

# Representing mental functioning: Ontologies for mental health and disease

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## ABSTRACT

Mental and behavioral disorders represent a significant portion of the public health burden in all countries. The human cost of these disorders is immense, yet treatment options for sufferers are currently limited, with many patients failing to respond sufficiently to available interventions and drugs. High quality ontologies facilitate data aggregation and comparison across different disciplines, and may therefore speed up the translation of primary research into novel therapeutics.

Realism-based ontologies describe entities in reality and the relationships between them in such a way that - once formulated in a suitable formal language - the ontologies can be used for sophisticated automated reasoning applications. Reference ontologies can be applied across different contexts in which different, and often mutually incompatible, domain-specific vocabularies have traditionally been used. In this contribution we describe the Mental Functioning Ontology (MF) and Mental Disease Ontology (MD), two realism-based ontologies currently under development for the description of human mental functioning and disease. We describe the structure and upper levels of the ontologies and preliminary application scenarios, and identify some open questions.

## 1 INTRODUCTION

Mental disorders are common in all countries, representing a significant portion of the public health burden. In the US, about one in four adults is diagnosed with a mental disorder in a given year, and about one in seventeen is thought to suffer from a serious and disabling mental illness. Mental disorders are the leading cause of disability in the United States and Canada for persons aged 15 to 44 (National Advisory Mental Health Council Workgroup, 2010). The cost of these disorders is immense, affecting not only patients but also their caregivers, rendering adults unable to work productively, destroying relationships and increasing the financial burden on society. Treatment options for sufferers are currently limited, with many patients failing to respond sufficiently to currently available interventions, which include psychotherapeutic, somatic, and pharmacological actions. And, while there is enormous variance in individual responses to therapeutic agents, there is often little alternative for the clinician other than trial and error in determining the best treatment strategy for the patient's genetic, physiological, or behavioral profile.

The volume of data, information and knowledge, both in patient records and in scientific literature, is steadily increasing. Computer-based methods able to harness such data are mandatory for supporting decision-making processes in the treatment of individual patients as well as in the interpretation of scientific findings. Whereas, traditionally, most relevant information has only been available as free text, machine processing increasingly requires the adherence to terminological standards (Freitas *et al.*, 2009). This need has been addressed by the development of controlled vocabularies such as SNOMED CT (International Health Terminology Standards Development Organization, 2012), and classification systems such as the International Classification of Diseases (World Health Organization, 2012) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 2000). DSM provides not only a classification of disorders but also guidance as to the diagnostic criteria for these disorders in the form of checklists of symptoms, with counts of how many symptoms of a various sort are required for the condition to be diagnosed. The DSM is currently in its fourth revision, but the fifth revision is scheduled for release in May 2013 (Regier *et al.*, 2009), and a draft version of the revisions have been released for public review at [www.dsm5.org](http://www.dsm5.org). Some issues that the revision will try to address are a high occurrence of co-morbidity of disorders according to the diagnostic criteria and the high use of 'catch-all' categories such as 'not otherwise specified'. To address these, the revision is expected to emphasize dimensional measures of symptoms that cross diagnostic category boundaries.

Terminology systems and controlled vocabularies address some of the requirements of computational support for data management, but in recent years a more powerful solution has become available in the form of formal ontologies. Realism-based ontologies are formalized descriptions that are based on scientific theories about the nature of entities in reality and the relationships between them (Smith, 2008; Munn and Smith, 2009; Rubin *et al.*, 2008). These ontologies may be expressed in a formal language and enhanced with standard identifiers, labels and definitions that are intended to facilitate unambiguous interpretation and annotation. A key advantage that such ontologies confer, over and above the mere standardization of terminologies, is that their underlying logical formalisms are natural language-independent and formally rigorous. This allows these ontologies to form the backbone of sophisticated automated reasoning applications, and to be applied across contexts

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in which multiple competing domain-specific vocabularies have traditionally been used (Stenzhorn *et al.*, 2008). Especially in the domain of biomedicine, ontologies have found a broad acceptance.

In the next section, we will describe the structure and upper levels of the Mental Functioning (MF) and Mental Disease (MD) ontologies. Thereafter, we provide a preliminary listing of possible application scenarios for these ontologies. Finally, we identify some open questions in the ontology of mental functioning.

