A taxonomy of white matter architecture

Introduction

The systematic, scientific study of the brain has been ongoing for more than two centuries now, and in that time the predominant foci, methods, and paradigms of the field have evolved alongside our understanding of this complex organ. Some of the earliest efforts to study the brain were concerned with determining what it was the brain was actually doing and what features of its structure were most central to it carrying out those functions. While we have clearly made great progress in coming to understand the brain, it is interesting to note that modern studies often still have this same flavor. Other scientific disciplines, like chemistry, astronomy, and physics have established multi-level, mechanistic frameworks for their domains and have moved on to study how the constituent pieces of those systems interact in increasingly complex scenarios. In neuroscience though, we are still trying to figure out what the pieces are, what properties they have, and what phenomena they actually give rise to. Our boundary conditions may now be more specific and the research questions more highly contextualized, but the overarching project largely remains the same. Moreover, while we may like to think that our progress has been continuous and monotonic, the reality of how neuroscience has progressed is somewhat more complicated and indirect. Due to dynamics of information access, shifts in disciplinary boundaries, and changes in ideological currents, entire schools of thought within neuroscience have faded into obscurity, only to arise again decades later as the foundation of a major paradigm shift. With this as our backdrop, we can get an initial sense as to how and why neuroscience has found it challenging to build upon itself to form comprehensive accounts of behavior, disease, and function. Despite these considerable challenges though, one way for the field to make modest, but nonetheless definitive progress is by improving the conceptual framework we use when endeavoring to study the brain.

In this paper I will suggest that one fundamental way we can make such an improvement is by attempting to provide meaningful structure to the broad, nuanced, and at times, convoluted

body of neuroscientific insight that already exists. That is, we can work to develop a conceptual framework which succinctly and usefully encapsulates the the entities we study and their relations and thereby reflects the “true” structure of the brain. Admittedly, due to the utter complexity of the brain and the corresponding breadth of neuroscience, it would be an immense undertaking to do this in a fully comprehensive fashion, through several such efforts exist [1–3]. Instead, this paper will limit its focus to a consideration of the brain’s white matter and the organizational schemas which could be used to capture and organize, in part or in whole, the entities that it is composed of. Several such schemas have already been proposed and, while they may provide various means of sorting white matter tracts into categories, it will be argued that they nonetheless fail to provide a framework which actually “does the work” we would expect of a taxonomic hierarchy in science. Having critically analyzed these existing proposals, this paper will identify a novel, developmentally-based approach for forming a hierarchical structuring of white matter and will then use this approach to propose a specific, though provisional, taxonomy. From the outset, it is not presumed that a “historical approach” [4] of this sort is inherently superior to other approaches, nor that applying it to white matter will result in in an obviously useful framework. Instead, throughout this paper a significant effort will be made to identify the issues that are relevant to the evaluation of a taxonomy of this sort and how the various pre-existing proposals seek to address them. To this end, one preliminary issue that needs to be considered is how, in practice, the field of neuroscience interacts with conceptual hierarchies and how these interactions shape the formation and subsequent use of such frameworks.

For many of those engaged in highly specialized and highly technical neuroscientific research, efforts to construct or infer conceptual hierarchies can appear to be of little practical value. For such individuals, it may seem that the true and meaningful progress that has been made in the field was hard earned through protracted and detailed experimental, observational, or clinical work. Indeed, when one reflects on major insights developed within the field of

neuroscience, the examples that readily come to mind seem to confirm this. The dynamics of the action potential [5], the localization of cognitive functions like face perception [6,7] in specific cortical areas, and the impact of various compounds on neurochemistry and behavior were all revealed through rigorous empirical work. None of these were the obvious consequence of an attempt to form an ontology or a structured hierarchy *from existing knowledge and insight*. The closest examples are likely the work of Brodmann [8], Golgi and Ramón y Cajal [9], whose work enumerated the entities forming the cortex at macro and micro levels. It must be noted though, that it was directly as a consequence of their work in the laboratory that their hugely impactful conceptual insights were made. As such, it is understandable why contemporary researchers in neuroscience may be skeptical about the prospects or utility of the predominantly theoretical work involved with forming or using conceptual hierarchies. Simply put, there simply don't seem to be high-profile examples of it in neuroscience. However, this disciplinary resistance is, to a certain extent, counter to the norms of broader science.

Among the hallmarks of progress in a given domain of science is the establishment or identification of "natural kinds" [10] that are pertinent to the domain in question. These natural kinds are conceptual groupings of entities which are purported to reflect the "actual structure of the world", and are thus observer-independent. For example, the chemical elements constitute natural kinds, in that their groupings are understood to genuinely correspond to features of the world that exist independent of our perception or understanding of them. Likewise, astronomical classifications like planets, stars, and galaxies are taken to correspond to genuine properties of the entities they are applied to. The ontological, metaphysical, and epistemic status of natural kinds is a topic of intense debate within philosophy [10]. However with respect to the conduct of science, we can see that, in practice, these groupings are absolutely essential to the formation of theories, explanations, and predictions. This presents a unique challenge for the field of neuroscience. What are the natural kinds of neuroscience and how can we identify them? The groupings resulting from the work of Brodmann and Golgi can serve as potential examples.

Although cortical and neuronal groupings are based on microscopic biological features, they are found to be highly relevant to relatively distinct and discriminable processes/phenomena which are of specific interest to neuroscience. Whether or not these represent natural kinds that are as clear, exclusive, and genuine as chemical elements can be debated, but here we have preliminary evidence for the utility and role of proximate natural kinds in neuroscience. Why and how is neuroscience's approach to natural kinds for white matter different from these examples?

The cortex, as instantiated by the brain's outermost layer of grey matter, has been a primary focus of research in the brain sciences, both historically and in more modern times. This is as compared to the amount of research directed towards the study of the white matter, which corresponds to 35% of the overall volume of the human brain [11–13]. The initial cause for this differential focus could be due to the cortex (and its surface morphology) being the most overt, striking, and easily accessed aspect of the brain. Indeed, it is in virtue of the striking cytoarchitectural patterns of the grey matter that Brodmann and Golgi were able formulate their schemas. The continued focus even in modern research may be attributable to the accessibility of methods which target the grey matter, the continued fecundity of research focusing on the soma of the neuron (i.e. receptor and transmitter focused neurobiology), or perhaps even lingering localizationist tendencies within the field more broadly. Regardless of the specific causes, the result of this trend has been an overwhelming displineary focus on structures and processes contained within the grey matter, and a corresponding dearth of investigative attention being paid to the white matter of the brain. Such a bias is regrettable on its face, but is seen to be all the more short sighted when considered by way of analogy.

Across many disciplines, and for many different explanatory purposes, the brain is often compared at a macro level to a computer. Given its role in information processing and guiding behavior it is perhaps unsurprising that this would be the case. However, considered at a more meso level, the brain is also found to be aptly compared to another computer-related system: the internet. In this analogical framework, the many billions of neurons of the grey matter are

taken to be like computers, manifesting computations in virtue of activities. These individual "neural computers" are, in a non-trivial sense, all connected to each other, just as the individual computers comprising the internet are interconnected to some degree. However, as is the case with the real internet, the major information transmission connections between neurons are necessarily physical, as opposed to some biological equivalent of WiFi or Bluetooth (the endocrine system notwithstanding). Not only is direct information transmission predicated upon the existence of such connections--after all, without a physical connection the computers can't directly communicate with each other--the very *character* of those transmissions are shaped by the properties of the connection. That is, just as with the internet, where the difference between a phone line and fiber optic is quite stark, the brain too has various grades of physical connection based upon neurons' axons and their myelination. In both cases these differences can impact the biological equivalents of "bandwidth" (transmission rate), "latency" (conduction delay), and "packet loss" (transmission failure/signal degradation). Thus, in both cases, we see that effective and reliable communication isn't merely a function of the activity of isolated computers or neurons, but is instead dependant on the continual interactivity of these components, as facilitated by their connections. This analogy highlights the centrality of white matter's connective role, and further underscores the potential oversight committed by focusing primarily on the cortex. However, this is not to say that white matter has been wholly ignored, either historically or in modern research, but rather that a confluence of factors has led to our understanding of white matter lagging far behind our understanding of grey matter.

Even before modern computational systems offered themselves up as a convenient conceptual analogy, early neuroanatomists were intrigued by the heterogeneous, but nonetheless structured architecture of the white matter. Nicholaus Steno was one of the first to marvel at the architecture of the white matter and, in virtue of its complexity, see evidence for a important role in sensation and behavior [14,15]. Slightly later, Thomas Willis was likewise "astonished" as he examined the white matter of the brain, as revealed by a scraping

methodology, and speculated as to the functional consequences of the architecture he observed [14,15]. With the advent of more directed and methodologically systematic approaches to dissection in the 1800s an initial understanding of white matter architecture began to take shape. Indeed, in 1810 Franz Gall and Johann Spurzheim published the foundational *Anatomie et physiologie du système nerveux [16]* which exemplified some of these early insights. Although they were proponents of a cortico-centric conception of brain function, this work nonetheless provided one of the first comprehensive descriptions of white matter anatomy. Throughout the 1800s work from researchers like Charcot, Meynert, Dejerine, and Wernicke began to form an increasingly robust account of the brain's white matter [1,14,17,18]. While this work was inarguably fundamental for neuroscience, the focus of neuroanatomical investigations would shift in the first decades of the 19th century.

In the early 1900s two major trends led to a gradual dissipation of research focusing on the brain's white matter and its architecture. The first of these was the eventual eclipsing of more integrative (i.e. incorporating multiple lines of evidence) approaches to brain cartography and mapping by predominantly cytoarchitectural approaches. This is illustrated most strikingly by the modern ubiquity of Korbinian Brodmann's cytoarchitectural mapping and the comparative obscurity of Alfred Campbell's mapping, which instead leveraged properties of both white and grey matter [19]. The second of these trends was the shift from French and German to English as the standard language of scientific communication after the first world war [20,21]. The historical consequence of this linguistic shift has been a reduced *direct* influence of work by early French (Charcot, Dejerine, Broca, etc.) and German (Meynert, Brodmann, Wernicke, Flechsig, etc.) neuroanatomists on modern research programs. This is not to say that this early neuroanatomical work has been without consequence--after all, the insights of Broca, Wernicke, and Brodmann almost guaranteed to covered in any introductory neuroscience or psychology course/text. Rather, it seems that the nuanced details, which are nonetheless of great importance, may not be readily accessible to modern researchers, as illustrated by the

“rediscovery” and “recharacterization” of white matter tracts [22,23]. Indeed, the failure to adequately and systematically leverage the insights of these precursors towards the formation of natural kinds or conceptual hierarchies may partially explain why modern investigations of white matter so closely resemble work conducted a century or more ago.

In modern neuroscientific research we still find that the cortex receives a great deal of attention, even if the trend has begun to shift back towards the direction of a balance. Initially though, with the discovery of the BOLD signal and the subsequent rise of functional magnetic resonance imaging (fMRI) [24,25] researchers obtained a method for *in-vivo* measurement (if indirectly) of brain activity with minimal risk to subjects (as compared to methods using radioactive tracers). The opportunity presented by this development was not lost upon the field, and the study of links between cortical activity and behavior blossomed. The utter fruitfulness of this work has, in turn, created something of a “streetlight effect” wherein research and insight formation became focused in the domain(s) where it is easiest to search--in this case in the grey matter. As has been noted above though, the functioning of the brain is not solely determined by the activity of the grey matter, and so, as a consequence of this streetlight effect, our understanding of white matter has not advanced in step with our understanding of grey matter. Indeed, it was not until the advent of diffusion magnetic resonance imaging (dMRI) based methods [26–28] more than a decade later that modern, *in-vivo* investigations of white matter became tractable. Even though more than a decade has passed since the development of dMRI methods, the white matter sub-field of research still finds itself playing catch-up relative to the general acceptance and methodological refinement of fMRI methodologies. Even considered independently of comparable neuroimaging methodologies, the contemporary work in the fields of dMRI and tractography appears to be retracing the footsteps of neuroanatomists from previous centuries, perhaps due to a lack of foundational insight or understanding of white matter.

During the initial forays into the systematic study of white matter, one of the most central developments was the creation of neuroanatomical atlases. These atlases served as a common reference for neuroanatomists, serving both as a record for described structures and as a guide for subsequent investigations. These include previously noted works by Gall and Suprzheim [16], Brodmann [8], and Campbell [29], in addition to works by Gray [30], Arnold [31], Gratiolet [32], and Dejerine [33]. In these works neuroanatomists catalogued the coherent (morphologically and compositionally distinct) "tracts" of white matter that they were able to reliably observe in their dissections. In doing so they began to establish the first natural kinds for white matter. As a contemporary reflection of this, one of the most active branches of modern digital white matter research is the creation of new white matter atlases, either in print [14,17,34] or in digital forms [35–38]. Indeed, a cottage industry of characterizing and describing subsets of white matter tracts is quite active in the field [39–47]. This modern work is noted to be quite reminiscent of work from a century or more ago, in which neuroanatomists struggled to develop a comprehensive white matter ontology. Indeed, one of the more common lines of work involves presenting evidence *against* the existence of tracts described by others. The implications of this renaissance are intriguing--issues of historical correspondence, interobserver consistency, and *reconciliation* [1,48,49] have all arisen. In spite of the challenges these issues present, might it be possible to leverage our current understanding of white matter towards the formation of a conceptual hierarchy? How might we begin this process? As we shall see, biology provides a case study of how a scientific field progresses when it identifies natural kinds, forms a conceptual framework, and begins to structure its constituent knowledge. The insights garnered from such a consideration will prove to be quite useful as we examine available conceptual frameworks for white matter.

The scientific field of biology, and in particular organismal biology, is often used as one of the prime exemplars of scientific progress and development [50–53]. There are many possible explanations for this including the long lineage of the field, it's ability to serve as as a case study

in hypothesis formation and theory development, and its relation to one of the most prominent theoretical developments in all of science (i.e. evolution). However, for the purposes of this paper, and to illustrate the role played by knowledge organizations systems (KOSs) in the development of scientific disciplines, our interest in the field of biology is specific to three semi-distinct aspects of categorization work conducted within biology. Explicitly, these are: the identification, delineation, and enumeration of types/species; the clustering and grouping of like types/species; and finally the structuring of the relations of these groups/clusters. Natural kinds are found to play a central role in these processes and, overall, this framework will prove to be useful for our consideration of white matter structures.

The aforementioned aspects of categorization exhibited by organismic biology are not taken to be a rigidly sequenced series of developmental phases, but rather as an interconnected sequence of disciplinary endeavors which can (and often do) influence one another. To begin then, we start by considering the work characterized by identification, delineation, and enumeration. With these endeavors, the primary goal is the development of an ontology which biologists build by comprehensively or even exhaustively classifying organisms at some "fundamental" level. This often involves the establishment or collection of "holotypes" (reference examples or prototypical specimens, [54,55]), requires the identification of characteristic features, and can result in the designation of a species. By establishing a holotype, biologists are proposing a natural kind of sorts, in that they are claiming that the grouping they have delineated corresponds to a non-arbitrary collection of individuals whose grouping reflects a natural category. In reality though, the status of a species as a natural kind is a hotly debated topic [10], and is greatly complicated by the details of how species are specified in practice. Moreover, implicit in the above description is the very notion of a species, which corresponds to a "foundational" or "most granular" level of categorization for biological natural kinds. Indeed, as implied by the earlier examples from chemistry and astronomy, and their notions of "elements" and "astral bodies" respectively, it is possible to gather these

“foundational” natural kinds into a larger group which nonetheless corresponds to an ostensibly meaningful category.

The process of identifying natural kinds doesn’t stop with the identification of an enumerative set of most basic categories. If this were the case, this would result in a flat taxonomy populated by a disparate and disjunct set of categorical entities whose relations would be, to some extent, inscrutable. This is because, while the act of enumerating the most basic categories may be comprehensive enough to assign *all* individual examples to some group (based on some decidable criterion), it doesn’t in and of itself provide a means of assessing the differences and relations *between* those groups. As such, in addition to requiring some formal specification for delineating what constitutes a species, a broader framework or set of proscriptions is necessary in order to systematically compare and relate species. Indeed, within the field of biology it is possible to adopt one of several approaches and thereby group species in accordance with distinct arrays of shared features or properties [4,56,57]. For example, one could group species with and without fur, with and without scales, or with and without teeth. Naturally then, there are significant consequences associated with the selection of a “meta-grouping” schema. Perhaps most obvious of these is that different grouping schemas result in different groups. Categories that were grouped together in one framework might well be in separate categories under a different framework, as exemplified with whales’ historical classification as fish [58]. Beyond these local discrepancies though, there are broader implications for the structure of the hierarchy that results from the classification framework.

