The utility of IFS (INECO Frontal Screening) for the detection of executive dysfunction in adults with bipolar disorder and ADHD

Sandra Baez [a,b,c,d], Agustin Ibanez [a,b,c,d,f], Ezequiel Gleichgerrcht [a,b,d], Ana Perez [a,b], María Roca [a,b,d], Facundo Manes [a,b,c,d,e], Teresa Torralva [a,b,d,*]

[a] Institute of Cognitive Neurology (INECO), Favaloro University, Buenos Aires, Argentina
[b] Institute of Neuroscience, Favaloro University, Buenos Aires, Argentina
[c] National Scientific and Technical Research Council (CONICET), Argentina
[d] UDP-INECO Foundation Core on Neuroscience (UIFCoN), Diego Portales University, Santiago, Chile
[e] Australian Research Council (ACR) Centre of Excellence in Cognition and its Disorders, Australia
[f] Universidad Autónoma del Caribe, Barranquilla, Colombia

ARTICLE INFO

ABSTRACT

Bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD) in adults share clinical symptoms. Both disorders present with executive functioning impairment. The detection of executive dysfunction usually requires the administration of an extensive neuropsychological battery. The Institute of Cognitive Neurology (INECO) Frontal Screening (IFS) is an efficient tool, which has been demonstrated to be useful for the detection of executive deficits in other diseases involving the prefrontal cortex. This study assessed the usefulness of the IFS in detecting the executive dysfunction of BD and ADHD adults, by means of a receiver-operating characteristic curve analysis and a multigroup discriminant function analysis. Twenty-four BD, 25 ADHD patients and 25 controls were assessed with a battery that included the IFS and other measures of executive functioning. Our results showed that both patient groups performed significantly lower than controls on the IFS total score. Using a 27.5 point cut-off score, the IFS showed good sensitivity and acceptable specificity to detect executive impairments in BD and ADHD patients. The IFS discriminated between controls and each patient group more reliably than other executive functions measures. Our results suggest that this tool could be a useful instrument to assess executive functions in BD and ADHD patients.

1. Introduction

Executive functions (EF) refer to the capacities involved in formulating goals, planning, and carrying out plans effectively (Lezak, 1982). Several psychiatric disorders are characterized by EF deficits, including bipolar disorder (BD) and adult attention deficit/hyperactivity disorder (ADHD), among others. These disorders usually share clinical symptoms, present high rates of comorbidity and are challenging to differentiate from one another clinically (Wingo and Ghaemi, 2007; Chang, 2010; Klassen et al., 2010). Besides these similarities, both BD (Bearden et al., 2001; Agarwal et al., 2008; Lin et al., 2011; Ibanez et al., 2012) and ADHD patients (Seidman et al., 2004; Depue et al., 2010; Ibanez et al., 2012) present abnormalities in brain regions relevant to EF tasks, such as the dorsolateral prefrontal cortex and the anterior cingulate cortex

(Stuss and Benson, 1986; Fuster, 1997). Thus, it is likely that abnormalities in the prefrontal cortex circuitries may be reflected in executive impairment in BD and ADHD.

Individuals with BD have deficits mainly in abstraction capacity, response inhibition and set shifting ability (Mur et al., 2007; Gruber et al., 2008; Bora et al., 2009; Torralva et al., 2012). Impairments in working memory and verbal fluency have also been reported (Robinson et al., 2006; Bora et al., 2009). These executive deficits are present not only during mood episodes, but persist even during periods of euthymia (Robinson et al., 2006; Mur et al., 2007; Oliveira et al., 2011; Elshahawi et al., 2011).

Regarding ADHD, research among adult populations is relatively scarce. Nevertheless, neuropsychological studies (Nigg et al., 2005; Biederman et al., 2006; Adler, 2010; Barkley, 2010) have consistently reported that adults with ADHD exhibit deficits in a wide range of EF including planning, working memory, set shifting, cognitive flexibility and response inhibition.

Although an accurate evaluation of EF is critical for the neuropsychological assessment of these two disorders, the detection of

* Corresponding author. Tel./fax: +54 11 4807 4748.
E-mail address: ttorralva@ineco.org.ar (T. Torralva).

executive dysfunctions usually requires an extensive battery that has to be administered by trained neuropsychologists. Given this difficulty, an efficient screening tool that is easy and quick to administer, yet shows high sensitivity and specificity, would be of great importance to clinicians.

Although several cognitive screening tools have desirable diagnostic and psychometric properties (Cullen et al., 2007), few have been designed to specifically evaluate EF. Furthermore, these screening tools have been mainly used to assess general cognitive functioning in neurodegenerative diseases, rather than in psychiatric conditions. No tools have yet been developed to be efficient, sensitive and specific in the detection of executive dysfunction in psychiatric disorders.

Because of this, our group recently created a tool aimed at detecting executive dysfunction: the IFS (INECO Frontal Screening) (Torralva et al., 2009). This is an easy-to-administer and brief (approximately 10 min) test which was designed to provide health professionals with an executive functioning screening tool to detect frontal impairment in everyday clinical settings or even at bedside. The IFS was designed to include several subtests in order to measure, in an efficient way, as many EFs as possible. This tool has been shown to be useful to discriminate controls from individuals with dementia (Torralva et al., 2009). It was further shown to be a sensitive and specific tool to differentiate the behavioral variant of frontotemporal dementia (bvFTD) from Alzheimer's disease (Torralva et al., 2009; Gleichgerrcht et al., 2011).

Because of its ability to detect the executive impairment of populations with prefrontal cortex involvement (i.e. bvFTD), the IFS may be useful in psychiatric populations, such as BD and ADHD. Thus, the goal of the present study was to assess the clinical usefulness of the IFS in detecting the executive dysfunction of adults with BD and ADHD. In order to do so, we employed two different methods. We initially determined the sensitivity and specificity of the IFS to discriminate between (a) healthy controls and BD patients and (b) healthy controls and ADHD patients, by means of a receiver-operating characteristic (ROC) curve. Likelihood ratios were also calculated. In addition, we performed a multigroup discriminant function analysis (MDA) to assess the capacity of the IFS, compared with classical executive measures, to discriminate between (a) healthy controls and BD patients and (b) healthy controls and ADHD patients.

We predicted that the IFS would show high sensitivity and specificity for the detection of executive deficits in BD and ADHD patients. We also hypothesized that the IFS total score would discriminate better than other EF measures between (a) healthy controls and BD patients and (b) healthy controls and ADHD patients.