## 2 ONTOLOGY STRUCTURE AND CONTENT

### 2.1 Mental Functioning Ontology

Based on the Basic Formal Ontology (BFO, Grenon and Smith (2004)) and being developed in the context of the OBO Foundry (Smith *et al.*, 2007) library of interrelated modular domain ontologies, the Mental Functioning Ontology (MF, (Hastings *et al.*, 2012)) is a modular domain ontology aiming to represent all aspects of mental functioning, including mental processes such as cognitive processes and qualities such as intelligence. MF grounds mental functioning entities in an upper level ontology, and gives a framework within which mental functioning can be related to ontological descriptions of related entities in other domains such as neuroanatomy and biochemistry. Modules of MF that are actively under development are those for cognition, perception and emotion.

Figure 1 illustrates the upper levels of the ontology, based on the framework laid out in (Ceusters and Smith, 2010a), together with the alignment to BFO. At the top level, BFO introduces a distinction between continuants and occurrents. Occurrents are processes and other entities that unfold in time, i.e. entities that have temporal parts. Continuants, on the other hand, are those things that exist in full at all times that they exist, have no temporal parts, and continue to exist over an extended period of time. This distinction can be seen in the context of mental functioning between, for example, an organism, or a part of an organism's *anatomy*, that continues to exist over time (thus is a continuant), and an organism's *thinking process* that spans over a few minutes (unfolding in time) before it is completed (thus is an occurrent). Within continuants, BFO further distinguishes between those entities that are independent and those that are dependent. Independent continuants can exist by themselves, while dependent continuants are those sorts of things that need a "bearer" in order to exist, such as colours, social roles, or behavioral dispositions that are realized in behavior, an occurrent entity. 'Functioning' is defined as the realization of a function, where a function is a special type of disposition that is realized in end-directed activity that is appropriate for the kind or kinds of contexts for which the bearer is designed or in which the bearer has evolved (Arp and Smith, 2008). In the domain of the mental, therefore, mental functionings are those mental processes that are realizations of functions; processes that have been positively selected for by human evolution. While cognition, remembering, and emotion can all be examples of mental functionings, examples of mental processes that are not functionings include the auditory perception involved in tinnitus and, contentiously, possibly dreaming (if dreaming realizes a function at all, which function it realizes is disputed).

The illustrated upper levels of MF show several important distinctions in the framework to annotate and describe mental functioning allowing interrelationships across a wide variety of different levels of description. The organism is the fundamental independent continuant in which mental functioning takes place. A mental

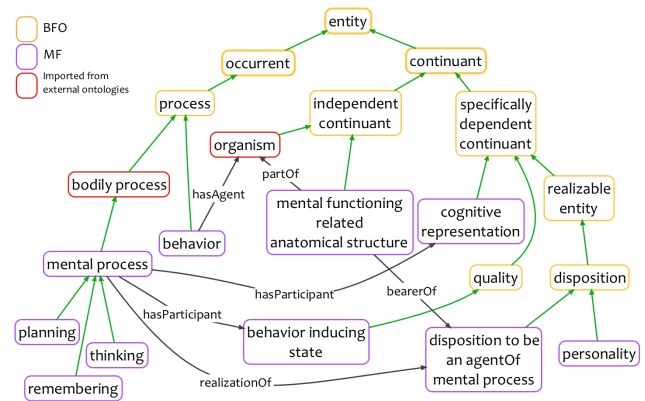


Fig. 1. The Mental Functioning Ontology upper level aligned to BFO. Unlabelled arrows represent subsumption relations.

functioning related anatomical structure is that part of an organism that bears a disposition to be the agent of a particular mental process. So, for example, the particular neuronal and biochemical configuration (i.e. the bona fide group of receptors and neurotransmitters (Ceusters and Smith, 2010b)) that gives rise to a particular person's feeling of sadness is a mental functioning related anatomical structure. Neurons and brain chemistry are themselves described as continuants in other ontologies such as CHEBI for the neurotransmitters, the Protein Ontology (PR, Natale *et al.* (2011)) for the receptors, and NeuroLex and BIRNlex (Bug *et al.*, 2008) for neurons and neuronal systems. These components can be linked together as parts of the corresponding mental functioning related anatomical structure, the boundaries of which are to be determined with the advance of our understanding of the neurobiology and neurochemistry of the physical basis of the various mental processes involved. The links from entities in MF to the known biochemical and neurobiological bases will be maintained in bridging modules, ensuring that different levels of granularity and description can be separately maintained. References to other vocabularies such as ICD and BIRNlex will be annotated in the ontology where applicable.

