Author's response to reviews

Title: A randomized trial for an evolutionary-driven psychological intervention for depression

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Author's response to reviews: see over
Dear editor,

Please find our answers interspersed below.

Thank you for your consideration,

Cezar Giosan, Ph.D.

Reviewer's report
Title: Darwinian-driven cognitive therapy for depression: A therapy protocol
Version: 2 Date: 17 September 2013
Reviewer: Tara Donker

Reviewer's report:
This paper describes the design of a RCT aimed to develop and examine an evolutionary-driven cognitive therapy protocol for depression. While evidence-based treatments for depression exist, a substantial amount of patients do not respond to this. Therefore, efforts to improve evidence-based treatments are important. The current clinical trial is designed to contribute to this desideratum. The manuscript is well-written, and is well-organized. The manuscript provides an account of the rationale and methodology of a study. However, a detailed account of the hypothesis has not been described and some methodological details are not provided.

1. Will the study design adequately test the hypothesis?

The trial aims to compare the effect of an evolutionary-driven Cognitive Therapy (ED-CT) to Cognitive Therapy (CT). The study has been set up as a randomized controlled trial. As mentioned previously, a detailed description of the hypothesis is lacking. Therefore, I cannot assess whether the study design will adequately test the hypothesis.

Because the two conditions are both active treatments, the design will be a (randomized) non-inferiority, equivalence or superiority trial (e.g. is one treatment non-inferior, equivalent or superior to the other treatment?). Since the authors state that the trial is designed to contribute to the efforts to improve evidence-based treatments, the appropriate design of the study would be a superiority trial, with the hypothesis that ED-CT will be superior to CT.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

The method section contains detailed information and is well organized. However, a few details which are currently not described need to be added to allow replication of the work:
- Information on the background of the therapists giving CT and ED-CT and whether there will be different therapists for the two conditions? If not, there can be a contamination effect which will might bias the results.
- Training of assessors
- Plans to promote participant retention and complete follow-up is missing

3. Is the planned statistical analysis appropriate?

The power calculations seem to be appropriate for a RCT-design. However, the design of the study seems to be a superiority-trial. The power calculations and needed sample size to reach sufficient power for a RCT, or a non-inferiority, equivalence, or superiority trial differ from each other.

Furthermore, the authors suggest using ANCOVA to analyze the data. However, given the different methods of data recruitment (several clinics, newspapers, etc.) which might attract different types of populations, and expected drop-out which could be analyzed with more sophisticated methods, I would recommend multilevel analyses (e.g. linear mixed models, mixed models repeated measures [MMRM]. The MMRM is able to account for correlations among repeated measurements for participants and can include participants with missing data. The MMRM use all available data and yield unbiased and efficient estimates of effectiveness under missing completely at random (MCAR) and missing at random (MAR) assumptions.

Besides a possible power problem, and the lack of a description how to analyze mediators, I do not believe the authors can conduct mediator analyses with this type of design, due to the lack of a control-group (CT is an active treatment).

4. Is the writing acceptable?
The manuscript is well-written and acceptable for publication.

Notes to the author

Major Essential Revisions

1. Please add a detailed account of the hypothesis to the manuscript.

The trial aims to compare the effect of an evolutionary-driven Cognitive Therapy (ED-CT) to Cognitive Therapy (CT). The study has been set up as a randomized controlled trial. Since the authors state that the trial is designed to contribute to the efforts to improve evidence-based treatments, should the appropriate design of the study not be a RCT, but a superiority trial, with the hypothesis that ED-CT will be superior to CT? When the two conditions are both active treatments, the design could be a (randomized) non-inferiority, equivalence or superiority trial (e.g. is one treatment non-inferior, equivalent or superior to the other treatment?). If so, this will have implications for the sample size needed to achieve sufficient power.
The trial was indeed designed as a superiority trial. The main advantage of this design is that all participants receive an active treatment for depression symptoms while allowing us to determine whether ED-CT is superior to the standard CT therapy. As suggested, we have replaced “randomized clinical trials” with “randomized trial” throughout the manuscript and included the trial hypothesis and design in the manuscript (see page 7). The revised power analysis reads now as follows (page 18): “The sample size to provide adequate power (≥ 0.80) for this study, with moderate effect sizes (Cohen d = .45) and ICC =.5, is calculated at 98 participants. A dropout rate of 25% and a 10% no-show after the first evaluation are assumed, necessitating a total of 140 initial participants”.

Minor Essential Revisions
Title:
2. Please add the design of the trial to the title (e.g. RCT, superiority trial?)

Abstract:
3. Methods/design: please include with which diagnostic instrument diagnoses are assessed

To evaluate the clinical status of the participants, we used the following parts of the Structured Clinical Interview for DSM-IV (SCID): the Overview, Mood Episodes module, and Anxiety Disorders module. As suggested, we have introduced this clarification in the Abstract section of the manuscript.

Methods:
4. CT and ED-CT: Please provide information on the background of the therapists giving CT and ED-CT (e.g. their educational background, specific training for the CT and ED-CT). Will there be different therapists for the two conditions? If not, there can be a contamination effect which might bias the results.

The CT and ED-CT protocols are each delivered by two different psychotherapists. All four psychotherapists are certified by the Romanian Board of Psychologists and have extensive training in CT, completed through the Romanian Association of Cognitive and Behavioral Psychotherapies. The two psychotherapists delivering the ED-CT protocol have received additional training in evolutionary psychology (e.g., optional graduate-level courses) and specific instructions regarding the evolutionary components of the ED-CT protocol1: they went through six weeks of training, based on the protocol manual for the ED-CT group, under the direct supervision of the principal investigator. As suggested, we have introduced the information on the background of the therapists in the Procedure section of this manuscript (see page 13).