2. Methods

2.1. Participants

Seventy-four participants (BD: $n=24$; ADHD: $n=25$; controls: $n=25$) received a full clinical assessment and a complete evaluation of EF. Patients in the BD and ADHD groups were selected from the outpatient population of the Institute of Cognitive Neurology (INECO) using the following inclusion criteria: (1) subjects older than 18 years old; (2) diagnosed with Type-I/II BD or adult ADHD according to the diagnostic and statistical manual of mental disorders (DSM-IV) criteria (American Psychiatric Association, 1994), using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1996). BD patients had no ADHD comorbidity and ADHD patients had no BD comorbidity. Eleven patients (45.8%) had diagnosis of BD type I and 13 (54.1%) of BD type II. All BD patients were in euthymic state, defined by scores less than or equal to 8 points according to the Montgomery–Asberg depression rating scale (MDRS) and less than or equal to 6 according to the Young mania rating scale (YMRS) for at least 8 weeks (see Table 1), and with no change in medication type or dosage over 4 months. All ADHD patients were recruited from the adult ADHD clinic of INECO. ADHD diagnosis was made by three experts, independently. In addition to a clinical evaluation and the structured clinical interview, participants completed the ADHD rating scale for adults (Barkley and Murphy, 1998), which provides a symptom profile (see Table 1) from the inattention and hyperactivity/impulsivity scores.

Nineteen BD patients (79%) were taking mood stabilizers, 10 (42%) SSRI antidepressants and eight (33%) benzodiazepines, either alone or in combination. Thirteen (52%) ADHD patients were taking methylphenidate, two (8%) atomoxetine, two (8%) benzodiazepines, either alone or in combination. Eight (32%) patients were not taking any medication.

Exclusion criteria were (1) other axis-I diagnoses, except for generalized anxiety disorder given its high comorbidity; (2) history of substance abuse/dependency; and (3) history of mental retardation, neurological disease, or any clinical condition that might affect cognitive performance. Patients who received antipsychotic medication were not included in this study.

We recruited 25 healthy controls matched for sex, age, handedness, and years of education from a larger pool of volunteers who did not have a history of drug abuse or a personal or family history of neurodegenerative or psychiatric disorders. All participants provided written informed consent in agreement with the Helsinki declaration. The Ethics Committee of the Institute of Cognitive Neurology approved this study.

2.2. Instruments

2.2.1. Clinical, symptomatic and neuropsychological assessment

Taking into account that anxiety and depression are factors that could affect executive functioning, all participants completed a series of psychiatric questionnaires in order to establish a profile of psychiatric clinical symptoms. The Beck Depression Inventory-II (Beck et al., 1996) was used to rate depression. The state-trait anxiety inventory (STAI) (Spielberg et al., 1970) was used to assess anxiety. In

Table 1
Demographic and clinical profiles of patients and controls.

Demographics	BD ($n=24$)	ADHD ($n=25$)	CTR ($n=25$)	BD vs. CTR	ADHD vs. CTR
Age (years)	39.0(11.2)	32.7(14.6)	35.8(10.15)	N.S	N.S
Gender (F:M)	8:16	4:21	11:14	N.S	N.S
Education (years)	15.7(2.8)	14.6(4.2)	16.3(1.9)	N.S	N.S
Handedness (R:L)	21:3	22:3	21:4	N.S	N.S
Clinical profile					
MADRS	3.3(3.7)				
YMRS	0.3(0.9)				
Barkley					
Inattention		11.7(6.4)			
Hyperactivity		11.7(5.8)			
BDI-II	15.2(10.8)	16.9(21.6)	6.2(6.9)	N.S	0.03
STAI state	29.6(6.4)	32.8(13.4)	15.0(8.6)	0.0002	0.0001
Trait	32.4(9.3)	33.2(11.9)	19.0(6.69)	0.0001	0.0001

BDI-II=Beck Depression Inventory; MADRS=Montgomery–Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale; STAI=State-Trait Anxiety Inventory.

addition, all participants were evaluated with the IFS (Torralva et al., 2009) and several EF measures (see below).

The clinical and symptomatic scales were administered by two expert psychiatrists. Tests of EF, including the IFS, were administered by two trained neuropsychologists.

2.2.1.1. INECO Frontal Screening (IFS). The IFS is an efficient and easy screening test to assess executive functions (Torralva et al., 2009), which includes the following eight subtests:

Motor programming (three points) (Luria, 1966; Dubois et al., 2000). This subtest asks the patient to perform the Luria series, "fist, edge, palm" by initially copying the administrator, and by subsequently doing the series on his or her own, then by repeating the series six times alone. This subscale assesses motor programming capacity, depending on the extent of frontal lesion or degeneration, some patients may not be able to complete the series in the correct order on their own, and others may not even be capable of copying it. If subjects achieved six consecutive series by themselves, the score was 3, if they achieved at least three consecutive series on their own, the score was 2; if they failed at achieving at least three consecutive series alone, but achieved three when copying the examiner, the score was 1; otherwise the score was 0.

Conflicting instructions (three points) (Dubois et al., 2000). This subtest is a measure of sensitivity to interference. Subjects were asked to hit the table once when the administrator hit it twice, or to hit the table twice when the administrator hit it only once. To ensure the subject had clearly understood the task, a practice trial was performed in which the administrator first hit the table once, three times in succession, and then twice, three more times. After the practice trial, the examiner completed the following series: 1-1-2-1-2-2-2-1-1-2. If subjects made no errors, the score was 3; for one or two errors the score was 2; for more than two errors the score was 1, unless the subject copied the examiner at least four consecutive times, in which case the score was 0.

Motor inhibitory control (three points) (Dubois et al., 2000). This task was administered immediately after the previous task and it is a measure of motor inhibitory control. Subjects were told that now, when the test administrator hit the table once, they should hit it once as well, but when the examiner hit it twice, they should do nothing. To ensure the subject had clearly understood the task, a practice trial was performed in which the administrator hit the table once, three times in succession, and then twice, three more times. After the practice trial the examiner completed the following series: 1-1-2-1-2-2-2-1-1-2. If subjects made no errors, the score was 3; for one or two errors the score was 2; for more than two errors the score was 1, unless the subject copied the examiner at least four consecutive times, in which case the score was 0.

Backward Digit Span (six points) (Hodges, 1994). This task assesses temporary storage and online manipulation of information (verbal working memory). Subjects were asked to repeat a progressively lengthening string of digits in the reverse order. Two trials were given at each successive list length, beginning at two and continuing to a maximum of seven. If subjects passed either trial at a given list length, then the next length was administered. The score was the number of lengths at which the subject passed either trial, maximum 6.

Verbal working memory (two points) (Hodges, 1994). This subscale also evaluates verbal working memory capacity. The patient was asked to list the months of the year backwards, starting with December. If subjects made no errors, the score was 2; for one error, the score was 1; otherwise the score was 0. This task evaluates the same function as the previous subtest but with a slightly different load because the series is highly overlearned for most individuals.

Spatial working memory (four points) (Wechsler, 1987). This is a measure of the visuospatial components of working memory. In this task, the examiner presented the subject with four cubes and pointed at them in a given sequence. The subject was asked to repeat the sequence in reverse order. There were four trials, with sequences of two, three, four, and five cubes, respectively. The score was the number of correctly completed sequences.