The specification of a particular meta-grouping schema has broad consequences. The binary examples cited above (e.g. with and without fur) results in a hierarchy with a secondary category level featuring only two categories. Such a schema is easily adjudicated (relatively speaking), but results in an exceedingly coarse granularity and fairly uninteresting groups. The focus on fur has precluded expanding upon this hierarchy, in that the specifications of the categorizational structure do not provide additional tools for forming sub-classifications within

these two groups. It is possible however, to apply an approach to categorization which can be iterated (to some degree) to create a “deep” and thus highly granular hierarchy. Indeed, this is the standard approach adopted in systematic formation of biological taxonomies. Even with this iterability maxim, there are a range of options available to taxonomists. For example, a phenetic approach [56] to biological classification groups species based on their phenotypic similarity, and structures the relations of these groups based on the phenotypic “distance” they are determined to exhibit [4]. Other examples of comprehensive yet distinct approaches to biological classification include the work of Aristotle, Linnaeus, and, of course, Darwin. This discussion of approaches to classification in biology should provide some context as we consider classification schemas in neuroscience. However, from a utilitarian standpoint, it remains unclear what the consequences of forming these hierarchies are for biology, and what we might hope to gain for the study of white matter.

Although the aspects of classification described above may not, in and of themselves, constitute strictly empirical endeavors (i.e the formation and attempted falsification of hypotheses), they nonetheless provide a number of benefits for biologists. First, formal classification systems provide system for referring to entities pertinent to the field. As amply illustrated by Linnaeus’s introduction of binomial nomenclature, the provision of a formal classification system helped establish a *lingua franca* for biology. Without a system like this, it is quite possible to have the same species listed multiple times in a taxonomy due to multiple reference terms. In turn, this can lead to a descent into a “tower of babel”-like situation, wherein lax nomenclature practices result in a proliferation of names for the same entities, along with a consequent balkanization of research as lines of inquiry become irreconcilable. Indeed, despite the best efforts of taxonomists this already occurs in biology [48,55,59] and has proven to be a huge challenge for the study white matter [1,2]. In both fields, problems resulting from nomenclature confusion are further compounded (or facilitated) by slight discrepancies in the descriptions provided for species or tracts, despite the different names referring to the same

categorical entity [21,60]. It is unclear how this will ultimately be resolved for the study of white matter, but within the field of biology one of the essential roles for taxonomists is to guard against this sort of degeneracy. From a more positive perspective though, the adoption of a formal classification schema is noted to have improved the overall interoperability, accessibility, and reproducibility of research conducted within biology. It stands to reason that similar efforts would provide a comparable benefit for the study of white matter as well. Beyond these incremental benefits though, there has been a more profound consequence of establishing a standard categorizational hierarchy for biology, and it hints at the possibility of equally profound consequences for the conduct of neuroscience.

No discussion of biology, categorization, and hierarchies would be complete without a consideration of the theory of evolution. Indeed, a sufficiently detailed depiction of the hierarchy manifested by the lineage of the species may well be thought of as essentially tantamount to a proposal of the theory of evolution itself. Inherent within the nested relations and their sequencing are the central tenets of the theory and, taken in their totality, they represent an incredibly strong, bold, and specific hypothesis. Should any of the lineages purported in the hierarchy fail to be corroborated, the theory and proposed mechanisms must be reconsidered. In this way, we see that a hierarchical classification system needn't simply be a tool of cognitive expedience for grouping entities. Rather, here in the case of evolution, we find that the endeavor to accurately enumerate the natural kinds of biology and specify their relations has essentially provided an explanation or account of a process--namely speciation and the diversity of species. Moreover, the hypothesis instantiated by this specific hierarchy is not at all a dead end. Instead, serves as the starting point for a wide range of research endeavors. What is it about the theory of evolution's approach to hierarchy formation that facilitated this? It may well be that the approach it takes to classification is best at "carving nature at it its joints" [61], and thereby delineating natural kinds. Even granting this though, it isn't immediately clear what aspect of it permits this. A consideration of Ereshefsky's analysis of classification [4], reveals

that the likely culprit is the implicit placement of causation at the heart of the classification schema.

As implied by the above discussion of biological taxonomies--as well as the earlier appeals to classification systems in chemistry and astronomy--classification schemas can be developed for all manner of subject matter. Despite the potential diversity exhibited by such schemas, there are nonetheless particular aspects of classification schemas that can be compared and analyzed. Notably, while most, if not all, endeavors to form classification schemas entail the successful discernment of natural kinds as an intermediate goal, there are several distinct approaches they adopt to achieve this. Ereshefsky [4] describes three such general approaches that can be adopted to serve as the basis for forming a system of classification: **essentialism**, **cluster analyses**, or the **historical approach**. Importantly, the appropriateness of a particular approach is relative to the domain being structured--what works for one domain may not work at all for another. As we shall see, the same features which make the historical approach work for biology may be well suited to structuring the study of white matter too.

Arguably, the sharpest and most clear cut approaches are essentialist in nature. **Essentialism** is characteristic of the work of Plato, Aristotle, Linnaeus, Putnam, and Kripke, and centers around the search for properties that are “essential” for membership in a specified group. An essentialist classification system ascribes membership in a particular group based on whether or not an entity meets specific *necessary* (and sufficient) conditions which are fundamental to it being that particular kind of thing. The paradigm example cited by Ereshefsky is the periodic table, which is structured in accordance with the the essential atomic properties of the various elements. In isolating and highlighting a certain set of necessary traits essentialist classification schemas are taken to capture the genuine structure in the world and thereby quite directly specify a natural kind. While this may seem like an optimal approach to classification, it is generally found to be difficult to apply in practice because “the essential

features" of particular kinds are often elusive, if at all discernable. Endeavors to specify a necessary property often fall prey to counterexamples which demonstrate an entity's membership in a group in spite of not possessing the presumed necessary property. Given these practical challenges to establishing essentialist categories, other approaches are commonly adopted.

An alternative to finding the essential feature(s) of a group is identifying some cluster of properties which all members exhibit some subset of, though no two members necessarily overlap exactly in exhibited properties. Such an approach is characteristic of **cluster analyses**, which are based on finding sets of jointly *sufficient* (but not necessary) properties that characterize membership in a group. Ereshefsky cites Wittgenstein and Hempel as individuals whose work exemplifies this approach and, in particular, Wittgenstein's example of "games" as a group which can only be delimited using sufficient characteristics as no single feature is exhibited by all games. Hempel attaches the additional criteria of practical utility (relative to science), such that only clusterings based on properties that are useful for the conduct of science are emphasized. Within the realm of biology, phenetic approaches to taxonomy construction, in which organisms are grouped according to observable phenotypes (i.e. morphology), are found to be an example of clustering analyses. However, clustering-based approaches may not always be decidable, in that some categorization actions may ultimately be arbitrary due to insufficiently specific criteria. In such cases, it may be necessary to adopt a different approach.

The final classification strategy described by Ereshefsky concerns the use of entities' historical origins as the basis for grouping. This approach is referred to as "**the historical approach**", and is quite famously central to Darwin's theory of speciation and evolution. With historical categorization schemas, membership in a group is achieved via a shared origin. Thus, entities X, Y, and Z form a sensible grouping if they can appropriately trace their current state back to a shared effect of A. Interestingly, historical approaches place causation (and thus

mechanism [62]) at the heart of systems of categorization. As Ereshefsky notes, there are broader philosophical implications to this emphasis. However, even a superficial consideration of historical approaches suggests that they would be quite fitting for scientific endeavors which are preeminently concerned with providing causal accounts/explanations. Given this broad, overarching framework for approaches to classification, we can consider how existing white matter classification systems manifest aspects of these approaches and how they fulfil their role as classification systems in virtue of these traits.

The need for a hierarchical system of white matter has not gone unnoted [1]. Indeed, as illustrated in **Figure 1**, several potential systems have been proposed.

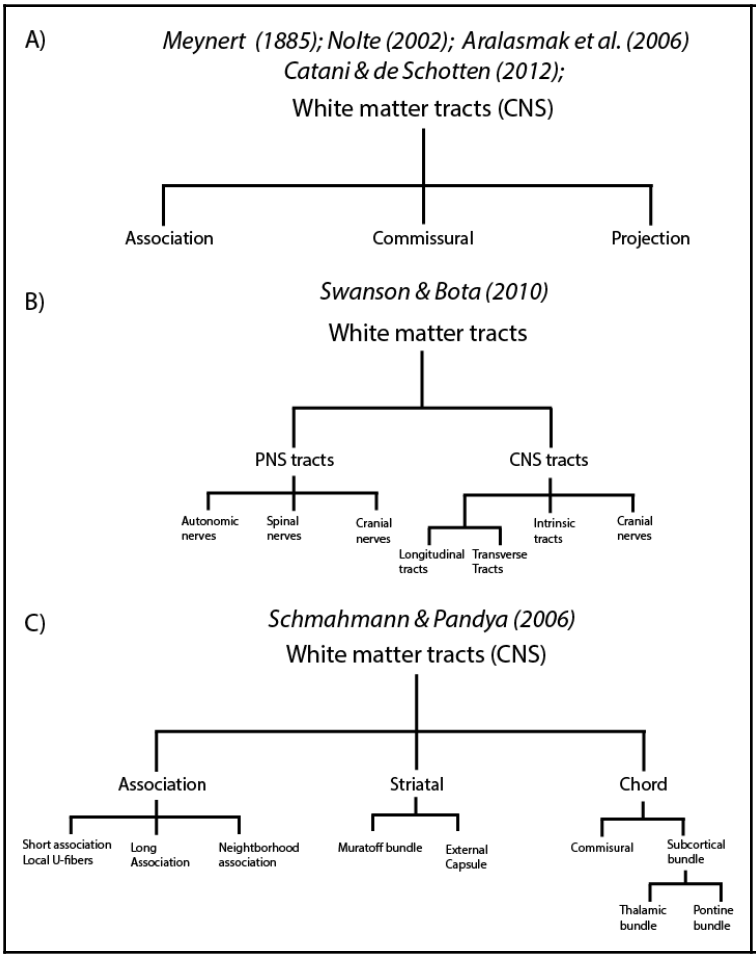

Figure 1. Proposed white matter classification schemas. Panel **(A)** depicts the schema initially proposed by Meynert, and currently held by a number of other investigators. Panel **(B)** depicts the schema held by Swanson (2015). Panel **(C)** depicts the schema held by Schmahmann & Pandya (2006).

One of the earliest and longest lasting organizational schemas was initially proposed by Theodor Meynert [14,22,63,64]. In it Meynert classified tracts into 3 primary groups:

1. **Projection:** tracts which correspond to those tracts conducting information to or from motor or sensory targets.
2. **Commissural:** tracts which correspond to those tracts conducting information between the hemispheres (i.e. the corpus callosum and its subcomponents).
3. **Association:** tracts which correspond to cortico-cortical connections within the same hemisphere.

Even more than a century later, this schema (**Figure 1A)** is found to have a lasting impact on modern neuroanatomists. Indeed**,** a number of researchers still utilize this same basic framework, albeit with minor changes [14,64–67]. This Meynert-based categorization has been noted [14] to basically correspond to the primary orientation of a tract's course (i.e. rostro-caudal, dorso-ventral, or mediolateral), and is thus seen to represent a fairly straightforward schemas. However, more complex schemas are available as well.

Theodor Meynert is not the only historical neuroanatomist found to exert an influence on modern white matter classification systems. Larry Swanson, whose work often focuses on rodent models and extends to the full nervous system (e.g. central nervous system and peripheral nervous system), bases his schema [1] on the work of Alexander Monro [68] and John & Charles Bell [69]. In this schema (**Figure 1B**) he specifies four types of white matter tracts in the central nervous system:

(1) **Longitudinal:** tracts which "extend between rostrocaudally ordered central nervous system secondary topographic divisions".

(2) **Transverse:** tracts which are either a sub branch of a longitudinal tract or "form a commissure between between the right and left sides of a primary or secondary topographic division".

(3) **Intrinsic**: tracts which "stay within a primary topographic division".

(4) **Central roots**: tracts corresponding to the craniospinal nerves.

This schema is noted to be somewhat different from the Meynert-based categorization. Instead, Swanson's initial categorization is based off of connectivity features, particularly connectivity within or between primary (forebrain, midbrain, and rhombicbrain) and secondary (endbrain, interbrain, midbrain, hindbrain, medulla and spinal cord) topographic divisions. The significance and distinctness of these anatomical delineations is established via an appeal to the historical anatomists Monro, Bell, and Bell. An alternative to basing a schema on orthodoxy is to leverage findings from contemporary investigations.

Connectivity and planar orientation are not the the only bases for classifications schemas currently utilized by neuroanatomists. Jeremy Schmahmann and Deepak Pandya, whose work is primarily based in non human primates, utilize a schema (depicted in **Figure 1C**) based on the morphological and anatomical character of a tract as it exits the grey matter. This results in the delineation of three primary categories of white matter tracts:

1. **Association:** tracts which run either immediately beneath the cortex to adjacent gyri (in the case of u fibers) or proximal to the cortex to more distal regions (in the case of neighborhood association fibers).
2. **Striatal:** tracts intermingle with association tracts as they exit the cortex, but become more distinct as they move towards their terminations in the caudate, putamen and claustrum.
3. **Cord**: tracts which form a cord as they move interiorly towards the deeper parts of the gyral white matter.

Whereas the previous two schemas were primarily based upon the work of historical precursors, Schmahmann and Deepak is distinctly reflective of the tracer methodologies they employ. Their attention to cortical proximity and structural uniformity is a consequence of observations made from sequential autoradiographic sections taken from postmortem brains [17].

The general frameworks proposed by these approaches results in distinct groupings of established anatomical tracts (**Table 1**). The differences between these systems can be

observed by directly comparing them to one another. However, a more informative examination results when they are considered relative to the previous discussions of classification and classification approaches.

Catani & de Schotten (2012)	Nolte (2002)	Aralasmak et al. (2006)	Schmahmann and Pandya (2006)	Swanson (2015)
Projection	**Projection**	**Projection**	**Striatal**	**Central root***
Internal capsule	Optic radiation	Optic radiation	Muratoff bundle	(various)
Corona adiata	Thalamocortical radiation	Acoustic radiation	External capsule	
Fornix	Internal Capsule	Internal capsule		**Transverse***
		Fornix	**Chord**	Fornix
Commisural	**Commisural**		Corpus callosum	Anterior commisure
Corpus callosum	Corpus callosum	**Commisural**	Anterior comissure	Corpus callosum
Anterior commissure	Anterior commissure	Corpus callosum	Internal capsule	Arcuate fibers
	Hippocampal commissure	Anterior commisure	sagittal stratum	Uncinate fascicle
Association		Hippocampal commisure		Inferior longitudinal fascicle
Short association (U) fibers	**Association**	Habenular commisure	**Association**	External capsule
Arcuate fasiculus	Short association (U) fibers	Posterior commisure	Local (U) fiber system	Superior longitudinal fascicle
Inferior fronto-occipital fasiculus	Arcuate fasiculus	Tectal commisure	Neighborhood fiber system	Cingulum
Uncinate fasiculus	Superior occipitofrontal fasiculus		Arcuate fasciculus	
Cingulum	Inferior occipitofrontal fasiculus	**Association**	Superior longitudinal fasciculus 1	**Longitudinal***
Superior longitudinal fasiculus (2011)	Uncinate fasiculus	Short association (U) fibers	Superior longitudinal fasciculus 2	Middle Longitudinal fascicle
	Cingulum	superior longitudinal (arcuate) fasiculus	Superior longitudinal fasciculus 3	Corticospinal tract
		Superior occipitofrontal (subcallosal) fasiculus	Middle longitudinal fasciculus	Fornix
		Inferior occipitofrontal fasciculus	Fronto-occipital fasciculus	Internal capsule
		Inferior longitudinal fasiculus	Inferior longitudinal fasciculus	
		Uncinate fasciculus	Uncinate fasciculus	**Intrinsic***
		Cingulum	Cingulum bundle	Lateral olfactory tract
			External capsule	Periventricular bundle of thalamus
				Principal mammillary tract

Table 1. Assignment of anatomical tracts under various classification schemes. Under the most superficial grouping (highest hierarchical division), the membership of established white matter tracts in specified groups, as designated by the schema indicated by the author heading. Asterisks adjacent to Swanson's groups indicate that only a subset of tracts categorized are displayed here. Partially adapted from [65].

The Meynert-based schema appears to be an essentialist approach at first glance (**Figure 1A**), in that it specifies a necessary property, namely direction of orientation, and categorizes fibers accordingly. However, an examination of the tracts designated in **Table 1, columns 1, 2,** and **3** reveals the ambiguity inherent in this system. Despite Catani and de Schotten's observation about planar orientation [14], we find several tracts which do not appear to conform to this norm. First and foremost, it should go without saying that not all tracts run orthogonal to one of the anatomical planes. For example, the fornix is an extremely curved structure (even moreso than the arcuate fasciculus), and so it is unclear what plane it is perpendicular to. Likewise, the internal capsule is found to be a decidedly heterogenous "tract" (and may be better thought of as an amalgam of several sub tracts) with fibers traveling both rostro-caudally and dorso-ventrally, and yet we would likely find ourselves strongly disinclined to

reassign its sub-components based on the planar traversal maxim. As such, it's unclear what principle we should appeal to when "primary direction of traversal" fails to return a definitive proscription. Beyond this ambiguity though, the Meynert-based schema is also found to foster "mislabelings"--categorizations which flout the presumed norm--a feature which may belie a deeper truth about this schema.

