Measuring Cognitive Functions: Hurdles in the Development of the NeuroPsychological Testing Ontology

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ABSTRACT

The NeuroPsychological Testing Ontology provides a set of classes for the representation and annotation of neuropsychological tests and the associated data. These classes are intended to enable the integration of results from a variety of neuropsychological tests that assay similar or overlapping domains of cognitive functioning. Neuropsychological testing is an important component in developing the clinical picture used in the diagnosis of patients with a range of neurological diseases. A core assumption in designing and implementing these tests is that their results provide more than just a description of a patient's behavior. We contend that cognitive functioning assays provide information about the state of the patient's cognitive functioning. Cognitive impairment is, in part, responsible for the patient's observed behavior and can be linked to the medical condition that caused the impairment. Many theoretical and practical issues arise in the course of representing cognitive functioning assays, cognitive functions, and measurements of cognitive functions. In this paper, we discuss how to best represent cognitive functioning assays and the resulting measurements of cognitive functions within the framework of the Ontology for Biomedical Investigations using the handedness assay as a model.

1 INTRODUCTION

The NeuroPsychological Testing Ontology (NPT) provides a set of classes for the representation and annotation of neuropsychological tests and the associated data (Diehl et al., 2013). The purpose of this ontology is to allow for the integration of results from a variety of neuropsychological tests that assay similar or overlapping domains of cognitive functioning. Neuropsychological testing is an important component in developing the clinical picture used in the diagnosis of patients with a range of neurological diseases, such as Alzheimer's disease (AD) and multiple sclerosis, and following a stroke or traumatic brain injury. Two initial applications of NPT are to test hypotheses regarding the diagnosis of AD and to identify patient populations likely to convert from mild cognitive impairment to dementia and AD. A longer-term application is to support the development of an Alzheimer's patient registry in Buffalo, NY for use by clinicians and researchers. So far, NPT includes detailed representations of the Folstein Mini-Mental State Examination, Montreal Cognitive Assessment, and Alzheimer's Disease Assessment Scale. Work is also being done to represent additional neuropsychological assessments such as the Trail-Making Test, Hopkins Verbal Learning Test, and Wechsler Memory Scale.

NPT is a corollary project of the Neurological Disease Ontology (ND), which represents entities relevant to the diagnosis, treatment, and study of neurological diseases (Cox et al., 2012). The initial phase of development is focused on representating cognitive functioning assays relevant to the study of AD; specifically on the representation of cognitive tests that are used as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Weiner et al., 2012). ADNI is a public-private partnership to "develop a multisite, longitudinal, prospective, naturalistic study of normal cognitive aging, mild cognitive impairment (MCI), and early Alzheimer's disease as a public domain research resource to facilitate the scientific evaluation of neuroimaging and other biomarkers for the onset and progression of MCI and Alzheimer's disease" (NIH/ADNI, 2013).

Neuropsychological tests are used to assess cognitive domains such as attention, visual-spatial ability, memory, executive function, and language comprehension and expression. In addition to representing the structure of these neuropsychological tests, NPT represents the cognitive processes and functions that they involve as well as the data they produce. NPT is being developed to allow the integration of outputs from different neuropsychological tests and subtests. One immediate benefit of this is that data for patients who have been tested using different protocols can be queried and studied based on similar measurements of the same or closely related cognitive functions. NPT provides more than a list of terms necessary for the annotation of neuropsychological testing data. A core developmental goal is to construct logical definitions to connect these terms in a meaningful manner. We expect the most innovative uses of NPT to be those that take advantage of these connections.