Abstraction capacity (*Proverb interpretation*) (three points) (Hodges, 1994). This subscale assesses the capacity to interpret the metaphoric meaning of three proverbs. In this task, three proverbs were read to the subjects and they were asked to explain their meaning. For each proverb a score of 1 was given when the subject gave an adequate explanation, and a score of 0.5 for a correct example. Otherwise, the score was 0.

Verbal inhibitory control (six points). This task, inspired by the Hayling test (Burgess and Shallice, 1996), measures a subject's capacity to inhibit an expected response. Materials were six sentences, each missing the last word and constructed to strongly constrain what it should be. In the first part (three sentences), subjects were read each sentence and asked to complete it correctly, as quickly as possible. For example, "I put my shoes on, and I tie my… (laces)". In the second part (remaining three sentences), subjects were asked for a completion that was unrelated to the sentence in meaning. Only the second part was scored. For each sentence, a score of 2 was given for a word unrelated to the sentence, a score of 1 for a word semantically related to the expected completion, and a score of 0 for the expected word itself.

The IFS has a maximum possible total score of 30 points and takes less than 10 min to be administered and scored.

2.2.1.2. Other executive functions measures. Trail Making B (Partington and Leiter, 1949) was used to assess speed processing, sequencing, mental flexibility, visual search and set shifting. Inhibitory control was evaluated using a computerized go-no go task, providing the percentage of correct, incorrect and omitted responses and the mean reaction time. Backward Digit Span, Letter–Number Sequencing and the Arithmetic tests of the WAIS-III (Wechsler, 2007) were used to assess mental manipulation and working memory. We also determined the Working Memory Index according to WAIS-III instructions (Wechsler, 2007). In addition, a phonological fluency task was included. In this task, participants were given 1 min to generate as many words as possible beginning with the letter "P" (Lezak et al., 2004).

2.3. Data analysis

The demographic, neuropsychological, and experimental data were compared between the groups using ANOVA and Tukey's HSD *post-hoc* tests (when appropriate). The ANOVA results were also corrected for multiple comparisons using Tukey's test. To control for the influence of depression and anxiety symptoms on EF tasks, we applied an ANCOVA test adjusted for BDI-II and STAI scores. We reported only effects that were still significant after covariation. When analyzing categorical variables (e.g., gender), χ^2 tests were applied. The α value for all statistical tests was set at 0.05.

In order to compare the usefulness of the IFS in detecting the executive dysfunction of adults with BD and ADHD, we determined the sensitivity and specificity of this test to discriminate between (a) healthy controls and BD patients, and (b) healthy controls and ADHD patients. This was done by means of a receiver-operating characteristic (ROC) curve (Hanley and Mcneil, 2010), detecting the optimal cut-off scores. The area under the ROC curve was used as a measure of discriminatory accuracy. Likelihood ratios were also calculated.

A multigroup discriminant function analysis (MDA) (Porebski, 1966; Stevens, 1996) with the step inclusion method (Wilki's Lamba) was performed to determine the feasibility of the IFS (compared with classical executive measures), to discriminate between healthy controls and each patient group. The working memory index was not considered as a predictor, since the inclusion of this measure together with Arithmetic, Backward Digit Span and Letter–Number Sequencing subtests may affect the MDA results. For every significant discriminant function, the level of variables' prediction in every group was tested by means of the module of classification of MDA's cases, using Statistical Package for Social Sciences (SPSS) version 18.0.

MDA combines independent variables by selecting and assessing the discriminant power of combined measures (predictor variables) applied in each group. Once the best predictors were selected, a final model was run without the selection method in order to determine the accuracy of the discriminant function. The MDA is based on a factor analytic method, which can classify the participants in different groups according to the discriminate ability of the selected predictors, and the results can be used to visually represent the position of groups relative to each other in a discriminant space. This technique was chosen since it is used for classifying subjects into groups on the basis of a battery of measurements, as well as on its parsimonious interpretation (Stevens, 1996). Moreover, this method can be used in small or medium sample sizes (Porebski, 1966). Previous studies in psychiatric populations with similar sample sizes (Pardo et al., 2006; Martin et al., 2007; Shur et al., 2008; Huepe et al., 2012) showed feasible results. It has been proposed (Hair et al., 1992) that at least five observations for each independent variable are needed, which are adequate for our data.

3. Results

3.1. Demographic data

No significant differences in age ($t(1, 29)=1.62$, $P=0.20$), gender ($\chi^2(2)=4.65$, $P=0.10$) or years of formal education ($F(2, 71)=1.72$, $P=0.18$) were observed between the groups. Table 1 shows the overall results from the demographic and clinical assessments.

3.2. Clinical assessment

We observed a between-group difference for BDI-II scores ($F(2, 71)=3.63$, $P<0.01$). Post-hoc comparisons (Tukey's HSD test, $MS=211.17$; d.f.$=71.00$) revealed higher levels of depression for participants with ADHD ($P<0.05$) compared with controls. In addition, significant differences between groups for STAI-state

$(F(2, 71)=15.43, P<0.01)$ and STAI-trait $(F(2, 60)=15.62, P<0.01)$ scales were observed. State scale posthoc comparisons (Tukey's test, HSD, $MS=124.74$; d.f.$=71.00$) showed that BD $(P<0.01)$ and ADHD $(P<0.01)$ participants had higher scores than controls. Post-hoc comparisons $(MS=88.95$; d.f.$=71.00)$ also showed higher scores for the trait scale in BD $(P<0.01)$ and ADHD $(P<0.01)$ patients compared with the control group.

In brief, BD patients had higher levels of anxiety than controls. ADHD patients showed higher scores of anxiety and depression than controls. Taking the differences between groups into account, we considered the BDI-II and STAI scores as covariables in the EF performance analysis.

3.3. Executive functions assessment

3.3.1. INECO Frontal Screening (IFS)

IFS and other executive measures results are provided in Table 2. The IFS total score showed significant differences between the groups $(F(2, 71)=4.85, P<0.01)$. Posthoc comparisons (Tukey's HSD, $MS=7.17$, d.f.$=71$) revealed that compared with controls, BD $(P<0.01)$ and ADHD $(P<0.01)$ patients had lower performances.

A detailed comparison of the performance on each of the eight IFS subtests indicated that the groups differed significantly $(F(2, 71)=4.21, P<0.01)$ on the digit backward span. The posthoc analysis demonstrated that ADHD patients had lower scores than controls $(P<0.05)$. We also observed group differences $(F(2, 71)=3.74, P<0.05)$ on spatial working memory. Posthoc comparisons (Tukey's HSD, $MS=0.99$, d.f.$=71$) showed that both patients groups, BD $(P<0.05)$ and ADHD $(P<0.01)$ performed worse than controls. Furthermore, differences between groups were observed in abstraction capacity $(F(2, 71)=2.45, P<0.05)$. The posthoc analysis revealed (Tukey's HSD, $MS=0.30$, d.f.$=71$) lower scores in ADHD patients compared with controls $(P<0.05)$.

