SOLOMON: An Ontology for Sensory-Onset, Language-Onset and Motor-Onset Dementias

Martin Skarzynski, Adam Craig and Carl Taswell
Brain Health Alliance, Ladera Ranch, CA 92694 USA
Email: ctaswell@BrainHealthAlliance.org

***Abstract*—The PORTAL-DOORS system (PDS) has been designed as a resource metadata management system intended to support applications such as automated searches of online resources and meta-analyses of published literature. PDS comprises a network of Problem Oriented Registry of Tags and Labels (PORTAL) lexical registries and Domain Ontology Oriented Resource System (DOORS) semantic directories. Here we introduce a PDS-compliant concept-validating registry and hypothesis-exploring ontology that organizes focal-onset dementias including Sensory-Onset, Language-Onset and Motor-ONset (SOLOMON) dementias with novel classifying and relating concepts. This approach facilitates semantic search of resources and exploration of hypotheses related to neurodegeneration. SOLOMON interoperates with other PDS registries and ontologies including BrainWatch, ManRay and GeneScene.**

***Index Terms*—PORTAL-DOORS System, ontology, meta-analysis, dementia, sensory-onset, language-onset, motor-onset.**

I. Introduction

Within the framework of the PORTAL-DOORS System (PDS) [1], [2], we have maintained the goal of supporting tools that facilitate automated searches of online resources and meta-analyses of the published literature. Ontologies used by PDS serve as critical components that determine the scale and scope of these searches and meta-analyses. Our initial application problem area focuses on the dementias, neurodegenerative disorders and brain imaging. We introduce here a PDS-compliant concept-validating registry and hypothesis-exploring ontology that organizes focal-onset dementias [3], [4] including Sensory-Onset, Language-Onset and Motor-ONset (SOLOMON) dementias.

II. Informatics for neurodegenerative disorders

Given the rapid rate at which research studies, clinical trials, and anonymized patient data are accumulating and the diversity of knowledge domains used in the different testing methods, it is unrealistic to expect any one researcher to be able to read and access every new piece of evidence as it becomes available. Furthermore, the number of samples and subjects available for any one study also may limit the statistical power of that study. Meta-analyses [5] address both problems. Researchers perform a meta-analysis by gathering together reports of individual studies that examine the same effect using methods similar enough to allow comparison of results. They then analyze the results of the studies for statistical trends in order to look for consensus results regarding the significance and effect size. A clear consensus across multiple studies is more convincing than a single result, and a single paper presenting that consensus takes less time to read and review than to do for numerous reports of individual studies.

A biomedical field currently undergoing rapid changes in the state of scientific understanding that could benefit from a novel approach to ontology development is the study of progressive neurodegenerative diseases leading to an irreversible cognitive decline known as dementia. Various neurodegenerative diseases, including Alzheimer's disease, Lewy body disease and Parkinson's disease may result in dementia. Correctly diagnosing the disease afflicting a patient remains critical to choosing the proper treatment in a clinical setting and also to studying the disease in a research context with clinical trials. During the course of these neurodegenerative diseases [6], damage may spread to multiple areas of the brain so that symptoms in the later stages overlap extensively. However, in their early stages, they tend to affect different parts of the brain, causing different sets of symptoms to appear initially. This progression of pathophysiology makes it useful to classify dementias by type of clinical onset (see Table I).

For example, in Alzheimer's disease, diminished ability to form memories often arises first [11], so one could describe the resulting dementia as a "memory-onset" dementia. On the other hand, if visual hallucinations are the earliest symptoms to manifest as often happens in Lewy body disease [6], [12], the resulting dementia can be described as "sensory-onset". Because loss of motor skills and coordination precedes cognitive decline in Parkinson's disease [12], the description "motor-onset" dementia applies. The most common type of frontotemporal dementia, first affecting the frontal and temporal lobes of the cortex, is "language-onset" dementia characterized by progressive aphasias such as semantic aphasia with a decline in the ability to remember the meanings of words or by a non-fluent aphasia with difficulties producing coherent speech [13]. All of these examples fall under the broader category of focal degenerative dementia syndromes [3], or focal-onset dementias, which can be linked to specific anatomical regions of the brain [4]. The combination of clinical relevance and orderly semantic structure make this approach to classification of dementias a logical choice as the basis for an ontology.