While we might hope that ambiguous cases could be adjudicated with further refinement of the categorization system, we should still be able to expect that, in practice, it is applied consistently in accordance with guiding principles of the system. However, there are several examples where it is fairly evident that this is not the case. Most flagrantly, we can note that the optic radiation simply *does not* run dorso-ventrally in the white matter, but instead rostro-caudally, and should therefore be categorized as an association tract rather than a projection tract. Admittedly though, it would likely strike us as inappropriate to group the optic radiation with association tracts as they do not seem to be "of the same kind". In this same vein, there's the omission of a number of tracts whose designated categorization, were they to be included, would strike most observers as counterintuitive--a theme we will come across again when considering other white matter categorization systems. Among these omitted tracts are the frontal aslant tract (FAT) [70–72], vertical occipital fasciculus (VOF) [22,40,73,74], and the posterior arcuate (pArc) [40,42], all of which have vertical traversals, but would likely feel out of place under the projection heading. These issues reveal several hidden flaws within the Meynert-based schema.

In light of the problems noted above, the previously noted discrete and straightforward character of the planar-based system may now seem less like a virtue and more like a shortcoming. This aspect of Meynert's schema, and its consequences, have been noted previously [22,64,75]. Specifically, key to Meynert's theory was the decree that association tracts *definitionally* run with an anterior-posterior orientation. The initial characterization of the vertically oriented VOF by Obersteiner, Sachs, and Wernicke [22] thus created a tension with

this claim, which was ultimately and unfortunately resolved by the exclusion of this tract from anatomical texts--a mistake that wasn't corrected until more than a hundred years later. Indeed, the historical consequences of this Meynert's theory serve as a cautionary tale about how we construct our conceptual framework for white matter architecture and reminds of the profound and long lasting impact this process can have. Were this schema to have actually picked out an "essential" property of white matter tracts (in keeping with Ereschefsky's characterization of essentialism) it likely would have had more success in "carving" the white matter at its joints. Even adjusting our analysis of this schema to treat it as a cluster analysis approach does little to improve the prospects of the planar-based approach--it isn't clear what disjoint set of properties this schema is supposed to reflect or capture. Perhaps more importantly, it doesn't seem that this approach satisfies Hempel's criteria of scientific utility in that no predictions or explanations readily avail themselves of these categories. Indeed, although modern revisions of this schema have emphasized connectivity (similar to [1]), it isn't clear what the practical implications of these categories are (though some potentially surprising implications may exist, see "Biological aspects of white matter and their implications for computational models". In the end, it appears that the Meynert-based system was structured more for cognitive expediance rather than correspondence to intrinsic characteristics of the tracts themselves. The same likely cannot be said for the remaining categorization systems, which are found to be less intuitive.

In some cases, it might be worthwhile to look beyond surface level characteristics to try and devise a classification schema. As described earlier, Swanson's schema (**Figure 1B**) is primarily based off of connectivity features as determined from set of primary and secondary divisions. It results in groupings as illustrated in **Table 1 column 5**. There are a number of initial observations that can be made about this schema. First among these is the inclusion of a "central root" category which corresponds to craniospinal nerves, a distinction not made in other schemas. There are indeed a great many such fibers--the facial central nerve root, the gracile fascicle and others, for example. However, most contemporary digital neuroanatomists are not

able to make use of this fine grained delineation due to the inability of modern methods to detect or appropriately model these tracts. Consequently, purely for the sake of pragmatics, these tracts are given scant attention in this analysis. The other category that is of particular note is "intrinsic tracts" which corresponds to tracts which stay within a single primary topographic division. Included among Swanson's intrinsic tracts are the principal mammillary tract and the middle commissure. Again though, we note that these are arguably obscure tracts, at least for contemporary researchers utilizing *in-vivo* imaging methodologies. Moreover, these tracts are found to constitute only a small proportion of the total tracts enumerated in Swanson's schema. This leaves a great deal of the conceptual "heavy lifting" to be done by the longitudinal and transverse categories--a task that they don't quite seem up to, as we shall see.

The preponderance of the tracts covered by Swanson's schema are categorized as either longitudinal or transverse. Indeed, it is here that we find all of the tracts typically discussed in modern tractography studies (and *overwhelmingly* under the transverse heading). As such, the granularity that this schema may have been presumed to have--on account of utilizing 4 primary categorical divisions--is found to be illusory, at least for contemporary researchers utilizing *in-vivo* imaging methodologies. Whatever taxonomic work this system may be doing in this regard is actually being done by 2 categories rather than 3 (as done in Meynert's and Pandya's systems; see **Figure 1A & C**). Moreover, we find that this schema exhibits problems similar to Meynert's: counterintuitive groupings and questionably defined/applied rules.

For reasons that will later be discussed, it is actually somewhat difficult to pull the two aforementioned issues apart in some cases. Given the implications for systematically implementing this approach though, the latter of the two (i.e. questionably defined/applied rules) is generally taken to be more pernicious. Counterintuitive groupings, defined as the categorization of two tracts that do not seem (intuitively, at least) to be "of the same sort" under the same heading, include the optic radiations' inclusion alongside the corpus callosum as well

as the corticospinal tract with the thalamic radiations. Such counterintuitive groupings are not seen as an issue in and of themselves--after all, there is no requirement that the "true" groupings of reality conform to our intuitions--however, it does raise a concern about the systematicity of this approach. Indeed, a close consideration of the criteria for each group reveals the pervasive flaw inherent in this schema.

As discussed earlier, Swanson's reliance on primary and secondary divisions of the brain may be less intuitive for researchers who work with modern neuroimaging and tractography-based methods. Swanson's background in rodent work and consideration of the nervous system in its totality (i.e. central *and* peripheral) provides a significantly increased granularity for "lower" brain structures and their connections. These structures don't often factor into imaging based studies of the brain and behavior, and so they may be less familiar to researchers using these methods. However, the system of topographic divisions used in this categorization schema ends up being far coarser for "higher" brain structures, leading to the *entire* telencephalon being treated as a secondary area (and a therefore a *subsection* of a primary area). While this clear and well defined framework may facilitate the establishment of an essentialist framework [4], it also presents a fairly significant problem.

Swanson's framework is, to an extent, presented in an explicit fashion [1]. In it, intrinsic tracts are very clearly defined as those tracts which "stay entirely within a primary topographic division". This statement is preceded by the qualifier "Intrinsic tracts are distinct from longitudinal and transverse tracts [because of the aforementioned property]". However, further consideration reveals this to simply be a non sequitur. An overwhelming number of tracts listed as longitudinal and transverse stay within the same primary division--indeed all cortico-cortical connections stay within the same *secondary* division. This claim is quite perplexing in that it presumes a distinction where, as the classification system has defined it, none exists. In defense of the schema, we can understand why we would be inclined to want to treat "longitudinal" and "transverse" tracts differently from the remainder of white matter tracts, but

this inclination doesn't serve as a justification. A classification system should be non-arbitrarily decidable though, and the invention of a category which flouts the guiding framework being used undermines the system's face validity, internal consistency, and extensibility. Schmahmann and Pandya's schema is based off of work in non-human primates, and therefore is more "forebrain-centric", but nonetheless has problems of its own.

The final of the three general schemas is that posed by Schmahmann and Pandya [17]. Like Meynert's schema it features three primary categories: striatal, cord and associative. Unlike either of the preceding schemas though, it's approach to classification is based off of a meso level property of white matter tracts, namely their path through the white matter of the brain. Under this schema, the relatively unique category of striatal fibres is delineated. This category corresponds to the Muratoff bundle and the external capsule, which are taken to be similar in their exit motif from gyral white matter and their shared source in layer Va [17]. Notably though, it is *exclusively* composed of these two tracts--no other tracts are characterized as being included under this heading--and both of these cases (viz. putative tracts) are unique for their own reasons. This means that this is a distinctly brittle category for two reasons. First, given that there are only two items in this group, it could be argued it is an arbitrary distinction. For any two tracts, it may well be possible to select a seemingly significant trait that they alone share without it being a "meaningful" similarity (akin to a conceptual type 2 error). Second, in the event that the uniquely distinguishing characteristic or property of one of the tracts are called into doubt, this results in a group with a single tract in it, which is taxonomically suspect. Both of these concerns arise while considering this categorization schema.

The external capsule is an interesting inclusion in any taxonomy of white matter. This is because it more accurately described as a volumetric region than a tract; it it isn't a discrete white matter structure with a uniform morphology or connectify profile. Instead, it is composed of "association fibers from the superior and the inferior longitudinal fasciculi, the uncinate fasciculus, and the pyriform cortex" [76]. There is a precedent for this however, in that the

inclusion of volumetric regions in white matter atlases or parcellations is quite common (i.e. the extreme capsule, internal capsule, and external capsule; see [14,17,37,77]). This is a curious choice for a white matter taxonomy, though. Given standard definitions of tracts [1,78] it is unclear why such entities would be considered in an enumerative white matter taxonomy. Contrary to this understanding of the external capsule, Pandya and associates have argued that the external capsule represents a unique and distinct tract [41,79,80]. If this were true, it could lend credence to the the inclusion of this tract in a white matter taxonomy as well as the existence of Schmahmann Pandya's unique category, however the evidence supporting this is dubious.

The initial claims about the existence of a unique extreme capsule tract (see [79]) were predicated upon its purported morphological and connective distinctiveness relative to nearby, established tracts. However, the evidence presented to support this claim is not entirely convincing. Notably, the anatomical feature cited exhibits a great deal of heterogeneity (see figures 5 and 6 [79]; note the extreme bifurcation exhibited in the subcallosal region). Perhaps more troubling is this tract's homology with classical descriptions of the inferior fronto-occipital fasciculus (IFOF) and middle longitudinal fasciculus (MdLF) (see figures 5 and 6 [79]). An attempt to address this is made by arguing that the connectivity of the putative fibers is distinct in specific areas. This claim is suspicious given their tractography seeding method (note no specification of seeding method for IFOF or MdLF) and the use of deterministic tractography. Consideration of other research casts further doubt on the claims made regarding the external capsule.

Overall, Pandya et al.'s claim about the extreme capsule is found to be anomalous relative to preceding [37,76] and subsequent reports [78,80–83] of the white matter in this area. Indeed, the consensus in those subsequent studies appears to be that this area is simply a dense crossroads of known associative fibers. Even if we are to grant that the purported tract exists, the validity of the striatal category is not assured. It's not clear why this tract, which

would otherwise seem to be a standard cortico-cortical connective associative fiber, would exhibit the purportedly unique white matter traversal path or what its import would be. Given it's inarguable connective and path similarity to the MdLF and IFOF, it would be quite remarkable if these tracts demonstrated clearly distinct properties--relative to the categorization criteria--and yet no such observation is made. Indeed, the designation of the purported extreme capsule tract is “inverted” in some sense, in that the tract is delineated by the designation a single, small white matter volume, whereas all other tracts are specified by a connectivity motif and characteristic pathway. If no unique extreme capsule tract exists, or if no particular tract in this region actually exhibits the property required for this category, it seems that the viability of the strital category depends on the Muratoff bundle.

The Muratoff bundle, also referred to in other publications by Pandya and associates as the subcallosal fasciculus [17], Muratoff’s bundle [84], and the subcallosal fasciculus of Muratoff [23], is a tract putatively connecting the frontal lobe to the caudate nucleus and has historically been confused with the hotly debated superior fronto occipital fasciculus (sFOF/FOF) [21,23,60]. Recent attempts at clarifying the nature of this tract appear to be hampered by a “tower of babel” effect wherein a number of different names including the medial subcallosal fascicle [85], fronto-striatal tract(s) [70,86], and caudate tract [87]--all in addition to the aforementioned terms--have been used to refer to this structure. Perhaps as a consequence, the actual connectivity of this structure is ambiguous [88].

Although a number of recent papers have discussed the Muratoff bundle, there are contradictory accounts of it’s morphology. Some have reported connectivity to the supplementary motor area [72,84–86,89,90] while others have reported connections in orbitopolar areas [21,70,87,91]. Regardless, it is sufficient to say that a tract akin to what Schmahmann & Pandya referred to exists in some form or another. The inherent ambiguity of this tract makes it is somewhat less clear if it can be said to have the the pathway character asserted by Schmahmann & Pandya, though--even Pandya and associates’ depictions of this

tract portray it at various points as a dorso-ventrally and anterio-posteriorly oriented tract (mutually exclusive characteristics). Beyond this though, it must be noted that Schmahmann & Pandya's enumeration of cortico-subcortical connections is not at all exhaustive (see **Table 1, column 4**), and we are therefore left to wonder if this category would simply be analogous to a Meynert based system's projection tract category. Indeed, others have characterized this tract as a projection fiber [92]. As such, neither the validity nor the practical utility of this schema are found to be sufficiently established.

Having considered the three systems analyzed above, we find that all are deficient for one reason or another. Overall, a classification schema should not simply be a post-hoc summary of amassed findings, but rather it should serve as a framework which can easily and systematically incorporate new entities and elaborated upon. However, the existing schemas do not meet this standard. Furthermore, it's not clear if the existing groupings would be useful as empirical constructs--what aspects of these tracts would we expect to vary systematically, in accordance with their memberships in these groups. As such we are left to wonder what sorts of approaches could we adopt with respect to forming a new classification schema. Going back to the work of Ereshefsky [4], we find a potential strategy. Reflecting on the existing systems we see that they either manifest themselves as essentialist or clustering-based approaches. With this in mind, we can opt for a different approach.

One strategy that could be adopted to form a classification schema for white matter would be to use a historical approach. However, given that we are attempting to classify entities which are all found in a typical subject of interest, it is not immediately clear how to do this--the model provided by evolution is only of so much use here. Fortunately, Ereshefsky provides some guidance with the observation that the organizing principle for groups under this approach is the presence of shared causal relations. In the case of white matter tracts presents something of a dilemma. Do we build our hierarchy based on developmental processes (ie. ontogeny) or evolutionary processes (i.e. philogney)? Contrary to Ernst Haeckel's maxim of

“ontogeny recapitulates phylogeny” the two processes are not mirror images, though they can still shed light on one another [93]. The previous consideration of Larry Swanson’s topologically based schema [1], which was implicitly structured around the evolutionary structure of the brain, suggests that our goal of categorizing the white matter of the telencephalon may not be well served by a phylogenetic approach. This intuition is supported by the observation that a uniquely large component of postnatal neural development in primates is the extended process of myelination [94]. As such, the hierarchy that is proposed in this paper will primarily be based on evidence obtained from ontogenetic studies of white matter, though appeals to phylogenetic sources of evidence may be made when appropriate as well. A consideration of the relevant evidence is thus in order.

Although neural development is one of the more prominent research foci in the field of neuroscience [95], the specific study of how white matter features in this process is decidedly less prevalent. One of the foundational researchers in this domain is Paul Flechsig, a german neuroanatomist who was active around the turn of the 20th century. Among the contributions he made to neuroscience was his foundational work on myelogenesis, the process by which axons of the central nervous system become myelinated over the course of early development. Indeed, one of his most impactful insights was his mapping of the cortex (**Figure 2** and **Supplemental Table 2** for standard cortical nomenclature) based upon the sequence in which their contributory white matter became myelinated [15,96–99]. Beyond this though, was the establishment of **Flechsig’s rule** [96,100,101], which was postulated as “no long association system is known which connects two primordial zones that are to be regarded as sensory centres”. This “rule” asserts that there are no direct connections between cortical regions that develop (e.g. myelinate) early as the brain matures. These insights were later refined and expanded upon by the work of Yakovlev and Lecours, as well as Geschwind.

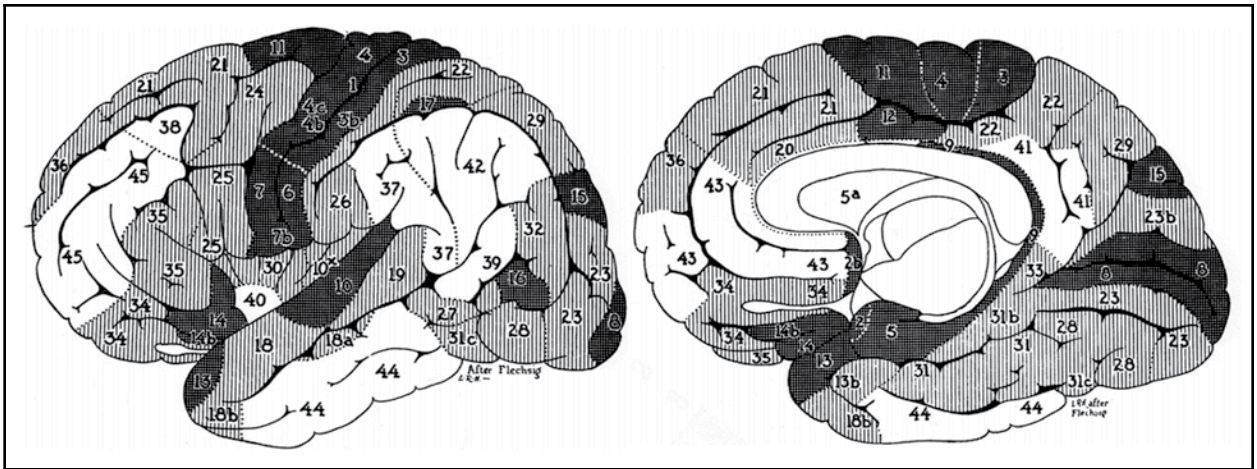

Figure 2. Lateral and medial views of Flechsig's zones of cortical myelogenesis. Numbering is in sequence of developmental primacy. Shading corresponds to general areas of myelogenesis; Dark shading corresponds to "primordial centers", grey shading corresponds to "intermediary centers", and no shading corresponds to "terminal centers". Figure taken from [102].