No significant differences between BD and ADHD patients were found on either the total score or any of the IFS subtests. Details on these comparisons are provided in the Supplementary material.

Table 2
IFS and other executive measures raw scores. Comparisons between patient groups and controls.

	BD (n=24)	ADHD (n=25)	Control (n=25)	BD vs. CTR	ADHD vs. CTR
IFS					
Total score	24.3(3.8)	24.3(2.9)	27.5(2.4)	**0.007**	**0.008**
Motor series	2.5(0.8)	2.9(0.2)	2.8(0.04)	N.S	N.S
Conflicting instructions	2.8(0.3)	3.0(0.0)	3.0(0.0)	0.06*	N.S
Go-no go	2.7(0.5)	2.7(0.5)	3.0(0.0)	N.S	N.S
Backward digit span	4.3(1.0)	4.1(1.1)	5.0(1.0)	N.S	**0.05**
Verbal WM	1.9(0.2)	1.7(0.6)	2.0(0.0)	N.S	N.S
Spatial WM	2.7(1.1)	2.4(0.9)	3.5(0.7)	**0.01**	**0.003**
Abstraction capacity	2.5(0.6)	2.3(0.8)	2.9(0.2)	0.06*	**0.03**
V.I. control	4.5(1.3)	4.9(1.0)	5.2(0.8)	0.07*	N.S
Other executive functions measures					
T.M.T-B	83.2(33.1)	76.4(33.6)	68.0(25.0)	N.S	N.S
Go/no-go task					
Correct responses (%)	93.7(17.2)	98.0(4.6)	100(0.0)	N.S	N.S
Commission errors (%)	9.3(17.6)	4.3(5.4)	0.2(0.8)	N.S	N.S
Omission errors (%)	6.3(17.2)	2.0(4.9)	0.0(0.0)	N.S	N.S
Reaction time (ms)	403.0(100)	359.6(142.6)	400(48.2)	N.S	N.S
Digit backward span	4.8(1.2)	4.7(1.1)	5.5(1.1)	N.S	**0.05**
L–N sequencing	10.7(3.4)	10.0(2.6)	12.8(2.4)	0.06*	**0.03**
Arithmetic	13.4(3.8)	12.6(4.6)	15.1(3.9)	N.S	N.S
WM index	103.4(13.3)	94.3(14.7)	110.5(13.7)	N.S	**0.006**
Phonologic fluency	17.0(6.2)	16.2(3.8)	22.7(7.2)	**0.01**	**0.01**

Statistically significant differences are in bold.

* Tendencies to statistical significance. IFS=INECO Frontal Screening; WM=working memory; V.I Control=verbal inhibitory control; TMT-B=Trail Making Test-B; L–N sequencing=Letter–Number sequencing.
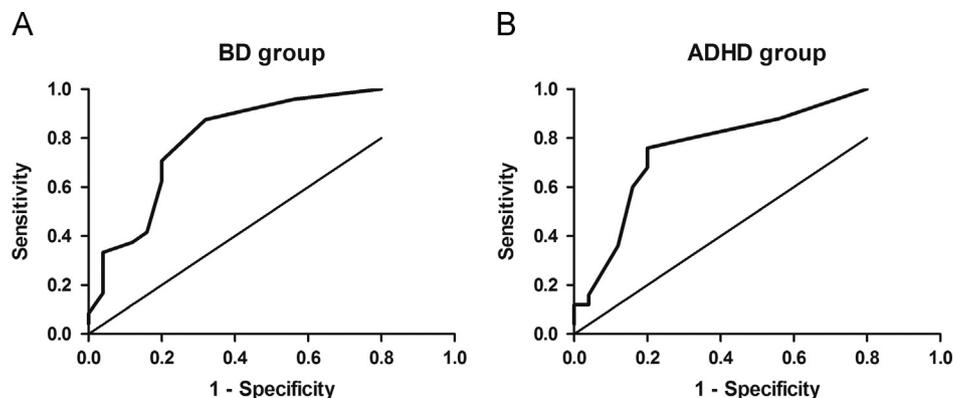
Fig. 1. INECO Frontal Screening (IFS) receiver operating characteristic (ROC) curve. (A) ROC curve analysis between BD patients and controls. The area under the curve was 0.82. A cut-off score of 27.5 points showed a sensitivity of 87.5% and a specificity of 68%. (B) ROC curve analysis between ADHD patients and controls. The area under the curve was 0.79. A cut-off score of 27.5 points showed a sensitivity of 80% and a specificity of 68%.

Table 3
Likelihood ratios and diagnostic odds ratios.

	Positive likelihood ratio	Negative likelihood ratio
BD vs. controls	2.72 (CI: 1.53–4.84)	0.18 (CI: 0.06–0.54)
ADHD vs. controls	2.50 (CI: 1.38–4.48)	0.27 (CI: 0.12–0.67)

CI=confidence interval.

Table 4
Standardized coefficients of discriminant functions.

Predictor variables	BD vs. controls	ADHD vs. controls
IFS total score	0.94	0.78
Correct responses (go-no go task)	0.59	–
Phonological fluency	–	0.58

3.3.2. Other executive functions measures

We found differences between groups on most of the working memory measures. The score on Backward Digit Span evidenced significant differences between groups ($F(2, 71)=2.65$, $P < 0.05$). A posthoc analysis (Tukey's HSD, $MS=1.36$, d.f.$=71$) revealed that ADHD ($P < 0.05$) patients had a worse performance than controls. Furthermore, the groups differed significantly ($F(2, 71)=3.67$, $P < 0.05$) on the Letter–number sequencing task. Posthoc comparisons (Tukey's HSD, $MS=7.67$, d.f.$=71$) indicated that ADHD ($P < 0.05$) patients had lower scores compared with controls. We also found differences between groups ($F(2, 71)=3.68$, $P < 0.01$) in the Working Memory Index. The posthoc analysis showed (Tukey's HSD, $MS=175.18$, d.f.$=71$) that ADHD group had lower performance than controls ($P < 0.01$).

The score on the verbal phonological fluency task also evidenced significant differences between groups ($F(2, 71)=2.85$, $P < 0.05$). Posthoc comparisons (Tukey's HSD, $MS=41.42$, d.f.$=71$) showed lower performance for both ADHD ($P < 0.05$) and BD ($P < 0.05$) groups.

3.4. Receiver operating characteristic (ROC) curve analyses

Fig. 1 illustrates the ROC curves for BD and ADHD groups. These show the sensitivity and specificity corresponding to different choices of IFS cut-off. The ROC curve analysis between BD patients and controls generated a cut-off score of 27.5 points, with a sensitivity of 87.5% and a specificity of 68%. The area under the ROC curve was 0.82 (CI: 0.70–0.93; $P < 0.01$). Likewise, comparing ADHD patients and the control group, a 27.5-point cut-off showed 80% of sensitivity and 68% of specificity. The area under the ROC curve was 0.79 (CI: 0.66–0.91; $P < 0.01$). In brief, the IFS showed an adequate sensitivity and specificity to detect executive impairments in both BD and ADHD patients. The area under the ROC evidenced that the IFS had a good discriminatory accuracy for EF deficits in both patient groups.

