Author’s response to reviews

Title: ADHD in adolescents with borderline personality disorder

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Author’s response to reviews: see over
Paris, the 23th of august, 2011

To the Editor in Chief

*BMC Psychiatry*

Dear editor,

We have carefully read all the interesting commentaries raised by the reviewers on our first version of the paper “ADHD in adolescents with borderline personality disorder” (manuscript N°1660765808570547) and we would like to submit a revised version of the paper to BMC Psychiatry.

We have tried to answer to each point individually explaining the reasons of our choices and the modifications we would like to introduce to the text. In particular, we have clearly acknowledged the limitation of the cross-sectional design of the study and we have better described the sampling procedure. Upon discussion with our statistical adviser (who is now included among the authors), we have modified the statistical plan to answer to the issue of the hierarchical nature of the design and of the between-center variability of the participants. The tables have been modified.

The proposed modifications have been integrated in the manuscript in underscored characters. We join to the manuscript a document with all the answers to the reviewers.

We would like to thank the journal and the reviewers for the opportunity to read our work and we hope that this new version will fulfill the standards of BMC Psychiatry.

We look forward to reading from you.

Sincerely yours,

Signature of the corresponding author
Mario Speranza MD PhD

For all correspondence:

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ADHD IN ADOLESCENTS WITH BORDERLINE PERSONALITY DISORDER

Manuscript №1660765808570547

ANSWERS TO REVIEWERS’ COMMENTS WITH MODIFICATIONS WE WOULD LIKE TO INTRODUCE TO THE TEXT. THE PROPOSED MODIFICATIONS ARE HIGHLIGHTED IN YELLOW IN THE DOCUMENT

Editors comment:
Major concerns: the issue of the developmental pathway; the issue of pre-screening and potential for clinical bias; the issue of the hierarchical nature of the design that reflects a type of nested sampling.

Answer and proposed modifications
We have carefully read the reviews and tried to answer to each point resumed by the editor and raised by the reviewers. For each commentary, we have given an explanation and an indication of the proposed modifications. The modified texts are in yellow in this document and have been integrated in underscored characters in the manuscript.

Concerning the issue of the developmental pathway, we have acknowledged the limitation of the cross-sectional design of the study but also its interest in better defining the clinical profile of comorbid disorders in specific populations, such as adolescents. We have also pointed the short time leg between childhood and adolescence and the high diagnostic stability between past and current ADHD diagnosis which can support the hypothesis of a subtype of BPD with a childhood history of ADHD, hypothesis that has been recently confirmed by Stepp and colleagues in a longitudinal study on adolescent girls. This study (published during the reviewing process) has been added and commented in the text. See also answers R1-A5 and R2-A1.

Concerning the issue of pre-screening and potential for clinical bias, we have better described in the methods section the sampling and research procedure of the study. We have argued that we have used a two-stage procedure to increase the validity of the diagnosis of BPD for the final sample. The screening procedure was conducted by experienced clinicians informed and supervised by the research team and using a screening questionnaire with DSM-IV criteria. This procedure seems to us sufficiently adequate for a clinical research whose aim was to have a well-defined group of BPD adolescent. This is why we paid special attention to the diagnostic phase in the research protocol with repeated training and assessment of interrater reliability for Axis-I and Axis-II diagnoses. Final diagnoses were established in a consensus conference on the basis of the interviews and the clinical records, thus strengthening the validity of BPD diagnosis and reducing the risk of misdiagnoses. See also answers R2-A2.

Concerning the issue of the hierarchical nature of the design and the between-center variability of the participants, we have modified the statistical plan and used the Mantel-Haenszel chi-square statistic for categorical variables and the nested ANOVA statistic controlling for the recruitment centers for the continuous variables. The variable “recruitment centers” was also introduced as an independent variable in the regression analyses. To reduce the number of statistical comparisons and comparisons with few observations, Axis-I and Axis-II diagnoses were included as groups of related disorders. All the tables have been modified to introduce the new statistical analyses. See also answers R1-A2 and R2-A3.
Answers to reviewer N°1 J. Joêl Paris

R1-C1. It should also be noted that the sample size is too small for generalizability, but that the findings generally confirm the previous study in BJP.

R1-A1. The limitations of the small sample size of the study and generalizability of the results have been acknowledged in the limitations section of the paper.

Modifications included in the revised text

In the “limitations” section
The second limit concerns the small sample size of the study and the potential sample selection bias of the screening phase conducted by the consulting clinicians without performing a systematic between-center inter-rater reliability. This may have reduced the statistical power of the analyses and the generalizability of the results. However, the sample of BPD participants was reasonable compared to other studies, particularly since it was limited to adolescents with a well-characterized BPD diagnosis. Results however, should be interpreted with caution as to know what the likelihood might be that the sample is actually representative of BPD adolescents.