Yakovlev and Lecours [103] expanded upon the findings of Flechsig through extensive histological study of more than 200 fetal and neonate brains which were stained to reveal myelin. This work carefully examines the typical onset, duration, and resolution of myelination processes in early development, and even follows up these analyses with corresponding analyses of myelination in more mature brains. From the data they collect they produce a table summarising their findings for a number of structures in the brain (**Figure 3**). Yakovlev notes that components that are of "special functional importance" begin myelinating earlier, but have more drawn out myelination cycles, while components with "more universal and less specific functions" begin myelinating later, but complete the myelination process more quickly [103]. He further makes the interesting observation that newborns reach a level of myelination (as indicated by staining intensity) comparable to an adult rhesus monkey within about 3 to 4 months of development. Moreover, he notes that the rate of myelogenesis in the monkey is "incomparably faster than in man", indicating that humans have an unusually slow cycle of myelogenesis. Yakovlev's work was significant in its own right, but also in virtue of its impact on other researchers active at that time.

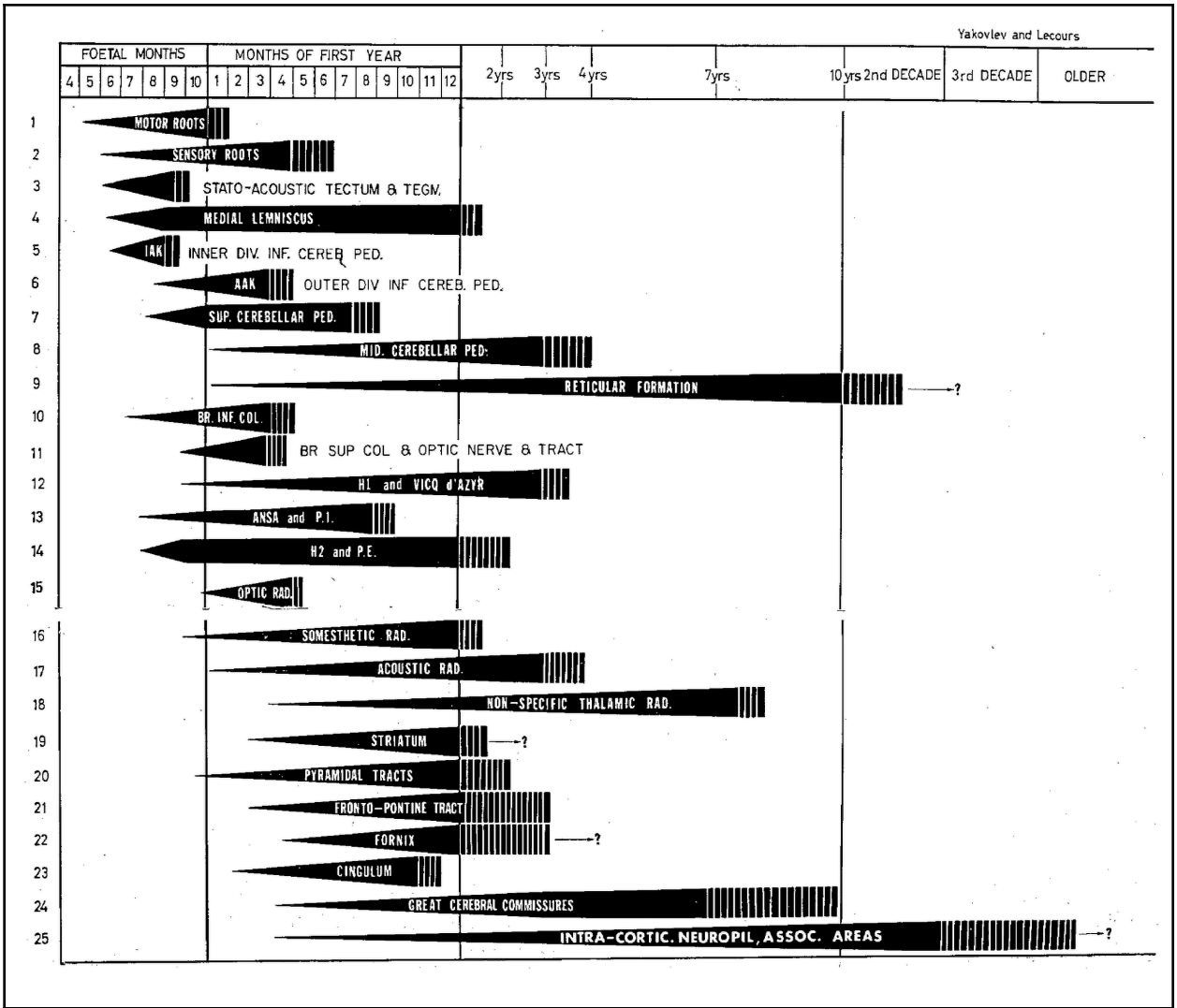

Figure 3. Standard process of myelination in the the central nervous system. Onset of myelination, as indicated by staining, is indicated by the initiation of a lateral graph line on the left hand side of the chart. The width of this object corresponds to the observed intensity of staining. Vertical striping, observed on the right hand side of the lateral graph lines, indicates typical range of termination for myelination processes. From [103]

Among Yakovlev's contemporaries was Norman Geschwind, who is notable for, among other things, his expansion upon Flechsig's rule. While his primary interest was in developing and analyzing the recently revitalized notion of "disconnection syndromes", his theories were thoroughly predicated upon the work of Flechsig. He expanded upon Flechsig's rule, which precluded direct connections between sensory regions, by extending the restriction to include interhemispheric or motor connections [20,100,104]. In turn, this set of prescriptions leads to a particular architectural motif for white matter connections of the brain, characterized by primary

cortical processing areas, adjacent intramodal association areas, and specialized multimodal association areas, all operating in parallel to a limbically-mediated network of connections. To help explain these observations he made an appeal to evolution and phylogenetic processes. Specifically, he noted the evolutionary appearance and expansion of association regions which serve as intermediary connections between sensory and motor regions as species evolved. These connections, he suggested, permitted the transfer of information via non-limbic routes, and thereby facilitated the development of more complex behavioral repertoires [100,104]. Indeed, on Geshwind's account, it was this move away from limbic connections to the use of specialized multimodal association areas that permitted the development of capacities like language and semantics [19,100]. Having considered this previous work, we are now in a position to make an initial grouping for a subset of white matter tracts.

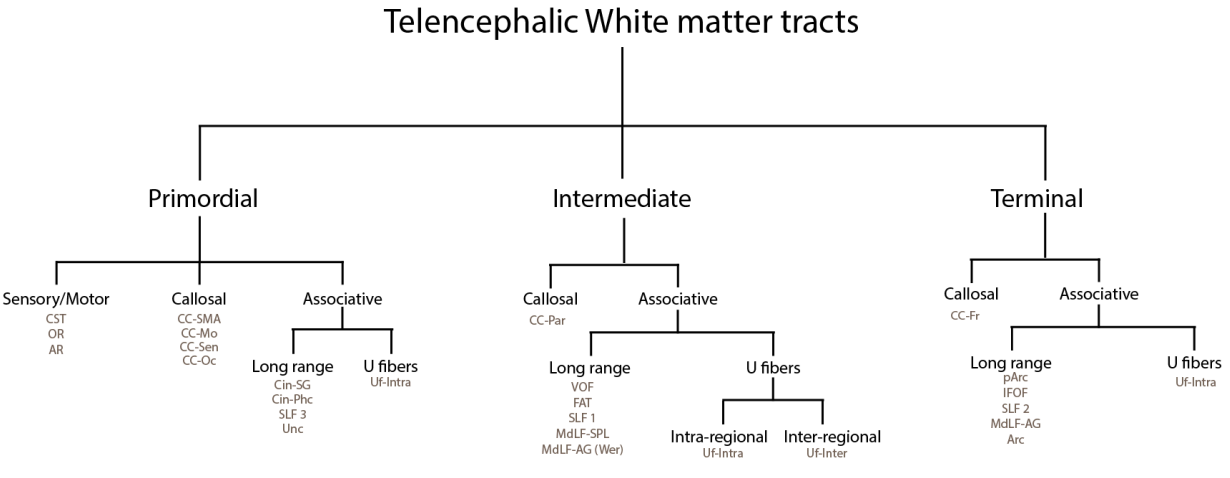

Figure 4. A preliminary hierarchy of telencephalic white matter tracts, with developmental groupings. A proposal for a structure organizing white matter tracts in accordance with order of myelination and other characteristics. Primordial, intermediate and terminal nomenclature adopted from Flechsig. Specific tracts listed in gray, with naming conventions found in **Supplemental Table 2.**

In **Figure 4** we find a hierarchy whose initial grouping is based on Flechsig's myelogenetic mapping. In it we find tracts sorted into initial categories of primordial, intermediate and terminal based on the myelogenetic sequence of the regions they terminate in.

Generally speaking, tracts which terminate in regions exhibiting different myelogenetic groupings (See shading in **Figure 2**) were assigned to the “latest” (later in development) category, on the presumption that “early” myelination of the tract would have been observed in the “later” (i.e. intermediate or terminal) area if it had occurred. Subsequent groupings are based in part on the Meynert-Catani conventions. A number of observations can be made about this hierarchy.

It should go without saying that is a highly speculative proposal, based primarily on previous literature. Even so, it avails itself of several interesting observations. The primordial grouping is noted to be the only category featuring a set of sensory motor tracts. This is unsurprising given Flechsig and Yakovlev’s observations about the myelination of such systems early in development. Callosal fibers are found to be categorized across all myelogenetic groupings. The corpus callosum is a brain structure found to occur since the evolution of placental mammals [105,106], however the structures they connect are not uniformly present throughout mammals, and so it was the presumed evolutionary sequence of these areas, along with Flechsig’s mapping that led to this arrangement. Moreover, there is precedent for this sub segmentation [107,108]. U fibers are found across all three myelogenetic groups as well. This is predicated upon the expectation that U fibers connecting within primordial areas will be utilized and thus myelinate in conjunction with their cortical milieu. However, connections to adjacent unimodal association areas (see **Figure 2,** primarily in gray intermediate areas) would not themselves myelinate until target areas were at least partially myelinated, and likewise for terminal areas. Two tracts are noted to be subdivided up in a potentially unintuitive fashion, the SLF and the cingulum. Both tracts have been noted to have subdivisions [46,109], and were categorized in accordance with their cortical terminations. In the case of the cingulum, this grouping is further supported by previous work showing the subgenual component exhibiting distinct quantitative properties in addition to the distinct connectivity pattern [109]. Finally, the uncinate fasciculus is noted to be a perplexing inclusion in the primordial grouping given that it

does not conduct sensory or motor information. However, there is independent evidence for this (beyond Flechsig's mapping), in the form of dMRI findings indicating the early appearance of this tract in fetal development [110]. What are the broader virtues of this schema though?

As noted in our earlier consideration of white matter classification schemas, the groupings are typically only useful insofar as they correspond to some causal process and thereby constitute something approximating a natural kind. Here, we have used development as our guide, which results in our schema having some very worthwhile applications. Recent research has implicated deviations in standard early white matter developmental processes in the later development of mental disorders [111–114]. White matter has been found to be particularly vulnerable to disruptions of developmental processes [115], and so what we are provided with in this model is a probative method for testing these hypotheses. Given the timing of a developmental insult, we can make predictions about which tracts are still developing and thus uniquely vulnerable to insults which would disrupt this process. For example, exposure to teratogens [116] are known to have differential effects depending on the time of exposure [117–119]. A hierarchy based on developmental sequencing of myelination would allow us to infer if there may be a developmental component to a disorder based on variation in particular grouping of fiber tracts. This can be done *a priori*, through use of previous work noting alterations in individual tract properties relative to clinical diagnoses, or *a posteriori* by seeing if the set of tracts exhibiting variance in a clinical population are noted to all be under development at the same time. This has the further benefit of hinting at specific mechanism, with the potential to implicate particular critical developmental time points wherein an insult might have arisen. As such, we see the potential utility of this approach to categorization and why it would be worthwhile to further develop such hierarchies.

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Supplemental Material

Primordial areas		Intermediary areas		Terminal areas	
#	Name	#	Name	#	Name
1	Middle precentral gyrus(?), Middle central sulcus	18	Anterior superior temporal lobe, middle superior temporal sulucs (?)	37	Posterior supermarginal gyrus, anterior angular gyrus
2	Entorhinal pole, subcallosal area	19	Posterior inferior superior temporal gyrus (inefrior to wernicke's area)	38	mid middle frontal gyrus (superior to intermediate frontal sulcus)
3	Superior postcentral gyrus, posterior paracentral lobule	20	anterior midcingulate cortex	39	superior temporal gyrus (between the ascending and horizontal superior temoral sulci)
4	Superior precentral gyrus, middle paracentral lobule	21	Middle and posterior superior frontal gyrus	40	insula (adjacent to central insular sulcus or posterior central insular sulcus
5	Entorhinal gyrus	22	Anterior superior parietal lobule	41	Posterior cingulate cortex, gyri limbici retrospleniales
6	Inferior postcentral gyus	23	gyrus descendens, sublingual gyrus (inferior to subcalcerine sulcus, middle saggital gyrus (superior to inferior saggital sulcus)	42	Posterior angular gyrus
7	Inferior precentral gyrus	24	posterior middle frontal gyrus	43	Anterior cingulate cortex, medial inferior frontopolar gyrus, medial middle frontopolar gyrus
8	Occipital pole, superior lingual gyrus, inferior sagittal gyrus, (pericalcarine cortex)	25	inferior frontal gyrus (basilar part), inferior frontal gyrus (ascending part), inferior frontal gyrus (opercular part), pars opercularis, posterior broca's area	44	Middle and anterior middle and inferior temporal lobes
9	Posterior cingulate gyrus (extremely proximate to body of corpus callosum), posterior callosal sulcus	26	Anterior supermarginal gyrus	45	Anterior middle frontal gyrus
10	Posterior, superior temporal gyrus (Wernicke's area)	27	extreme posterior inferior middle temporal gyrus		
11	Extreme posterior superior frontal gyrus (superior/medial to frotal paramidline sulcus);	28	Extreme posterior fusiform gyrus, inferior temporal gyrus (posterior to preoccipital		

	Supplimental motor area , anterior paracentral lobule		notch)		
12	Middle cingulate gyrus (between anterior midcingulate cortex and posterior midcingulate cortex)	29	Posterior superior lobule		
13	Temporal Pole	30	Insula, gustatory cortex (?)		
14	Posterior orbital gyrus, posteromedial orbital lobule	31	Anterior fusiform gyrus, inferior temporal gyrus between preoccipital notch and inferior temporal sulcus		
15	occipitoparietal arch (aka arcus parieto occipitalis)	32	Superior middle occipital gyrus		
16	Anterior, inferior middle occipital gyrus	33	isthmus of cingulate gyrus, perisplenial region		
17	extreme inferior superior parietal lobule, adjacent to inferior parietal sulucs; inferior pareital sulucs (?)	34	Inferior frontal gyrus, orbital part, straight gyrus, rostral gyrus		
		35	Inferior frontal gyrus (Triangular part), pars triangularis, anterior broca's area		
		36	anterior superior frontal gyrus		

Supplemental Table 2. Nomenclature associated with cortical regions numbered in figure 3. A table providing standard names for the cortical regions implicated in the preliminary myelogenic hirearchy, and grouped in accordance with his characterization.

Primordial Tracts		Intermediate Tracts		Terminal Tracts	
Abbreviation	Name	Abbreviation	Name	Abbreviation	Name
CST	Corticospinal Traact	VOF	Vertical Occipital Fasiculus	CC-Rs	Cingulum retrosplenial
OR	Optic radiation	FAT	Frontal Aslant	pArc	Posterior arcuate
Unc	Uncinate (?)	SLF 1	Superior longitudinal fasciculus 1	Arc	Arcuate fasiculus
Cing-Sg	Cingulum - subgenual	CC-Par	corpus callosum - parietal	IFOF	Inferior fronto occipital fasiculus
Cing-Phc	Cingulum - parahippocampal	MdLF-AG (Wer)	Middle longitudinal fasiculus, angular gyrus component--Wernicke's subcomponent	TPc	Temporo-parietal conenction
SLF 3	Superior longitudinal fasiculus 3	MdLF-SPL	Middle longitudinal fasiculus, superior parietal lobule component	SLF 2	Superior longitudinal fasciculus 2
CC-SMA	Corpus callosum - supplimental motor area	Uf-Inter	inter-regional: unimodial association - primordial area	MdLF-AG	Middle longitudinal fasiculus - Angular gyrus component
CC-Mo	Corpus callosum - motor cortex	Uf-Intra	intra-regional: unimodial association	Uf-inter	unimlodal-associative <-> multimodal associative U fibers
CC-Sen	Corpus callosum - sensory cortex			CC-Fr	corpus callosum - Frontal
CC-OC	Corpus callosum - occipital cortex (?)				
AR	Acoustic Radiation				
Uf-Intra	Intra-regional U fibers: primordial areas				

Supplemental Table 1. Nomenclature associated with white matter tracts in figure 3. A table providing standard names for the white matter tracts organized in the preliminary developmental white matter hierarchy. Grouped in accordance with primary category.