Taking into account the results of the ROC curve analyses, we used the sensitivity and specificity values to calculate likelihood ratios for each group. These values are shown in Table 3.

3.5. Multigroup discriminant function analysis (MDA)

IFS total score and the other EF measures were included into the MDA as independent variables. We performed a stepwise MDA for each patient group vs. controls, individually. For BD vs. controls, two variables (total IFS score and the percentage of the correct responses of the computerized go-no go task) were selected by their best contribution in differentiating the groups. One discriminant function was calculated from the predictors with

a Wilks's $\lambda=0.51$, $\chi^2 (2)=16.4$, $P < 0.01$. This function accounted for 100% of the total variance. The IFS total score discriminated most reliably between healthy controls and BD patients, followed by the percentage of correct responses of the go-no go task. Employing this model, 77.6% of participants were correctly classified, 75% of BD patients and 80% of control subjects.

Defining ADHD and control groups as dependent variables, two variables (total IFS score and phonological fluency) were selected by the stepwise discriminant procedure. One discriminant function was calculated between the predictors with a Wilkis's $\lambda=0.50$, $\chi^2 (2)=20.11$, $P < 0.01$. This function accounted for 100% of the total variance. The IFS total score also discriminated most reliably between healthy controls and ADHD patients, followed by the phonological fluency task. With this model, 78% of participants were correctly classified, 80% of ADHD patients and 76% of control subjects. Standardized coefficients of the variables selected are shown in Table 4.

4. Discussion

The goal of this study was to determine the efficacy of the IFS to detect executive dysfunctions in BD and ADHD adults using two different methods, the ROC curve analysis and a MDA. We showed that the IFS has a good sensitivity and acceptable specificity for the detection of executive dysfunctions of both patient groups. We also found that this screening tool has a good prediction accuracy to differentiate healthy controls from BD and ADHD patients, compared with other EF measures. Our results suggest that the IFS is a useful instrument to assess EF in BD and ADHD adults.

In this way, the IFS seems to be the first screening test that has been proved to be useful in assessing the executive functioning of adults with BD or ADHD. The appropriate sensitivity, specificity and discriminatory accuracy, make this test an adequate tool both for clinical and research settings, especially when time available is very limited. Thus, this screening test provides health professionals with an easy-to-administer and useful tool to detect frontal impairment in everyday clinical settings or even at bedside. Furthermore, our results further support the use of the IFS not only in patients with frontal degenerative pathologies (bvFTD), but also in patients with psychiatric disorders, in which frontal lobe abnormalities are less pronounced and systematic.

4.1. The executive profile in BD and ADHD patients

BD and ADHD patients showed lower scores than controls on the IFS total score. This is expected, since both BD (Mur et al., 2007; Gruber et al., 2008; Bora et al., 2009; Torralva et al., 2012) and ADHD adults (Nigg et al., 2005; Biederman et al., 2006; Adler, 2010; Barkley, 2010) show impairments in several executive domains, which are assessed by the IFS.

Congruent with previous reports (Dowson et al., 2004; Clark et al., 2007; Schecklmann et al., 2011), the performance on the IFS subscales showed that both patient groups had spatial working memory deficits. As previously reported (Nigg et al., 2005; Biederman et al., 2006), ADHD patients also exhibited verbal working memory and in abstraction capacity impairments (Johnson et al., 2001).

Regarding the other EF measures, in line with previous studies (Martino et al., 2008; Schecklmann et al., 2008; Bora et al., 2009), both patient groups showed deficits in phonological fluency. Furthermore, both patient groups had working memory difficulties (Torralva et al., 2011), but ADHD patients had deficits in a greater number of measures. In coherence with this finding, impaired working memory (Dowson et al., 2004; Nigg et al., 2005; Biederman et al., 2006; Clark et al., 2007; Torralva et al.,

2011) and abnormal task-related brain activation (Schecklmann et al., 2008) have been confirmed in adults with ADHD. Indeed, working memory has been proposed (Barkley, 1997) to be a core deficit of the ADHD.

In summary, results of IFS and other executive measured showed that both BD and ADHD patients performed lower than controls on the IFS total score. The comparison of the performance on the eight IFS subscales showed that both BD and ADHD patients compared with controls, had spatial working memory impairments. ADHD patients also exhibited difficulties in verbal working memory and abstraction capacity. Regarding other EF measures, both patient groups showed phonological fluency deficits. Although both patient groups had working memory difficulties, ADHD patients were impaired in a greater number of measures.

4.2. The efficacy of the IFS in ADHD and BD executive assessment

Using a 27.5-point cut-off, the IFS showed good sensitivity and acceptable specificity to detect executive impairments in both BD and ADHD patients. We used these sensitivity and specificity values to calculate likelihood ratios. For both groups, positive likelihood ratios indicated that a patient with executive dysfunction is about 2.5 or 3 times more likely to have a score below the IFS cut-off than a person without EF deficits. Likelihood ratios are measures of usefulness of a diagnostic test (Akobeng, 2007). However, the IFS is not a diagnostic test per se; rather, this is a screening tool that aims to detect executive dysfunction in a wide variety of conditions. Thus, although positive likelihood ratios were relatively small, these are expected and are similar to those of other cognitive screening tests (Larner, 2007; Paquay et al., 2007). Regarding negative likelihood ratios, in the BD group, the probability of having a normal score for individuals with executive dysfunction was 0.19 compared to individuals without executive dysfunction, whereas in the ADHD group this probability was 0.26. This means that individuals without executive dysfunction are about 4 to 5 times more likely to have a score above the IFS cut-off than individuals with EF deficits. These results suggest that the IFS is useful to exclude executive dysfunction.

The IFS was also proved to be useful for the detection of executive dysfunction in other diseases involving the prefrontal cortex (i.e. bvFTD) (Torralva et al., 2009; Gleichgerrcht et al., 2011). Furthermore, the IFS has shown higher sensitivity and specificity for the detection of dementia, higher discriminatory accuracy to differentiate bvFTD and Alzheimer's disease patients, and stronger correlations with executive tasks than other executive screening tests, such as the Frontal Assessment Battery (FAB) (Gleichgerrcht et al., 2011).