Dispositions are properties that inhere in their bearers and consist in the potential for certain processes in the bearer to occur when this bearer comes into the right circumstances, for example, a glass breaking when it is dropped onto a hard surface. An example of a disposition in the domain of mental functioning is human personality. Personality (or character) is the kind of thing that is realized in the behavioral interactions of a human being with the external world, along with characteristic patterns of thought, such as in task performance when learning new things. Personality may be measured by standardised tests (which are information content entities concretized in, for example, the paper assessment questionnaires handed out to subjects). Such tests - ideally - can be linked using something like a 'measures' relation to the representation of personality in MF.

On the side of occurrents beneath BFO, MF includes mental processes, which are defined as the processes that bring into being, sustain or modify cognitive representations. Cognitive representations are dependent continuants that specifically depend on the cognitive structures of an organism and contain cognitive content which can take the form of thoughts or memories, representing such

things as tables, people, smells, and colors. Mental processes – manipulating those cognitive representations – include all of the standard processual examples of mental functioning such as thinking, planning and learning or remembering. This is not say it is straightforward to formalize these common notions of the entities of mental functioning, but MF will focus as a major point of its development on providing the most accurate representation for these entities possible and appropriate at this level of description.

MF is being developed modularly, allowing different teams with different core areas of expertise to focus on the extension of the overall ontology to describe the entities relevant to their scientific area. One such extension is the Emotion Ontology (Hastings *et al.*, 2011), describing entities of relevance to all aspects of affective science. Another extension covers the domain of mental disease.

## 2.2 Mental Disease Ontology

The Mental Disease Ontology (MD) is a separate ontology module that aims to describe and categorize mental disorders based on the strategy outlined in (Ceusters and Smith, 2010a). MD extends not only the MF but also the Ontology for General Medical Science (OGMS). OGMS is designed to interrelate ontologies in the medical domain to support research on Electronic Health Record (EHR) technology and on the integration of clinical and research data. It provides definitions for ‘disease’, ‘diagnosis’ and ‘disorder’, among others, based on the terminology in (Scheuermann *et al.*, 2009).

Following OGMS, a mental disease is defined as a disposition to undergo pathological mental processes. A mental disease is a clinically significant deviation from mental health. Mental health is conformity of perception, emotion, and behavior internally and in relation to the external real-world environment. In contrast, pathological mental processes are those that hinder well-being. Thus, mental disease is a deviation from mental health that hampers the bearer in his or her mental well-being (Ceusters and Smith, 2010a). Figure 2 shows an extract of entities from MD for the domain of substance addiction, a mental disease characterised by substance use and phenomena such as tolerance, craving and withdrawal.

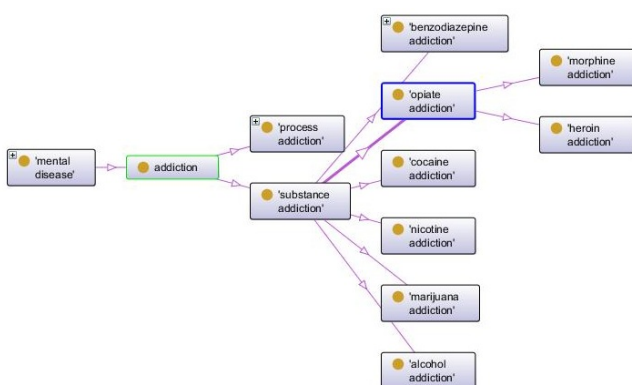


Fig. 2. Addiction in the Mental Disease Ontology.

For each mental disease, the ontology contains representations of the symptoms and signs that are manifested in the disease course, including pathological behavior. By differentiating a disease from a disease course and by explicitly representing symptoms and signs

within a logically rigorous ontological framework that includes a definition for mental disease, MF aims to address some of the challenges that have been observed with the DSM approach, such as high levels of co-morbidity and the use of catch-all ‘not otherwise specified’ placements. The DSM approach, termed ‘descriptive psychiatry’, focuses on symptom assessment and confers disorder status on specified thresholds of symptoms in terms of counts of symptom types and tokens and durations of symptom episodes. For example, a major depressive episode is stated to be diagnosable if five of a set of nine symptoms are found to obtain within the same two-week period. Symptoms include ‘insomnia or hypersomnia nearly every day’ and ‘fatigue or loss of energy nearly every day’. (Notice how these are not likely to be mutually exclusive.) The DSM-5 proposal has also been criticised for promoting medicalisation of *normal human experiences*: grief, a normal human emotion in response to bereavement, has been proposed as a type of depression, a mental disorder (Cacciatore, 2012).