In the “limitations” section
Notwithstanding these limitations, the results of this study confirm, in an adolescent sample, previous studies conducted in adult samples (reference to BJP) showing that…

R1-C2. Please provide clarification regarding what, if any, corrections for multiple comparisons were used.

R1-A2. We decide to not perform corrections for multiple comparisons because of the exploratory design of the study. As suggested by some authors (see Bender et al. Journal of Clinical Epidemiology 54, 343–349, 2001), adjustments for multiple testing are required in confirmatory studies whenever results from multiple tests have to be combined in one final conclusion and decision. In exploratory studies, in which data are collected with an objective but not with a prespecified key hypothesis, multiple test adjustments are not strictly required. However, to reduce the number of statistical comparisons and comparison with few observations, Axis-I and Axis-II diagnoses were included as groups of related disorders. This was possible without losing important information concerning individual diagnoses. See also R2-C3 for modifications of the statistical plan.

Modifications included in the revised text

In the “statistical analysis” section
To reduce the number of statistical comparisons and comparisons with few observations, Axis-I and Axis-II diagnoses were included as groups of related disorders.

R1-C3. The section at the top of page 12 that justifies the superiority of clinician rated measures over self-report measures is unnecessary for the paper and can be removed.

R1-A3. We have removed this paragraph from the text.

R1-C4. Two typos were noted:
On the bottom of page 13, there is “DMS-III” which should be “DSM-III”
At the top of page 14, line 3, should say “micro-psychotic” instead of “mini-psychotic”

R1-A4. The typos have been modified in the text.
R1-C5. Overall, this paper is novel and presents an interesting description of a possible subtype of adolescent BPD. It should however be acknowledged that since these diagnostic constructs tend to overlap, particularly in the realm of impulsivity.

R1-A5. We agree that the diagnostic constructs of ADHD and BPD overlap. However is interesting to note that symptoms of inattention, hyperactivity and impulsivity were evenly distributed across the sample. This points to the fact that all types of ADHD symptoms, not solely impulsivity, are frequently found in BPD adolescents. Moreover, comorbidity rates did not change when diagnosis was made without including impulsivity, thus reducing the criticism of an overestimation of ADHD diagnosis in BPD due to symptom overlap.

A part of this comment was already present in the discussion. A paragraph on the diagnostic overlap has been added in the limitations of the study.

Modifications included in the revised text

In the “limitations” section
First, the main limit of the study is its cross-sectional design with data on childhood ADHD diagnosis collected retrospectively. Only longitudinal studies can directly support the identification of the developmental pathways leading from childhood to adult psychopathology. This is even more important if we consider that these diagnostic constructs tend to overlap, particularly in the realm of impulsivity.

R1-C6. The authors used well-known measures, although there is no real evidence to support the use of DIB item scores as indicators of severity.

R1-A6. We agree that DIB scores could be more appropriately considered as a way to characterize the clinical profiles of these patients. Moreover, this is in line with the suggestion raised in the literature, on which we agree, that the association between ADHD and BPD could define a specific subtype of BPD.

The heading of the section and the text have been modified to indicate a difference in the borderline symptomatological profile of patients according to ADHD.

Modifications included in the revised text

In the “results” section

BPD-ADHD adolescents showed a different profile of borderline symptoms as assessed by the DIB compared to BPD adolescents.
Answers to reviewer n°2. Andrea Fossati

R2-C1. One of the major limitations of this study is the cross-sectional study of the interface between BPD and ADHD … providing no original data on the developmental process starting from childhood ADHD and ending with adult or adolescent BPD.

R2-A1. We agree that the cross-sectional design of the study cannot directly support the identification of a developmental pathway from childhood ADHD to adolescent BPD. We have clearly acknowledged this point in the limitations of the study. However, it is worth saying that on adolescent samples even cross-sectional studies are lacking, although they can cast some light on the developmental dynamics of ADHD children. In our study we observed a high diagnostic stability between past and current ADHD diagnosis, a finding that indirectly supports the hypothesis of a subtype of BPD with a childhood history of ADHD. During the reviewing process, we found on the medline, the first longitudinal study to examine ADHD and ODD symptom trajectories as specific childhood precursors of BPD symptoms in adolescent girls, which apports interesting data concerning a developmental subtype of BPD. Stepp and colleagues (2011), performed a series of latent growth curve models on two cohorts of girls annually assessed between the age of 8 and 14. They found that higher levels of ADHD and ODD scores at age 8 uniquely predicted BPD symptoms at age 14; over and above depression symptoms at outcome. This study has been included and commented in the revised text.

