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A prototype symbolic model of canonical functional neuroanatomy of the motor system

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Abstract

Recent advances in bioinformatics have opened entire new avenues for organizing, integrating and retrieving neuroscientific data, in a digital, machine-processable format, which can be at the same time understood by humans, using ontological, symbolic data representations. Declarative information stored in ontological format can be perused and maintained by domain experts, interpreted by machines, and serve as basis for a multitude of decision support, computerized simulation, data mining, and teaching applications.

We have developed a prototype symbolic model of canonical neuroanatomy of the motor system. Our symbolic model is intended to support symbolic lookup, logical inference and mathematical modeling by integrating descriptive, qualitative and quantitative functional neuroanatomical knowledge. Furthermore, we show how our approach can be extended to modeling impaired brain connectivity in disease states, such as common movement disorders.

In developing our ontology, we adopted a disciplined modeling approach, relying on a set of declared principles, a high-level schema, Aristotelian definitions, and a frame-based authoring system. These features, along with the use of the Unified Medical Language System (UMLS) vocabulary, enable the alignment of our functional ontology with an existing comprehensive ontology of human anatomy, and thus allow for combining the structural and functional views of neuroanatomy for clinical decision support and neuroanatomy teaching applications.

Although the scope of our current prototype ontology is limited to a particular functional system in the brain, it may be possible to adapt this approach for modeling other brain functional systems as well.

Keywords: Functional neuroanatomy; Ontology; Neural network; Motor system; Basal ganglia; Disease model; Parkinson's disease; Chorea; Hemiballism; Neural circuit

1. Introduction

The brain is arguably the most complex organ of the human body, and our understanding of its structure and function is fragmentary. The past few decades have seen an enormous accumulation of neuroscientific data, making it impossible for any one individual to comprehend and assimilate more than a fraction of the available data. This fact becomes evident while performing a simple search of the literature databases, such as Medline. For instance, a recent search in the Medline database performed by the authors, entering the term "brain", yielded 1,003,745 entries (http://www.ncbi.nlm.nih.gov/entrez, accessed on 01/25/2007).

Recent advances in bioinformatics have opened entire new avenues for organizing, integrating and retrieving neuroscientific data, in a digital format, which can be at the same time understood by both humans and machines, using ontological, symbolic data representations [1]. In addition to providing an understanding of the physical organization of the nervous system, neuroanatomy may also serve as a common frame of reference for organizing all types of neuroscience data [2].

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In a general sense, there are two complementary views of neuroanatomy: (a) a *structural view*, concerned with shape, dimensions, spatial location and relationships, and embryologic origin of neural structures, and (b) a *functional view*, dealing with functional (physiologic) relationships between entities assembled into neural functional systems (connections between these entities via neural pathways, physiologic actions—e.g. excitation or inhibition—of one entity on another exerted via neural pathways); these entities often do not share a common embryologic origin and may be spatially remote. The two perspectives are by no means mutually exclusive. On the contrary, they must be viewed as complementary, as both are essential for problem solving, in the basic as well as clinical neuroscience domain.

The Foundational Model of Anatomy (FMA), developed by Rosse and colleagues, is an excellent example of modeling the structural view of a biomedical domain [3]. The FMA is a comprehensive domain ontology describing the concepts and relationships that pertain to the structural organization of the human body, including the nervous system, from the molecular to the macroscopic level. The FMA has been successfully used for developing knowledge-based applications that rely on inference to support clinical decision-making, such as reasoning about consequences of penetrating chest injuries [4–8].

Structural information contained in the FMA enables queries such as: "*which structures are adjacent to or continuous with other structures*?", or "*what are the parts of a particular anatomic structure*?". However, structural information is insufficient to support logical inferences on the functional consequences of anatomic lesions.

The entities in the FMA are grouped according to embryologic origin and spatial adjacency criteria. Functional systems in the brain, on the other hand, include multiple, often spatially remote, and embryologically unrelated structures. For instance, from a structural point of view, the striatum and globus pallidus are part of the telencephalon, the ventral anterior nucleus of thalamus and the subthalamic nucleus are part of the diencephalon, while substantia nigra is part of the midbrain. From a functional perspective, all these structures are part of a single subcortical neural network, controlling the initiation of voluntary movement (Fig. 1).

The purpose of the present study was to develop a prototype symbolic model of canonical functional neuroanatomy of the motor system in an ontology, representing normal and disease states, based on a set of declared principles, Aristotelian definitions, and a high-level schema. We chose the motor system because it displays little anatomic variability and its function is better characterized than that of other, more complex functional systems in the brain. Furthermore, the motor system is involved in a host of pathologic processes with high impact on public health, such as movement disorders.

Our current prototype ontology, based on the principles of functional connectionism, is limited to a single functional system. However, since functional connectionism applies to the entire brain, it may be possible to extend the modeling approach we describe in this paper to other brain functional systems as well. As we will show in the following sections, the ontological modeling approach we are proposing can be employed to describe normal, as well as pathologic states.

Symbolic models of functional neuroanatomy, alone or in combination with MRI-based digital brain atlases, could open the way for developing knowledge-based applications for clinical decision support (e.g. surgical planning applications capable to identify potential targets for functional stereotactic surgery), and computer applications for neuroanatomy teaching.

2. Materials and methods

First, we extracted the relevant functional neuroanatomical information from authoritative neuroscience textbooks [9–11]. In addition, we collected information on movement disorders that result from impaired connectivity between key anatomical components of the motor system.

Next, we created an ontology of functional anatomy of the motor system, based on the anatomic knowledge we extracted in the previous step. The ontology was created using a disciplined modeling approach, inspired by that adopted by the developers of the Foundational Model of Anatomy [3]. Our ontology was implemented using the Protégé suite of tools (http://protege.stanford.edu), a frame-based ontology editor.

In this section, we provide a brief overview of the functional anatomy of the motor system. We then describe the theoretical framework and the principles we employed for developing our prototype functional ontology.

2.1. Functional anatomy of the motor system

Older classifications used to make a distinction between the "pyramidal" and "extrapyramidal" motor system. Modern neuroscience has outgrown this rather simplistic view, and it is currently well established that the concerted action of both these strongly interconnected groups of neural circuits is required for normal motor function.

2.1.1. The "Pyramidal" system

This functional system is responsible for voluntary movement. From a functional perspective, it is composed of two major types of neurons: upper motor neurons and lower motor neurons.