Computational Models of White Matter Structure
&
Related Biological Characteristics

Intro

When we endeavor to produce a structural model of an entity, our model is implicitly bounded by a number of constraints, many of which we may not have a full awareness or understanding of. Indeed, depending on how it was constructed, a given model abstraction may contain features which imply the existence of real world features which have either never been observed or cannot actually exist [1]. Assuming that our goal with modeling is to accurately reflect variance in the features occurring in the world, we may wish to take steps to decrease the probability of this happening. One way to do this would be to utilize a fully elaborated causal model to generate model tokenings (model entities presumed to correspond to real world entities). A comprehensive approach like this could conceivably permit the effect of every possible perturbation to the object/system to be modeled and studied, however this is simply not practical in the vast majority of cases--even “simple” models can become computationally intractable with the incorporation of a limited number of elements [2]. Instead, we can endeavor to impose constraints on such models given our amassed understanding of the entity in question. In this way, we can both improve models individually and adjudicate between competing models. In turn, this will allow us to move closer to models and modeling methods that are applicable at the individual level, and to finding more generalizable clinical applications for these models [3]. Setting this as a goal is straightforward enough, but knowing how to achieve this is another matter entirely.

One approach to model improvement of the kind described above could be to assess multiple outcomes (e.g. a parameter sweep or replications) from a modeling approach with regards to their consilience (agreement with findings obtained from other scientific approaches to the same general subject, [4]). More concretely and systematically, this would entail

developing a method for efficiently orienting and searching the hyperspace occupied by possible model tokenings to find sets of models [1,5] that are consistent with what is observed in the real world. Such an endeavor would be predicated upon a “dimensionalization” of the theoretical morphospace, wherein quantitative parameters of the model correspond to the axes of this conceptual space. The quantitative parameters used to do this could be those associated with the generating function or with the resultant model token. Perhaps as a means of prioritizing parsimony [6], the recommendation made here is to have the dimensionalization not be in terms of the generating model, but rather in terms of the model’s output, particularly as the output relates to the implicit or explicit biological properties of the entity being modeled.

In this paper I will consider model(s) used to represent the architecture of the brain’s white matter and its various associated properties, and find non-obvious criteria (e.g. non-connectivity based) that can be used to evaluate their plausibility. In doing so, this will provide some degree of dimensionalization or parameterization by which models can be assessed relative to one another. Overall, this endeavor will consist of three main phases: a thorough examination of the biological entities of interest (i.e. axons); an analysis of what idealized computational models of white matter might be, how they are generated in practice, and what their representational significance is; and finally a consideration of how the biological characteristics of axons might be incorporated into our computational or mathematical models models white matter. To begin we consider the biological nature of the brain’s white matter.

The study of the white matter of the brain has been a longstanding and important component of the broader endeavor to understand the brain, and has been characterized by fluctuations in methods, scope, and prominence. Indeed, the history of the study of white matter is a fascinating topic in and of itself, and has been presented in detail previously by other authors [7–12] as well as within this paper series (see “A Taxonomy of White Matter Architecture”). Overall, this amalgamated work has led to the establishment of a preliminary understanding of the white matter. To begin, the white matter is the tissue component of the

brain which is composed of the lipid-rich myelinated axons of the cortex, which give it is characteristic color and texture. In virtue of its being composed of axons in this fashion, the white matter is manifestly fashioned to form connections between the many neurons of the brain. Therefore, because the architecture of the white matter determines the flow of information in the brain, it stands as an obvious target of study to help understand how the brain's structure facilitates behavior--both in states of typical function and in states of disorder. To better grasp how this collection of axons instantiate the connectivity of the brain, it is necessary to consider how various aspects of their structure shape their functional role.

Axon-related Properties

The axon is the portion of the neuron, located in between the soma (cell body) and the terminal ends of the neuron, which facilitates connectivity to distal neurons or other systems (e.g. muscles or other tissues). In virtue of this positioning, their function is to conduct a signal, in the form of an electrochemical pulse (also known as an action potential), from one part of the body to another. Upon reaching its destination, the electrochemical signal triggers the release of signaling proteins (neurotransmitters or hormones) which, in turn, modulate the activity of target cells and tissues. Two of the distinguishing features between these signaling mechanisms--neurotransmitters and hormones--are the time courses and specificities that are associated with them. Generally speaking, neurotransmitters are released in a targeted fashion, from one cell to another, and conduct signals on a relatively short time scale (due, in part, to the dynamics of the synaptic cleft) [13]. Hormones, on the other hand, are typically released into the bloodstream and impact a number of cell types and tissues over a longer duration. In truth, the distinction between the hormonal and neurotransmitter systems is now understood to be less clear cut than was traditionally believed [14], but for the purposes of the discussion at hand this distinction will suffice. Continuing then, it is noted that, particularly for the neurotransmitter systems of the central nervous system, the issue of signal timing is of paramount importance to

the role of the axon. As we will see, the nervous system has implemented a number of design features in order to modulate the transduction of signals down the axon and which can serve as fruitful targets for investigation.

Nerve cells and tissue are found all throughout the body [15,16]. This is not surprising considering the need to control and coordinate the activities of cells and tissues that are at some distance from one another. Coordination of these cells and tissues is an incredibly time sensitive operation, and there are several ways that the speed at which signals are conducted down the axon can be modulated. By in large, these approaches achieve that end by somehow modulating the electro-conductive properties of the axon. An exhaustive examination of these features is beyond the scope of this paper and has been provided elsewhere [15–20]. Instead, we will briefly consider the structure of the neuron, how several structural modifications to the neuron (including axon diameter, myelination and node spacing) alter its functional characteristics, and how these structural characteristics come together to manifest higher-order properties of the brain. To begin we consider the general character of the neuron.

Although a number of different types of neurons exist [21,22] and exhibit different types of firing patterns [23], a consideration of the textbook model of a neuron's function is nonetheless informative [15,24]. Chiefly, the neuron is simultaneously an integrator and transducer of signaling information, operating dynamically at the timescale of microseconds. It's internal homeostatic mechanisms result in an intrinsic firing rate and pattern [23] which is subsequently modulated by external signaling influences (which either promote or inhibit the firing activity of the neuron in question). The net effect of these influences is an alteration of the membrane potential (the electrochemical potential instantiated by the actively maintained difference in the concentration of particular ions inside and outside the cell) within the integrative component of the neuron. As mathematically modeled initially by Lapicque in 1907 [25] and then comprehensively (and quite successfully) by Hodgkin and Huxley [26], once the integrated membrane potential of a particular, pre-axonal component of the neuron (i.e. axon hillock)

reaches a threshold value, a chain reaction of events is initiated. Voltage gated channels along the axon's membrane are successively triggered by the change in local membrane potential, leading to a down-axon "wave" (action potential) of electrochemical fluctuations which eventually reach the terminal ends of the neuron (terminal buttons). Here, in the distal ends of the neuron, the change in membrane potential facilitates the release of small containers (on the order of 39.5 nm in diameter [27]) of neurotransmitters into the space between this neuron and the receptive components of an adjacent neuron (~ 20 nm in span width [28]). Given the complex nature of this process, a number of features have been noted to change the dynamics of action potentials.

The factors modulating the speed of axonal transmission are worth considering for at least two reasons: their impact on reaction times [29–31] and the rate of information transmission between two distinct regions [18,32]. One such factor is the diameter of the axon. Previous research has found an approximately linear relationship between conduction velocity and axon diameter (in myelinated axons) such that conduction velocity (in meters per second) is measured to be roughly 6 times the diameter of the axon (in micrometers) [33,34]. For example, an axon with a diameter of 4 micrometers would have a conduction velocity of 24 meters per second. Thus we see that one way that developmental or evolutionary processes can modulate the speed of communication between regions is by changing the diameter of axons. As noted in an above aside though, these measurements were obtained in myelinated neurons, and so it is necessary to consider the structure and role of myelin.

As described by Hartline and Colman [31,35,36] rapid neural conduction times confer a distinct evolutionary advantage in the form of decreased reaction times. We have seen that one way to do this is by increasing the diameter of the axon. This achieves its effect by reducing the interior resistance of the axon, in virtue of resistance decreasing as a square of the diameter [31]. This, in turn, increases the rate at which adjacent membrane is charged with electric potential. Hartline and Colman refer to this as the "easy" solution". A second solution, they

note, would be to reduce the transverse capacitance of the membrane, such that less accumulated charge is necessary for the action potential to propagate down the axon. Indeed, this is the role played by myelin, which ensheaths portions of certain axons and thereby expedites signal transmission, while also acting to increase the transverse resistance. It is composed of multiple layers (~ 10 to 160 [20]) of dense lipids which are the the extensions of Schwann cells in the peripheral nervous system (PNS) or oligodendrocytes in the central nervous system (CNS) [16,24]. While increasing the number of layers of myelin can improve conduction speeds, there appear to be limits to the improvements achieved with each additional layer [17,24,31,37]. Myelin appears to have undergone convergent evolution several times, in that a number of unrelated species with distinct lineages exhibit it, without intermediate species also exhibiting it [31,35,36]. However, it is also worth noting that myelin, where it is present, does not cover the entirety of the axon and that this is also an important structural feature of the axon.

Another axonal factor which significantly impacts conduction speed is internodal distance. The covering provided by oligodendrocytes (or Schwann cells) is not continuous along the axon, and instead features “gaps” known as nodes of Ranvier [38]. Here, at the nodes of Ranvier, the axon is exposed and unmyelinated. As a consequence of this, the resistive and capacitive characteristics of the axon are quite different at these locations [16,24]. This leads to what is known as saltatory conduction, where the action potential “jumps” from node to node. In truth though, what is actually being observed is the *extreme* differences in conduction speeds between myelinated and unmyelinated sections of the neuron. The conduction speed along myelinated sections is not instantaneous, but rather a magnitude of order faster than conduction speeds along unmyelinated such that they appear instantaneous when considered at the timescale of conduction along unmyelinated sections [39]. Given that the conduction rate is thus a composite measure of conduction speeds along both of these sections, it stands to reason that the spacing of nodes of ranvier (and thus proportion of

exposed axon) is a major influence on overall conduction speeds. Indeed, research has shown that [17,31,34,37,39] this is the case.

One interesting class of observations has been the strong intercorrelations between axon diameter, myelination, and node spacing. For example, Hursh's analysis of axon properties also noted a striking correlation between axon diameter and internodal distance (see figure three in [34]), indicating that larger axons have slightly larger internodal distances. The notion of the "g-ratio" or the ratio of the inner-axonal diameter (the diameter of the axon itself) to the whole fiber diameter (i.e. the diameter including the myelin sheath) has also received a great deal of attention [34,37,40,41]. Rushton's theoretical work argued that a g-ratio of approximately .6 maximized conduction speeds relative to the increase in axon diameter, which corresponded to about the center of the range encountered with empirical work at that time (~ .5 to .75[20,37]). This was later bolstered by computational work by Smith and Koles using a 10.5 micrometer axon model, which showed that increasing myelination improved conduction speeds all the way out to a g ratio of .25 (i.e. 10.5 μm diameter axon with 42 μm myelin diameter), but that the efficiency of this peaked just above a g ratio of .6. Importantly this body of work has also noted that this ratio was only optimal for a particular range of axon diameters and that fibers outside of this range (e.g. < 1 μm [37] or > 20 μm [20]). The specifics of these observed interrelations, norms, and claims must be interpreted cautiously, however. Given the demands of the associated experiments (i.e. *post-mortem* or *in-vitro*), these were typically conducted on cephalopods, rabbits, cats or other animals and were often from PNS sources. As such we must consider whether work in animals is appropriate for extrapolation to the white matter of the human brain.

Although there is little reason to doubt the foundational work associated with the g ratio and conduction velocity, it remains unclear how applicable these observations are to human brain architecture. Indeed, some fibers may be as small as .1 μm in diameter [42] while those considered by the work discussed in the previous paragraph were typically larger (e.g. ~> 3 μm,

see figure 1C & D in [20] or even ~>= 5.8μm, see figure 1 in [34]). Quite shockingly, the majority of tracts (including major structures like the superior longitudinal fasciculus (SLF) and corpus callosum (CC)) had mean and median inner axon diameters of less than ~1-1.5 μm [18,19,42–45] in both humans and non-human primates. Moreover, some experimenters note that their methods (e.g. light microscopy, as opposed to electron microscopy) are unable to resolve tracts below .2-.3 μm [43]. Even accounting for g ratios of 1 or higher (which are very biologically implausible), this puts the overwhelming majority of tracts in the extreme left tail of the distributions considered in the early g-ratio and conduction velocity work. Contrary to Rushton's suppositions/observations [37], the majority of human white matter tracts are quite small (compared to the axon samples used in older work) but are nonetheless found to be myelinated (85 to >95%, [45]). Indeed, using a cross species comparison across the shrew, mouse, rat, marmoset, cat, and macaque, Wang et al. found that the proportion of myelinated axons increased with evolutionary sequence and brain size/weight (figure 1C & figure 4 [46]). This phylogenetic insight, along with the earlier work on conduction velocity, suggests that there are complex forces influencing the architecture of the human brain.

Clearly, there are additional, and as of yet unconsidered influences on myelination in the human brain. An important issue to reflect on is how evolutionary forces may have interacted to give rise to the observed architecture of the brain. Though it may seem trivially obvious, one important notion to keep in mind is that there is a functional implication to the distinction between white and grey matter: the connectivity manifested by the white matter is the result of an elaboration of an adaptive mechanism [47–49]. That is to say, white matter isn't simply a "spandrel" [50], but rather an architectural feature which serves a survival-essential role and that modulation of its features across phylogeny reflect adaptation to selection pressures. If minimizing reaction time were of singular importance to survival one solution would be to maximize the size and myelination of axons. However this is not observed empirically

[18,19,45,46,51], and theoretical models indicate that there are other constraints to the architecture of the brain. As such there must be other influences on its design.

As an evolutionarily generated system, the brain manifests a careful balancing of costs and associated benefits for various adaptive features [52]. Perhaps chief among these is space. Given that the brain is a physically instantiated object, the wiring (in the form of axons) needed to interconnect it incurs a volumetric cost--both for the axons themselves and the oligodendrocytes which support them. Thus, not only are there limits to overall myelination, but also regional balances that must be struck amongst various spatially proximal groups of axons [32,46,53,54]. With regards to whole brain limits, it has been noted that increasing the volume of the brain, either by inefficiently expanding the cortex to accommodate more neurons (i.e. without gyrification) or through overall increased white matter volume, has the consequence of increasing the distance between neural modules/components. This, in turn, incurs greater transmission delays and thereby necessitates the need for larger axons in order to obtain the necessary transmission speed once more--an unsustainable and self defeating cycle [49,54–57]. This observation provides some explanation as to why axons are not optimized solely for conduction speed, but it does not explain why the particular distribution of axon diameters--even within a single anatomical tract--is observed.

One striking feature that has been reported throughout research on this subject is the shape of the distribution of axon diameters within anatomical structures. Specifically, researchers have consistently found log normal distributions of this feature [18,43–46,58]. Conceivably, there are a number of alternative distributions of axon diameters that could exist for a given tract volume. For example, one might expect to find a tightly constrained distribution such that there is minimal variance in diameters, which would be in keeping with the expectation that maintaining synchronicity within a given fiber tract is important [59]. Alternatively, it could simply be that this variation is the result of a stochastic process, and so a normal distribution would be expected. Instead we find a log normal distribution. What could account for this?

One explanation for some degree of variation in axon diameters within a given anatomical structure could be that slight differences in axon length (due to variable path lengths between neuron-specific terminations) would necessitate fine modulation of conduction velocity via changes to axon diameter or myelination. Indeed, it has been shown that myelenation can be fine tuned in accordance with firing rates [17,60], and given that single oligodendrocytes myelinate several axons [16,24], the information needed to coordinate this process might be available to a given cell. However, this would not explain the presence of comparatively larger axons (e.g. .5 μm vs 5 μm) in the far right tail of the distribution within the same putative neuroanatomical module. Given the widely accepted standard for computing conduction velocity (~6 * axon diameter for myelinated axons, [34,46]), there appears to be significant heterogeneity in the rate of information flow into a given area [32]. This range is expanded when one considers the comparatively faster firing rate (e.g. 1 Hz vs 100 Hz) of larger axons [18,61]. It may well be that this is exactly the point of this distribution, and that this within-area information-rate heterogeneity isn't just an arbitrary characteristic of white matter fascicles, but an essential feature of brain architecture.