Previous studies have examined the efficacy of other screening tests to detect executive dysfunction. For instance, the Frontal Lobe Score (FLS) (Ettlin et al., 2000) is an instrument composed of 12 tests and two behavioral rating scales. This tool detects pure frontal lesions with a sensitivity of 92.3% and specificity of 75%, but its administration takes approximately 30 min (Wildgruber et al., 2000), which is not desirable for a screening tool. Another study (Forti et al., 2010) evaluated the utility of the Clock Drawing Test (CLOX) to detect executive impairments in patients with mild cognitive impairment. This instrument showed a fair specificity (72%), but unacceptably low values of sensitivity (28%) for screening purposes. Taking into account past and present results, the IFS can be considered an adequate screening tool to detect executive impairments in BD and ADHD patients and, possibly, in other psychiatric disorders.

In fact, consistent with the ROC curve analysis results, the MDA showed that the IFS total score was the variable that best discriminated between (a) BD patients and controls and (b) ADHD patients and controls. Comparing BD patients and controls, a

model that included the IFS total score and the percentage of correct responses on the go-no go task correctly classified 75% of BD patients and 80% of control subjects. Comparing ADHD patients and controls, we obtained a model that included the IFS total score and the phonological fluency tasks as the best predictors. Employing this model, 76% of ADHD patients and 80% of controls were correctly classified. These results suggest that the IFS total score discriminated between the healthy controls and the patient groups more reliably than other EF measures. This is not surprising since the IFS was designed to include several subtests in order to measure, in an efficient way, as many EFs as possible. Although an extensive and comprehensive neuropsychological assessment is maybe the best method to discriminate among BD and ADHD patients compared with controls, our results highlight the brevity, simplicity and clinical utility of the IFS.

4.3. Limitations and further assessment

Some limitations of this study should be acknowledged. First, although patients included in this study were not receiving antipsychotic medication, all of BD and the majority of ADHD patients were taking psychoactive drugs that can influence cognitive functioning. Second, the current cut-off points are applicable to individuals with high or middle education level. Future studies should assess the IFS performance of individuals with low levels of formal education. Another limitation is that our sample size was relatively small. However, it is similar to sample sizes used in previous studies comparing BD and ADHD patients (Mullin et al., 2011; Nandagopal et al., 2011; Torralva et al., 2011). Furthermore, previous studies in psychiatric populations with similar sample sizes (Pardo et al., 2006; Martin et al., 2007; Shur et al., 2008; Huepe et al., 2012) showed an adequate classification using the MDA method.

Although BD patients who participated in this study had no ADHD comorbidity and ADHD patients had no BD comorbidity, it is important to consider that these two disorders are often comorbid (Krishnan, 2005; Townsend et al., 2012). This should be taken into account in the assessment of these patients since individuals with comorbid ADHD have a more chronic and disabling course of BD (Nierenberg et al., 2005), which could affect their cognitive functioning. Furthermore, in the current study we included patients with types I and II BD. Future studies should assess the executive functioning of samples of each type of BD independently.

Our results showed that both BD and ADHD patients have similar executive dysfunction profiles, which could reflect the shared clinical symptoms and the high rates of comorbidity of these disorders. Further studies should be performed to confirm these findings assessing executive functioning by means of an extensive neuropsychological battery.

In addition, further studies should assess EF in larger samples, taking into account the subtypes of BD and ADHD. BD patients in manic, hypomanic or depressed episodes should also be evaluated. As well, it would be interesting to compare the executive functioning of BD and ADHD with that of individuals with other psychiatric disorders. Future studies should explore the utility of the IFS in detecting EF impairments in other psychiatric disorders.

5. Conclusions

The neuropsychological assessment of patients with BD and ADHD is a potentially useful source of information for differential diagnosis, complementary to the clinical interview. An accurate evaluation of EF is critical to the neuropsychological assessment of these patients. Although this assessment cannot rely exclusively

on an efficient screening tool, the IFS would be of great utility in everyday clinical practice. This tool does not replace a complete neuropsychological evaluation when available. The administration of the IFS should be complemented with instruments that assess other cognitive functions typically affected in BD and ADHD patients, such as attention and memory (Bearden et al., 2006; Tucha et al., 2009; Maalouf et al., 2010; Torralva et al., 2011). Thus, the results of a complete neuropsychological assessment should draw up the aims of cognitive training. These kinds of non-pharmacological treatments may have beneficial effects on cognitive functioning of ADHD and BD patients (McGurk et al., 2005; Rostain and Ramsay, 2006; Preiss et al., 2013). Indeed, improvements in executive functioning of BD patients have been associated with improvements in occupational functioning (Deckersbach et al., 2010).

To our knowledge, this is the first study to assess the utility of a screening instrument to detect executive dysfunctions in psychiatric populations. Although the complexity of EF makes it impossible for a single test to evaluate this cognitive process in its entirety, the present study indicates that the IFS is a solid, brief, and easy-to administer tool for the EF evaluation in BD and ADHD adults.

Funding

Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2014.01.020.

References

Adler, L.A., 2010. Monitoring adults with ADHD: a focus on executive and behavioral function. Journal of Clinical Psychiatry 71, 18.

Agarwal, N., Bellani, M., Perlini, C., Rambaldelli, G., Atzori, M., Cerini, R., Vecchiato, F., Pozzi Mucelli, R., Andreone, N., Balestrieri, M., Tansella, M., Brambilla, P., 2008. Increased fronto-temporal perfusion in bipolar disorder. Journal of Affective Disorders 110, 106–114.

Akobeng, A.K., 2007. Understanding diagnostic tests 2: likelihood ratios, pre-and post-test probabilities and their use in clinical practice. Acta Paediatrica 96, 487–491.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4 ed., American Psychiatric Press, Washington, DC.

Barkley, R., Murphy, C., 1998. Attention-Deficit Hyperactivity Disorder: A Clinical Workbook. Guilford Press, New York.

Barkley, R.A., 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychological Bulletin 121, 65–94.

Barkley, R.A., 2010. Differential diagnosis of adults with ADHD: the role of executive function and self-regulation. Journal of Clinical Psychiatry 71, 17.

Bearden, C.E., Glahn, D.C., Monkul, E.S., Barrett, J., Najt, P., Villarreal, V., Soares, J.C., 2006. Patterns of memory impairment in bipolar disorder and unipolar major depression. Psychiatry Research 142, 139–150.

Bearden, C.E., Hoffman, K.M., Cannon, T.D., 2001. The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. Bipolar Disorders 3, 106–150.

Beck, A., Brown, G., Steer, R., 1996. Manual for the Beck Depression Inventory-II. The Psychological Corporation, San Antonio.

Biederman, J., Petty, C., Fried, R., Fontanella, J., Doyle, A.E., Seidman, L.J., Faraone, S.V., 2006. Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. American Journal of Psychiatry 163, 1730–1738.

Bora, E., Yucel, M., Pantelis, C., 2009. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. Journal of Affective Disorders 113, 1–20.

Burgess, P.W., Shallice, T., 1996. Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia 34, 263–272.

Chang, K.D., 2010. Course and impact of bipolar disorder in young patients. Journal of Clinical Psychiatry 71, e05.