The upper motor neurons (UMN) are represented by the giant pyramidal neurons (Betz's cells), located in the internal pyramidal layer (layer V) of the primary motor cortex (precentral gyrus, motor strip).

The lower motor neurons (LMN) are located in the brainstem (motor nuclei of cranial nerves), and in the anterior horn of the spinal cord gray matter.

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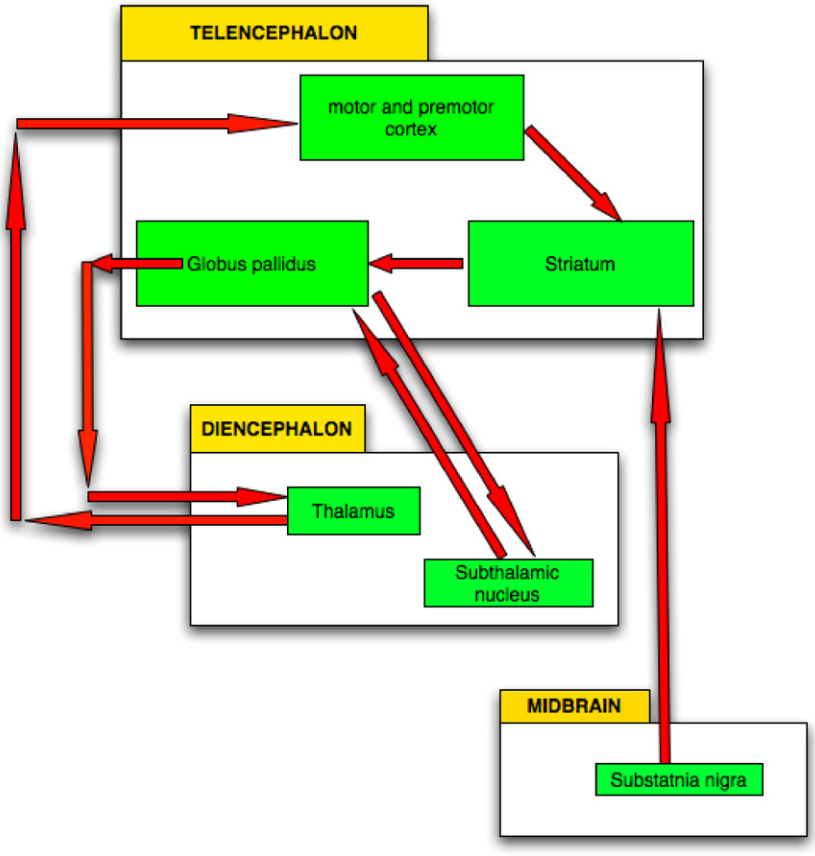

Q1 Fig. 1.

The precentral gyrus is located in the posterior frontal lobe. The central sulcus separates it from the postcentral gyrus (site of the primary somatosensory cortex). Medially, it is contiguous with the paracentral lobule, while inferiorly it is separated from the superior temporal gyrus by the lateral fissure (Sylvius). In the primary motor cortex, the different regions of the body are represented in a somatotopical fashion, with the foot and leg area located on the medial aspect of the cerebral hemisphere, followed by the trunk, upper limb and face areas, from medial to lateral (''*motor homunculus*''). The surface of the cortical representation is not proportional with the size of the respective body region, but rather with the complexity of movements performed by a particular part.

The axons of the upper motor neurons form the corticospinal (pyramidal) tract, which descends through the corona radiata and converge in the posterior limb of the internal capsule. After passing the internal capsule, these axons continue their descent through the ventral brainstem. At the brainstem level, some of these axons cross-over to the contralateral side and synapse with lower motor neurons located in the motor nuclei of the cranial nerves. From a clinical perspective, it is important to point out that the dorsal part of the facial nerve nucleus receives both contralateral and ipsilateral cortical input.

In the ventral medulla oblongata, the corticospinal fibers converge into two compact tracts, prominently visible at the surface (pyramids). At the junction between medulla and spinal cord, most (80–90%) of these axons cross-over to the contralateral side (pyramidal decussation), and continue their descent in the lateral spinal cord (lateral corticospinal tract). The uncrossed axons continue their descent in the anterior spinal cord, as the anterior corticospinal cord. This smaller contingent of fibers cross-over at the spinal cord level, shortly before reaching their target lower motor neurons. Most corticospinal axons synapse with their target lower motor neurons via spinal interneurons, while a smaller fiber contingent synapses directly on lower motor neurons.

2.1.2. The ''Extrapyramidal'' system (motor initiation system)

The motor initiation system consists of a family of parallel circuits linking subcortical structures with the motor cortex. Its principal components are the basal ganglia (striatum, globus pallidus), the subthalamic nucleus, the ventral anterior nucleus of thalamus, the substantia nigra and the motor cortex.

Input from the motor cortex (glutaminergic) reaches the basal ganglia via the striatum (caudate nucleus and putamen). The basal ganglia process this information and project back to the motor cortex, via the internal pallidal segment

and ventral anterior thalamic nucleus. The only output from the basal ganglia is inhibitory, and it originates in the GABA-ergic medium-spiny neurons of the internal pallidal segment.

The state of activity in the basal ganglia is regulated via two dopaminergic projection systems, originating in the substantia nigra pars compacta: the direct and the indirect projection systems (a.k.a. direct and indirect pathways). The facilitating effects on movement of the direct projection system are mediated by D1-dopamine receptors. The indirect projection system has an inhibitory effect on movement, mediated by D2-dopamine receptors (Fig. 2).

2.2. Diseases of the "Extrapyramidal" system (motor initiation system)

Lesions of the basal ganglia frequently result in movement disorders:

Parkinson's disease is a classical example of *hypokinetic* movement disorder. Clinically, this condition is characterized by impaired initiation of movement (*akinesia*), reduced velocity and amplitude of movement (*bradykinesia*), and resting tremor and increased muscle tone (*rigidity*).

The prevalence of idiopathic Parkinson's disease is estimated at 128–168 cases per 100,000 [12]. There is a dramatic increase in Parkinson's cases with increasing age. About 1% of the population aged 50–64 years suffers from Parkinson's disease. This rate increases to 14.9% in the 65–74 years age group and 52.4% of individuals over 85 years old [13].