5. Will the doctoral level clinical psychologist undergo SCID training? How will training take place of the diagnostic interview?

1 Details about the ED-CT manual can be obtained from the first author
The doctoral level clinical psychologists are certified by the Romanian Board of Psychologists, and are currently supervised in their clinical activity by senior psychologists. Also, they have been trained in using SCID for clinical assessments as part of their MA clinical psychology program, at Babeș-Bolyai University. Additionally, for the purposes of this study, all of them received specific practical training in administering the SCID modules used in this protocol. To ensure the adequacy of the assessment procedures, all the initial clinical evaluations are audio recorded and randomly verified by a senior clinical psychologist (i.e., the last author). Moreover, all the potential eligible cases are discussed with the same senior clinical psychologist before enrolling. We have introduced this additional information in the Screening section of this manuscript (see page 7).

6. Please move CSQ and other information about instruments and assessment times from the ED-CT group description to the instrument/assessment section

As suggested, we have removed the CSQ and other information about instruments and assessment times from the ED-CT group description to The Measures section of this manuscript (see page 12).

7. Please report on any plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

We thank the reviewer for raising this important issue. We’ve planned to use several strategies to promote participants retention and follow-up completion, described in the following paragraph, now included in the manuscript (see page 17):

“To promote participant retention and follow-up completion, we will use several strategies. First and foremost, the participants will receive a clear and complete description about the project, including, but not limited to, information regarding the type of psychotherapy offered - CBT, which is the standard of care in the psychological treatment for depression, having remission rates comparable to medication, and being more efficient than medication alone on the long term. The participants will also be explained that the treatment is provided for free by therapists trained in the most highly rated department of clinical psychology and psychotherapy in the country. (As in Romania psychotherapy sessions are not reimbursed by health insurance companies, we expect that this financial factor will act as a motivator to stay in treatment.). Furthermore, the therapy sessions will be scheduled in a flexible manner, according to the patients’ preferences. Additionally, the therapist will call the participant the day before the planned session for a brief check and to ensure continuation in therapy.

Most importantly, to ensure retention, at the end of each session the participants will complete the “Intend to attend” one-item scale, which is meant to promote the commitment in the therapeutic process as well as to detect any issues that might require the therapist’s special attention.

Lastly, the therapists will carefully prepare the end of the therapy and explain to the participants that they will keep in touch. The therapists will also remind the patients at this time

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2 See national classification of Romanian psychology programs and departments, at http://chestionar.uefiscdi.ro/docs/programe_de_studii.pdf
that the free treatment was possible because of a research grant, which makes the collection of follow-up measurements essential.”

8. The power calculations seem to be appropriate for a RCT-design. However, the design of the study seems to be a superiority-trial. The power calculations and needed sample size to reach sufficient power for a RCT, or a non-inferiority, equivalence, or superiority trial differ from each other. Also, please justify the effect size $d=0.45$. For two active treatments, a between-group difference of $d=0.46$ at post-test is quite large. This trial might suffer from power problems.

We reconsidered our analytical approach and, as suggested, we decided to employ mixed-effect models [MMRM] as an alternative methodology for this trial (see page 18). Though the ANCOVA method is appropriate for the analysis of BDI outcomes at the end of treatment, we agree that the mixed-effect methodology has advantages when modeling repeatedly measured clinical data, particularly in its ability to accommodate participants with missing data and examine sensitivity of results to the MCAR and MAR assumptions (Leon and Davis, 2009). As mentioned earlier, we collect data using the Intend to Attend scale, which has a utility in sensitivity analysis (see Leon, Demirtas & Hedeker, 2007).

Power calculations were repeated to accommodate for this analytic approach. Meta-analyses generally report medium effect sizes, and the standard deviation in numerous studies is $10$, yielding a group difference of $5$. In line with these reports, we assumed that the smallest clinically important difference between groups was $5$ points (standard deviation was assumed to be $10$), which translates into an effect size of roughly $.45$ and indicates that the mean of the experimental group is about half a standard deviation larger than the mean of the treatment-as-usual group. We believe that it is reasonable to expect this size of the effect based on findings from a recent meta-analysis (Cuijpers et al, 2010). Power calculations were based on the Diggle algorithm (Diggle et al, 2002) for longitudinal models. We set alpha at .05 two-tailed, ICC at .5, 4 measurement occasions (baseline, after session 4 and 8) and $d$ at $.45$. A sample size of 49 per group was found to be sufficient at 80% power to detect the effect. We plan to recruit a sample size that exceeds this amount (140 participants) to account for no-shows and attrition.

9. The authors suggest using ANCOVA to analyze the data. However, given the expected drop-out and more robust assumptions to estimate models, I would recommend using more sophisticated methods, such as GEE or mixed models (linear mixed models, mixed models repeated measures [MRMM]). The MMRM is able to account for correlations among repeated measurements for participants and can include participants with missing data. The MMRM use all available data and yield unbiased and efficient estimates of effectiveness under missing completely at random (MCAR) and missing at random (MAR) assumptions.

We addressed this concern in our answer to the prior comment. Please see above.

10. The method to assess mediators is missing (e.g., what do the authors expect which variables are mediating? Which analyses will be used?). Also, I wonder whether there will be sufficient power to assess mediators. Did the authors perform a power calculation for this? Besides this,
only mediator analyses can be performed when there is a significant difference between the two active treatments at post-test.

We agree that there is no sufficient power to assess the mediators. At the end of this study we will investigate, in an exploratory manner, whether there are group differences on what we assume are mechanisms of change. Should such differences be found, we will test their roles in mediation in a future study, on a larger sample and with adequate design.

Minor issues not for publication
11. There are some typographical errors and grammatical throughout the manuscript

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests