Response to reviewers

The Ontology of Mental Disease: a study preparatory to a realist representation of the Diagnostic and Statistic Manual of Mental Disorders

Werner Ceusters and Barry Smith

Version: 1 Date: 14 June 2010

Reviewer number: 1

This paper proposes definitions for mental disease-related terms, which constitutes a high-level ontology of mental diseases.
This artifact embraces realism-based ontology. The proposed definitions are analyzed in the context of DSM and Pie's staged model of mental disease. One particular mental disease, Tourette's, is presented as an illustration.

→ [R1] That is correct.

The authors claim they have clarified the terminology of mental diseases.

→ [R2]. That is not correct: we don't make that claim. We argued that the terminology used is ambiguous, as witnessed by what was (and still is) written in the section on the purpose of definitions: *"The definitions formulated in the foregoing are not definitions for familiar words or terms in their familiar usage. Thus our proposed definitions for the terms 'mental disease', 'disease course', and 'disorder' clearly do not capture the uses of these terms in the literature, not least because consistent distinctions between these and cognate terms are not in general drawn."*. We do claim however that there would be fewer ambiguities if the terms that we propose would be used exclusively in the sense that we proposed.

This work on mental disease ontology is relevant to JBMS. The paper is well written. It does not require any specific psychiatric knowledge. It should be of particular interest to this fraction of the readership with an interest in scholarly treaties and realism-based ontology.

This reviewer has two major reservations about this paper, regarding its objectives and organization.

Objectives
The statement of objectives is confusing. It is unclear throughout the manuscript whether the present work is an ontology of mental disease or a series of definitions, which will contribute to creating such an artifact in the future. My understanding is that these definitions constitute the top-level (i.e., the foundations) of such an ontology. If this is the case, this should be reflected more clearly in the title and throughout the paper.

→ [R3] We accept this proposal. We changed the title and shifted the focus of the paper on the foundations.

And a clear path toward the ontology of MDs should be articulated.
→ [R4] We added a section to this effect.

The list of definitions clearly constitutes the tangible contribution of this paper. It is unclear the extent to which the Tourette example actually helps make the case for the ontology, as it does not seem directly linked to the definitions. The referent tracking example in Table 5 resembles what one would expect to find in an EHR, but the proposed set of definitions does not directly apply to this example.

→ [R5] We agree that this does not show in this paper. Doing so would make the paper considerably longer. So we decided to leave this out and reserve it for a follow up paper.

Organization
Overall, the paper is extremely verbose and unnecessarily long.

→ [R6] We reduced it considerably in light of [R3] and [R5]

The authors have elected to follow the traditional plan of an experimental paper, with sections such as Hypothesis, Methods and Results. However, this work is NOT an experiment, but rather a reflection on approaches to describing and representing mental disease, resulting in the proposition of a set of definitions. As a consequence of this mismatch, the Methods section contains essentially background material (often harvested from previous publications of the authors). There probably should not be any Methods section in this paper.

→ [R7] We disagree in part. It is important for the reader, and for clear understanding and adoption of our methodology, that this methodology is explained. Too often, ontologies are built without a sound methodology. But we did limit this section in light of the proposed focus and changed the heading to ‘approach’ instead of ‘methods’.

Along the same lines, the validation of the so-called hypothesis is not clearly established.
The preference of this reviewer would be for the authors to rewrite this paper as a reflection on the definition of terms related to mental disease, removing the pseudo-experimental setting, and making the proposed set of definitions the main contribution of this paper.

→ [R8] We did so

The current Methods sections would then become part of the Background
section, which should be considerably shortened.

→ [R9] We kept the methodology section as argued for in [R7] with a new title, but shortened it.

A clear path to creating a full-fledged ontology of mental disease should be outlined, and the relations of this artifact to clinical classifications clarified.

→ [R10] We added a section to this effect (see also [R4])

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer number: 2

As an MD and practicing psychiatrist I am qualified as a domain expert in this field, including extensive experience with the Diagnostic and Statistical Manual of Mental Disorders. I am a predoctoral student in medical informatics, and have some formal and informal training with respect to ontologies, but am NOT an expert in this domain of medical informatics. I found that the paper was very understandable after reading some of the major references. I have truly enjoyed reading at, and have learned a great deal. Accordingly, some of my comments may be directed at making this paper more palatable to a wider audience, although this may or may not be desired for this journal and/or authors.