III. Hypothesis-exploring ontology development

Large encyclopedic reference ontologies can be cumbersome for both users and developers. For users, especially those not versed in predicate logic, searching through a large

TABLE I
EXAMPLES OF ONSET TYPE AND ASSOCIATED DISEASES, PROTEIN AGGREGATES AND ANATOMICAL REGIONS

Onset Type	Disease	Protein	Region	Citation
Memory	Alzheimer's Disease	Beta-amyloid	Hippocampus	[7]
Sensory	Posterior Cortical Atrophy	Beta-amyloid	Visual cortex	[8]
Language	Primary Progressive Aphasia	Tau	Insular cortex	[9]
Motor	Parkinson's Disease Dementia	Alpha-synuclein	Substantia nigra	[10]
Focal	Any of the above	Any of the above	Any of the above	[4]

tree of classes and examining their properties takes time and effort, especially when the ontology does not include the exact concept for which one is looking or a direct relationship between two concepts of interest so that the user must cobble together a more complex query from the existing classes and properties. For developers, updating nodes in an ontology with hundreds or thousands of classes and properties may introduce inconsistencies difficult to resolve, thus making large ontologies more difficult to maintain. Organizing the encyclopedia of concepts into smaller, modular ontologies that cover the lexicons of special topics makes both issues more manageable. A user can focus on searching for classes and properties within a module of interest, and a developer can work on a module with less concern about directly introducing errors in other modules.

The ManRay ontology, which focuses on radiopharmaceuticals, molecular imaging and nuclear medicine demonstrates a significant degree of modularity [14] in its design and was the first ontology designed for a PDS registry. The ManRay ontology contains modules that focus on specific entities such as imaging protocols, pharmaceuticals and radionuclides, all of which reference a shared foundational ontology [14]. The foundational ontology and modules, which together make up the ManRay ontology, can be used to investigate connections between genetic factors, imaging phenotypes and clinical symptoms [15]. Making the ManRay ontology interoperable with the PORTAL-DOORS system makes it useful for retrieving resources from the ManRay PORTAL registry, which provides metadata about relevant resources [16]. The PORTAL registry validates each resource a user attempts to register by checking that it references one or more subset of concepts included in the ManRay ontology, ensuring that each resource it accepts is relevant to nuclear medicine, radiopharmaceuticals, or molecular imaging [16]. In this way, the ManRay ontology and registry are fully integrated into the PDS resource metadata management system [1], [2], [17].

When designing the SOLOMON ontology (see Figure 1), we retained the key innovations demonstrated by the ManRay ontology by making the SOLOMON ontology PDS-compliant, concept validating and modular. However, even a large ontology divided into more partitioned sub-modules can still be too large for the kind of agile development cycle needed to keep up with the pace of modern biomedical science, necessitating a new strategy for designing lean, focused ontologies. With these concerns in mind, we established the following design principles (see Table II) to guide the construction of the SOLOMON ontology:

1) PDS compliance principle: SOLOMON must be compliant with the PORTAL-DOORS System [1], [2], [17]: PDS is a metadata network consisting of a distributed hierarchy of servers. The Problem-Oriented Registry of Tags and Labels (PORTAL) servers, known as the lexical side of PDS, allow registration [18] of URIs referring to online or offline resources associated with a specific problem domain. The Domain Ontology-Oriented Resource System (DOORS) servers, known as the semantic side of PDS, store those resource URIs in association with semantic tags that are part of a domain ontology, allowing for semantic searches of resources [2] using SPARQL queries [19]. Making SOLOMON interoperable with the PORTAL-DOORS Schema thus allows for live testing of the utility of the ontology for semantic search and allows SOLOMON to be used in conjunction with the resources registered with and tagged via the PDS.
2) Modularity principle: SOLOMON must contain all the concepts and relationships a researcher would need in order to search the literature for answers to key questions about hypotheses related to neurodegenerative disease and dementia. However, the more terms in the ontology, the longer it takes a user to find the right ones to use to formulate a query, and, the more intricately interrelated those terms, the more likely any change by a developer is to introduce errors into the relationships among terms. Thus, to optimize ease of use, maintainability, and adaptability, we sought to make SOLOMON no larger than needed to serve its purpose.
3) Interoperability principle: To make SOLOMON interoperable with any online resource, we defined the relationships between the terms in our ontology and terms in major neuroscience and medical publications and thesauri. This approach enables researchers to formulate queries in terms of the hypothesis-driven ontology and allows the reasoning engine to translate them into the language of the ontologies with which they are tagged.
4) Concept-validating principle (lexical and semantic side): The classes of the ontology should constitute a set of concepts such that a resource relating to one or more of those concepts [20] is relevant to the class of hypotheses of interest and is thus suitable for registry in the SOLOMON PORTAL registry.
5) Thesaurus-interfacing principle (lexical side): Because