2 METHODS

NPT is being built as an OWL2 ontology using Protégé 4.2 in accordance with ontological realism (Smith & Ceusters, 2010) and the Open Biological and Biomedical Ontologies (OBO) Foundry principles (Smith et al., 2007). We are

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working in connection with related efforts for the representation of Mental Disease (MD) and Mental Functioning (MF) (Hastings et al., 2012). NPT is being developed as an extension of the Ontology for Biomedical Investigations (OBI) (Brinkman et al., 2010). OBI is an integrated ontology for the description and annotation of biological and clinical investigations that represents the design, protocols, instrumentation, materials used, data generated, and types of analyses performed. OBI is closely connected with the Information Artifact Ontology (IAO) (IAO, 2013). IAO provides many mid-level classes needed to represent the results of neuropsychological tests in NPT. Both OBI and IAO are built under the framework of the Basic Formal Ontology (BFO) (Grenon, 2003).

While OBI and IAO provide most of the upper-level classes for NPT, questions arise regarding the nature of cognitive functions, test data, and more. Answering these questions required the top-down creation of some high-level classes. However, most development in NPT has come from the analysis of individual neuropsychological tests. This bottom-up examination of tests and their subtests lead directly to the development of most NPT classes. The initial attempt to represent a cognitive functioning assay in NPT was modeled after the handedness assay in OBI. Our test case was the Folstein Mini-Mental State Examination (MMSE) because it is short and involves a variety of subtests that are similar to many other neuropsychological tests. By representing the MMSE first, we expected to resolve many challenges that we would eventually face in developing NPT and to thereby gain insights into how to best represent a wide spectrum of cognitive functioning assays. This decision has proven rewarding.

3 RESULTS AND DISCUSSION

The neuropsychological assessments used in the ADNI project are useful for identifying the presence and degree of cognitive impairment in patients. Thus, the development of NPT necessitates reference to aspects of cognitive functioning. For example, the MMSE produces scores that are indicative of impairment in cognitive domains such as language, executive function, and memory. Clinicians and researchers use the term 'cognitive domain' to refer to and group the range of cognitive abilities with varying degrees of specificity. For example, within the domain of memory, immediate recall is distinguished from delayed recall and long-term memory (Lezak et al., 2004). A challenge we have encountered is how to connect these commonly described cognitive domains to what is occurring on the side of the organism. More specifically, what sort of entity is a cognitive domain and how do neuropsychological tests assess it?

3.1 Cognitive Functions

Before answering the second part of the preceding question, it is necessary to identify what sort of entity a cognitive domain is. Our position is that cognitive domains are best represented as cognitive functions. A cognitive function is a subclass of BFO:function, which is defined as "A realizable entity the manifestation of which is an essentially end-directed activity of a continuant entity in virtue of that continuant entity being a specific kind of entity in the kind or kinds of contexts that it is made for" (BFO_0000034). In other words, a function has a purpose or goal that it will fulfill or bring about when the conditions are right. For example, the function of a heart is to pump blood and the purpose of a kidney is to filter harmful substances out of the blood. Thus, cognitive functions may be thought of as those functions that bring about some form of cognition when presented with the right circumstances.

One might hold that neuropsychological tests are better understood as measuring certain qualities of the subject's cognition. On this view, what are measured are instances of BFO:quality and not, as we have proposed, instances of BFO:function. Another alternative is that neuropsychological tests are better understood as measuring a patient's observable behavior rather than the underlying mechanisms that give rise to them. On this view, what are measured are instances of BFO:process. While there are reasons to prefer either of these alternatives, neither account succeeds in providing an adequate description of what is occurring.

A compelling reason to hold that cognitive functioning assays measure cognitive qualities is that qualities are the sort of thing that we typically think of as capable of being measured. For example, we measure a child's temperature to determine whether she has a fever and we measure her height and weight to see how much she has grown since last year. Qualities are such archetypical objects of measurement that the only measurement relations in BFO, OBI, or IAO are IAO:'is quality measurement of' and its inverse. This is not entirely surprising though since it is difficult to think of something that we measure that is not a quality. Thus, it is reasonable to postulate that, if cognitive functioning assays measure anything, they measure cognitive qualities.

Yet, if the goal of cognitive testing is to measure cognitive qualities, these cognitive qualities must be qualities of something. The most immediate hypothesis is that cognitive qualities are qualities of the process of cognition; however, since BFO considers processes dependent entities, they are not permitted to be bearers of qualities (BFO 2.0, 2012; Grenon, 2003). Similarly, subclasses of BFO:function are dependent entities and cannot be bearers of cognitive qualities either. With these two options ruled out, it is far from obvious what cognitive qualities are qualities of. This difficulty is sufficiently challenging that it provides compelling evidence that one or more of the following is true: (i) there are no cognitive qualities; (ii) BFO's use of 'quality' is too restrictive and should be expanded to allow more than just subclasses of BFO:'independent continuant' to have qualities; or (iii) there is something other than cognitive qualities

that are measured by cognitive functioning assays. For the purposes of this paper, we set aside (i) and (ii) and endorse (iii). We maintain that the "something else" that is measured is the cognitive function.

One might object that this "something else" is the cognitive process (whether understood as the biochemical, physiological, or behavioral process) and not, as we claim, the cognitive function. This account is enticing when one considers that a cognitive function is a BFO:'realizable entity' and is, therefore, not directly observable. Behavioral processes, on the other hand, are often easily observed. Similarly, with the right equipment, a brain's physiological processes can also be observed. Yet, while the ability to observe something certainly makes it easier to measure that thing, it is far from necessary that something be directly observed in order to measure it. Furthermore, just as a cognitive process can bring about a behavioral process, a cognitive function gets realized as a cognitive process. Thus, behavior can tell us about the underlying cognitive process that gave rise to it and a cognitive process can tell us about the underlying cognitive function that it realizes. In this way, by measuring a patient's behavior and/or cognitive processes, we can measure his cognitive functions.

Admittedly, this picture is overly simplistic and the connections between behaviors and cognitive functions are far from straightforward. However, the challenge of resolving these difficulties falls on neuroscientists. NPT attempts to create representations that are consistent with the best current science and will be revised as progress is made in this area. It is important for our current purposes that there is an ontological connection between behavior, cognitive processes, and cognitive functions such that it is possible to measure the latter by observing the former. Given this connection, there is no need to restrict the development of NPT by making the less informative claim that cognitive functioning assays measure behavioral or cognitive processes. Of course, this is not to say that cognitive functioning assays do not also measure these entities—they simply are not the whole story and our commitment to ontological realism demands a more complete representation.

Furthermore, we contend that this account better represents the way that neurologists understand how a properly designed and administered neuropsychological test is supposed to work. It is not enough for the test to only result in a description of the patient's behavior. What is required is a pattern of behavior that can be found in a significant number of patients who suffer from the same problem as well as a theory that connects this pattern of behavior with a stable basis that can provide an explanation as to why these patients behave in this manner while others do not. Thus, theoretical considerations seem to require the existence of a stable cause for the behavior we observe. For the reasons provided above, we have assigned that role to cognitive functions. A single cognitive function can be realized any number of times as an instance of a cognitive process that, at least in part, produces the observed behavior. In this way, each time a patient participates in an instance of the same cognitive functioning assay, we can claim that the same cognitive function is being assayed. This is extremely useful for comparison across patients as well as for longitudinal

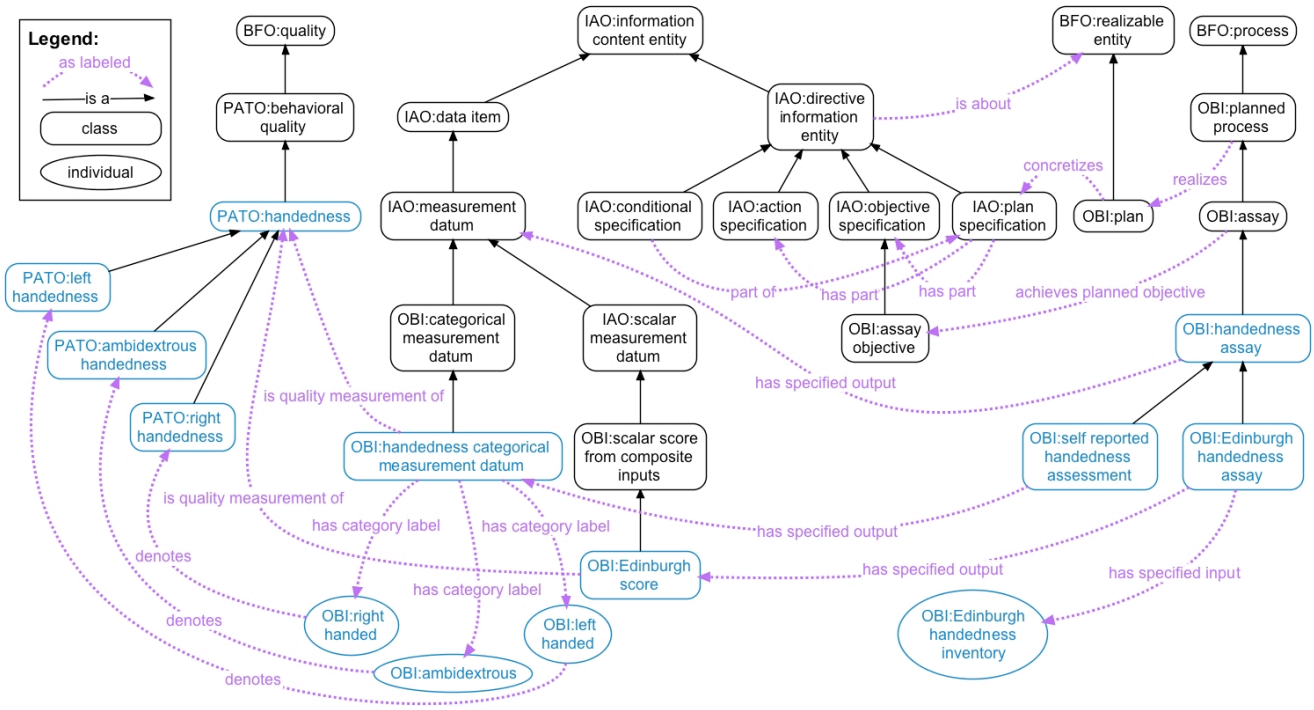

Fig. 1. A representation of the handedness assay in OBI.

studies of individual patients.

3.2 Representing Cognitive Functioning Assays

Having established that cognitive functioning assays assess cognitive functions, we now turn to the question concerning how this assessment takes place. In order to answer this question, we must first set the stage by representing the other entities involved in these types of assays.

The cornerstone of NPT is the class 'cognitive functioning assay'. We define 'cognitive functioning assay' as "An assay that measures one or more aspects of an evaluant's cognitive functioning." OBI:assay is "A planned process with the objective to produce information about some evaluant" (OBI_0000070). The initial attempt to represent a cognitive functioning assay was modeled after the representation of OBI:'handedness assay'. The handedness assay is a relatively straightforward assay intended to measure the "distribution of fine motor skill between the left and right hands" (OBI_0000944). There are currently two subclasses of handedness assay: OBI:'Edinburgh handedness assay' and OBI:'self reported handedness assessment'. The Edinburgh handedness assay has as its specified input a set of standardized questions provided by the Edinburgh handedness inventory and produces an Edinburgh score as its specified output (Oldfield, 1971). The Edinburgh score is a quality measurement of the evaluant's handedness. Handedness is a behavioral quality that has the subclasses 'left handedness', 'right handedness', and 'ambidextrous handedness'. The self reported handedness assessment asks evaluants to state which hand is dominant for them. Its specified output is a handedness categorical measurement datum, which is a quality measurement of the evaluant's handedness and is recorded using a category label – 'right handed', 'left handed', or 'ambidextrous'. These category labels denote their respective behavioral qualities. While the Edinburgh handedness assay and the self reported handedness assessment are similar in many ways, they present distinct models for representing assays. Both assays are shown in Figure 1.

Mirroring the format of the handedness assays to represent the Folstein Mini-Mental State Examination (MMSE) provided most of the necessary classes and structure. The resulting representation of the MMSE is shown in Figure 2. Since NPT aims to provide a complete representation of neurospychological tests, we created classes for the individual tests that comprise the MMSE as well as for their subtests. We also created classes for many of the cognitive processes involved in the various cognitive functioning assays and included them in the logical definitions of these assays as parts. For example, the MMSE recall assay, which involves asking the test subject to recall three words that she was told to remember a few minutes earlier, always has an episodic memory cognitive process as a part. One might object that not every instance of a cognitive functioning assay will include an instance of a specific cognitive process, or perhaps even an instance of any cognitive process. While this claim is prima facie appealing, its veracity ulti-

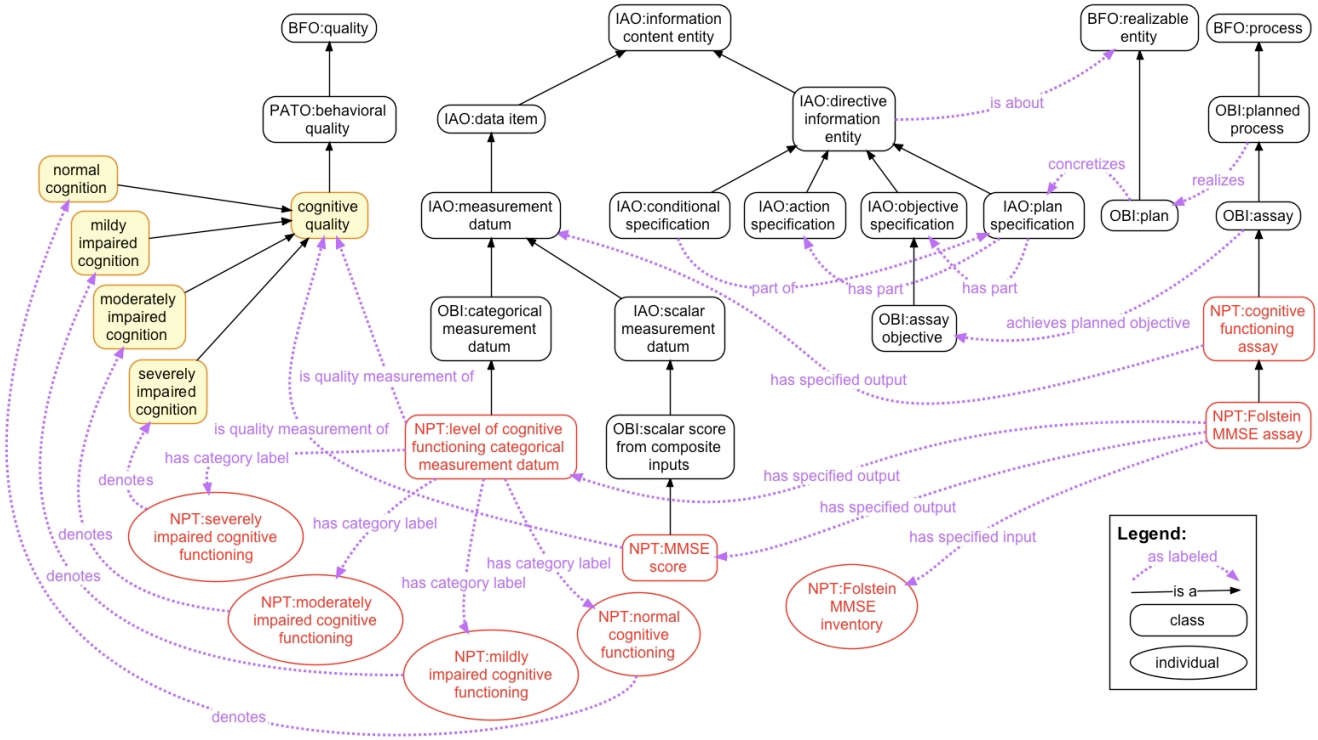

Fig. 2. A representation of the Folstein MMSE assay modeled directly on the handedness assay.
The shaded cognitive quality nodes on the left indicate where the model breaks down for cognitive functioning assays.

mately depends on how the classes are defined.

According to NPT, a cognitive functioning assay realizes a cognitive functioning assay plan, which is the concretization of a cognitive functioning assay design. The cognitive functioning assay design has as part an action specification. NPT gets finer grained about the action specification and includes classes for evaluant action specification and evaluator action specification. The evaluant and evaluator action specifications identify the actions that the assay participants must perform. NPT:'evaluant action specification' is "A directive information entity that describes an action an evaluant is required to perform as part of the realization of their evaluant role as a participant in an assay." These actions are part of the detail that NPT represents for each cognitive functioning assay. Given these logical and textual definitions, a particular cognitive functioning assay cannot be realized without the specified action or actions being performed. That is, a patient does not fulfill his role as a participant in the assay unless he participates in the manner required. We contend that performing the specified action requires the realization of the associated function because the function makes the action possible. Thus, we assert that every instance of a cognitive functioning assay has as part some cognitive process, which realizes some cognitive function. It is in this way that the results of cognitive functioning assays are connected to the cognitive domains—that is, the cognitive functions—that they are intended to measure.

One possible complication is a patient who is deliberately being difficult, perhaps by refusing to cooperate or by not trying to do his best. Another is a patient whose capacity to perform the assigned task is hindered by interference from a problem with something other than the cognitive function that the test is intended to measure. For example, a person who has a severe case of laryngitis might be temporarily incapable of responding. One consequence of this account is that, while a series of events may look like a particular cognitive functioning assay, it might nonetheless fail to be an assay. We take this to be a strength of our account. Indeed, it is common practice to exclude the results of certain tests when the data is corrupted. Thus, a representation of cognitive functioning assays that excludes some problematic cases is preferable over a less discerning account.

3.3 Measuring Cognitive Functions

Another shortcoming of using the handedness assay to model the MMSE is that, due to the treatment of qualities in BFO, problems arise for representing the measurement of cognitive functions. As we discussed in Section 3.1, a BFO:function cannot bear a quality. Furthermore, there is no measurement relation in BFO, OBI, or IAO that does not explicitly refer to a quality. At this point, we finally return to the question from the beginning of Section 3 concerning how cognitive functioning assays assess cognitive functions.

While the relation 'is quality measurement of' cannot be used to connect cognitive functioning assay scores to the cognitive functions they provide information for, we could use the relation 'is about'. IAO:'is about' is a "primitive relation that relates an information artifact to an entity" (IAO_0000136). Since many cognitive functioning assay outputs are information content entities, it is possible to use 'is about' to relate cognitive functioning assay measurement data to the pertinent cognitive functions. However, this solution is far from satisfactory since the relation is so general that almost any information content entity can be related to almost any other entity via 'is about'. Thus, using 'is about' does little to enhance the richness of NPT or its representation of cognitive functioning assays.