Several accounts of the lognormal axon diameter distribution--and resultant curious range of information rates within anatomical structures--have been provided. These include adherence to an optimality principle given spatial and informational constraints [32], mechanical consequences of microstructural properties of the axon [62], or that certain informational features may need to be encoded at higher informaton rates[18]. An alternate explanation may be the need to manifest and maintain multiple distributed patterns of neural oscillation (at a range of frequencies) in a coordinated fashion [48,59,63–66]. Although the general features of temporal dynamics in brain oscillations are preserved across mammalian taxa [48] it has been noted that the range of conduction delays is increased threefold between macaques and humans [63]. This is despite relatively "unextraordinary" nature of human brain anatomy overall when brain mass is controlled for [47,55,56,67], and the merely "modestly increased" mean

conduction delays observed in humans as compared to rodents (Supplemental note 4 [48]). Thus the wider range of delays may permit finer grained control of oscillation dynamics or even more complex dynamics between sets of oscillators [59]. Whatever the broader, downstream effects of the neuronal features discussed so far (e.g. g ratios, axon diameter distributions, conduction speeds, bit rates, etc.), it is also important to consider how this information can be incorporated into our models of the brain's anatomy. In order to do this though, it is worthwhile to consider what a model *is*, generally speaking, and what a structural model of white matter matter specifically might entail.

The Nature of Models

The term "model" is used in a number of different contexts throughout science. Generally speaking, the goal of a scientific model is to somehow "capture" or "represent" a specified object or phenomena. This can be achieved by different means. For example, a model can be static and represent a structure or physical arrangement, as is the case with the helical model of DNA, or it can be dynamic and thereby represent a process or system, as is the case with the Lotka-Volterra model of predator-prey dynamics. Furthermore, it can exhibit varying degrees of qualitative or quantitative properties. For example, the Atkinson and Shiffrin model of attention [68] qualitatively accounts for several aspects of attention while the Hodgkin–Huxley model of action potentials [26] provides a mathematical account of the dynamics of the neuron. There is even the possibility of developing generative models, the internal features or which are not presumed to correspond to any existent features of the world, but which nonetheless produce model "tokens" (i.e. instances of a model which putatively correspond to a specific event or structure). There are thus a wide range of characteristics that can be attributed to scientific models [69]. As such, in order to better understand how to improve upon or leverage our models of white matter, we should consider how they "represent" various aspects of the brain's architecture.

Given that the goal of a representational model is to somehow capture relevant aspects of the entity being modeled (without recapitulating the entire structure of that entity), we might take a step back and ask “what aspects of axons are we interested in?” Using tracer studies as our guide and as a comparison class [19,70–72], we can recognize that being able to focus in on the spatial traversal of an axon--in a highly accurate and granular fashion--is of paramount importance. This capability not only permits investigators to determine the deeper white matter areas traversed by an axon, but also the cortical areas it terminates in and (conceivably) what other terminations are near it--key tools for conducting connectomics ([73,74]. Furthermore, we we may wish to associate particular measures like g-ratio[20,37,41], diameter[19,42–44], or information rate [18] with particular axons or with particular locations along axons [75]. For a small organism it may be possible to represent the structure of the brain in a comprehensive, 1 to 1 fashion (i.e. atom-by-atom or cell-by-cell) [76]. However, in the case of the more complex organisms, it may be worthwhile to use an abstraction, such that axons are are represented by a centroid centered streamline sampled at a sufficient rate, in much the same way as contemporary tractography. Although features like g-ratio, diameter, transmission direction, and transmission rate are consequences of structural or geometric properties, these could likewise be stored in an efficient fashion as well (e.g. as an indexed numerical vector) [77]. In this way, such a model structure would capture information about geometry, connectivity, and biology which might be expected to vary in accordance with behavioral dispositions or states of disorder [12]. How does an ideal model framework for white matter like this compare to the kinds of models generated by modern neuroimaging though?

Key to understanding what modern, neuroimaging-derived models of white matter structure can be said to actually represent are the methods by which such models are derived. First and foremost, it must be reiterated that diffusion imaging [78–80] is *not* a direct measure of axons or white matter, but rather an impoverished and distal proxy measure of the aggregate movement of water molecules [81] within a given timeframe [82,83]. In turn, this motion is

understood to be differentially impacted by various tissue types like cell membranes and myelin [84,85], and thus capable of providing information about these features. The move from assessing an inferred tissue property to interpolating white matter architecture involves a number of intermediary steps. To begin, the data must be interpreted by a model which summarizes the voxelwise sampling of diffusion information (i.e. diffusion orientation density function [86,87] or fiber orientation density function[88–90]). Such models make a number of assumptions about tissue composition [91,92], are unable to reliably distinguish certain ground truth states, and are highly dependent on acquisition parameters [83]. Nonetheless, these intermediary models are then used to inform any of a number of algorithms [93–96] which use this information to infer the location and trajectories of amalgams of axons in the forms of putative white matter tracts [96–98], and exhibit reasonable degree of consistency with findings from other research modalities [71,72,99,100]. However, this move from information about diffusion orientations to the professed representation of white matter macro-structures has significant methodological consequences, and thus warrants deeper consideration. To what degree do these model features (i.e. streamlines) correspond to or represent anatomical features?

A first blush account of diffusion-derived models of gross white matter architecture is predicated upon the presumption that the model's constituent streamlines are (somehow) representations of putative tracts. With respect to their actual computational manifestation, streamlines take the form of an ordered set of nodes corresponding to the presumptive centroid of a putative "tract". The "smoothness" of a streamline is a function of the internode distance, and thus this discretization entails a tradeoff between representation compactness (i.e. storage demands of streamline representation) and real-world fidelity. This approach to encoding is not the only reason to scrutinize tractography based models of white matter, though. Indeed, the proper way to actually "interpret" these streamlines is a subject of much discussion [82,83].

It is taken for granted that streamlines do not correspond to individual axons. The ever-expanding--but nonetheless limited--capabilities of modern computational systems precludes the implementation of models which features 86 billion streamlines (which would correspond to one streamline per neuron [47,67]). As such, it further cannot be said that these entities accurately capture the morphology of specific axons, which are decidedly more tortuous than streamlines typically depict (see figure 1D [61], or [101]), and could exhibit branching. The historical anatomical work [102–104] along with the presumed norm of spatially adjacent axons (with similar connective properties) forming fascicles/bundles, suggest that a tenable interpretation might be that a given streamline corresponds to, or represents some subset of morphologically similar axons. Given the ambiguous character of streamlines (attributable to their inference from collective properties) it is unlikely that this correspondence can be mapped in an explicit fashion (i.e. axons 2134, 24523, and 4564 are specifically represented by streamline xyz) even in cases where ground truth is known. How does this impact our ability to make empirical claims about tractography models and their constitutive elements?

Conceivably, one virtue we may wish for our models of white matter architecture to have is the ability to be falsified. Although the specifics of the value of falsifiability have been the subject of much debate since Popper's initial writings on the subject [105], standard scientific practice suggests that it is still a generally desirable feature for scientific models. As such, we ought to consider how our tractography models can be subjected to tests of correspondence to real world observations. Clearly, we are presented with a challenge in that we cannot say that a particular streamline has axon-like properties (i.e. g-ratio, diameter, bit-rate). Likewise, it would be difficult to support a claim that a streamline corresponds to an amalgam (i.e. a distribution of properties) of *particular* axons. Without correspondence to a *particular* group of axons it is unclear how evidence could be presented to support or refute a claim about modeled biological properties. It may be possible to compare the modeled properties with measures obtained *post-mortem,* but this can only ever give us a sense of the degree of consistency between the

two. Definitive assessments and claims are not afforded by these models. For now though, that may be enough. Given the tools available to us there is still a great deal that can be done to improve our current models and to begin ensuring increasing consistency with established biological ranges. We should thus consider which biological properties would be most amenable to this process and how they could be incorporated into our investigations and models as anatomical priors.

Potential Anatomical Priors

Connectivity

One approach to evaluating general model credibility [106] might be through the study of connectivity [73,74,107]. Given the existence of certain ground truth measures of connectivity (i.e. CoCoMac [108,109]), network models of the brain are one way to subject our models to such a test--assuming the appropriate edge measure [73,74] is used. Indeed, the general format associated with network summaries [73,74,107] is likely well suited to summarizing a range of properties and characteristics of white matter architecture. This is in virtue of its ability to parcellate the white matter in a semi-consistent fashion across subjects and thereby facilitate multi-subject comparisons. Thus, for whatever measures that are subsequently proposed, in addition to doing a face comparison for white matter connections (however parcellated) and their relevant property, it may also be possible to conduct investigations of network properties using the given measure as an edge weight. This may not always lead to a sensible network analysis (e.g as one might expect in cases of tract length or g-ratio), but could lead to potentially interesting approaches (particularly for the hypothesized bandwidth measure).

Tract Length

One fairly obvious anatomical prior that could be applied to models of white matter architecture is a general principle connecting any two cortical regions in the most efficient way possible. This is in keeping with the general maxims of minimizing white matter volume and

conduction delay [57,110–113]. This would generally hold that, given any two patches of cortex, the fascicle(s) connecting these regions would be of the minimal length necessary to connect these two. This largely true [52], though there are exceptions (e.g. Meyer's loop [114,115] or the arcuate fasciculus [116,117]). One possible explanation for exceptions like these may be that there are additional constraints in the form of timing coordination or axonal density limits for particular volumes of white matter. Keeping this possibility in mind, a more nuanced version of this prior might be that the length of axons within any given tract are fairly homogeneous [19,43]. As such, model elements (i.e. streamlines) which excessively deviate from the norm (i.e. the the path centroid) for a given “tract” are likely spurious and should cast doubt on the overall plausibility of the model. Indeed, the logic underlying this prior is inherent in a number of algorithms like Cluster-viz [118], QuickBundles [119], and elements of Vistasoft (https://github.com/vistalab/vistasoft), which can be used to post-process streamline-based tractography models and eliminate dubious streamlines.

Axon Density

One biologically-based metric that has long been sought after is a plausible measure of axon density. Indeed, the search for such an axon based method or measure is of particular importance to investigations of brain networks as it would provide a biologically based and quantitative measure of connectivity--something that sorely lacking in contemporary studies [82]. For reasons discussed above, the counting of streamlines (or using this to create a density measure) cannot be relied upon to provide an accurate measure of connection strength. Methods for tractography validation have been pursued as a possible recourse for this issue [120]. Recently, there have also been efforts to develop imaging based methods for assessing fiber density more directly [121]. This method has the additional benefit of being “fixel”-based [122], which means that its measures are associated with fibers rather than voxels, which increases its robustness against issues arising in cases of crossing fibers. The authors of the associated paper [121] note that there is a great deal of terminological confusion on this issue,

with terms like “intra-axonal volume”, “fibre or axonal volume fraction”, or simply “density”. They therefore take great pains to define the term they use--”fibre density”--as “the volume of the intra-axonal compartment per unit volume of tissue”. This is a somewhat technical phrasing, but can be better understood with a consideration of other work relating to cellular densities in neural tissues.

Interestingly, the above work on track density relates to research in cross-species glial cell densities [67,123–125]. That body of research has found a linear relationship between white matter volume and non-neuronal cell numbers in the white matter (i.e. glial cells), indicating degree of constancy with relation to the non-neuronal component of the white matter volume. Given that glial cell proliferation is density-dependant, regulated by a fairly uniform (across species and structures) density-dependant mechanism, and that the average size of glial cells is invariant (relative to white matter volume), it has been suggested that changes in volumetric measures of neuronal or glial densities are a function of variation in neuron size [124]. Together, these insights (Herculano-Houzel et al. and Raffelt et al.) suggest that properly modeled investigations of tract densities may be surprisingly tractable, assuming issues relating to crossing fibers and fiber orientation can be reliably dealt with.

g-ratio

Another anatomical feature that we may wish to include in our models is the g-ratio. Although this is a property ascribed to individual axons, and is therefore not explicitly modeled in traditional tractography models, it could nonetheless be incorporated into models in such a way as to permit their assessment based on the biological plausibility of their predicted g-ratios. For example, we might expect consistent patterns of changes in these values across development ([126,127], see also “A taxonomy of white matter architecture”), that particular structures have typical g-ratio distribution patterns, or that particular disorders are associated with specific patterns of myelin degradation (see “A Developmental Model of Schizophrenia”). To that end,

Stikov et al [128] have proposed a method for measuring this value at a voxel-wise level. While this would surely be a useful capacity, some of concerns have been raised about the method.

The endeavor to develop imaging based approaches to studying g-ratios *in-vivo* faces a number of challenges. Several groups [129–131] have noted that the approach proposed by Stikov et. al makes the fairly curious assumption that g-ratios are uniform within a given voxel/volume. This is known to not be the case [131,132]. Furthermore, these groups have also noted that this model was only tested in the corpus callosum, which features no crossing fibers. Given that even in the revised models [129–131], this is a singular volumetric measure with no ability to ascribe g-ratios relative to distinct orientations or multiple axons, it is unclear how such an approach could distinguish between crossing fiber tracts, which are known to occur quite frequently in the brain. This is likely further complicated by the presence of a range of different g-ratio distributions across the brain. This range may actually turn out to be a boon though, given that particular tracts likely have characteristic distributions of g-ratios in the same way that particular tracts have distinct axon width distributions [18]. If so, g-ratios could serve as an important and informative component of a comprehensive model of white matter structure and properties which could be evaluated relative to established findings [132]. This may be particularly true when such measures are modeled in conjunction with other associated features like diameter.

Axon Diameter

As discussed earlier in this paper, and noted by imaging researchers investigating g-ratios [128,129], measures of g-ratios may of particular use when conjoined with measures of axon diameter given the their relevance to conduction speed [34,37]. Indeed, in light of the small range of variance observed in g-ratios [37,132] and their linear impact on conduction speed, it stands to reason that the comparatively extensive range of axon diameters [18,42] may prove to be a much more informative target for investigations of information dynamics in the white matter. To this end, Assaf et al.[133] have proposed an extension of the CHARMED

modeling approach [134] which permits the estimation of axon diameter distributions. This initial proposal had several shortcomings which were noted by the authors, however subsequent advancements by other groups working on similar methods have created more practicable applications which can even address issues associated with crossing fibers [135]. Taken together, the increasingly realistic prospect of incorporating measures of tract density, g-ratios, and axon diameters into our investigations of white matter suggest that unprecedentedly comprehensive *in-vivo* analyses of white matter. Indeed, this may even facilitate the development of entirely new composite/inferred measures which would be of particular interest to network studies of the brain.

Bandwidth/Bitrate

Given the above capabilities, it would seem that we could conceivably begin to form a method for modeling *in-vivo* information transfer rates [18,61,136] for white matter tracts. Even though we are unable to measure specific axon properties directly, the ability to access to information about (1) the overall distribution of axon diameters in a tract (2) the overall distribution of g-ratios in a tract, and (3) the density of axons in a given tract opens the door for computation of such a measure tract-wise. What's more, we have a relatively good baseline measured for these properties in the corpus callosum [19,44,45,58,128] and other structures [18,42]. These baseline measures can be used in the same way that measures of FA in the corpus callosum are used in other diffusion studies, and thereby ensure that our derived measures are consistent with established biological ranges. In turn, with these measures we can model the expected activity parameters for neurons [18,61] and begin incorporating information about encoding methods [136,137]. This, along with models for conduction speeds [34,37], will provide a rich source of data for studying how these dynamics give rise to phenomena like neuronal synchrony[138,139].

Implications for classification systems

Meynert-based systems

Although the planar-based delineation of association, projection and callosal fibers is not particularly plausible, categorical distinctions made within more refined versions of this schema may actually be found to correspond to (and thus be supported by) quantitative features. For example, projection fibers could be further subdivided into sensory/motor tracts and subcortical tracts (i.e. those associated with the thalamus, caudate, and putamen). We might expect that the timing demands for these two sub-classes to be vastly different. Given the coordination demands associated with the corticospinal tract and and the optic radiations, these likely have very low average conduction delays while the slower timescales associated with subcortical structures would suggest slower conduction speeds. Similarly, the division of association fibers into “long-range” fibers and u-fibers may be supported by differences in the distribution of axon diameters. Given the short range spanned by u-fibers it is unclear if massive axonal size ranges (and thus conduction speed ranges) would be of any functional utility, while (conversely) a limited number of minimal delay, high throughput channels in a long range connection could confer unique functional capacities.

Developmentally-based systems

The division of tracts into developmentally-based categories may actually receive even greater support than Meynert-based divisions. Indeed several recent studies have used MRI to investigate the development of white matter in infants [126,140–142]. Given the developmental time courses associated with white matter (see “A taxonomy of white matter architecture”), we would expect axons in the developing brain to start out unmyelinated but then sequentially myelinate as more functions come online. With respect to the quantitative properties discussed above, this would be observable as a shift in g-ratios, which would be expected to start out at low values but then increase to norms observed in adults. Given the influence of myelination on conduction speeds this process would also manifest as a sequential shift in information transfer rates. Thus, the primordial group of fibers would be expected to exhibit increases in this

characteristic before the intermediate group, and in turn, the intermediate group would shift before the terminal group. This hypothesized finding would lend credence to the overall categorization schema. Moreover, the temporal granularity provided by these studies would permit the establishment of a continuous spectrum of white matter development, rather than relying on somewhat arbitrarily binned developmental phases.