Modifications included in the revised text

In the “Introduction” section

Stepp and colleagues recently published the first longitudinal study to examine ADHD and ODD symptom trajectories as specific childhood precursors of BPD symptoms in adolescent girls [25]. They performed a series of latent growth curve models on two cohorts of girls annually assessed between the age of 8 and 14. They found that higher levels of ADHD and ODD scores at age 8 uniquely predicted BPD symptoms at age 14; over and above depression symptoms at outcome.

In the “limitations” section

First, the main limit of the study is its cross-sectional design. Only longitudinal studies can directly support the identification of the developmental pathways leading from childhood to adult psychopathology. However cross-sectional studies on comorbid disorders in specific populations, such as adolescents, can shed light on their clinical presentation and help identifying their specific therapeutic needs. Moreover, although indirectly, the high diagnostic stability between past and current ADHD diagnosis found in our study supports the hypothesis of a subtype of BPD with a childhood history of ADHD, hypothesis that has been recently confirmed by Stepp and colleagues in a longitudinal study on adolescent girls.

R2-C2. The sampling and research design of the current study are problematic.

R2-A2. We report here some arguments to answer to the commentaires concerning the sampling bias. As correctly pointed by the reviewer, BPD may be reliably diagnosed in adolescence (Becker et al., 1999) with prevalence rates in the community similar to those found in adults (Zanarini et al., 2003). If the notion of stability of BPD features from adolescence to adulthood is more controversial, however, this is not unique to adolescents (Zanarini et al., 2010).

In the present study, we choose to use a two-stage procedure to increase the validity of the diagnosis of BPD. The screening procedure was conducted by experienced clinicians in university settings who were informed of the research protocol and had previously participated in research meetings within the Network to discuss DSM-IV criteria for BPD diagnosis, in particular, the question of the one-year duration of the symptoms, the pervasive and persistent nature of the traits unlikely to be limited to episodes of an Axis-I disorder. Although we did not collect reliability data on this screening phase, we gave to clinicians a questionnaire specifying all BPD DSM-IV criteria that had to be fulfilled before referring to the research team. As correctly suggested by the reviewer, this part of the procedure can represent a potential sampling bias that could undermines the external validity of the diagnosis (its generalizability to the rest of the population). However, this is common to every clinical research studies on spontaneously consulting participants compared to prevalence studies. This is why we paid special attention to the diagnostic phase in the research protocol with repeated training and
assessment of interrater reliability for Axis-I and Axis-II diagnoses. Final diagnoses were established in a consensus conference on the basis of the interviews and the clinical records, thus strengthening the validity of BPD diagnosis and reducing the risk of misdiagnoses.

In the methods section we have tried to better describe the sampling and research procedure of the study.

The potential bias of the sampling has been acknowledged in the limitations of the study.

To better describe the clinical sample, we reported some comorbidity data concerning the sample in the results section.

**Modifications included in the revised text**

In the “methods” section

During the period between January and December 2007, all consecutively admitted adolescent in and out-patients (aged 15 to 19) were clinically screened by the consulting psychiatrists to look for a diagnosis of BPD according to the DSM-IV criteria. Before the beginning of the project, the outline of the study had been presented to clinicians in research meetings and specific questions concerning the DSM-IV criteria for BDP diagnosis had been discussed. Clinicians had to fulfill a questionnaire specifying all BPD DSM-IV criteria before referring the participants to the research team. Exclusion criteria were a diagnosis of schizophrenia or any chronic and/or serious medical illness involving vital prognosis. Adolescents fulfilling the criteria for BPD according to clinicians were further investigated with a research protocol which consisted in a diagnostic evaluation of Axis-I and Axis-II disorders (with confirmation of the BPD diagnosis with the SIDP-IV interview) and a self-report questionnaire eliciting socio-demographic data and psychopathological features. For the present study, only participants with a confirmed diagnosis of BPD according to the SIDP-IV interview were included in the final sample.

In the “results” section

The majority of adolescents met the criteria for at least one Axis-I disorder (N=76, 89%). Mood disorders were the most frequently observed comorbidity (N=47, 55.3%) followed by eating disorders (N=27, 31.8%), disruptive behavior disorders (N=22, 25.9%), and substance use disorders (N=17, 20%).

In the “Limitations” section

The second limit concerns the small sample size of the study and the potential sample selection bias of the screening phase conducted by the consulting clinicians without performing a systematic between-center inter-rater reliability. This may have reduced the statistical power of the analyses and the generalizability of the results. For instance, our sample included a majority of female patients. It is commonly agreed that ADHD is less frequent in females, with a predominance of purely inattentional forms. It is possible that the high levels of impulsive features associated with ADHD could be due to a referral bias of our specific clinical sample composed of severe forms of BPD female adolescents. Although the size of the sample of BPD participants was reasonable compared to other studies, particularly since it was limited to adolescents with a well-characterized BPD diagnosis, results should be interpreted with caution as to know what the likelihood might be that the sample is actually representative of BPD adolescents.