Pathophysiologically, degeneration of dopamine producing cells in the substantia nigra pars compacta leads to a decrease in the activity of the direct basal ganglia pathway relative to the indirect pathway activity. This, in turn, results in an increased inhibitory output from the internal pallidal segment (globus pallidus pars interna, GP_i).

The therapeutic approaches to Parkinson's disease include pharmacologic agents (dopamine agonists), and stereotactic functional surgery, such as ablation of the subthalamic nucleus or of the internal pallidal segment (GP_i).

Hyperkinetic movement disorders are characterized by excessive, uncontrollable motor activity resulting in abnormal, involuntary movements of the extremities, head and trunk, and decreased muscle tone (*hypotonia*). Depending on the anatomic structure affected, the involuntary movements can take the form of writhing movements of the arms and hands (*athetosis*), brief, non-rhythmic movements spreading from one muscle group to the next (*chorea*), violent, large amplitude movements of the proximal limbs (*ballism*).

Huntington's disease is a typical example of hyperkinetic movement disorder. It is an inherited, autosomal-dominant disorder with complete penetrance. Its prevalence in the United States is estimated at about five cases per 100,000. Huntington's disease is a slowly progressive condition,

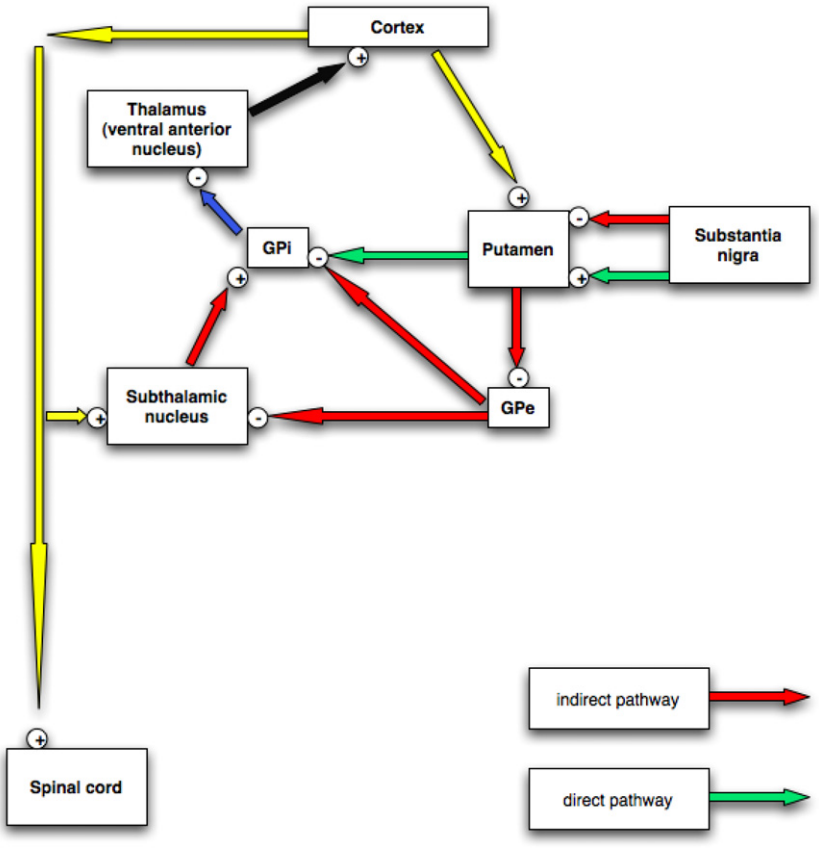

Fig. 2.

leading to death of the affected individual within 15–20 years from symptom onset [14].

The responsible gene is located on chromosome 4. This gene encodes a large protein, *huntingtin*. The function of huntingtin has yet to be characterized. It is theorized, however that huntingtin plays a role in triggering apoptosis (programmed cell death) in certain neuron populations in the central nervous system, including the basal ganglia.

As opposed to Parkinson's disease, the inhibitory internal pallidal output is decreased in hyperkinetic disorders, such as chorea and hemiballism.

Disease-induced alterations of the basal ganglia neural circuits in Parkinson's disease, chorea and hemiballism are presented in Fig. 3.

2.3. Ontological modeling

In developing our ontology, we adopted a disciplined modeling approach, as described by Rosse and colleagues in their seminal work on the Foundational Model of Anatomy (FMA) [3]. This development was accomplished in a four step process: (1) establishing the appropriate theoretical framework and identification of the biological concepts, attributes and relationships that will form the building blocks of the symbolic representation; (2) defining a rational modeling approach, the elements of the symbolic model structure (high-level schema), and the set of properties and modeling rules to be employed; (3) identification of an appropriate software authoring system, that will not only allow, but also enforce the modeling rules; (4) evaluation of the symbolic model. Our ontology was implemented using the Protégé suite of tools (http://protege.stanford. edu).

2.3.1. Theoretical framework

The functional organization principles of "cellular connectionism" (Wernicke, Sherrington, Cajal) provide the biological foundation for our symbolic model:

(1) *Neuron doctrine:* the elementary signaling unit in the nervous system is the neuron. Each neuron is a distinctive cell with distinctive processes (multiple dendrites, one axon).

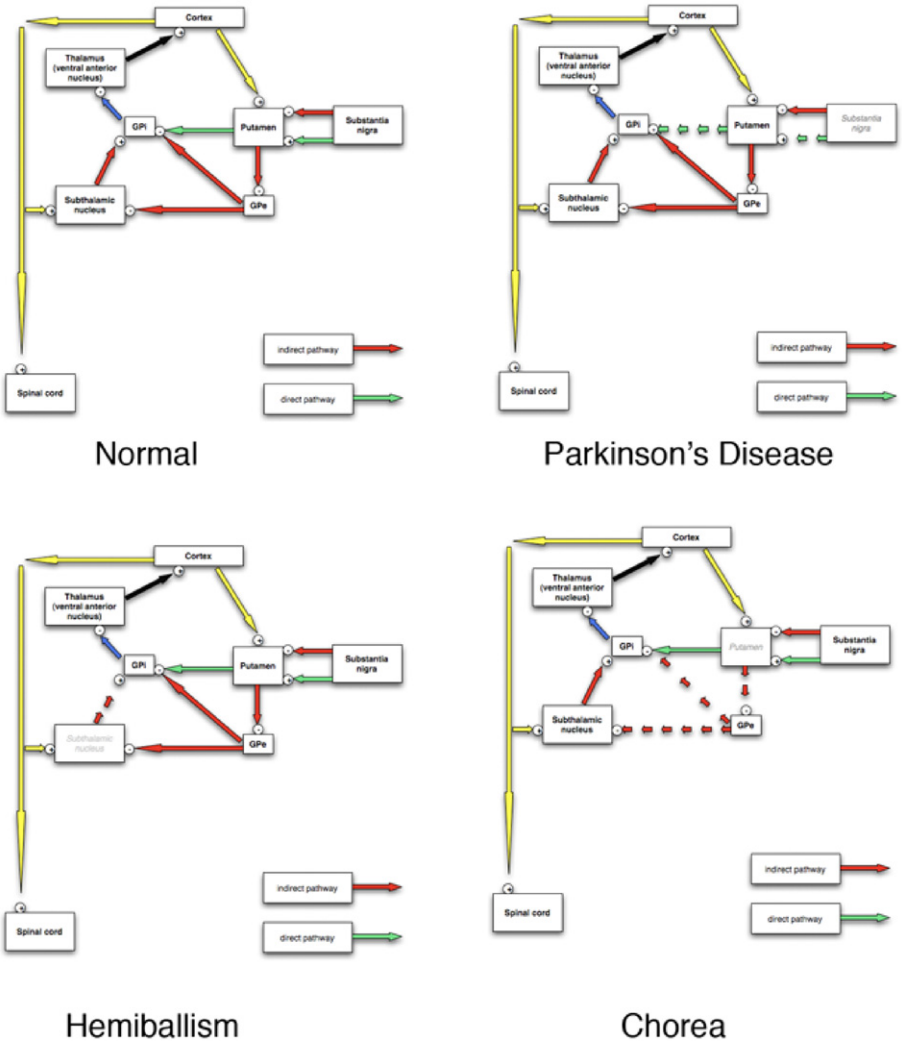

Fig. 3.

(2) *Dynamic polarization principle:* the signal (action potential) flow in the neuron is unidirectional, from the dendrites to the cell body to the axon.
(3) *Connectional specificity principle:* each neuron is connected with certain other neurons (target cells), but not with others. The connections between neurons provide the physical basis for signal processing, i.e. for brain function. Neurons are arranged in specific functional groups or *neural networks* (e.g. primary motor and somatosensory cortex, subcortical nuclei). Each neural network is concerned with specific *elementary signal processing operations*, as part of a specific neurologic function. These groups of neurons are linked via serial and parallel connections (neural pathways). Specific brain functions are divisible into elementary signal processing operations, performed by specialized neural networks. Consequently, a brain functional system (e.g. motor system) can be viewed as a collection of specialized neural networks.
(4) The signals are transmitted from one neuron to the other via *synapses*. This process is mediated by chemical *neurotransmitters*. Neurotransmitter release may lead to *depolarization* (*excitation*) or *hyperpolarization* (*inhibition*) of the postsynaptic membrane. For instance, glutamate is the most common excitatory neurotransmitter in the nervous system, while gaba-amino-butyric acid (GABA) is the most common inhibitory neurotransmitter.
(5) The action potential is the universal mechanism for signal transmission in the nervous system. The specificity of a given signal (e.g. motor, sensory) is determined by the neural network(s) it travels through.
(6) Somatotopic representation: individual parts of the body are represented at specific sites in the motor and somatosensory systems.

In summary, *elementary signal processing operations* are the building blocks of brain function, and *neural networks* provide the anatomical basis for these operations, i.e. they represent the *anatomo-functional units* of the nervous system. The defining feature of a network is the link (connection) between its nodes. As detailed in the following sections, the *neural network* concept plays a central role in our symbolic representation.

2.3.2. Disciplined modeling

One important requirement for ontological models is that they rigorously and consistently conform to the domain they are designed to model [3,15–19]. A common pitfall when developing symbolic models of anatomy is mixing spatial and functional information in the same hierarchy [3,15,20]. In order to avoid this problem, the scope of our ontology is strictly limited to representing *functional* anatomy, specifically the functional anatomy of motor neural networks (*abstraction level principle*) [3]. Consequently, our design plan conforms to a functional context (*unified context principle*) [3], and the entities of the symbolic model, along with their attributes and relationships are defined in respect to their functional role, and not to spatial relationships or embryologic origin criteria (*definition principle, relationship constraint principle*) [3].

Defining the dominant concept (*dominant concept principle*) and the organizational unit (*organizational unit principle*) [3] are crucial steps in ontology design. The dominant concept serves as reference for defining all classes (concepts) of the ontology.

As discussed in the previous section, the neural network is the anatomo-functional unit of the nervous system. Hence, in order to represent brain function, we identify the "*neural network*" concept as the dominant concept of our ontology. We define this concept as follows:

Neural network is a biological entity consisting of neurons and their processes, connected by synapses in a specific, genetically determined pattern, which performs specific elementary signal processing operations, and constitutes the functional organization unit of the nervous system.

Microscopic neuronal networks are grouped together into functionally specialized, gray matter structures (subcortical nuclei, cortical areas). Gray matter structures are connected in a specific, genetically determined pattern, via long axonal processes (*neural pathways, fiber tracts*), into functionally specialized *macroscopic neural networks* (e.g. networks of subcortical nuclei).

The organizational unit of our symbolic model is the *neuron*, since all elements (classes) of our symbolic representation can be derived from neurons or parts of neurons. At its current stage of development, our ontology represents anatomic structures at macroscopic scale.

In accordance with the *content constraint principle* [3], the largest entity that can be modeled is a functional system (collection of macroscopic neural networks performing elementary signal processing operations as part of a specific brain function, e.g. motor function), and the smallest entity that could be represented is a biological molecule concerned with synaptic transmission in the nervous system (neurotransmitter).

2.3.3. High-level schema

The general structure (high-level schema) of our ontology consists of the following elements: *anatomo-functional abstraction*, *neural network taxonomy*, and *neural network component taxonomies* (nodes taxonomy, connections taxonomy).

2.3.3.1. Anatomo-functional abstraction. The anatomo-functional abstraction describes the properties and relationships between the entities of the functional ontology.

There are two types of relationships that need to be represented in an ontology of functional anatomy: *meronymic* (*partitive*) and *functional* (*physiologic*) relationships.

(1) *Meronymic* ("*is part of*", "*has parts*") *relationships*. Each neural network *is part of* a functional system (e.g.

motor system, sensory systems), and *has parts*, i.e. network nodes (subcortical gray matter nuclei/cortical areas), and network connections (white matter fiber tracts, neural pathways), respectively.

Examples:

> "The motor initiation neural network *is part of* the motor system."
> "The motor system has parts: the voluntary motor neural network and motor feedback neural networks."
> "Globus pallidus *is part of* the motor initiation network, and thus it *is part of* the motor system."

White matter structures (white matter fiber tracts, neural pathways) are also parts of a neural network.

(2) *Functional* (*physiologic*) *relationships*. Neural networks provide the anatomic basis for neurologic function. Typically, the physiologic influence of one network node on another is conveyed via neural pathways (neural network connections). A pathway can only have one origin (cortical area/subcortical nucleus) and one target (cortical area/subcortical nucleus), and it conveys one type of physiologic effect to the target (excitation, or inhibition). The signal propagation is unidirectional, from the origin to the target (*dynamic polarization*).

Example:

> "The internal pallidal segment exerts an *inhibitory* influence on the ventral anterior thalamic nucleus; this inhibitory influence is conveyed via the pallido-thalamic pathway."

Since neural pathways convey the physiologic action of the origin node to the target node, they can be represented as verbs in the syntactic structure of the ontology, while the origin node can be represented as subject, and the target node as object (Fig. 4).

2.3.3.2. Neural network taxonomy and neural network element taxonomies. Since neural network elements cannot be represented in the form of "*is a*"—subclasses of the generic neural network class, we accomplished the goal of creating a comprehensive class-subsumption hierarchy in an operational manner.

First, we created a template taxonomy of neural networks, with "neural network" as its root class (Fig. 5).

Specific neural networks belonging to particular functional systems (e.g. motor neural network, somatosensory neural network) are represented as subclasses of the root class. We further elaborated the "motor neural network" class, by adding the following subclasses: "voluntary movement neural network", and "motor feedback neural network". The latter subclass also has two subclasses: "motor initiation neural network" and "motor modulation neural network". The right and left motor initiation neural networks are represented as instances of the "motor initiation neural network" subclass.

Second, using the template neural network taxonomy, we created separate taxonomies for each network element type (nodes and connections, respectively).

The classes in the nodes taxonomy were given the following properties: "is part of" (neural network), "*output*", "*input*". The "input/output" slots can only be filled with instances of classes from the network connections taxonomy.

One important feature of neural networks participating in the same brain function is the fact that they share some of their nodes. For instance, the motor cortex is at the same time part of the voluntary motor network and of the motor initiation network. The basal ganglia send output back to the motor cortex, where the initial motor command originates (see Fig. 1). We accounted for this feature by creating a "shared node" subclass of the "motor neural network node" class.

The classes in the connections taxonomy were given the following properties: "*origin*", "*target*", and "*physiologic effect*" (*excitation/inhibition*). The "origin" and "target" slots can only be filled with class instances from the nodes taxonomy.

In the final step, we combined the two network element taxonomies into a comprehensive functional ontology. In this design, the classes of the nodes taxonomy fill slots of classes in the connections taxonomy (Figs. 6 and 7).

2.3.3.3. Representing somatotopy and pathway cross-over. Specific sites of the motor system control the motor activity of different body regions (head, neck, trunk, limbs). This is called somatotopic representation. For example, the cortical area located on the medial aspect of the precentral gyrus controls voluntary movement of the contralateral leg, while voluntary movement of the face muscles is controlled by an area located in the inferior portion of the precentral gyrus. In order to represent somatotopy in our ontology, we added instances to the "neural network node" and "neural network connection" classes, according to the body regions they represent. For example, we added instances to the "motor cortex" class corresponding to leg, trunk, upper limb, lower limb, etc.

Due to the fact that the corticospinal tract crosses over to the contralateral side, voluntary movement of the two body halves is controlled by the contralateral motor cortex. Pathway cross-over is represented in our ontology in the following manner:

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origin node (right side) → pathway (instance of neural network connection) → target node (left side).
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3. Results

Using the approach presented in the previous sections, we developed of a prototype ontology describing the basic

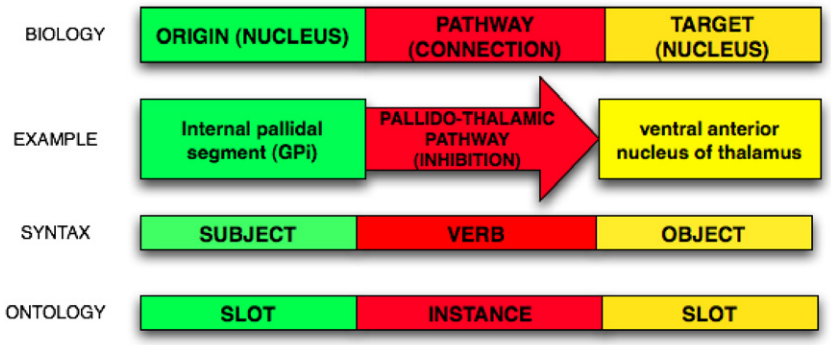

Fig. 4.

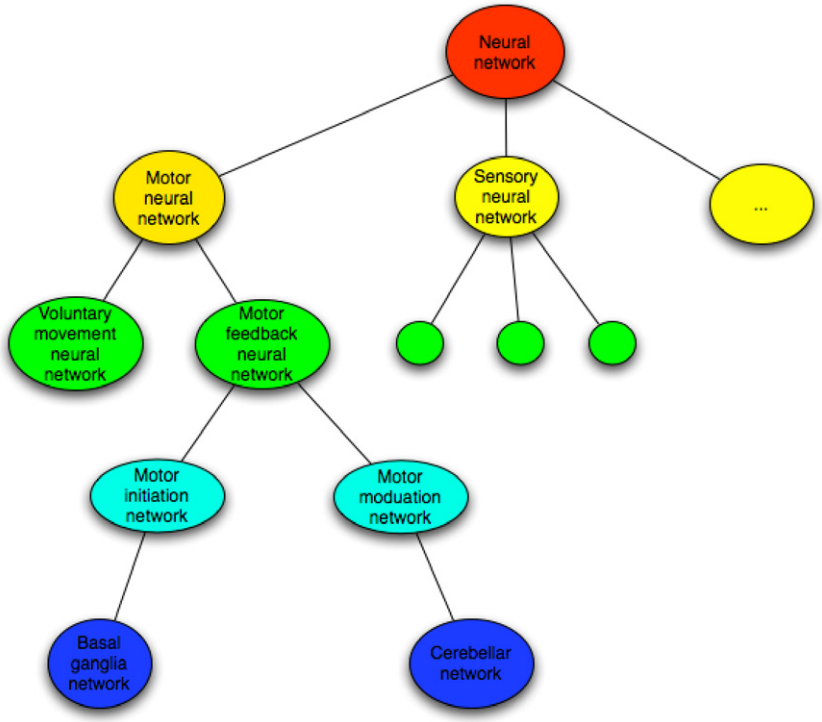

Fig. 5.

functional organization of the motor system. There is a one-to-one mapping from each instance in the ontology and a gray matter structure in the brain involved with motor function (e.g. right and left primary motor cortex, right and left putamen, globus pallidus pars interna and externa, etc.). For example, the internal pallidal segment is represented as an instance of the NeuralNetworkNode class. Furthermore, the connections (neural pathways) between gray matter structures, each having the appropriate attributes to specify their functional action on the target network node (gray matter structure), i.e. excitatory or inhibitory influence, are also represented in our ontology, as instances of the NeuralNetworkConnection class. The ontological representation of the different neural networks that compose the motor system is accomplished in an operational manner, i.e. the network is reconstructed from its elements: class instances of the neural network nodes taxonomy fill "target" slots of classes in the neural network connections taxonomy.

Our modeling approach is suitable not only for representing neural connectivity in the normal brain. It can be easily extended to represent impaired brain connectivity as well.

We used the prototype ontology described above to create a symbolic, computable model of neural connectivity and function of the motor initiation network in the normal brain (Fig. 8B). While this ontology-based symbolic model has a very similar appearance to the original graphical representation from which it was derived (Figs. 1 and 8A), the entire model is a computable representation. Each node and connection in the diagram represents an object in the ontology. For example, the arc connecting thalamus and cortex is an instance in the ontology in which the thalamus is linked with the motor cortex

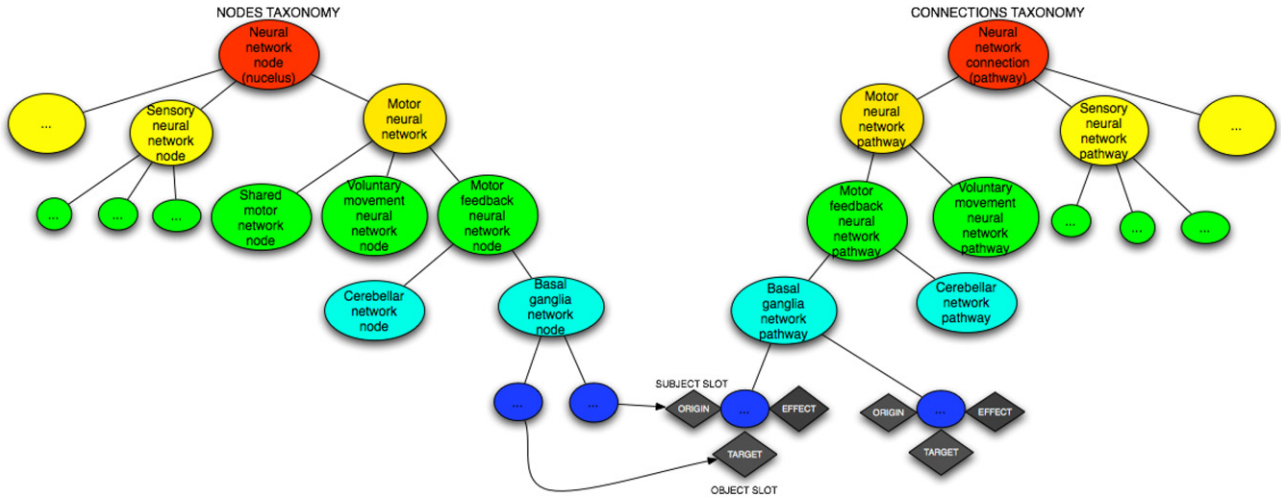

Fig. 6.

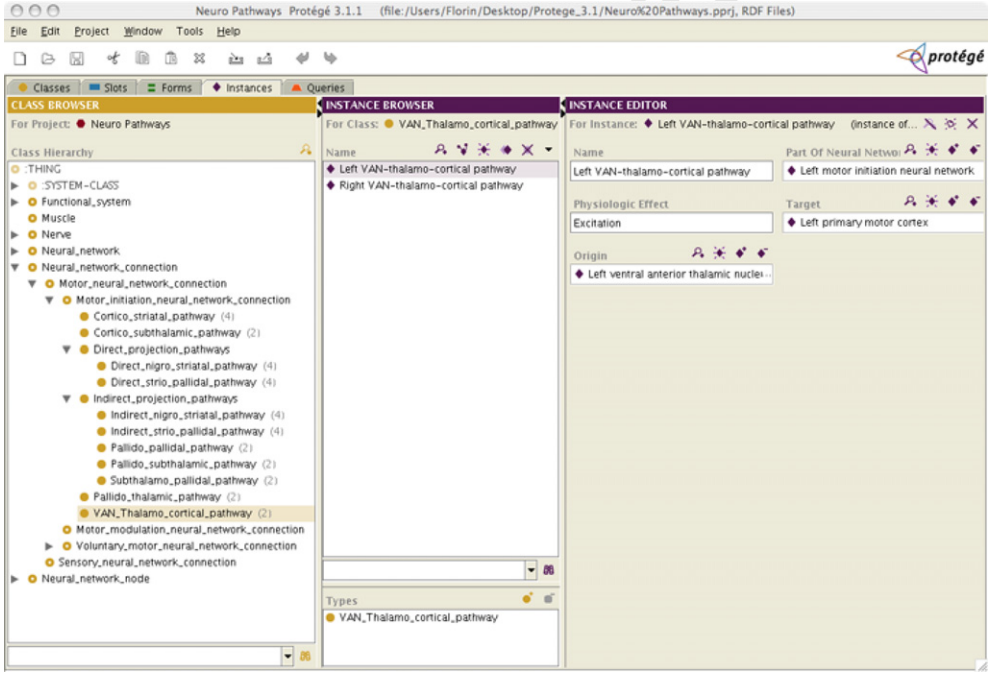

Fig. 7.

via an excitatory connection. This instance contains information about the structure from which it originates and the target structure to which it projects, as well as the type of physiologic influence it exerts on the target. Likewise, other connection objects are instances of an "inhibitory connection" class, meaning that they inhibit nodes to which they connect.

The entire model is computable, and by traversing all links, it is possible to compute the net excitation or inhibition of every anatomic structure.

To demonstrate the extensibility of our approach for representing pathologic conditions, we created a second model representing impaired neural connectivity in Parkinson's disease, by modifying the normal model. We replaced two arcs in the normal model with arcs that are of type "impaired excitatory neural connection". These arcs represent neural connections that produce less excitatory output than normal. Accordingly, the ontological representation of the Parkinson's disease model permits us to assess the consequences of the impaired connectivity—that there will be increased inhibitory activity in the internal pallidal segment (GP_i), and consequently increased inhibition of the motor cortex (Fig. 9). In a similar manner, we could model the consequences of impaired connectivity in hyperkinetic movement disorders, such as Chorea and Hemiballism by replacing links with the appropriate functional types according to the pathology of the disorder.

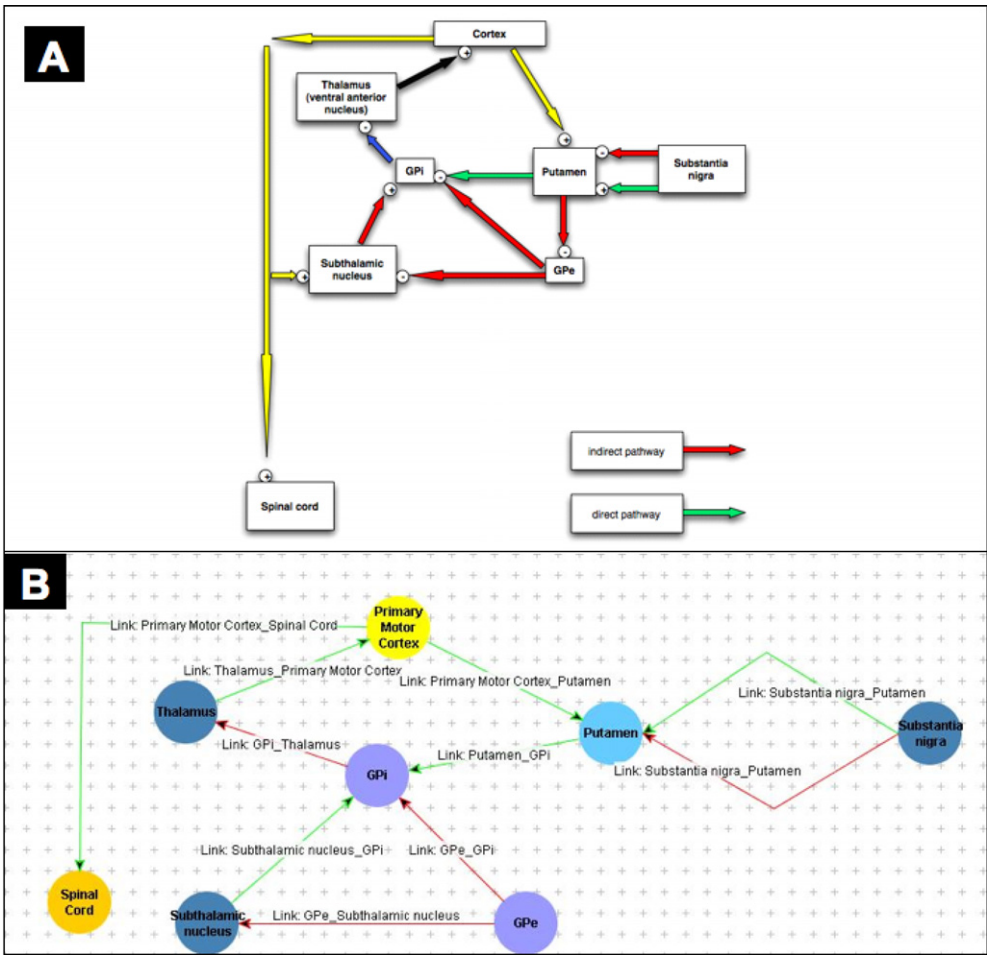

Fig. 8.

The net inhibitory effect of the internal pallidal segment on the motor cortex, via the anterior thalamic nucleus, is determined by the ratio between activation levels of the direct vs. indirect pathway (A_{DP}:A_{IDP}) [21]. Voluntary movement can only be initiated when the activation level of the direct pathway is greater than that of the indirect pathway. In hypokinetic movement disorders, such as Parkinson's disease, the A_{DP}:A_{IDP} ratio is lower than normal, whereas in hyperkinetic movement disorders (Chorea, Hemiballism), this ratio is higher than normal.

By attributing arbitrary strength values to the different network connections (positive for excitatory connections, negative for inhibitory connections), it is possible to create a computer reasoning application that computes the net excitation levels of the motor cortex under normal and pathologic circumstances, because our ontology-based model of neural connectivity is machine-processable and net excitation of all nodes can thus be computed (Figs. 8 and 9). For example, in the Parkinson's disease model, the ontological representation of the functional aspects of neural network connections would permit a computer reasoning service to evaluate the net activation in the different nodes of the `MotorInitiationNeuralNetwork` and conclude that there is net inhibition of the `PrimaryMotorCortex` node. Accordingly, the value of creating our ontological representation of the functional organization of the motor system is to make the anatomic and functional aspects of neural structures accessible to intelligent computer reasoning services.

Such reasoning services, combined with patient-specific imaging-based brain atlases, may be used in creating decision support applications to help surgical planning and personalized patient care. Image-based, geometric models of brain anatomy provide spatially accurate, implicit representations of brain structure. However, they lack explicit knowledge about their contents, such as the functional role of the anatomic structures they represent or the functional consequences of pathologic changes. By combining the explicit functional knowledge provided by ontology-based models with image-based geometric models of brain anatomy, it may be possible to develop surgical planning applications designed to predict consequences of injuries to brain structures resulting from particular surgical approaches, or to support identification of appropriate targets for stereotactic functional surgery in movement disorders, that can be highlighted on patient-specific image datasets.

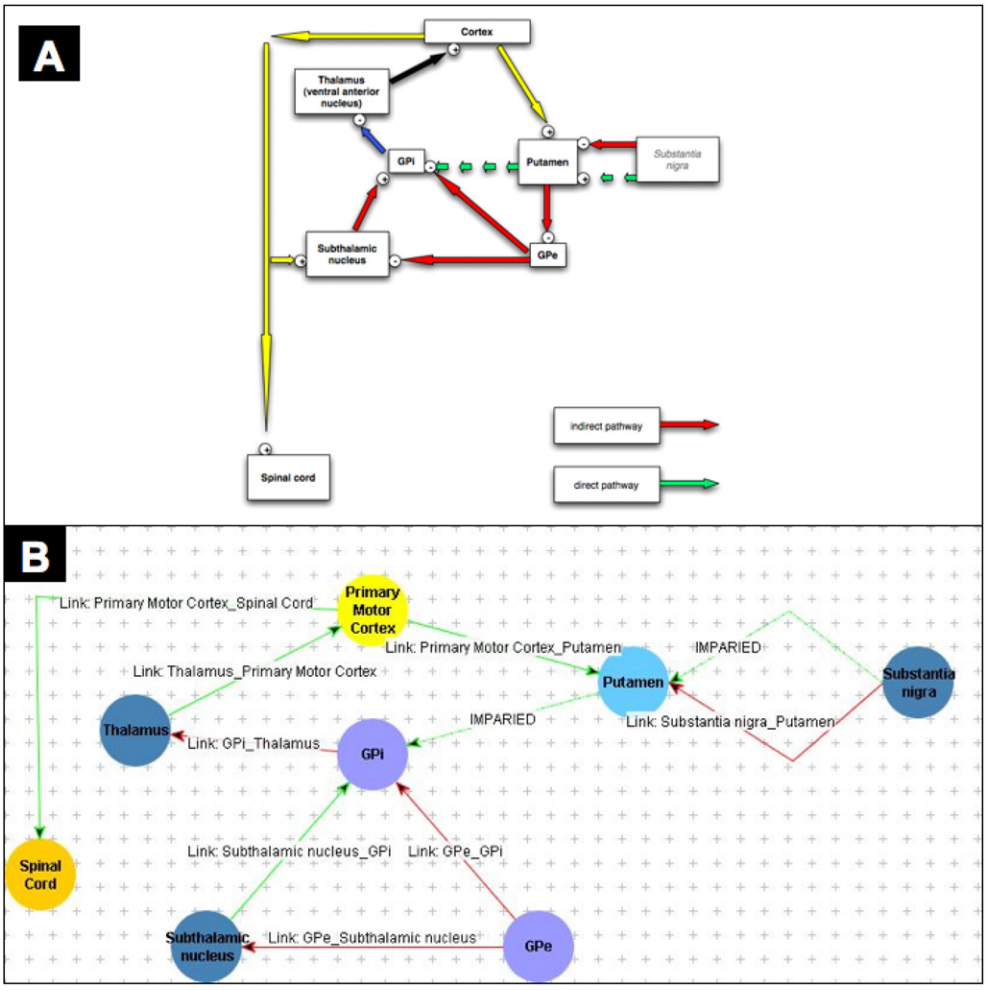

Fig. 9.

4. Discussion and conclusion

In this paper, we introduced an ontological modeling approach of functional neuroanatomy, and presented a prototype ontology of canonical functional anatomy of the motor system. Our ontology-based model is intended to support symbolic lookup, logical inference and mathematical modeling by integrating descriptive, qualitative and quantitative functional neuroanatomical knowledge. We have shown that our approach permits us to generate symbolic models of impaired brain connectivity under pathologic conditions, such as movement disorders. Our methods also provide a computational framework in which to create applications that can reason about the functional consequences of brain injuries.

Our functional ontology shares several important features with the Foundational Model of Anatomy (FMA) [3]: common vocabulary, common modeling principles, and a common modeling platform (Protégé). Aside from the limited coverage of our ontology compared to the FMA, one essential difference is the fact that these ontologies provide two different, but complementary views of neuroanatomy. While the FMA describes the *spatial organization* of the nervous system, our ontology describes its *functional organization*. The structural knowledge of the FMA enables automated identification of anatomic structures that may be affected by certain injuries with a given spatial distribution. However, structural knowledge is not sufficient to provide an understanding of how the neural structures work, or to predict functional consequences of injuries.

Recently, parameterized models have been designed for specific applications, such as simulating the effects of deep brain stimulation (DBS) on the activity of basal ganglia [22,23]. Such parameterized models incorporate actual clinical and experimental observations, and use systems of partial differential equations to describe temporal variations of physiologic signals in a quantitative manner. These parameterized models are highly specialized applications developed with the purpose of solving a particular clinical problem. They lack explicit declarative anatomic information about the components of which they are comprised.

To our knowledge, no ontology of functional neuroanatomy has been developed to date. As opposed to parametrized models, domain ontologies, are repositories of coherent, explicit knowledge, stored in a format understandable by both humans and computers. They are not

intended as end-user applications or designed for solving a specific problem. They represent generalizable and reusable sources of knowledge about a particular domain. Ontologies of functional neuroanatomy enable qualitative reasoning about functional consequences of abnormalities and can serve as basis for a multitude of specific applications, including parameterized modeling of neurologic function. Furthermore, they are extensible, and can be mapped to structural ontologies, such as the FMA, as well as to medical images.

One limitation of our ontology is that it currently covers only large macroscopic neural components. We are currently working on extending this representation to more granular levels of anatomic and functional detail.

Another limitation of our prototype ontology is the fact that it currently covers the narrow domain of functional organization and abnormal neural connectivity of the motor system. While our ontology is potentially useful to enable different types of intelligent applications, it may not be able to tackle a broader range of reasoning applications beyond the scope of our focused domain. However, since the principles of functional connectionism, that lay at the foundation of our ontological representation, apply to the entire brain, it may be possible to extend the scope of our ontological representation to incorporate other functional systems as well, with the final goal of creating a domain ontology of functional neuroanatomy.

In summary, in this preliminary report, we have shown that functional neuroanatomical knowledge about the motor system can be represented using an ontology, which can be exploited by computer reasoning applications. The declarative knowledge encoded in our ontology can be perused and maintained by domain experts, interpreted by machines, and serve as basis for a multitude of decision support, computerized modeling, and teaching applications.

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