Clark, L., Blackwell, A.D., Aron, A.R., Turner, D.C., Dowson, J., Robbins, T.W., Sahakian, B.J., 2007. Association between response inhibition and working memory in adult ADHD: a link to right frontal cortex pathology? Biological Psychiatry 61, 1395–1401.

Cullen, B., O'Neill, B., Evans, J.J., Coen, R.F., Lawlor, B.A., 2007. A review of screening tests for cognitive impairment. Journal of Neurology, Neurosurgery, and Psychiatry 78, 790–799.

Deckersbach, T., Nierenberg, A.A., Kessler, R., Lund, H.G., Ametrano, R.M., Sachs, G., Rauch, S.L., Dougherty, D., 2010. RESEARCH: Cognitive rehabilitation for bipolar disorder: an open trial for employed patients with residual depressive symptoms. CNS Neuroscience & Therapeutics 16, 298–307.

Depue, B.E., Burgess, G.C., Bidwell, L.C., Willcutt, E.G., Banich, M.T., 2010. Behavioral performance predicts grey matter reductions in the right inferiorfrontal gyrus in young adults with combined type ADHD. Psychiatry Research 182, 231–237.

Dowson, J.H., McLean, A., Bazanis, E., Toone, B., Young, S., Robbins, T.W., Sahakian, B.J., 2004. Impaired spatial working memory in adults with attention-deficit/hyperactivity disorder: comparisons with performance in adults with borderline personality disorder and in control subjects. Acta Psychiatrica Scandinavica 110, 45–54.

Dubois, B., Slachevsky, A., Litvan, I., Pillon, B., 2000. The FAB: a Frontal Assessment Battery at bedside. Neurology 55, 1621–1626.

Elshahawi, H.H., Essawi, H., Rabie, M.A., Mansour, M., Beshry, Z.A., Mansour, A.N., 2011. Cognitive functions among euthymic bipolar I patients after a single manic episode versus recurrent episodes. Journal of Affective Disorders 130, 180–191.

Ettlin, T.M., Kischka, U., Beckson, M., Gaggiotti, M., Rauchfleisch, U., Benson, D.F., 2000. The Frontal Lobe Score: Part I: Construction of a mental status of frontal systems. Clinical Rehabilitation 14, 260–271.

First, M., Spitzer, R., Gibbon, M., Williams, J., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinical Version (SCID-CV). American Psychiatry Press, Washington, DC.

Forti, P., Olivelli, V., Rietti, E., Maltoni, B., Ravaglia, G., 2010. Diagnostic performance of an Executive Clock Drawing Task (CLOX) as a screening test for mild cognitive impairment in elderly persons with cognitive complaints. Dementia and Geriatric Cognitive Disorders 30, 20–27.

Fuster, J., 1997. The Prefrontal Cortex, 3rd ed. Raven Press, New York.

Gleichgerrcht, E., Roca, M., Manes, F., Torralva, T., 2011. Comparing the clinical usefulness of the Institute of Cognitive Neurology (INECO) Frontal Screening (IFS) and the Frontal Assessment Battery (FAB) in frontotemporal dementia. Journal of Clinical and Experimental Neuropsychology 33, 997–1004.

Gruber, S.A., Rosso, I.M., Yurgelun-Todd, D., 2008. Neuropsychological performance predicts clinical recovery in bipolar patients. Journal of Affective Disorders 105, 253–260.

Hair, J., Anderson, R., Tatham, R., Black, W., 1992. Multivariate Data Analysis with Readings. Macmillan, New York.

Hanley, J., Mcneil, B., 2010. The meaning and use of the Area under a Receiver Operating Characteristic (ROC) curve. Radiology 143, 29–36.

Hodges, J., 1994. Cognitive Assessment for Clinicians. Oxford University Press, Oxford.

Huepe, D., Riveros, R., Manes, F., Couto, B., Hurtado, E., Cetkovich, M., Escobar, M., Vergara, V., Parrao, T., Ibanez, A., 2012. The relationship of clinical, cognitive and social measures in schizophrenia: a preliminary finding combining measures in probands and relatives. Behavioural Neurology 25, 137–150.

Ibanez, A., Cetkovich, M., Petroni, A., Urquina, H., Baez, S., Gonzalez-Gadea, M.L., Kamienkowski, J.E., Torralva, T., Torrente, F., Strejilevich, S., Teitelbaum, J., Hurtado, E., Guex, R., Melloni, M., Lischinsky, A., Sigman, M., Manes, F., 2012. The neural basis of decision-making and reward processing in adults with euthymic bipolar disorder or Attention-Deficit/Hyperactivity Disorder (ADHD). PLoS One 7, e37306.

Johnson, D.E., Epstein, J.N., Waid, L.R., Latham, P.K., Voronin, K.E., Anton, R.F., 2001. Neuropsychological performance deficits in adults with attention deficit/hyperactivity disorder. Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists 16, 587–604.

Klassen, L.J., Katzman, M.A., Chokka, P., 2010. Adult ADHD and its comorbidities, with a focus on bipolar disorder. Journal of Affective Disorders 124, 1–8.

Krishnan, K.R., 2005. Psychiatric and medical comorbidities of bipolar disorder. Psychosomatic Medicine 67, 1–8.

Larner, A.J., 2007. Addenbrooke's Cognitive Examination (ACE) for the diagnosis and differential diagnosis of dementia. Clinical Neurology and Neurosurgery 109, 491–494.

Lezak, M., 1982. The problem of assessing executive functions. International Journal of Psychology 17, 281–297.

Lezak, M.D., Howieson, D.B., Loring, D.W., 2004. Neuropsychological Assessment. Oxford University Press, New York.

Lin, F., Weng, S., Xie, B., Wu, G., Lei, H., 2011. Abnormal frontal cortex white matter connections in bipolar disorder: a DTI tractography study. Journal of Affective Disorders 131, 299–306.

Luria, A., 1966. Higher Cortial Function in Man. Tavistock, London.

Maalouf, F.T., Klein, C., Clark, L., Sahakian, B.J., Labarbara, E.J., Versace, A., Hassel, S., Almeida, J.R., Phillips, M.L., 2010. Impaired sustained attention and executive dysfunction: bipolar disorder versus depression-specific markers of Affective Disorders. Neuropsychologia 48, 1862–1868.

Martin, L.F., Hall, M.H., Ross, R.G., Zerbe, G., Freedman, R., Olincy, A., 2007. Physiology of schizophrenia, bipolar disorder, and schizoaffective disorder. American Journal of Psychiatry 164, 1900–1906.

Martino, D.J., Strejilevich, S.A., Scapola, M., Igoa, A., Marengo, E., Ais, E.D., Perinot, L., 2008. Heterogeneity in cognitive functioning among patients with bipolar disorder. Journal of Affective disorders 109, 149–156.

McGurk, S.R., Mueser, K.T., Pascaris, A., 2005. Cognitive training and supported employment for persons with severe mental illness: one-year results from a randomized controlled trial. Schizophrenia Bulletin 31, 898–909.

