PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A study protocol for a prospective cohort study examining the predictive potential of dynamic symptom networks for the onset and progression of psychosis: The Mapping Individual Routes of Risk and Resilience (Mirorr) study
AUTHORS	Booij, Sanne; Wichers, Marieke; de Jonge, Peter; Sytema, Sjoerd; van Os, Jim; Wunderink, Lex; Wigman, Johanna

VERSION 1 – REVIEW

REVIEWER	Peter Uhlhaas Univ. of Glasgow
REVIEW RETURNED	23-Aug-2017

GENERAL COMMENTS	Booij et al present an interesting study protocol of a project that examines the emergence of psychopathology in different clinical and non-clinical groups using a staging-model. Overall, I think that this protocol is useful in it its present form. I would appreciate, however, if the following points are addressed prior to publication: 1) It would be useful if the authors summarize key hypotheses 2) Discussion/Conclusion: Is very short. This section could be expanded summarizing the impact and potential implication of the findings. 3) Data-sharing: Will the data be made available?

REVIEWER	Angus MacBeth University of Edinburgh, Scotland, UK
REVIEW RETURNED	01-Sep-2017

GENERAL COMMENTS	The protocol is an admirable project, that seeks to deliver a more nuanced, sensitive and specific modelling of risk of progression within the full spectrum of psychotic phenomena, using dynamic measurement of functioning and symptoms. The project is novel and ambitious, but well described and sufficiently methodologically rigorous to meet it's stated aims. I have some minor queries, mainly around the presentation of the method and rationale. Abstract: Although there is a 'developmental' aspect to the strengths, I suggest 'developmental' could be confusing in this context, so perhaps retain 'dynamic' in the strengths bullet points?

	Intro lines 115 – 120: The evidence around clinical staging, although certainly theoretically valid and appropriate, seems to be based around review papers – could the authors be clearer on the empirical basis for staging? In contrast the paragraph on dynamic variation and predictive issues with static models is particularly clear. From a purely stylistic perspective, I thought that the "The Mirorr study" and "Aims and Hypotheses" would be better coming after the paragraph on "A network approach to psychopathology". Following from this, if these sections are re-formatted, does this introduce some redundancy between the "Aims and hypotheses" and the "Objectives" sections? Does the section explaining Figure 1 perhaps need some additional detail around how the network was constructed? Is this a theoretical schematic, or is there an empirical basis? Given the date of Trial registration, is the recruitment rollout timeframe in the Procedures accurate? E.g. start recruitment September 2015? The methodology of the trial is impressive, and speaks to a confidence and knowledge of the measures, and the implementation of a dynamic sampling approach. The analyses, although complex and somewhat novel appear to be powered adequately, and seem appropriate to the data. Although the authors estimate missing data, is there any inclusion of loss to follow-up? From an ethical perspective, is there a procedure for managing significant deterioration in an individual's functioning? This may be beyond the parameters of the project, but should perhaps be stated. It may be worth stating, that although the dynamic modelling should, in theory, give a richer and more nuanced picture of how functioning changes over time, the study will not be a direct test of dynamic modelling against static modelling of psychopathology (although perhaps I have misunderstood this point).

REVIEWER	Ian Kelleher Royal College of Surgeons in Ireland
REVIEW RETURNED	11-Sep-2017

GENERAL COMMENTS	This is a very well written protocol for an impressive study. I can think of little to criticise. Just one typo I noticed: "along with screening questionnaires and an informed consent form will be send to potential participants" typo: should be 'sent'.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 (Peter Uhlhaas)
Booij et al present an interesting study protocol of a project that examines the emergence of psychopathology in different clinical and non-clinical groups using a staging-model.
Overall, I think that this protocol is useful in it its present form. I would appreciate, however, if the following points are addressed prior to publication:

1) It would be useful if the authors summarize key hypotheses.

Reply: We agree that this might be useful. Therefore, we have added a sentence to the paragraph: 'Aims and hypotheses', page 9/10:

"With the Mirorr study, we aim to investigate the hypothesis of dynamic symptom networks as the basis of psychopathology in general and psychosis in particular. The key hypothesis to be tested centers on the question whether individual networks of a broad scope of transdiagnostic symptoms can predict course and outcome of early psychopathology in young individuals at increased risk for psychosis and other severe mental illness. Furthermore, ….".

2) Discussion/Conclusion: Is very short. This section could be expanded summarizing the impact and potential implication of the findings.

Reply: We have expanded the conclusion section (page 24/25) by addressing multiple potential implications for science and clinic. In addition, we added a concluding statement regarding these implications:

"Current diagnostic systems are increasingly criticized by mental health professionals, researchers and users of mental health care [9, 12, 26, 111]. Conceptualization of psychopathology in terms of (i) clinical staging (at macro level) and (ii) dynamic, individual symptom networks (at a more micro level), which is the purpose of this study, represents a promising avenue to tackle both scientific and clinical problems. From a scientific perspective, improving our understanding of the factors driving the development of psychopathology by investigating how symptoms influence each other will enhance our ability to identify valid phenotypes to predict onset of (psychotic) mental disorders and to link with other relevant information (e.g., genetic or endophenotypic variation). From a clinical perspective, a better understanding of why psychotic symptoms can lead to a need for care in some, but resolve spontaneously in others, will help mental health professionals to adequately recognize the early needs of individuals who are likely to develop mental illness or functional impairments. This is important because interventions are both more effective and less invasive when applied early in the course of illness[112]. In more progressive clinical stages, deeper knowledge of the dynamic ways symptoms impact on each other will help to differentiate between those likely to recover or to deteriorate and between those likely to be responsive or resistant to treatment. Using symptom networks will improve the application of individually tailored, person-based interventions, adapted to one's current clinical stage and symptomatology, as different stages require different types of intervention. Since personalised interventions better fit individual needs, they will result in enhanced treatment response[113], reducing the costs of mental disorders at both personal and societal level. Thus, the use of symptom networks will assist in improving and fine-tuning dynamic models of psychopathology, which will stimulate both clinical (in terms of both diagnostics and intervention) and scientific progress."

3) Data-sharing: Will the data be made available?

Reply: Yes, data will be available upon request after the study has ended and the main study results have been published. This is stated in the Ethics and dissemination section, page 24:

”Data gathering was not completed when this manuscript was submitted. After the study has ended and the main results have been published, the data obtained by this study will become available on reasonable request. Requests should be sent to j.t.w.wigman@umcg.nl with the topic name MIRORR data.”

Reviewer: 2 (Angus MacBeth)
The protocol is an admirable project, that seeks to deliver a more nuanced, sensitive and specific modelling of risk of progression within the full spectrum of psychotic phenomena, using dynamic measurement of functioning and symptoms. The project is novel and ambitious, but well described and sufficiently methodologically rigorous to meet its stated aims. I have some minor queries, mainly around the presentation of the method and rationale.

1) Abstract: Although there is a ‘developmental’ aspect to the strengths, I suggest ‘developmental’ could be confusing in this context, so perhaps retain ‘dynamic’ in the strengths bullet points?

Reply: We feel this is a good suggestion and have changed ‘developmental’ to ‘dynamic’ in the third point under ‘Strengths and limitations of the study’.

2) Intro lines 115 – 120: The evidence around clinical staging, although certainly theoretically valid and appropriate, seems to be based around review papers – could the authors be clearer on the empirical basis for staging? In contrast, the paragraph on dynamic variation and predictive issues with static models is particularly clear.

Reply: The reviewer is right that a lot of work around clinical staging is still heuristic, and awaits thorough testing. To make it more clear what is known and what is not known, we have now summarized the empirical evidence for clinical staging of psychosis. We added this to the introduction section, page 7:

“This model offers a theoretical representation that seems to fit better to the true nature and development of psychopathology [9-11, 26], and hence may improve diagnostic accuracy. It has been developed most extensively in the context of psychosis [23, 25, 27], but needs further empirical validation. Longitudinal studies assessing predictive validity of the model have mostly concentrated around the transition from stage 1b (ultra-high risk) to stage 2 (first psychotic episode), and found 3-year transition rates of 36% [29]. In addition, some biological and cognitive measures seem to be more abnormal in more severe stages, and these measures seem to change in patients who progress in stage [28, 30]. Finally, some treatments seem more effective for individuals in early stages [30]. Taken together, these studies provide at least some support for the clinical staging model of psychosis. However, many questions still remain, e.g. about what drives progression through subsequent stages and how the thresholds between the stages should be defined exactly.”