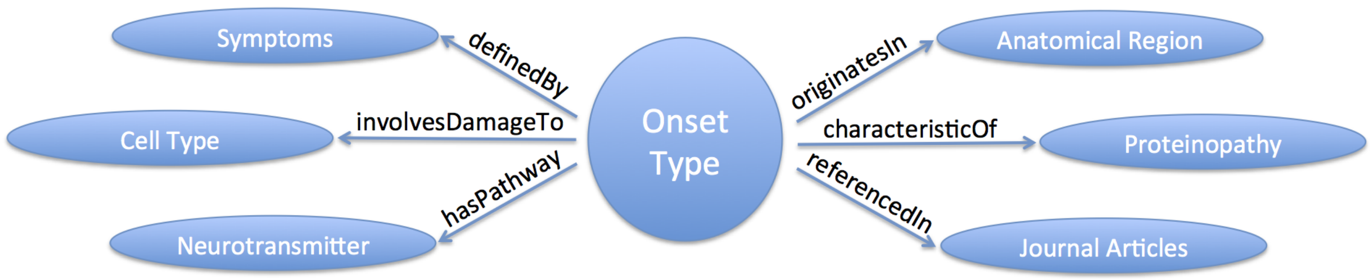

Fig. 1. Shows the relationships between the central concept of onset type and examples of other concepts

TABLE II
DESIGN PRINCIPLES GUIDING CREATION OF THE SOLOMON ONTOLOGY

Principle	Benefit
PDS compliance	resource discovery through the PORTAL-DOORS System
Modularity	coverage of domain of interest, ease of use and maintenance
Interoperability	discovery of resources tagged with well-established ontologies
Concept-validating (lexical and semantic side)	relevance of resources registered with PORTAL registry
Thesaurus-interfacing (lexical side)	discovery of resources employing synonyms of the target terms
Ontology-interfacing (semantic side)	discovery of resources employing target concepts in the desired context
Hypothesis-exploring (lexical and semantic side)	ease of use for biomedical end-users interested in the hypothesis space

experts in different fields and even in the same field speaking in different contexts may refer to the same concept by different names, it is important that the axioms of the SOLOMON ontology equate classes with their synonyms in reference ontologies, allowing these to serve as thesauri [21]. A lexical search for a term of interest can then find resources containing the term itself or a synonym.

6) Ontology-interfacing principle (semantic side): Because the SOLOMON ontology itself must not be encyclopedic in scope, it must reference other ontologies that are. These reference ontologies place the terms used in SOLOMON in their proper context in the larger network of relationships among terms, allowing reasoning engines to determine not only whether a term is used in a resource or not but whether it is used in a way that makes the resource relevant to the current search.
7) Hypothesis-exploring principle (lexical and semantic side): The SOLOMON ontology must maximize the ease with which biomedical researchers can formulate queries exploring hypotheses that attempt to explain the distinct onset-types and progressions of different types of dementia. The translation of a hypothesis into a query for resources that support it or for those that refute it must be direct and readily apparent so that the end user only needs expertise in the biomedical domain of interest and some basic knowledge of SPARQL.

IV. AN INTEGRATED HYPOTHESIS-EXPLORING SYSTEM

The PORTAL-DOORS System (PDS) [1], [2] is a bootstrapping, self-referencing, self-describing resource metadata infrastructure system [16]. A major innovation of this hybrid system is that it connects and relates both the lexical web and the semantic web with each other by linking the lexical Problem Oriented Registry of Tags and Labels (PORTAL) registries and the semantic Domain Ontology Oriented Resource System (DOORS) directories. In the PDS infrastructure, the PORTAL-DOORS Schema serves as the foundation for the management of resources by the PORTAL-DOORS System, defining the record types stored in each type of server and the fields those records contain. The SOLOMON ontology references terms from the PORTAL-DOORS schema to ensure that searches using the SOLOMON ontology can retrieve the resource metadata most relevant to the search in a manner compliant with PDS. Thus, the terms and relations for the SOLOMON ontology are embedded in the the metadata record stored in the PDS root server that defines, declares and describes the SOLOMON PORTAL registry. The SOLOMON registry and ontology, accessible through the Brain Health Alliance registrar, are both components of the PDS. Brain Health Alliance maintains the BHA Registrar as a PDS registrar and the SOLOMON Registry as a PDS PORTAL registry to store and manage URIs and metadata for resources registered as relevant to exploration of hypotheses related to neurodegenerative disease onset-type and a DOORS directory to store subject-predicate-object triples describing those resources in terms of the SOLOMON ontology. The introduction of the SOLOMON registry as a brain science and medicine reference ontology-interfacing and neurodegeneration hypothesis-exploring ontology is part of Brain Health Alliance's ongoing development of the semantic side of its implementation of PDS beyond the already implemented lexical side of the infrastructure.