Most of my comments relate to typographic, structural, and organizational issues. I think the psychiatric domain is well represented and examples are explained. Arguably, Tourette's Syndrome and related disorders have some of the clearest symptoms(e.g. vocal and motor tics) in the field of psychiatry. This does not refute any of the observations or conclusions in the paper, but this fact may be worth mentioning in the paper or the conclusion.

→ [R11] We removed the example from the shortened, more focused paper as requested by the other reviewers. We will for sure address the point in a follow paper focused on the use of the ontology in a clinical setting.

The paper is excellent and provides a well-thought out and explained introduction to realist based ontologies, and ontologies of mental illness, even to a more generalist audience. This is a very important and thoughtful analysis of a crucial problem in psychiatry, and researchers in this domain will greatly benefit from reading this article.
The introductory portion of the paper is excellent, and does a concise but complete job of summing up major existing problems in psychiatric classification, including describing the current standard definitions(s) of a mental disorder,

describing the dimensional vs categorical tension in the field, and addressing cultural issues. The referent tracking section adeptly uses examples relevant to psychiatry.

→ [R12] We left some of these aspects out here, to pick them up again in the follow up paper.

It may be helpful to insert a table summarizing Pies model (particularly the 5 stages) into the paper, as as it is referred to very frequently.

→ [R13] The summary was provided in the text. We used bullets to make it more clear.

Itemized comments:

Page 13. in L2 may want to explicitly state that cognitive representations of this reality as embodied in observations and interpretations on the part of patient(in addition to clinicians and others), as this is referred to on page 21 of the paper.

→ [R14] we did so

Page 16. This sentence fragment in the middle paragraph is awkward--"all members of a GRP that exist at some given time are further themselves such as to exist at that time."

→ [R15] deleted that sentence. It was redundant.

Page 21. In the paragraph below the insertion of Figure 1(or possibly earlier in the paper), it would be helpful to clinicians to reiterate the formal definition of a disease as a disposition,

→ [R16] we referred for this to the discussion section

along with the other definitions and relational terms in Table 2,

→ [R17] that would make the paper, already claimed to be verbose, even more verbose, unfortunately. We believe the definitions are clear, and the essential ones are addressed in depth in the discussion section. More information can be found in the referenced papers which are publicly available.

and possibly place in a diagram of these terms and relations.

→ [R18] that has been done: we added a Figure 2

Although the paragraph is clear and makes sense, the loose definitions of disease and disorder that clinicians use make the first read through of these concepts confusing, and it may be helpful to at least explicitly state(again) the definition of these terms in contrast to the their (vague) meanings when used in a clinical setting.

→ [R19] we did so in the discussion

I think some elaboration on the definition of a disposition at this point, as opposed to the relation disposes to will also be helpful. Though the term disposition has been clearly defined in the references, for a non expert audience, it will be helpful to explicitly state the definition and relations that are relevant.

→ [R20] We did so in the discussion.

This elaboration is not necessary for the terms process, representation, and quality, as their definitions are more in line with their use in the clinical setting.... These issues are nicely addressed in the discussion, but earlier iteration may make the manuscript easier to follow for readers....Obviously this comment is only relevant if the authors wish to reach a broader audience.....

Page 22. I think NRRU should be NRU for consistency with Table 1.

→ [R21] This typo has been corrected

Page 23. In the Definitions for stage 1, bullet # 2 uses the term bodily process, while bullets 4-8 use the terms quality, processes, process, and interpersonal process. Should/can the word bodily also precede the above terms in bullets 4-7 and precede process (after interpersonal) in bullet 8?

→ [R22] That would be redundant. The new figure 2 makes it clearer however

Page 25. May want to explicitly state in example that in 1988 DSM-III was in use and in 1994 DSM-IV was in use.

→ [R23] The example has been removed due to the shift in focus

Page 31. At end of first sentence is sentence fragment(Diseases,disorders, and illnesses)
The conclusion is excellent. As stated above, the paper may benefit from inserting some of the information earlier for non specialist readers.

→ [R24] This has been done.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer number: 3

The authors describe their approach of constructing an ontology of mental disease. They make reference to theoretical background knowledge that has to be considered when constructing such an ontology.

They do not give evidence, how the ontology has been applied nor how it has been evaluated.

→ [R25] This has been done by means of Pies' model.

The considerations presented by the authors are certainly relevant to the scientific community and to the journal.

Unfortunately, the whole paper suffers from the fact that the introduction and the method section is not well focused and not well structured to explain the “results” presented later on. Altogether the manuscript would profit from reducing the arguments to what is needed to explain the choices taken for the design of the ontology.

→ [R26] This has been done .

The title “method” is certainly not appropriate for the section that is basically an extension of the motivation or introduction section.

→ [R27] We changed it to ‘approach’.

The publication has to be reduced to the design principles and the decisions for the design principles that leads to the development of the ontology as presented in the tables at the end of the manuscript. This will help to judge the manuscript better.

→ [R28] This has been done.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Response to reviewers

Foundations for a Realist Ontology of Mental Disease

Werner Ceusters and Barry Smith

Version: 2 Date: Oct 28 2010

Reviewer number: 1

This is a second review. The manuscript has improved significantly. It is shorter and more focused, rid of extraneous material. This reviewer still sees several major issues with the current version, which hopefully can be addressed in the next round of revisions.

There is some confusion between background information and method. There is currently no Background section …

→ Now we are confused. The title of section 1 in the revision is called 'Background', so there is one. Or does this reviewer means there is no *method* section? But this reviewer stated specifically in his first review: "*There probably should not be any Methods section in this paper*." That is why we replaced it with an 'approach' section.

… and reference information (about BFO, granular partition theory, OGMS and Pie's model) is presented together with methods in the Approach section. This is inappropriate as it makes it difficult for the reader to tease out what the contribution of the current work precisely is. Background information should be moved to a Background section.

→ We moved the initial discussion on disease classifications and the controversies involving the nature of mental disorders to the introduction, and used the Background section only to describe the fundamentals of the resources that we used as basis for our work: BFO, granular partition theory, OGMS and Pies' model

Moreover, only aspects of these background resources having a direct impact on the methods should be introduced here. For example, in the presentation of BFO, realism-based aspects seem highly relevant, whereas distinctions between occurrents and continuants, and between dependent and independent entities are not later used in the methods and should be dropped (or later referenced in the methods).

→ We kept the distinctions in the Background section because they are essential elements of ontological realism, and therefore, as requested, explained in the methods how they are used. We further labeled in the tables whether the terms denote occurrents or continuants.

Along the same lines, it is unclear how the discussion section about "Diseases as dispositions" is relevant here. Probably not unless it addresses specific issues about mental disorders, not diseases in general. If rewritten to this effect, it should probably be moved to the background (for

the introductory notions) and methods, if it contributes at all to shaping the foundations of your ontology.
→ this section is very important as the idea of disease as disposition is new, and not at all well understood in the biomedical informatics community. Disposition is further used in our definition of mental disease, thus is essential here. But we agree with the reviewer that the section should be in the Background and thus moved it there.

The description of the methods is extremely limited (currently to the introduction to section 2). The description is vague and does not support reproducibility by others, in stark contrast with the claim for a scientific approach to building ontologies made by the authors.
Here are specific sentences describing the approach:
- "our method starts with the identification of the sorts of entities that exist in the salient portion of reality thereby drawing on the best current scientific understanding."
- "were then used to assess whether the representational units of BFO and OGMS were adequate"
More than scientific method, these statements sound like "a good ontologist knows one when s/he sees one". The Methods section should clearly establish how the various resources (BFO, GP theory and OGMS) contribute to the foundation of an ontology of mental disorders and which process was used to derive such foundation from these resources. Similarly, the manuscript should better explain how the proposed framework was tested against Pie's model.

→ We agree, and expanded the methodology section to this effect.

Finally, most of the manuscript remains extremely generic and lacks specific examples related to mental disorders (e.g., in relation to GP theory, OGMS and Pie's for stages 2-5). Such examples should be added systematically throughout the manuscript.

→ We checked and we provided examples throughout the entire Background section and discussion. If the reviewer however means that there are no specific examples of types of mental diseases (psychosis, schizophrenia, manic depression, …) worked out formally using our foundations, then he is right, but that is intentional: as we explain in the future work section that is work in progress on which we will report in a later paper. First we address: what is a mental disease?; in this second paper we will address: What is psychosis? What is schizophrenia? Etc.

In the discussion, the authors acknowledge the lack of clinical relevance of their ontology. Part of the discussion should be devoted to assess the limitations in terms of adoption of the proposed ontology by the community, unless the present effort is purely an academic exercise (which would also be fine).

→ In this paper, we discuss the foundations, the results of a very difficult academic exercise indeed. When we have formally represented, for instance, a chapter of DSM in terms of these foundations, then adoption by the community is indeed very important.

Specific comments

- In the Results section, it might be best to present entities before introducing the relations in which these entities participate (?)

→ We did so. The paragraph introducing the relations has been moved to the Background section since these relations apply to any disease and were introduced in OGMS.

- Unclear why most entities defined in 3.1 do not appear in Fig. 2

→ We checked and they all are in that figure. Perhaps the result of the problem this reviewer had with printing this figure? (see his next comment)

- Fig. 2 does not print well

→ we leave this to professionals of the journal

- the claim "Moreover, the DSM's classification scheme does not mesh neatly with that of the ICD or with other systems describing mental disorders." should be substantiated or dropped.

→ the claim was substantiated in our example and tables referring to the evolution of the classification of Tourette's syndrome over time – which this reviewer asked us to remove. But we agree that without that example, there is no point in keeping that statement in the paper, so we dropped it.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer number: 3

The manuscript covers a significant scope of work in defining mental diseases. The authors demonstrate their background knowledge on the different definitions of mental diseases sections of the manuscript.
The manuscript is now better structured, but the course of arguments in the first section does not support the reader in understanding how the definitions for mental disorders made progress over the past years.

→ Well, we were asked during the previous review to remove the long analysis in this respect of the Tourette's syndrome, which we did. The reason was that only one example was given. More examples would make the paper much longer, and length was already considered to be problematic. We therefore will cover this question in the later paper.

The sections 2, 2.1 and 2.2 are very general and less informative for a scientist having some experience in the development of ontologies. This part should be shortened and focused to the most essential parts.

→ There are only five or six persons I can think of that really understand these issues and are able to apply the principles, 99% of the people 'with experience in the development of ontologies' being happy if they produced something in OWL, but not asking themselves the question whether what they built reflects the structure of reality. These sections are primarily for them.

The result section gives definitions mental disorder, behavior, mental disease, diagnosis of mental disease. These definitions are very general but certainly worth having and/or discussing about . It is not obvious how the experience of the past efforts in categorizing mental diseases is reflected in the definitions, but this could be worked out.

→ See some earlier comments. This paper is not about the various sorts of mental diseases, but about a formal definition for 'mental disease'. Such a definition is lacking in the literature.

The discussion is quite interesting, at least in parts, but far too long and it is difficult to follow the course of arguments. The first 3 parts (4.1, 4.2, 4.3) are pretty straight-forward, but the last part (4.5) is very difficult to understand.

→ Ontology is hard indeed. We hope that the reorganization of the Background section helps to make that particular section better understandable.

I think it is in general less certain to derive from the clinical phenotype the disease phenotype than the other way around, since the disease phenotype should be causal to the clinical phenotyp.

→ This is a topic at the level of OGMS, not mental disease in particular. But to address the issue in point: the relationship between disease phenotype and clinical phenotype, as can be seen from the definitions in table 2, is not one of causality, but of subtype: all disease phenotypes are clinical phenotypes. But there are clinical phenotypes for which there is no relationship with a specific disease. Example: inflammation. This is for sure something we will cover in a following paper when talking about how views on mental disease have changed over time.

Conclusion: interesting paper, interesting ideas, but would profit from a more stringent flow of arguments in the different sections.

→ We hope to have achieved this in the current revision.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Response to reviewers

Foundations for a Realist Ontology of Mental Disease

Werner Ceusters and Barry Smith

Version: 3 Date: Nov 28 2010

Reviewer number: 1

With this second round of revisions, the authors have managed to align the methods and results of their paper with the objectives and title. They propose a set of definitions for entities related to mental disease, which they link to BFO and OGMS. They acknowledge the limited relevance of their work to contemporary clinical practice and outline a path to a realism-based ontology of mental disease. Overall, this paper has come a long way compared to the initial version and is now suitable for publication.
This reviewer only has minor comments and suggestions at this point, which the authors are invited to take into consideration when preparing the final version of their manuscript.

Minor comments and suggestions

- p. 7: John -> Jim
→ Corrected

- "L2. cognitive representations" unnecessary dot after L2 (several occurrences)
→ Corrected

- bold italic is used to denote things other than relations (e.g., POR)
→ Corrected

- Table 1 is not referred to anywhere in the body of the paper
→ It was referred to on page 18, We added an additional reference earlier and moved the table accordingly.

- The description of Fig. 1 in text should be both more thorough and more consistent.
→ Corrected

Patient should be introduced as an organism instance.
→ We removed in the figure the word 'patient' by 'instance', and in the text the word 'patient' by 'person' in order to avoid the additional complexity that being a patient is a role performed by a person.