One symptom of substance addiction, for example, is a preoccupation with use of the substance in question, a kind of non-canonical (i.e. not in accordance with the environment, not conducive to well-being) thinking process (since the organism is not able to control the thinking process as they would in canonical thinking processes). Furthermore, pathological (or non-canonical) processes are related to the canonical versions of those processes. This interlinking of symptoms to diseases and to canonical related processes in a computable framework allows bridging from research involving different diseases to research exploring ordinary functioning or underlying mechanisms. It also allows hypotheses of mechanisms underlying diseases to be made explicitly testable in terms of supporting data.

## 3 APPLICATIONS OF THE ONTOLOGIES

### 3.1 Standardisation

Ontologies are already widely used to facilitate *standardised database annotations* throughout the biomedical sciences. To be truly successful, this use case necessitates adoption of the principles of the OBO Foundry such as the use of semantics-free stable unique identifiers and the annotation of clear textual definitions for each entity in the ontology. Databases containing data that could potentially be annotated with mental functioning terminology include those in neuroscience such as BrainMap (Laird *et al.*, 2005), a curated database of functional neuroimaging research studies. Many more neuroscience databases are aggregated in the NIF webpages (Gardner *et al.*, 2008)). Beyond neuroscience, mental functioning annotations are of increasing relevance in systems biology contexts such as the BioModels database (Li *et al.*, 2010). Mental functioning is also particularly relevant for defining chemical influences in biological systems, as done in ChEBI (de Matos *et al.*, 2010).

An additional context where standardisation is of paramount importance is in the organisation and maintenance of biobank data in which human samples are stored for purposes of clinical research (Krestyaninova *et al.*, 2011). Often, in order to research underlying mechanistic factors in rare diseases, samples from patients bearing the condition may need to be sourced from multiple biobanks in multiple countries or regions. Traditional systems which use local (language and country-specific) terminologies to annotate the sample databases will certainly not be straightforward to integrate and search across different sample collections. It is even more difficult to interrelate sample data with EHR data and with known indicators

in medical and biological knowledgebases such as those collecting annotated genetic sequence information.

### 3.2 Behavioral and Cognitive Testing

Neuropsychological and psychometric tests are designed to obtain information about brain functioning through behavioral expressions to determine the kind and dimension of dysfunction present in a subject. These tests have putative links to various cognitive domains like attention, language, episodic or semantic memory, executive function, as well as general intellectual functioning, etc. (Lezak *et al.*, 2004). Tests are typically used as part of the clinical picture that a physician develops to make a diagnosis in cases of patient injury, neurodegenerative diseases like Alzheimer's disease and related dementias or deliriums, or paradigmatic mental diseases such as dissociative or autistic spectrum disorders. The Neuropsychological Testing Ontology (NPT) is currently under development to represent many of these test procedures by describing the stimuli, methods and responses, along with associated plan specifications (Cox *et al.*, 2012). These need to refer to mental functioning.

### 3.3 Population research: clinical questionnaires

Genetic and psychiatric population-wide research often relies on diagnostic interviews which standardise the collection of data into aspects of psychiatric functioning such that the data can be compared and aggregated across large groups of patients. In the domain of mental functioning, this is a particularly pressing problem since many aspects of mental functioning are not directly observable, and the assessment of mental functioning therefore relies on the subjective assessment of the trained practitioner and on self-reports by the patient, who of course has no access to alternative experiences of mental functioning other than his/her own. Standardised questionnaires are thus an essential element of population research into mental functioning. An example of such a questionnaire is the Diagnostic Interview for Genetic Studies (Nurnberger *et al.*, 1994), a questionnaire used in clinical interviews to assess major mood and psychotic disorders and related spectrum conditions. Linking the symptoms assessed in such questionnaires to ontologies of mental functioning provides the capability to standardise the collected data across multiple such questionnaires. Furthermore, it allows multi-level aggregation, rather than only aggregation at the level of whether a particular disorder is diagnosed or not – which in some cases may obscure rather than illuminate shared underlying mechanisms and pathologies.