We created the SOLOMON ontology as a demonstration of our principles for design and application of an ontology with a clear focus on the exploration of a specific biomedical problem. We designed SOLOMON around the sensory, language and motor impairments that arise as the initial manifestations of dementia and neurodegeneration, because the early clinical presentations of dementia are more readily distinguishable from each other, unlike the general cognitive impairments associated with later stages of dementia. Our first application of this ontology will be semantic tagging and analysis of literature and data sets related to the current hypothesis that proteinopathies (diseases caused by aberrant proteins or protein aggregates and their abnormal deposition or accumulation) are the central etiologic component of neurodegenerative disorders and dementia. This task remains formidable because of the complexity of neurodegenerative disorders on the molecular, cellular and anatomic levels. Furthermore, relevant datasets are large and heterogeneous, ranging from genetic sequencing to brain imaging scans. Despite the inherent intricacies of this field of study, the SOLOMON ontology will facilitate exploration of hypotheses related to its problem-oriented domain by allowing reasoning engines to logically expand queries into the terminology of relevant reference ontologies, such as the ManRay ontology for concepts related to nuclear medicine, radiopharmaceuticals, and imaging, and and other brain science and medicine ontologies [22] for concepts related to the investigation, diagnosis and treatment of brain disorders and diseases.

V. Conclusion

Continuing development of PDS with lexical registries and semantic directories of resource metadata for the organization, classification and analysis of data sets and literature remains an important approach to managing the growth of published data and information from basic research and clinical trials. When supported with tools that enable automated search for resources and automated meta-analyses of the literature, ontologies, such as SOLOMON, BrainWatch and ManRay, will facilitate exploration of hypotheses that address neurodegeneration, brain imaging, and nuclear medicine. These ontologies and associated software applications will serve as necessary components of a knowledge engineering workbench for brain imaging and the study of dementias.

References

[1] C. Taswell, "DOORS to the semantic web and grid with a PORTAL for biomedical computing," *IEEE Transactions on Information Technology in Biomedicine*, vol. 12, no. 2, pp. 191–204, Feb 2008, in the Special Section on Bio-Grid.

[2] ——, "A distributed infrastructure for metadata about metadata: The HDMM architectural style and PORTAL-DOORS system," *Future Internet*, vol. 2, no. 2, pp. 156–189, 2010, in Special Issue on Metadata and Markup. [Online]. Available: http://www.mdpi.com/1999-5903/2/2/156/

[3] Z. Arvanitakis and N. Graff-Radford, "Focal degenerative dementia syndromes." *Clin Geriatr Med*, vol. 17, no. 2, pp. 303–318, May 2001.

[4] C. Taswell, V. L. Villemagne, P. Yates, H. Shimada, C. E. Leyton, K. J. Ballard, O. Piguet, J. R. Burrell, J. R. Hodges, and C. C. Rowe, "^{18}F-FDG PET improves diagnosis in patients with focal-onset dementias." *J Nucl Med*, vol. 56, no. 10, pp. 1547–1553, Oct 2015. [Online]. Available: http://doi:10.2967/jnumed.115.161067

[5] M. Ressing, M. Blettner, and S. J. Klug, "Systematic literature reviews and meta-analyses: Part 6 of a series on evaluation of scientific publications," *Deutsches Ärzteblatt International*, vol. 106, no. 27, pp. 456–463, 07 2009. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719096/

[6] J. Quinn, Ed., *NIP- Neurology in Practice : Dementia*. Wiley-Blackwell, 2013.

[7] S. S. Sisodia, E. H. Koo, K. Beyreuther, A. Unterbeck, and D. L. Price, "Evidence that beta-amyloid protein in Alzheimer's disease is not derived by normal processing." *Science*, vol. 248, no. 4954, pp. 492–495, Apr 1990.

[8] S. Alladi, J. Xuereb, T. Bak, P. Nestor, J. Knibb, K. Patterson, and J. R. Hodges, "Focal cortical presentations of Alzheimer's disease." *Brain*, vol. 130, no. Pt 10, pp. 2636–2645, Oct 2007. [Online]. Available: http://dx.doi.org/10.1093/brain/awm213

[9] G. D. Rabinovici, W. J. Jagust, A. J. Furst, J. M. Ogar, C. A. Racine, E. C. Mormino, J. P. O'Neil, R. A. Lal, N. F. Dronkers, B. L. Miller, and M. L. Gorno-Tempini, "Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia." *Ann Neurol*, vol. 64, no. 4, pp. 388–401, Oct 2008. [Online]. Available: http://dx.doi.org/10.1002/ana.21451

[10] W. S. Kim, K. Kågedal, and G. M. Halliday, "Alpha-synuclein biology in lewy body diseases." *Alzheimers Res Ther*, vol. 6, no. 5, p. 73, 2014. [Online]. Available: http://dx.doi.org/10.1186/s13195-014-0073-2

[11] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services task force on Alzheimer's disease." *Neurology*, vol. 34, no. 7, pp. 939–944, Jul 1984.

[12] I. G. McKeith, D. Galasko, K. Kosaka, E. K. Perry, D. W. Dickson, L. A. Hansen, D. P. Salmon, J. Lowe, S. S. Mirra, E. J. Byrne, G. Lennox, N. P. Quinn, J. A. Edwardson, P. G. Ince, C. Bergeron, A. Burns, B. L. Miller, S. Lovestone, D. Collerton, E. N. Jansen, C. Ballard, R. A. de Vos, G. K. Wilcock, K. A. Jellinger, and R. H. Perry, "Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on dlb international workshop." *Neurology*, vol. 47, no. 5, pp. 1113–1124, Nov 1996.

[13] M. Gorno-Tempini, A. Hillis, S. Weintraub, A. Kertesz, M. Mendez, S. e. a. Cappa, J. Ogar, J. Rohrer, S. Black, B. Boeve *et al.*, "Classification of primary progressive aphasia and its variants," *Neurology*, vol. 76, no. 11, pp. 1006–1014, 2011.

[14] C. Taswell, B. Franc, and R. Hawkins, "The ManRay project: Initial development of a web-enabled ontology for nuclear medicine," in *Proceedings of the 53rd Annual Meeting of the Society of Nuclear Medicine, San Diego, CA*, Jun 2006, p. 1431.

[15] C. Taswell, "Knowledge engineering for pharmacogenomic molecular imaging of the brain," in *Proceedings of SKG 2009 The 5th International Conference on Semantics, Knowledge, and Grid*. IEEE Computer Society, September 2009, pp. 26–33.

[16] ——, "Alternative bootstrapping design for the PORTAL-DOORS cyberinfrastructure with self-referencing and self-describing features," in *Semantic Web*, G. Wu, Ed. Vukovar, Croatia: In-Teh, 2009, ch. 2, pp. 29–37. [Online]. Available: http://sciyo.com/books/show/title/semantic-web

[17] ——, "PORTAL-DOORS infrastructure system for translational biomedical informatics on the semantic web and grid," in *Proceedings of the American Medical Informatics Association Summit on Translational Bioinformatics, San Francisco, CA*, Mar 2008, p. 43.

[18] ——, "Implementation of prototype biomedical registries for PORTAL-DOORS," in *Proceedings of the American Medical Informatics Association Summit on Translational Bioinformatics, San Francisco, CA*, Mar 2009, pp. AMIA–0036–T2009.

[19] B. DuCharme, *Learning SPARQL*. " O'Reilly Media, Inc.", 2013.

[20] C. Taswell, "Concept validating methods for maintaining the integrity of problem oriented domains in the PORTAL-DOORS system," *AMIA*, 2010.

[21] ——, "Use of the MeSH thesaurus in the PORTAL-DOORS System," in *Proceedings AMIA 2010 Symposium on Clinical Research Informatics, San Francisco CA*, 2010, pp. AMIA–033–C2010.

[22] S. D. Larson and M. E. Martone, "Ontologies for neuroscience: What are they and what are they good for?" *Front Neurosci*, vol. 3, no. 1, pp. 60–67, May 2009. [Online]. Available: http://dx.doi.org/10.3389/neuro.01.007.2009