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**R2-C3.** The between-center variability of the participants must be entered in the design of study and in the statistical analyses

**R2-A3.** In what concerns the between-center variability of the participants, which could be considered as a potential bias in the results, we proceed in two ways: 1) we compared the centres on age, educational level, numbers of borderline criteria and in/outpatient ratio and 2) we modified the statistical plan and we used the Mantel-Haenszel chi-square statistic for categorical variables and the nested ANOVA statistic controlling for the recruitment centers for the continuous variables. The variable “recruitment centers,” was also introduced as a independent variable in the regression analyses. To reduce the number of statistical comparisons and comparisons with few observations, Axis-I and Axis-II diagnoses were included as groups of related disorders. This modified statistical plan resulted in some minor modifications in the strength, but not in the direction or type, of the observed associations.
Modifications included in the revised text

In the “statistical analysis” section
To take into account the variability between centers, we used the Mantel-Haenszel chi-square statistic for categorical variables, preceded by the Breslow-Day test to assess the homogeneity of the odds ratios of the recruitment centres. For the continuous variables, we used the nested ANOVA statistic controlling for the recruitment centers. To reduce the number of statistical comparisons and comparisons with few observations, Axis-I and Axis-II diagnoses were included as groups of related disorders.

In the “results” section
There were no significant differences between the recruitment centres in terms of subject age and educational level, numbers of borderline criteria and in/outpatient ratio.

R2-C4. Use of the adolescent version of the BIS-11.

R2-A4. We agree that it could have been more interesting in our sample to use the adolescent version of the BIS-11. However, up to now, we do not dispose of a validated version of the adolescent scale, whereas the adult version of the BIS-11 has been translated and validated in French in a sample which included a large number of adolescents (paper submitted, Caci et al.). Although the use of the adult version of the BIS-11 in adolescents older than 15 can be found in the literature on impulsivity, we have acknowledged this point in the limitations of the study.

Concerning the results of the relationships between the types of impulsivity and BPD-ADHD adolescents, it must be noted that the Cognitive dimension of the BIS-11 (which is a second-order factor) is constructed on the basis of the first-order factors attention and cognitive instability. It refers to the ability to focus on the task at hand and to the cognitive speed in decision making). For this reason this factor is currently labeled Attentional/Cognitive Impulsiveness ad as so it will be called in the text (see the International Society for Research on Impulsivity’ webpage and JH Patton et al., Journal of Clinical Psychology, 51, 768-774).

Modifications included in the revised text

In the “limitations of the study” section
Finally, to assess impulsivity, we used the validated adult version of the Barratt Impulsiveness Scale. Although the use of the adult version of the BIS-11 in adolescents can be found in the literature on impulsivity [58, 59], it could have been interesting to use the adolescent version of the scale which has been shown to present a different structure from the adult one.

R2-C5. There are no agreed upon data showing that the DIB-R represent a severity index of DSM-IV BPD, particularly in adolescence.

R2-A5. We agree that DIB scores could be more appropriately considered as a way to characterize the clinical profiles of these patients. Moreover, this is in line with the suggestion raised in the literature, on which we agree, that the association between ADHD and BPD could define a specific subtype of BPD. The heading of the section and the text have been modified to indicate a difference in the borderline symptomatological profile of patients according to ADHD.

Modifications included in the revised text

In the “results” section
BPD-ADHD adolescents showed a different profile of borderline symptoms as assessed by the DIB compared to BPD adolescents.
The authors report a prevalence of current ADHD symptoms of 11% which is the lowest among all the studies that the authors reported in the introduction.

Although the current prevalence observed in our study may appear not very high, up to 46% of the subjects presented at least one symptom with a clinical or subclinical significance and some impact on functioning, eventually qualifying for a diagnosis of ADHD-NOS. However, this is not the same as a full diagnosis of ADHD which requires the association of a pervasive pattern of symptoms with a significant impact on the overall functioning of the subject. This comment was already present in the discussion. A comment on the generalizability of the results has been added.

**Modifications included in the revised text**

In the "limitations" section

Results should be interpreted with caution as to know what the likelihood might be that the sample is actually representative of BPD adolescents.

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The lack of a control group of non-BPD adolescents strongly undermine the specificity of the findings of the present study.

The overall project of the study, included a control sample of normal adolescents (for more details, see Corcos et al., 2010 and Caihol et al., accepted in JPD). For this study we decided not to present these data because our aim was to contrast BPD adolescents with and without ADHD. All BPD participants had a severe clinical profile with almost all comparisons (Axis I or self-questionnaires) being significant compared to normal controls. This choice was also made to avoid multiple comparisons and facilitate the reading of the text. Data are available if necessary.