A concrete example here is a project funded by the National Institutes of Health (NIH) designed to obtain better insight into the complexity of pain disorders, specifically concerning the assessment of different pain types in the orofacial region, as well as into pain-related disablement and its association with mental health and quality of life. Five existing data collections compiled independently from each other have been made available for this study. The data collections cover the same domain, but are distinct in various respects: (1) some variables are identical across collections, others involving, for instance, somatization, depression and anxiety, are different because measured with in total 22 distinct assessment instruments; (2) these instruments contain each between 50 and 500 unique assessment items, but, although frequently sharing intent, do not share a similar presentation across forms, supporting detail, instructions regarding the sources of information that can be used to complete each item, or severity/frequency response scales that

are comparable across instruments; (3) because of their distinct origins, the data collections incorporate cultural influences related to pain report that have an impact on the comparability of the collections, despite the use of common instruments. One specific aim of the project is to make these data collections comparable by building a realism-based reference ontology for pain-related disablement, mental health and quality of life (OPMQoL) following the principles of Ontological Realism (Ceusters, 2012).

### 3.4 Translational research

Increasing the speed and throughput of the translation of primary research in brain and mind science into novel therapeutic agents, and ultimately clinical interventions, has been highlighted as a pressing current concern for mental health research and practice (National Advisory Mental Health Council Workgroup, 2010). However, this effort is hindered by the disconnect between the different communities involved in primary research and the different levels needed for the translation into therapeutics. Understanding the processes involved in mental disorders requires research and integration of knowledge across all the different levels of life science, from the most fundamental such as genetic and biomolecular, through medical, brain and neurosciences, to the psychological and psychiatric perspectives which focus on the behavioural and functional aspects. Recent breakthroughs in basic science in all of these different levels have the potential to be exploited towards novel interventions and therapeutics, but severe obstacles remain in the path of translation, and there is still a resulting shortage of new agents and approaches in the therapeutic pipeline (National Advisory Mental Health Council Workgroup, 2010). Most importantly, ontologies offer a common language that enables automated bridging between different disciplines, facilitating translation as research becomes increasingly interdisciplinary. Furthermore, sophisticated querying and hypothesis testing frameworks are able to be developed around the ontologies.

## 4 OPEN QUESTIONS

A core open question for any effort to create an ontology for mental functioning is in how to relate descriptions at the level of the *brain* with descriptions at the level of the *mental functioning*. While most modern biomedical researchers reject extreme views such as mind-body dualism or outright eliminativism in favour of some form of pragmatic embodied cognition, nevertheless the question of the nature of the ontological relationship between mental functioning entities and the purported corresponding brain processes is disputed. The realism framework that MF is based on does not imply physicalist reductionism, since we allow that there are mental functionings which can be experienced in the first person, and which are first-class entities in their own right.

The precise nature of the physical and neural basis for a mental process is the subject of neuroscientific research, an appropriately empirical question. MF aims to offer a framework within which different types of empirical data can be compared as evidence for different theoretical models. The problem of linking different levels becomes more detailed when different levels of brain description are considered – there is brain anatomy, brain activity as measured by various different technological platforms, neuronal systems, neuronal, and synaptic electrical and biochemical activity. Each of these

different levels of description need to be categorised and related to the description of the mental functioning of which they are a part.

Our approach follows that of (Ceusters and Smith, 2010a) in that the definition of mental disease as “a clinically significant deviation from mental health [...] that hampers the bearer in his or her mental well-being.” Determining what counts as a clinically significant deviation from mental health can be challenging, as this can differ depending on the environmental context. Another open challenge is that it is not possible to straightforwardly link symptoms, such as behaviour, to the diseases that they are indicative of, since such symptoms are usually not necessary conditions for the disease (except in the case of markers). A challenge for MD and MF will be to provide bridging modules that reconcile these aspects.

## 5 CONCLUSION

The ontology efforts that we have described aim to place mental functioning in a central role within a broader evolving biological and medical scientific context. Ontologies show great potential for addressing many of the challenges of data management and data-driven research in the post-genomic age of computer-assisted science. However, to be successful such ontologies have to be adopted by a wide, diverse community of users across different but overlapping domains. We have highlighted some use cases where adoption of the ontologies described could lead to benefits, and raised some open questions where we believe interdisciplinary discussions would contribute to the evolution of the framework.

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