Disease instance should be distinguished from disease universal more systematically.
→ This has been done

Please use either type or universal and use it consistently in the figure and its description in the manuscript.
→ has been done. We removed 'type' wherever it was used as synonym for 'universal'.

- p. 12: it is not clear why "disorders are independent continuants", not is it self-evident at the time this statement is made.
→ we added a sentence motivating this.

- Fig. 1: Organism (Patient) => Organism instance
→ has been corrected

- Fig. 2: Labels are not attached unambiguously to specific relations (e.g., realizationOf, inheresIn, partOf). One solution would be to use additional visual distinctions (e.g., dotted arrows for isa relations).
→ has been corrected

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer number: 3

The structure of the paper is better now. The logical discourse is also better laid. Due to its length it happens that some arguments are repeated and other arguments seems to be less focused to the core line of arguments.
For example, the authors repeat in several parts of the document the observation that there are cultural differences in the perception of the clinical significance of mental disorder symptomes.
→ we removed the first mention of it

The paper would hugely profit from taking away
(1) parts that are not core to the line of arguments,
→ we didn't spot any

(2) take out redundancy,
→ we did so insofar we identified redundancy.

(3) shorten the paper in general.
→ it has been shortened a lot from the very beginning. What is left is necessary for readers that are not familiar what this sort of ontological approach, which is the majority of readers.

The methods and the result section are rather short in comparison to Background and Discussion. The authors have to determine, whether they want to convey existing background knowledge or their methodology.

→ the methodology and the motivation thereof would be very difficult to comprehend without the background knowledge. Also the length of the discussion is a result of clarifications the reviewers requested. These clarifications might not be essential anymore for them, but other readers might probably have the same questions.

The first two sections only raise the perception that the definition of mental disorders was tackled from several researchers. These two parts do not explain why it is now possible nor necessary to provide a formal specification of the mental disorders. (Nice to have!!)
→ we do not understand the request here.

The Background information on pages 6/7 could be shortened.
→ We disagree. The reviewers raised at many occasions several questions which could only be answered comprehensibly on the basis of background information of the sort given. Still now, for example, the first reviewer wondered why disorders are independent continuants. This reviewer has questions what it means to be the agent of a process. This clearly indicates that even very basic background information is required.

The Level staging in Section 2.2 is quite important and will be reused in the Results sections. Please make sure that the labelling of the three different levels (page 9) is more prominent. The labels (L1-L3) serve as enumeration. It should be more prominent that we talk about three different lefels. You could do: "(1) Level L1: ..."
→ We did so.

Page 11, top: it is not a well founded statement to explain that OGMS is "the best ontology effort in the whole .. by far" (personal statement). Deliver the proof or leave it out.
→ We have the proof in writing by means of a dated email. We provided these details in the paper.

Page 12: It would be good to list a source for the definition of the disposition. I know that there is some debate about the correct interpretation of disposition. The definition is acceptable.
→ We did so, stating that this definition comes from BFO.

Page 13: The example around the hypothetical organism is quite hypothetical and not very helpful. How does it relate to the realism approach?
→ We removed it, thus shortening the paper a bit more.

On Page 17, finally, we get some results. Would be good to shorten the previous sections to make them more concise.
→ During the previous round, this reviewer asked for a better description of how Pies' model relates to our work, how we used it, etc. We provided this info in the section here. Thus we leave it as it is.

Page 18: I am not sure what the definition of "agent" is and therefore it is difficult to figure out what an agent of a Mental Process is. I think that we talk about an "assumed agent".
→ No; "assumed agent" is a term for which there is no place in a realism-based ontology since it mixes ontology with epistemology which is to be avoided.

To avoid confusions of this sort in other readers, we gave an example of the agent relation in the background section and clarified it further in the discussion.

The discussion is again very long and sometimes lacks focus. Could be shortend, but is not really harmful.
→ we modified where deemed better

On page 24 returns the example with the cultural differences of mental disorders.
→ we left it here but removed the prior reference.

Minor comments:

- “it still remains unspecified”: I would argue that they are not formally specified, but there is a medical / clinical specification, well more or less in a freeform description
→ no that is wrong. We had a very lengthy documentation for this argument in the first version of our paper, but were asked to shorten it. We leave it the way it is.

- Page 7: “to development level”
→ this is a literal quote from the DSM

- Page 11, bottom: some stylistish issues .. “standardly” and “as erroneous thought formation”. The latter does not look like a medically well defined term.
→ we changed it into "erroneous thoughts"

- Page 14: dis-ease
→ this is also a literal quote

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.