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A Developmental Model of Schizophrenia

One of the most pervasive and maligned challenges associated with studying schizophrenia and schizotypy is the heterogeneity exhibited by this class of disorders. Even setting aside the difficulties with establishing valid and practicable clinical diagnostic categories, there remains a decided lack of structure to schizophrenia's phenomenological characterization. Using Ereshefsky's framework for classification schemas [1], we see that this grouping is a paradigmatic manifestation of a cluster analysis-based approach. As such, no specific feature or set of features is ultimately essential for membership in the taxonomic group. More explicitly, no particular set of behavioral or pathogenic features are decisively characteristic of individuals exhibiting schizophrenia. Rather, manifestations of the disorder are all taken to share various properties, though none is found in all cases and, indeed many of these properties may be found in manifestations of other disorders. This, in turn, suggests that overarching approaches to mental disorder classification schemas may also be based on cluster analysis approaches. Regardless, instances of schizotypy or schizophrenia are taken to exhibit a disjunctive "family-resemblance" to one another, broadly characterized by disorganized thought, hallucinations, and paranoia/delusions. Vague and ill-defined categorical boundaries like this present a challenge for those who would attempt to provide etiological accounts of the disorder. What specific *explananda* should such accounts target? Schizophrenia's notable resistance to accommodating conceptual or mechanistic accounts has led some to take a step back and reconsider the very *kinds* of conceptual and analytic approaches that are used for such endeavors.

In this paper I will utilize previous conceptual work and empirical work to develop a model of the etiology of schizophrenia. This will begin with a consideration of two frameworks proposed for considering neuropsychological disorders. Having established that framework I will then make an explicit proposal of the model and discuss the general sequence of events

that it entails. This will be followed by a more specific consideration of the various processes involved and the empirical evidence for them. Finally, a consideration of the implications of this model will close the discussion.

Conceptualizing models of schizophrenia

In their 1990 article Tsuang et al. [2] set out to consider the general form of models which could be used to adjudicate between "unitary multifactorial polygenic" (MFP) and "discrete-subtype" models of schizophrenia. Key to establishing their conceptual framework for considering models of schizophrenia is delineating three levels of "indicators", a move that they take to be heuristic in nature. It is here suggested though, that this move is somewhat more significant than they claim. What the authors are doing here is dividing up the domain of indicators in accordance with either a causal (in that lower level indicators cause higher level indicators) or reductionist (in that higher level indicators "supervene" [3] on, or can be otherwise reduced [4] to, lower level indicators) approach. Thus, this tactic isn't merely for cognitive expedience as it actually reflects certain properties of the world--it would be *wrong* to place behavioral phenomena in the lowest level of these schemas. Moreover, this arguably represents a historical approach to classification [1] for characteristics of schizophrenia and schizotypy, which may lead to a more useful system of classification than would otherwise be achieved, as we have seen previously (see Paper 1: *A taxonomy of white matter architecture*). To continue, Tsuang et al. specify these three levels as "Etiology", "Pathophysiology", and "Symptoms" and, after discussing the method of assignment for phenomena to a given level, move on to the cross-level patterns of association between these phenomena. Indeed, they argue that it is the specification of these cross level associations (along with the specification of coherent, within-level groupings or classifications) that distinguishes various potential model classes of schizophrenia. They summarize this by depicting six potential instantions of these model classes (See **Figure 1**) which will be worthwhile to consider very briefly.

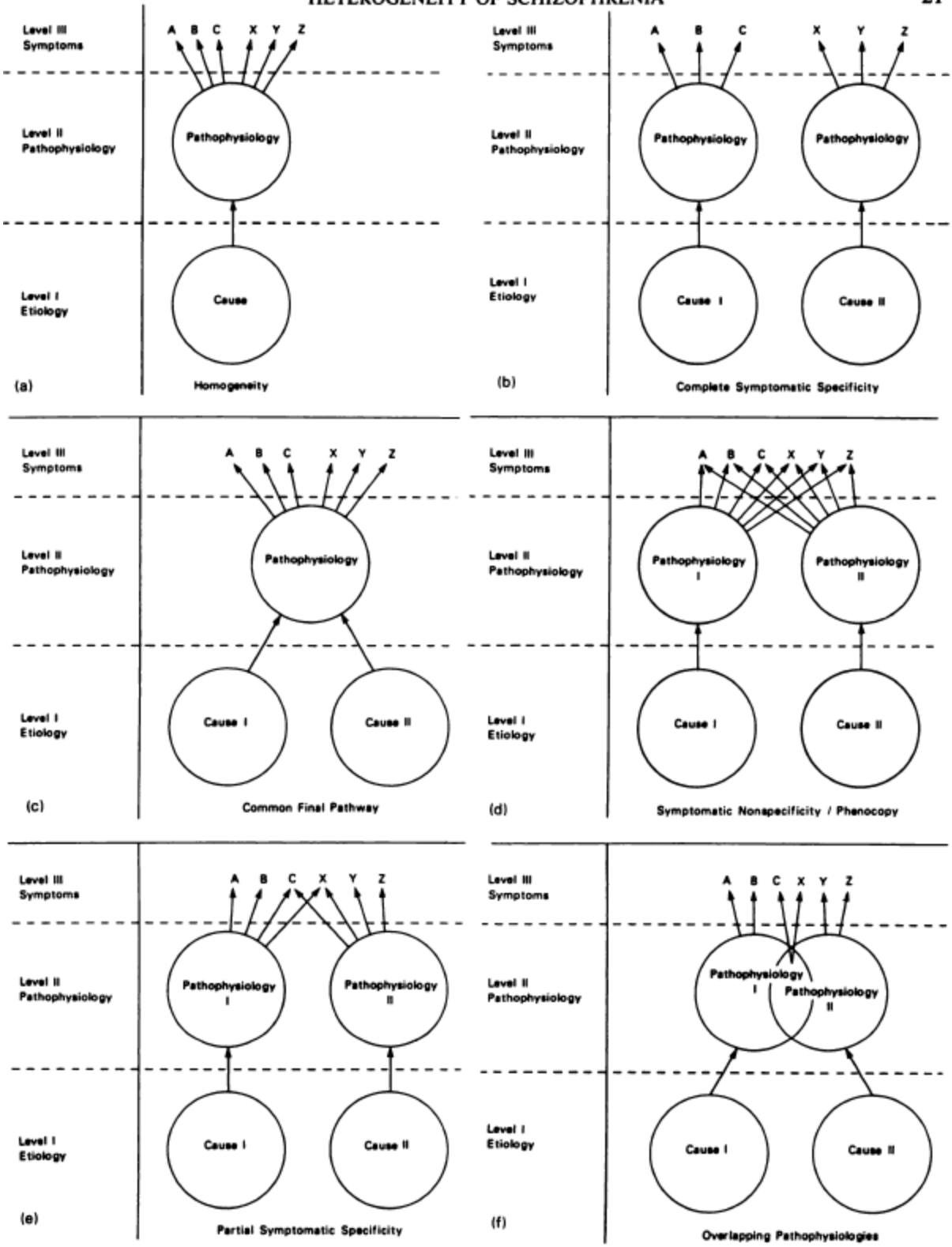

FIG. 1 Models for investigating the heterogeneity of schizophrenia.

Figure 1, (a-f): six potential general models of cross-level relations between indicators of schizophrenia. Within each sub-panel, phenomena are divided into (potentially overlapping) categories, as depicted by circles (or merely letters, in the final level), while the cross level relations are specified by feed-forward arrows. Dotted lines correspond to shifts in the causal or reductive level, while the vertical progression through levels corresponds to subsequent causal events or "higher order" phenomena. Taken from [2].

Although it is not an exhaustive parcellation of the potential "model-space" for schizophrenia, it is nonetheless useful to consider the the types of models enumerated by Tsuang et al. To begin, **Figure 1, panel A** depicts a "homogeneity" model, which corresponds to a situation in which a single cause is both necessary and sufficient to give rise to schizophrenia and that there are no true subcategories of schizophrenia. There is some history to this class of model, but contemporary understanding of schizophrenia casts doubt on the plausibility of such models. **Figure 1, panel B** depicts a "complete symptomatic specificity" model, in which some number of distinct etiological processes give rise to distinct pathophysiological processes which, in turn, give rise to distinct clusters of symptoms. Thus, sub categorizations of schizophrenia manifestations would be completely determined by initial etiological factors. Schizophrenia's ongoing resistance to easy subclassification is taken to be evidence against such models. **Figure 1, panel C** depicts a "common final pathway" model, wherein distinct etiological processes give rise to the same pathophysiology with no resultant clusters of behavioral symptoms. In these scenarios there would be multiple etiological routes to the same foundational pathophysiology. **Figure 1, panel D** depicts a "symptomatic non-specificity" model. In such a model distinct etiological processes give rise to the distinct pathophysiologies, which nonetheless give rise to the same range of behavioral symptoms. **Figure 1, panel E** depicts a "partial symptomatic specificity" model. This corresponds to a scenario which is somewhat similar to symptomatic non-specificity (**Figure 1, panel D)**, except that some of the level 3 symptoms may be specific to particular pathophysiologies (and thus etiologies), suggesting that they may be informative for attempts at subcategorization. Finally, **Figure 1, panel F** depicts "overlapping pathophysiologies. This is the most complex possibility

presented, and would characterize a scenario in which distinct etiologies gave rise to partially overlapping pathophysiologies, each combination of which could give rise to distinct behavioral symptomatology. Although the model that will ultimately be proposed in this paper is somewhat more complex than the overarching framework provided by Tsuang et al, it nonetheless serves as a good starting point for thinking about how to structure the relations between various aspects of schizophrenia phenomenology. Further consideration of the general features and aspects of Tsuang et al's approach is thus warranted.

Although somewhat minimal, in that it precludes complex factor interactions, the proposals outlined by Tsuang et al. provide a basic framework for considering and comparing potential etiological scenarios for schizophrenia. Perhaps first and foremost, there is an empirical aspect to what they discuss--this isn't merely a conceptual exercise. Indeed, the later portion of their paper is dedicated to a discussion of how to implement a "maxcov-hitmax" taxonomic search algorithm [5–7] in order to adjudicate between the the various taxonomic architectures they outline. Inherent in this approach is the acknowledgement that, in order to develop a meaningful understanding of schizophrenia, it isn't sufficient to catalogue predictors and/or symptom clusters--it is also necessary to unlock the associations between these various aspects of the disorder. Thus, the overarching goal isn't to find a conceptual structure that is easy to comprehend, but one that accurately captures the true structure of the world (i.e. "natural kinds" [8]; see also "*A taxonomy of white matter architecture*"). This is evident in their closing remarks, where they note the "seductive" appeal of a MFP model which appears to accommodate the many diverse lines of evidence and manifestations of schizophrenia. They caution against "vague notions of multicausality" and "omnicausality" (wherein every factor is somehow, nonspecifically relevant to the outcome) which are not amenable empirical verification. The general framework they present, along with the specific scenarios, are structurally designed to avoid cases of overdetermination (i.e. cases where multiple disjunct sets of causes are deemed to have been sufficient to cause a particular event). Finally, its also

worth noting that although this framework was presented within the context of adjudicating between multiple genetic factors, it can also be expanded to accommodate non-genetic etiological factors as well. A more recent review by Kenneth S Kendler reflects on what has been obtained by genetic-based studies across this period and, importantly for our purposes, considers the potential ways in which our understanding of schizophrenia may evolve in the near future.

Predicting the character and extent of scientific progress is a tricky proposition. Paradigm shifts are abound, and what is today's dogma may well be tomorrow's pseudo-science. However, as we have seen from Tsuang et al.'s work [2], there is value in considering the range of general forms that the "truth" may take in neuropsychology. In a 2013 review article, Kenneth Kendler considers the scientific fruits obtained from past studies of the heritability of psychiatric disorders (via both traditional family studies and more modern genetics-based methods), and what the future may hold for these investigative endeavors [9]. Just as with Tsuang et al., throughout the discussion there is the central recognition that there is a need to engage in concerted prospection as we study the brain and the disorders which may manifest in it. Also, like Tsuang et al., Kendler initially focuses on the interrelation between genes and psychological disorders before moving on to a broader consideration of progress in the study of psychological disorders. Although the article's conceptual analysis is not specific to schizophrenia, we will see that many of the the issues that it discusses are essential to the forming proposed model of schizophrenia etiology.

Given that Kendler's retrospective/prospective is situated within psychiatric genetics, the discussion understandably begins with a consideration of "family, twin, and adoption studies" (FTA studies), the historical bedrock of heritability studies in psychology. FTA studies' contributions and limitations are noted, with the observation that even if traditional FTA studies have not implicated specific mechanistic pathways (and cannot do so), they have nonetheless been of great use in definitively establishing a framework for how to approach studying mental

illness. Although the discussion of advances in genetic psychology is informative, it is the discussion of FTA studies' third weakness that will be seen to be of particular insightfulness, both within the context of the paper and with respect to the later discussion in this paper. Here, using the hypothetical example of a heritable construct "LLR" (left handedness, a long nose, and red hair) Kandler notes that although this construct will exhibit heritability it doesn't actually correspond to a "coherent category" and will thus have "no comprehensible unifying underlying biology". Thus, heritability is no guarantee that the phenomenon being studied will admit of some sensible structure at lower levels of analysis [4]. Although the phrase "coherent category" isn't explicitly cashed out in these terms, the essence of what is being appealed to here is the notion of a natural kind [8]--a coherent, observer independent category which reflects the actual structure of the world. Major issues from the philosophy of science again rear their head as Kandler moves into his consideration of potential patterns of findings in future genome wide association studies (GWAS).

The conceptual thrust of Kandler's discussion is centered around the interplay of two main factors that are expected to influence the results seen from future GWAS for mental disorders: the etiological heterogeneity of the disorder and the "biological level" which it arises at. There are two major observations to be made about this specification. The first is that the "etiological heterogeneity" of a disorder is necessarily predicated upon the coherence of that disorder as a construct--that is, as a natural kind. An "arbitrary concatenation of etiologically distinct symptoms", as Kandler puts it, like LLR will not be found to have a coherent structure in the etiological processes which give rise to it. Conversely, a mental disorder construct which accurately reflects a natural kind will almost certainly be found to have appropriately structured etiological underpinnings simply in virtue of the definition of what a natural kind is. Whether or not we can parse that structure is a different matter, though. The second observation corresponds to the issue of disorders manifesting at particular "biological levels". Here, Kandler is speaking to the "level of analysis" [4,10] that the etiology or disorder is considered at.

Although this topic will be discussed more later, it is important to note here that there is an implicit assumption that the processes which give rise to a disorder all occur at the same "level". However, there is no reason to believe that all processes which foster a disorder "act" or "manifest" at the same level, irrespective of whether they are necessary or sufficient. Indeed, Kendler provides a disclaimer to this effect, citing his focus on genes and biology, but the point nonetheless warrants being made explicitly here. Having established these two issues as the primary factors, Kendler then moves on to setting up a minimalistic spectra of scenarios that, may characterize future outcomes in GWAS.

Like Tsuang et al., key to Kendler's analysis is the establishment of a conceptual framework. Here though, the concern is less about the models used to describe mental disorders, and more about the possible "ground truth" scenarios that characterize them. To this end he arranges his possible scenarios in accordance with the relative coherence of the genetic factors studied, with nonexistent coherence at one end (scenario 1) and maximal coherence at the other (scenario 4). Although it risks belaboring the point, its worth considering how Kendler is cashing out this notion of coherence, which is being used to arrange this spectra. He states "...by coherence, I mean the genes whose altered expression or structure is indexed by the detected common or rare genetic variants or CNVs **tell a sensible biological story**" (emphasis added). Here again we see issues of natural kinds and cognitive utility arise. There seems to be the assumption that natural kinds are inherently "sensible" and that they would straightforwardly factor into a "biological story" (i.e. an explanation). This may or may not be a valid assumption, and there may ultimately be natural kinds which are baffling to us. Regardless, insofar as their scientific tractability is concerned, the "book-ends" of the senario spectra serve as worst and best case outcomes, respectively. That is, scenario 4 would be manifest if all of the identified genetic factors corresponded to a single biological pathway, as would be the case with a Mendelian disorder. Alternatively, scenario 1 would be manifest if there was minimal discernable association between identified genetic factors (a "mess", as

Kendler puts it). Given our contemporary understanding of many mental disorders, these cases are highly unlikely; there appears to be at least some structure in the genetic factors associated with many disorders, but in the vast majority of cases they do not coalesce into a single coherent etiology (for any single disorder). As such, the most plausible outcomes are somewhere in between and are likely better captured by scenarios 2 or 3.

Kendler saves what he takes to be the most plausible scenarios for last. Although they are not diametrically opposed with one another, they nonetheless represent distinct outcomes. Senario 2 corresponds to the case(s) in which genes implicated by GWAS would be found to form small interrelated custers, but would generally fail to indicate the existence of major pathways. Two examples of how this state of affairs could arise are given. The first would be a case similar to "LLR" syndrome, in which an arbitrarily designated construct fails to exhibit interrelations between sub-components because there is no actual underlying biological relation between those features. That we can force the subcomponents of something like "LLR" (left handedness, a long nose, and red hair) under the same categorical heading does nothing to guarantee that nature is, in fact, arranged in that fashion. The second example is presented as the hypothetical heritable trait "liking roller coasters". This trait could itself be sub-composed of several sub-traits ("risk for nausea, hedonic effects of rapid acceleration changes and thrill-seeking") which would, on some (likely lower) level be influenced by genetic factors. Though there may well be links between the factors underlying these sub-traits (and thus "liking roller coasters"), because the overarching category is couched in terms of decidedly unnatural construct these weakly linked genetic factors are unlikely to arrange themselves in a more sensible superstructure. It is here noted that both of the examples provided stem from issues related to construct specification, again suggesting that correspondence to "natural" categories is of extreme importance. The last scenario is somewhat similar, but slightly more optimistic.

