controlled designs and neuroimaging could improve our understanding of this possible effects of ayahuasca and the possible association between them and the therapeutic properties of ayahuasca.

Finally, another area that should be better investigated is related to the individual effects of DMT and the β-carbolines. Indeed, recent studies suggest that endogenous DMT, through the sigma-1 receptor, could be involved in physiological processes such as immunity and inflammatory responses, and also tissue protection and regeneration[11,12]. The fact is that we still do not know what DMT is doing in our bodies, so this is a very interesting topic to further investigate[9,10]. Moreover, preclinical studies suggest that DMT and the β-carbolines have not only antidepressive, anxiolytic, and antiaddictive proprieties[39,40], but also neuroprotective and neurotrophic potentials[69,77-79]. For instance, a recent neuropsychological study in ayahuasca user suggested that ayahuasca may indeed improve cognition and have "nootropic" effect[80]. However, although the preclinical data on antidepressive, anxiolytic, and antiaddictive potentials of ayahuasca and its alkaloids has been replicated to some extend in preliminary observational and clinical studies in humans, with the exception of the neuropsychological study just commented, studies on possible neuroprotective and neurotrophic effects are still on the basic level. Future studies should further explore this area.

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Letter to the editor

The risk of initiating fluoxetine for motor deficits after ischemic stroke in patients with bipolar disorder

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Dear Editor,

In 2011, the fluoxetine for motor recovery after acute ischemic stroke (FLAME) trial described a significant improvement in motor deficits among patients who were prescribed fluoxetine while recovering from an ischemic stroke[1]. Following the publication of FLAME and similar trials[2,3], there is growing evidence that providers should consider prescribing a selective serotonin reuptake inhibitor for a patient who has experienced a stroke[4]. However, the psychiatric consequences or diagnostic contraindications of this therapy have not been discussed.

We examined the effects of initiating fluoxetine in a patient with bipolar 2 disorder following left posterior inferior cerebellar artery ischemic stroke. The patient's medical and psychiatric history, physical and neurological examinations, pertinent family history, social history, and laboratory data were used in our assessment and subsequent treatment of their condition. The patient's anonymity was maintained by withholding identifying information.

The patient was hospitalized for treatment of left posterior inferior cerebellar artery ischemic stroke roughly two weeks after stopping their home medications consisting of insulin, metoprolol, and lithium. While recovering from their stroke, the patient resumed taking metoprolol and insulin though refused lithium or another mood stabilizer. To treat residual symptoms of their ischemic stroke, fluoxetine 40 mg by mouth daily was initiated without a concurrent mood stabilizer. Soon thereafter, the patient developed symptoms concerning for hypomania: increased rate of speech, irritability, psychomotor agitation, tangential thought process, and reduced need for sleep. The patient's urine toxicology was negative for drugs of abuse, and aside from fluoxetine the patient had not been treated with medications associated with drug-induced mania. Though the patient refused medication to treat symptoms of hypomania, they agreed to discontinue fluoxetine. Over the course of multiple days, the patient's symptoms improved, and the patient did not require inpatient psychiatric treatment for acute stabilization.

We report that initiation of fluoxetine for motor recovery after ischemic stroke carries the risk of inducing hypomania in a patient with bipolar 2 disorder who is not taking a mood stabilizer. Fluoxetine is one of many medications that can induce symptoms of mania[5]. The risk of triggering medication-induced mania is heightened among patients with bipolar disorder[6-8]. Among patients with known bipolar disorder, treatment with an effective mood stabilizer or atypical antipsychotic is necessary prior to starting an antidepressant to mitigate the risk of triggering mania[9,10]. Providers should understand the benefits of conducting a psychiatric review of systems and appreciate the risks of prescribing fluoxetine following an ischemic stroke to patients with a history of bipolar disorder.

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Resolution of antipsychotic-induced amenorrhea using aripiprazole

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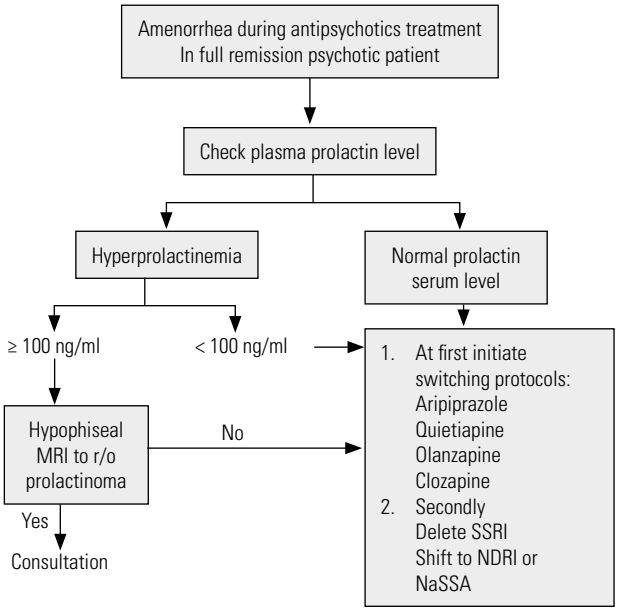
Dear Editor,

Antipsychotic-induced[1] amenorrhea is a serious concern among premenopausal women suffering from mental disorders. Among many women, menstruation is a symbol of femininity that indicates the ability to become pregnant naturally, or is a basis to determine if they are menopausal[2]. Some patients believe the lack of menstruation signifies menopause and contributes to emotional instability or aggravation of their mental disorder. Patients with amenorrhea often seek help from gynecologists to induce menstruation. Peuskens *et al.*[3] reported that amenorrhea occurred in 22-50% of women treated with antipsychotics. The prevalence of menstrual irregularities and amenorrhea is considered to be 15-97% in women receiving therapy for a psychotic disorder[4]. It is also common for patients to discontinue antipsychotics due to amenorrhea, which in turn triggers relapses.

I will discuss two cases here: a patient with schizoaffective disorder and another with bipolar I, manic episodes with psychotic features. Both patients achieved full remission of psychotic symptoms, but wanted to switch medications due to lack of menstruation and weight gain. Both patients were middle-aged women in their 40s, with multiple past records of discontinuing their medication that triggered relapses and led to hospitalization. Therefore, I prescribed aripiprazole to facilitate a gradual process of switching medications. Table 1 summarizes the history of past medications, medication switching process, and results of therapy for the two patients. Notably, amenorrhea does not only occur among patients with hyperprolactinemia, but also among premenopausal patients with normal blood prolactin levels, even when using multi-acting receptor targeted antipsychotics (MARTAs), which have an extremely low probability of causing amenorrhea.

Among antipsychotics, hyperprolactinemia is most commonly induced by sulpiride, amisulpride, risperidone, and paliperidone. Paparrigopoulos *et al.* found that the prevalence rate of hyperprolactinemia induced by amisulpride was 100%, and this was observed more in women than in men[5]. The prevalence of menstrual side effects such as amenorrhea in patients on risperidone is reported to be 1-10%[6]. In addition, serotonin-dopamine antagonists (SDAs) are more likely to induce hyperprolactinemia than MARTAs. Psychiatrists thus often use MARTAs, such as olanzapine and clozapine[1], to treat female psychotic patients with amenorrhea. However, it has been reported that even olanzapine may lead to hyperprolactinemia[7].

Aripiprazole is regarded as a second- or third-generation antipsychotic, mainly because it provides a control mechanism for the dopamine "see-saw". It reduces the dopaminergic neuron activity in brain regions with dopamine hyperactivity, while increasing the dopaminergic neuron activity in regions with hypoactivity, thereby reducing the number of side effects; regarding reduced side effects, the resolution of hyperprolactinemia has attracted the most attention. Aripiprazole can be used to resolve hyperprolactinemia induced by risperidone[8], amisulpride, and ziprasidone[9]. However, the use of aripiprazole to resolve MARTA-induced amenorrhea has rarely been reported, especially in amenorrhea without hyperprolactinemia. Some may believe that since aripiprazole can reduce amenorrhea, we should attempt to use it in the early stages of disease onset in women. It should be noted that in Case 2, aripiprazole was used during the early stages of disease onset. However, due to its slow antimanic effect, it was combined with zotepine after four weeks, and was only completely replaced by zotepine (100 mg/d) after eight weeks, followed by a switch to aripiprazole after the unexpected occurrence of amenorrhea. In both cases, full D2 antagonists were used initially for rapid therapeutic effect until full remission of the mental disorder, and then were successfully replaced by aripiprazole completely over one to two months. This was a viable therapeutic strategy.



SSRI: selective serotonin reuptake inhibitors; NDRI: norepinephrine-dopamine reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressants.

Figure 1. Summary of the clinical algorithm used patients are suspected of antipsychotic-induced amenorrhea[7].

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Table 1. Summary of past medications, medication switching process, and results of therapy for the two patients

	Patient 1	**Patient 2**
Diagnosis	Schizoaffective disorder	Bipolar I, manic episode with psychotic features
Age	44	43
Past medications	2011 Risperidone 2 mg/d 2013/1 Zotepine 100 mg/d 2013/8 Olanzapine 10 mg/d + sertraline 50 mg/d (body weight increased 20 kg) 2014/9 Risperidone 3 mg/d 2014/12 Began to visit gynecologist every month till 2015.10.14 2015.9.16 Last prescription at gynecology out-patient department Above are the past discharge medications, out-patient medications and gynecological follow-up visits	2009 Lithium 900 mg/d+ Valproic acid 900 mg/d+ Risperidone 4 mg/d 2010/3 Lithium 600 mg/d+ Valproic acid 1000 mg/d+ Risperidone 3 mg/d 2010/7 Valproic acid 750 mg/d+ Risperidone 3 mg/d 2013 Valproic acid 500 mg/d+ Risperidone 3 mg/d 2014 Lithium 600 mg/d + Risperidone 3 mg/d Above is the past discharge medication list. Below are the medications prescribed during this hospitalization 2016/5/13 Aripiprazole 30 mg/d 2016/5/25 Aripiprazole 30 mg/d Dogmatyl 200 mg/d 2016/6/8 Aripiprazole 30 mg/d Zotepine 50 mg/d 2016/7/4 Zotepine 75 mg/d+ Lithium 900 mg/d 2016/7/5 Zotepine 100 mg/d+ Lithium 900/d 2016/7/13 Zotepine 100 mg/d+ Lithium 600 mg/d
Medication switching process	2015.8.19 LMP (last menstrual period) 2015.8.29 PRL (prolactin) = 92.92 ng/ml 2015.10.22 Risperidone 2 mg/d+ Aripiprazole 10 mg/d X 21 days 2015.11.12 Risperidone 1 mg/d+ Aripiprazole 20 mg/d X 14 days 2015.11.26 Aripiprazole 20 mg/d (delete risperidone) 2015.12.16 PRL = 6.93 ng/nl 2016.2.4 PRL = 6.65 ng/nl	2016.8.7 LMP 2016.10.18 Zotepine 50 mg/d+ Aripiprazole 10 mg/d+ Lithium 600 mg/d 2016.10.19 PRL = 8.01 ng/ml 2016.10.26 Aripiprazole 20 mg/d+ Lithium 600 mg/d (delete zotepine) 2016.11.4 PRL = 5.42 ng/ml 2016.11.14 Norethisterone (5) 1#tid x 3 days (progestin challenge) 2016.11.15 Normal CEA/CA125; CEA (carcinoembryonic antigen); CA (carbohydrate antigen) r/o ovarian cancer
Result	2015.12.15 Menstruation resumed naturally without assistance from gynecological drugs, and body weight decreased by 3-4 kilograms	2016. 11.22 Menstruation resumed

In conclusion, when using antipsychotics among premenopausal women, we should consider the possibility of self-discontinuation of medications due to amenorrhea. Hence, after achieving rapid symptom alleviation using non-aripiprazole antipsychotics, the patient should be switched to aripiprazole, which prevents amenorrhea and may also achieve weight loss. Further clinical studies are needed to explore possible solutions to amenorrhea induced by antipsychotics. Figure 1 summarizes the clinical algorithm used when patients are suspected of antipsychotic-induced amenorrhea[7].

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