What is needed is a relation that is more specific than 'is about' but is not specifically tied to qualities. A step in the right direction is to create the relation 'is measurement of'

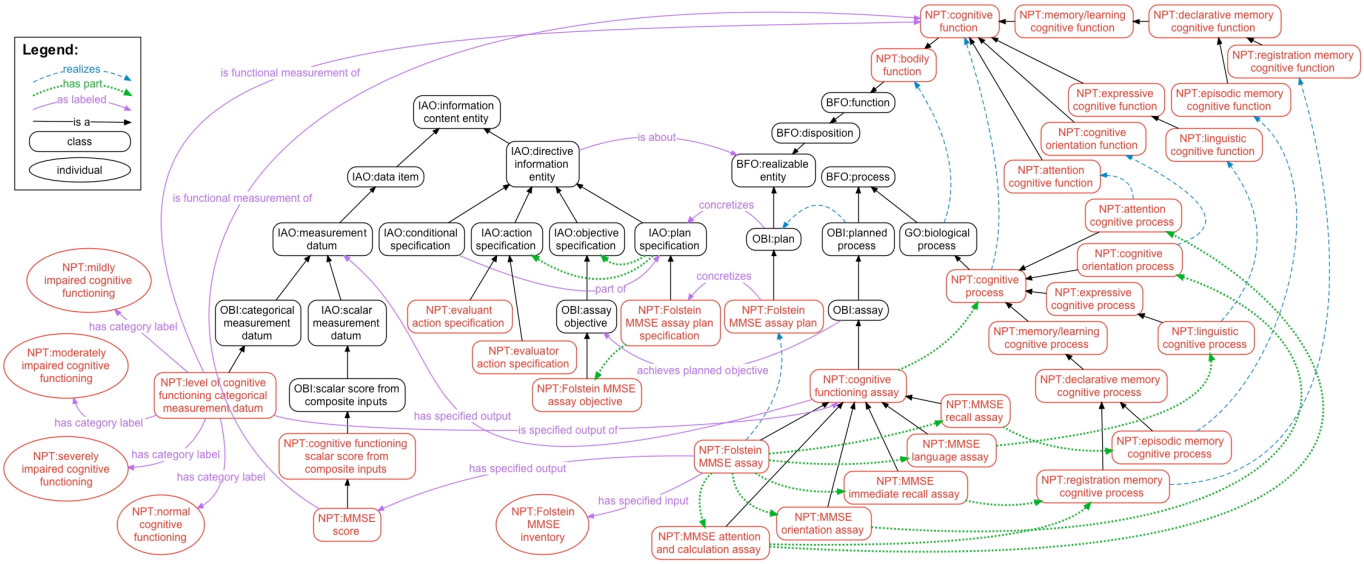

Fig. 3. A partial visualization of our proposed representation of the Folstein MMSE assay.

as a subproperty of 'is about' and the superclass of 'is quality measurement of'. While this relation specifies that certain assay data measure certain cognitive functions, more specificity is desirable. Thus, we also propose the addition of the relation 'is functional measurement of'. This relation is a subproperty of 'is measurement of', a sister-class to 'is quality measurement of', and connects measurement data to functions. Thus, an instance of an MMSE recall score is a functional measurement of the patient's episodic memory cognitive function.

An objection might be raised that only qualities can be measured. According to this view, the only measurement relation needed is 'is quality measurement of'. While this position is tempting, it imposes significant limitations on what can be expressed using ontologies. There are also independent reasons to reject it. For example, we use clocks to measure the passage of time, but neither time nor processes are permitted to be the bearers of qualities within the BFO framework (BFO 2.0, 2012). Given the naturalness with which we make claims to measure time and other entities that cannot bear qualities, accepting the view that only qualities can be measured comes at a high cost.