3) From a purely stylistic perspective, I thought that the “The Mirorr study” and “Aims and Hypotheses” would be better coming after the paragraph on “A network approach to psychopathology”.

Reply: We think this is a very helpful suggestion for improving the structure of the manuscript. We have now placed the paragraph “A network approach to psychopathology” before the aims and hypotheses and the unique properties of the Mirorr study. We also agree (see point 4) that there is now some redundancy between the “Aims and hypotheses” and “Objectives”. We feel that the section “Aims and hypotheses” best describes the purpose of the Mirorr study. Hence, we removed the “Objectives” section.

4) Following from this, if these sections are re-formatted, does this introduce some redundancy between the “Aims and hypotheses” and the “Objectives” sections?

Reply: Please, see our response to the previous point.

5) Does the section explaining Figure 1 perhaps need some additional detail around how the network was constructed? Is this a theoretical schematic, or is there an empirical basis?

Reply: This figure is indeed a theoretical figure, created purely for illustrative purposes. We have added this to the figure legend.

6) Given the date of Trial registration, is the recruitment rollout timeframe in the Procedures accurate? E.g. start recruitment September 2015?

Reply: The recruitment indeed started on September 2015. Studies can be registered at official trial registers as long as they are still in the data collection phase.

7) The methodology of the trial is impressive, and speaks to a confidence and knowledge of the measures, and the implementation of a dynamic sampling approach.

Reply: Thank you.

8) The analyses, although complex and somewhat novel appear to be powered adequately, and seem appropriate to the data.

Reply: Thank you.

9) Although the authors estimate missing data, is there any inclusion of loss to follow-up?

Reply: It is hard to estimate the potential loss to follow-up. However, we try to minimize this by a) explaining clearly at the beginning of the study that all follow-ups are also an important part of the study to ensure optimal commitment, b) keeping elaborate contact info of the participants on both cell-phone numbers and email addresses, c) investing in personal contact that is matched, as far as possible, to individual needs of our participants.

10) From an ethical perspective, is there a procedure for managing significant deterioration in an individual’s functioning? This may be beyond the parameters of the project, but should perhaps be stated.

Reply: We have several protocols for situations where clinical care may be warranted, e.g. in case of disclosure of suicidal thoughts, or in case of UHR status in one of the lower-risk groups. In case of poor functioning or high levels of mental problems in participants of subgroup 1, we advise participants to seek help with, for example, their GP. Participants in the other subgroups (2-4) are already in clinical care. A sentence is added to the "Ethics and dissemination" section, page 23:

"Several protocols have been developed for situations where clinical care may be warranted, e.g. in case of disclosure of suicidal thoughts, or in case of UHR status in one of the lower risk groups."

11) It may be worth stating, that although the dynamic modelling should, in theory, give a richer and more nuanced picture of how functioning changes over time, the study will not be a direct test of dynamic modelling against static modelling of psychopathology (although perhaps I have misunderstood this point).

Reply: The reviewer raises an important point here. We feel that this approach should not so much be seen as a radical alternative to static modeling of psychopathology, but rather as a complementary approach, as each approach we can take offers relevant information for other types of questions. Although we do aim to test the predictive value of more dynamic network models against that of more static assessments, we are mainly interested in the additional information we can learn from taking this dynamic, transdiagnostic approach. As it was not clear for the reviewer whether we explicitly test the dynamic modelling against static modelling, we now explicitly mention in the "Aims and hypotheses" section (page 10) that we will compare the network characteristics to more static assessments of symptom severity:

"Finally, we will evaluate the predictive potential of these characteristics against (more) static assessments of symptom severity."

Reviewer: 3 (Ian Kelleher)
This is a very well written protocol for an impressive study. I can think of little to criticise.
Just one typo I noticed: "along with screening questionnaires and an informed consent form will be send to potential participants" typo: should be 'sent'.
Reply: Thanks to the reviewer for the compliments. The typo has been corrected.

VERSION 2 – REVIEW

REVIEWER	Angus MacBeth University of Edinburgh, Scotland, UK
REVIEW RETURNED	02-Oct-2017

GENERAL COMMENTS	The revisions are robust and well-handled. The response from the authors is both thoughtful and considerate. I have no further issues to raise with the manuscript.