Mullin, B.C., Harvey, A.G., Hinshaw, S.P., 2011. A preliminary study of sleep in adolescents with bipolar disorder, ADHD, and non-patient controls. Bipolar Disorders 13, 425–432.

Mur, M., Portella, M.J., Martinez-Aran, A., Pifarre, J., Vieta, E., 2007. Persistent neuropsychological deficit in euthymic bipolar patients: executive function as a core deficit. Journal of Clinical Psychiatry 68, 1078–1086.

Nandagopal, J.J., Fleck, D.E., Adler, C.M., Mills, N.P., Strakowski, S.M., DelBello, M.P., 2011. Impulsivity in adolescents with bipolar disorder and/or attention-deficit/ hyperactivity disorder and healthy controls as measured by the Barratt Impulsiveness Scale. Journal of Child and Adolescent Psychopharmacology 21, 465–468.

Nierenberg, A.A., Miyahara, S., Spencer, T., Wisniewski, S.R., Otto, M.W., Simon, N., Pollack, M.H., Ostacher, M.J., Yan, L., Siegel, R., Sachs, G.S., 2005. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biological Psychiatry 57, 1467–1473.

Nigg, J.T., Stavro, G., Ettenhofer, M., Hambrick, D.Z., Miller, T., Henderson, J.M., 2005. Executive functions and ADHD in adults: evidence for selective effects on ADHD symptom domains. Journal of Abnormal Psychology 114, 706–717.

Oliveira, S., Kapczinski, F., Camey, S., Trentini, C., 2011. Assessment of executive functions in a Brazilian sample of bipolar subjects. Spanish Journal of Psychology 14, 859–868.

Paquay, L., De Lepeleire, J., Schoenmakers, B., Ylieff, M., Fontaine, O., Buntinx, F., 2007. Comparison of the diagnostic accuracy of the Cognitive Performance Scale (Minimum Data Set) and the Mini-Mental State Exam for the detection of cognitive impairment in nursing home residents. International Journal of Geriatric Psychiatry 22, 286–293.

Pardo, P.J., Georgopoulos, A.P., Kenny, J.T., Stuve, T.A., Findling, R.L., Schulz, S.C., 2006. Classification of adolescent psychotic disorders using linear discriminant analysis. Schizophrenia Research 87, 297–306.

Partington, J., Leiter, R., 1949. Partington's pathway test. Psychological Center Bulletin 1, 11–20.

Porebski, O., 1966. Discriminatory and canonical analysis of technical college data. British Journal of Mathematical and Statistical Psychology 19, 215–236.

Preiss, M., Shatil, E., Cermakova, R., Cimermanova, D., Ram, I., 2013. Personalized cognitive training in unipolar and bipolar disorder: a study of cognitive functioning. Frontiers in Human Neuroscience 7, 108.

Robinson, L.J., Thompson, J.M., Gallagher, P., Goswami, U., Young, A.H., Ferrier, I.N., Moore, P.B., 2006. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. Journal of Affective disorders 93, 105–115.

Rostain, A.L., Ramsay, J.R., 2006. A combined treatment approach for adults with ADHD-results of an open study of 43 patients. Journal of Attention Disorders 10, 150–159.

Schecklmann, M., Dresler, T., Beck, S., Jay, J.T., Febres, R., Haeusler, J., Jarczok, T.A., Reif, A., Plichta, M.M., Ehlis, A.C., Fallgatter, A.J., 2011. Reduced prefrontal oxygenation during object and spatial visual working memory in unipolar and bipolar depression. Psychiatry Research 194, 378–384.

Schecklmann, M., Ehlis, A.C., Plichta, M.M., Romanos, J., Heine, M., Boreatti-Hummer, A., Jacob, C., Fallgatter, A.J., 2008. Diminished prefrontal oxygenation with normal and above-average verbal fluency performance in adult ADHD. Journal of Psychiatric Research 43, 98–106.

Seidman, L.J., Valera, E.M., Bush, G., 2004. Brain function and structure in adults with attention-deficit/hyperactivity disorder. Psychiatric Clinics of North America 27, 323–347.

Shur, S., Shamay-Tsoory, S.G., Levkovitz, Y., 2008. Integration of emotional and cognitive aspects of theory of mind in schizophrenia and its relation to prefrontal neurocognitive performance. Cognitive Neuropsychiatry 13, 472–490.

Spielberg, C., Gorsuch, R., Lushene, R., 1970. Manual for the Stait-Trait Anxiety Inventory. Consulting Psychological Press, Palo Alto.

Stevens, J., 1996. Applied Multivariate Statistics for the Social Sciences. Lawrence Erlbaum Associates, New Jersey.

Stuss, D., Benson, D., 1986. The Frontal Lobes. Raven Press, New York.

Torralva, T., Gleichgerrcht, E., Torrente, F., Roca, M., Strejilevich, S.A., Cetkovich, M., Lischinsky, A., Manes, F., 2011. Neuropsychological functioning in adult bipolar disorder and ADHD patients: a comparative study. Psychiatry Research 186, 261–266.

Torralva, T., Roca, M., Gleichgerrcht, E., Lopez, P., Manes, F., 2009. INECO Frontal Screening (IFS): an efficient, sensitive, and specific tool to assess executive functions in dementia. Journal of the International Neuropsychological Society: JINS 15, 777–786.

Torralva, T., Strejilevich, S., Gleichgerrcht, E., Roca, M., Martino, D., Cetkovich, M., Manes, F., 2012. Deficits in tasks of executive functioning that mimic real-life scenarios in bipolar disorder. Bipolar Disorders 14, 118–125.

Townsend, J.D., Sugar, C.A., Walshaw, P.D., Vasquez, R.E., Foland-Ross, L.C., Moody, T. D., Bookheimer, S.Y., McGough, J.J., Altshuler, L.L., 2012. Frontostriatal neuroimaging findings differ in patients with bipolar disorder who have or do not have ADHD comorbidity. Journal of Affective disorders 147, 389–396.

Tucha, L., Tucha, O., Walitza, S., Sontag, T.A., Laufkotter, R., Linder, M., Lange, K.W., 2009. Vigilance and sustained attention in children and adults with ADHD. Journal of Attention Disorders 12, 410–421.

Wechsler, D., 1987. Wechsler Memory Scale-Revised. Psychological Corporation, New York.

Wechsler, D., 2007. Wechsler Adult Intelligent Scale III, 3rd ed. The Psychological Corporation, San Antonio, TX.

Wildgruber, D., Kischka, U., Fassbender, K., Ettlin, T.M., 2000. The Frontal Lobe Score: Part II: Evaluation of its clinical validity. Clinical Rehabilitation 14, 272–278.

Wingo, A.P., Ghaemi, S.N., 2007. A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. Journal of Clinical Psychiatry 68, 1776–1784.