4 CONCLUSIONS

In developing NPT, we have attempted to provide a detailed realist representation of cognitive functioning assays. In this paper, we discussed some challenges encountered along the way. In particular, we focused on how to represent the measurement of cognitive functions. In doing so, we argued that cognitive functions are the appropriate object of study for cognitive functioning assays. We further argued for the addition of the relation 'is functional measurement of'. This commits us to the view that qualities are not the only things that can be measured. It should be noted that, while this relation is a novel proposal, various candidate subproperties of 'is about' have been proposed, but none have been included in IAO due to a lack of strong definitions (IAO_0000221). It is our contention that the relation 'is functional measurement of' should be included in IAO. Once this relation is available, the connection between cognitive functioning assay outputs and cognitive functions becomes relatively straightforward. A partial representation of the MMSE assay is shown in Figure 3. We contend that our solution is an accurate and useful representation of cognitive functioning assays and should serve as a model for representing additional neuropsychological tests.

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REFERENCES

BFO 2.0. (2012). Basic Formal Ontology 2.0 Reference.

Brinkman, R. R., Courtot, M., Derom, D., Fostel, J. M., He, Y., Lord, P., Malone, J., Parkinson, H., Peters, B., Rocca-Serra, P., Ruttenberg, A., Sansone, S. A., Soldatova, L. N., Stoeckert, C. J., Jr., Turner, J. A., Zheng, J., & consortium, O. B. I. (2010). Modeling biomedical experimental processes with OBI. *J Biomed Semantics, 1 Suppl 1*, S7.

Cox, Alexander P., Jensen, Mark, Duncan, William, Weinstock-Guttman, Bianca, Szigeti, Kinga, Smith, Barry, & Diehl, Alexander D. (2012). *Ontologies for the Study of Neurological Disease*. Paper presented at the ICBO 2012: 3rd International Conference on Biomedical Ontology, Graz, Austria. http://bit.ly/T6TkZB

Diehl, Alexander D., Cox, Alexander P., & Jensen, M. (2013). NPT Google Code page. from https://code.google.com/p/neuropsychological-testing-ontology/

Grenon, Pierre. (2003). BFO in a Nutshell: A Bi-categorial Axiomatization of BFO and Comparison with DOLCE: Institute for Formal Ontology and Medical Information Science (IFOMIS) at the Faculty of Medicine of the University of Leipzig.

Hastings, J., Smith, B., Ceusters, W., Jensen, M., & Mulligan, K. (2012). *Representing mental functioning: Ontologies for mental health and disease*. Paper presented at the ICBO 2012: 3rd International Conference on Biomedical Ontology, Graz, Austria. http://kr-med.org/icbofois2012/proceedings/ICBOFOIS2012Workshops/ICBO2012MFO/ICBO-2012-MFO-WS.pdf

IAO. (2013). Information Artifact Ontology. from http://code.google.com/p/information-artifact-ontology/

Lezak, Muriel Deutsch, Howieson, Diane B., & Loring, David W. (2004). *Neuropsychological assessment* (4th ed.). Oxford: Oxford University Press.

NIH/ADNI. (2013). from http://www.nia.nih.gov/research/dn/alzheimers-disease-neuroimaging-initiative-adni

Oldfield, Richard C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Smith, B., Ashburner, M., Rosse, C., Bard, J., Bug, W., Ceusters, W., Goldberg, L. J., Eilbeck, K., Ireland, A., Mungall, C. J., Consortium, O. B. I., Leontis, N., Rocca-Serra, P., Ruttenberg, A., Sansone, S. A., Scheuermann, R. H., Shah, N., Whetzel, P. L., & Lewis, S. (2007). The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration. *Nat Biotechnol, 25*(11), 1251-1255.

Smith, B., & Ceusters, W. (2010). Ontological realism: A methodology for coordinated evolution of scientific ontologies. *Appl Ontol, 5*(3-4), 139-188.

Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Green, R. C., Harvey, D., Jack, C. R., Jagust, W., Liu, E., Morris, J. C., Petersen, R. C., Saykin, A. J., Schmidt, M. E., Shaw, L., Siuciak, J. A., Soares, H., Toga, A. W., Trojanowski, J. Q., & Alzheimer's Disease Neuroimaging, Initiative. (2012). The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. *Alzheimers Dement, 8*(1 Suppl), S1-68.