Finally, scenario 3 corresponds to situations in which moderate coherence is found. In such cases although no single pathway will be revealed, several parsable subclusters may be

found which would contribute to disorder manifestation. It is postulated that these cases may arise in the event of “classical biochemical genetic heterogeneity” or if the disorder arises at some higher level of nervous system organization. For genetic heterogeneity, Kendler speculates that the independent pathways could, in fact, also be leading to subtly different manifestations within the same clinical diagnosis, but may remain undetected until future techniques are applied. This difficulty could be due to cross-level noise, pleiotropy, or other complex interactions. The second proposed possibility, interaction at higher levels, could remain hidden due to individual variation associated with development and environmental exposures. Ultimately, Kendler suggests that the truth is likely between scenarios 2 and 3. The proposal of this paper (presented next) is decidedly closer to senario 3 and predicts an appreciable level of coherence within the etiological evolution of the disorder.

A proposed etiological model of schizophrenia

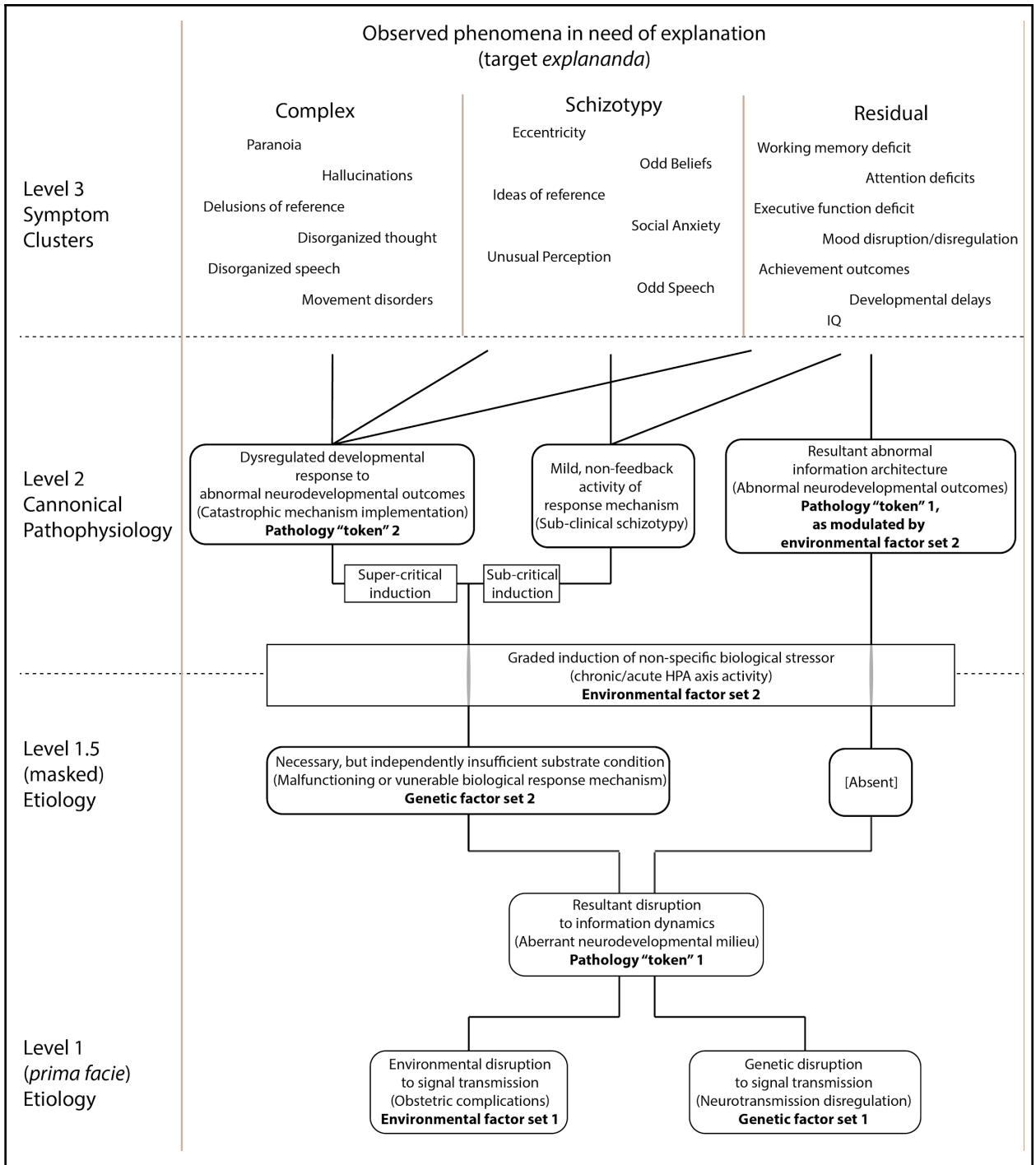

Figure 2: Proposed etiological model for schizophrenia. A general framework for schizophrenia etiology based off of the format used by Tsuang et al., 1990 [2]. 3 broad levels of causal activity are demarcated in the left hand column, with the first level being subdivided to illustrate a low-level interaction amongst etiological factors. Etiological factor sets are labeled in bold in accordance with their source (genetic or environmental). Likewise, outcome pathologies (clinically characterizable physiological disorder states) are labeled in bold as "tokens". Interconnecting lines represent the causal progression of mechanisms as processes move from lower to higher-order [4].

Figure 2 presents the proposed etiological model for this paper. This model is not taken to be entirely novel. Many (if not all, given that this is a review paper with no original empirical work) processes or features represented in the model have been discussed by other researchers. Instead, value of this model is taken to be associated with three characteristics: (1) the linking of semi-specific processes--all the way from fetal development on through to initial onset of schizophrenia, (2) the specification of multiple etiological processes which may be independently sufficient to give rise to disorder precursor states, and (3) the framing of this model relative to the work of Tsuang et al. and Kendler. Subsequently, the scenario(s) the model represents will be briefly outlined. After that, the conceptual relevance of topics and frameworks presented by Tsuang et al. [2] and Kendler [9] will be discussed. Following that discussion, research supporting specific components this model will be reviewed in some detail. Finally, falsifiable/empirically testable aspects of the model will be discussed. As such we proceed to the model description.

Model specification

The model presented in **Figure 2** is divided into 3 major levels which correspond to the general levels of causation claimed to be at work in schizophrenia as presented by Tsuang et al. [2]. Notably though, level 1 (Etiology) features a subdivision into *prima facie* and masked etiological factors. This is due to the hypothesized existence an intermediary pathology state, **Pathology "token" 1**: Aberrant neurodevelopmental milieu, which can be reached via any one of many etiological precursor states. These etiological precursor states are divided into two broad categories, one corresponding to environmentally mediated insults and labeled as **Environmental factor set 1**: obstetric complications, while the other corresponds to genotype variants, **Genetic factor set 1**: Neurotransmission dysregulation. It is acknowledged that it is unclear whether or not this is truly a clean distinction or if this division fully encompases the entire range of etiological factors for schizophrenia, but it is found to be largely reflective of the

discussion of etiological factors in the field. Individual members of these categories correspond to individually sufficient or a collection of *inus* ("insufficient but necessary part of a condition that is itself unnecessary but sufficient for the result"[11], see also [9] box 1) etiological factor(s). In this way, any appropriate factor is taken to be (in conjunction with otherwise "normal" neural system activity) sufficient to give rise to the some degree of manifestation of the aberrant neurodevelopmental milieu of **Pathology "token" 1**. Furthermore, it is presumed that in cases of co-occurrence the individual severities of environmental factors from set 1 would lead to concomitant increases in the severity of **Pathology "token" 1**, and would accumulate additively. Likewise, the effect of the presence of multiple genetic factors is presumed to accumulate (more or less) additively with respect to the severity of **Pathology "token" 1**, and could also co-occur and interact additively with environmental factors from set 1 (or vice-versa). Assuming that **Pathology "token" 1** has manifested, the etiology of schizophrenia is next impacted by the presence of a second set of genetic factors, **Genetic factor set 2:** Malfunctioning or vulnerable biological response mechanism.

The proposed model bifurcates after the establishment of **Pathology "token" 1.** In the most straightforward case genetic factors from **Genetic factor set 2** are altogether absent. However, this does not mean such an individual would present as neurotypical. Instead, the neurodevelopmental aberrations from **Pathology "token" 1** would remain in place and give rise to disordered behavioral outcomes (enumerated under the "Residual" heading of Level 3 Symptom Clusters). The manifestation of these non-schizotypal outcomes are presumed to be modulated (i.e. exacerbated) by **Environmental factor set 2:** chronic/acute HPA axis activity, as is the case with mental disorders in general [12,13]. In the event that factors from **Genetic factor set 2** are present a potentially complex interaction takes place. To begin, there is the assumption that the pathological state represented by **Pathology "token" 1** is manifest. Interestingly, although not depicted, it is certainly possible that factors from **Genetic factor set 2** could be present *without* **Pathology "token" 1** being in place--this possibility will be discussed

briefly later in the paper. Continuing, **Pathology "token" 1** serves as the substrate for factors from **Genetic factor set 2** to act upon. Specifically, it is hypothesized that the severity of **Pathology "token" 1** is correlated with the degree to which mechanisms corresponding to the activity of members of **Genetic factor set 2** (thus taken to be compensatory for or responsive to **Pathology "token" 1)** are recruited. That is, as the neurological disruptions from **Pathology "token" 1** become more severe, there will be an increased need to engage the biological pathways associated with members of **Genetic factor set 2**. Here though, there is mediation by **Environmental factor set 2:** chronic/acute HPA axis activity, which is hypothesized to increase the probability of critical, pathogenic engagement of **Genetic factor set 2** processes, leading to a catastrophic feedback-loop of brain-structure disruption. Indeed, it is the interaction of **Genetic factor set 2** and **Environmental factor set 2** that is taken to give rise to the the stereotypical etiological character of schizophrenia.

Prior to the induction of **Genetic factor set 2** the neurological structure and observable behavior of individuals with and without these factors is taken to be largely similar and primarily a reflection of **Pathology "token" 1.** Admittedly, there may be pre-catastrophic induction (i.e. prior to the first identified episode of psychosis) effects of **Genetic factor set 2**, however this model currently does not furnish any specific hypotheses regarding what those effects would be. Once the processes associated with **Genetic factor set 2** are recruited though, the outcome is primarily determined by two factors: the (additive) severity of the genetic disruption(s) from **Genetic factor set 2** and the mediating effect of **Environmental factor set 2.** The activation of the hypothalamic pituitary adrenal (HPA) is taken to act not on its own, but rather through a disrupting effect of processes associated with **Genetic factor set 2.** In this way, more moderate disruptions of **Genetic factor set 2** processes can nonetheless lead to **Pathology "token" 2**: Catastrophic mechanism implementation if an adequate stress response is manifest (either acutely or chronically). Likewise, sufficiently severe disruptions of **Genetic factor set 2** processes can lead to **Pathology "token" 2** even in the absence of appreciable HPA axis

activation. With the underlying neuropathology in place, the behaviors associated with canonical schizophrenia, general schizotypy, and general developmental disorders become manifest.

Ultimately, results of canonical pathophysiologies from level 2 are observed clinically in the presentation of symptom clusters from level 3. These symptom clusters are, under this model, arranged into three overarching categories: complex, schizotypy and residual. Respectively, these correspond to the symptoms canonically associated with clinically diagnosed manifestations of schizophrenia, sub-clinical or familial/relative manifestations of schizotypal behaviors, and deficits to general cognitive processes or capacities. Naturally, symptoms from the complex category are expected to be present only in cases where **Pathology "token" 2** is also present. Depending on whether or not complex symptoms are interpreted as being more severe manifestations of schizotypy, schizotypal behaviors may be present as well. Along with these, the initial neurostructural disruptions associated with **Pathology "token" 1** remain in place (having not been ameliorated during the intervening period) and give rise to the various general cognitive deficits observed in schizophrenia (and other psychological disorders, for that matter). In individuals characterized by sub-critical induction of **Genetic factor set 2**, various schizotypal behaviors may be observed along with whatever neurological deficits arise from **Pathology "token" 1**. Finally, as described earlier, individuals with no pathology associated with **Genetic factor set 2** are expected to exhibit general cognitive deficits as enumerated in the "Residual" category. These outcomes, and the previously described etiological pathways that give rise to them, constitute the model proposed here. However, there remains the question of how Tsuang et al. [2] and Kendler's [9] work have influenced the construction of this model.

Model framework

Although undeniably distinct from the conceptual analysis and frameworks provided by Tsuang et al. and Kendler, the current model represents an extension of their work. Perhaps the

most obvious similarity is the division of causal priority into categories mirroring Tsuang et al.'s three levels (Etiological, Pathophysiological, and Symptoms). The model proposed above modifies this slightly by dividing the etiological level into *prima facie* and masked components. As discussed earlier, this distinction is made in order to reflect the myriad base level etiological factors which have been identified. In turn, one or more these factors (**Genetic factor set 1** and **Environmental factor set 1**) give rise to the intermediary **Pathology "token" 1**, which serves as the proximal and necessary substrate for **Genetic factor set 2**. Tsuang et al.'s original model was unable to accommodate an early instance of multiple individually sufficient causes occuring within the level of base etiological factors. Likewise, it was unable to accommodate the moderating effect of **Environmental factor set 2** and the subsequent threshold induction of **Genetic factor set 2** to give rise to **Pathology "token" 1** (or not, as the case may be). The modifications to the general framework described above permit these complex interactions, but perhaps come at the cost of elegance or simplicity. Overall this model is taken to most closely resemble the last scenario they present (**Figure 1, panel F**) in that there are multiple, partially overlapping pathophysiologies giving rise to distinct behavioral complexes. Moreover, given the potential heterogeneity of how **Genetic factor set 1**, **Environmental factor set 1**, and **Genetic factor set 2** could manifest, along with the graded manifestations of **Pathology "token" 1**, **Pathology "token" 2**, and **Environmental factor set 2**, the diversity of behavioral manifestations (i.e. "sub-types") may also be accounted for by this model as well. Additional influences from Kendler warrant consideration as well.

Although the proposed model extends beyond the level of genes and gene interactions, Kendler's analysis has nonetheless exerted an influence on its formation. This is largely due to his consideration of topics traditionally considered to be the purview of the philosophy of science. Chief among these topics is the repeated emphasis--both implicit and explicit--on the importance of the constructs and categories used in the formation of models or explanations. This can be seen in his approbation of 'bottom–up' approaches to etiology. Such approaches

are definitionally agnostic about the *a priori* structure of higher order constructs, though it is this same agnosticism which gives rise to the uncertain "sensibility" of future GWAS results. The emphasis can also be noted in his consideration of scenario 2 where "LLR" syndrome and "liking of roller coasters" are found to be ill suited for study using biological approaches. Indeed, the model proposed in this paper steadfastly eschrews appeals to constructs which might fail to be reduced to biological phenomena. These biological processes needn't all occur at the same level of analysis though, which is reflected in his concern about the appropriateness of exclusively trying to understand mental disorders at the level of genes. This paper's model acknowledges an etiological role for genes, but argues that their effect is achieved via the manifestation of a higher order state (namely **Pathology "token" 1**), and which can be achieved via other etiological processes (i.e. items from **Environmental factor set 1**). Finally, Kendler's sidebar regarding Fodor's notion of multiple realizability [9,14,15] and Mackie's notion of inus causes [9,11] paves the way for hypothesizing one and the same pathophysiological state as being reachable from multiple, distinct etiological starting points. Thus we can see the conceptual influence of Kendler's review. Having outlined the processes and interactions entailed by the model, as well as the influences which gave rise to the model's formatting and structure, there remains the task of actually justifying the claims made by the model.

Evidence for the model

The processes and structure of the model are not presumed to stand on their own without any additional explication. As such, evidence for important aspects of the model will be presented subsequently. This explanation will begin with the initial etiological processes, and then move through important components of the model in sequence.

Foundational Etiologies - Environmental factors

One of the most central features of the model are the two categories associated with the base etiological processes purported to give rise to **Pathology "token" 1**. With respect to **Environmental factor set 1**, it has long been noted that complications during pregnancy are

associated with increased risk of developing schizophrenia. One of the most prominent examples of this are findings implicating prenatal exposure to influenza [16–18]. In the litterature this has occasionally manifested as an association between season of birth and incidence rates of schizophrenia [19,20]. Obviously, a season cannot, in and of itself, exert a mechanistic influence on the developing brain, however further research on this subject has specifically linked these effects with influenza exposure [16–18,20]. Furthermore, the developmental window of vulnerability has been narrowed down to either the first [16] or second [17–19] trimester (with several noting a particularly strong association with exposure during the 6th month of gestation). Influenza is not the only infectious agent to have been associated with schizophrenia though.

Beyond influenza, there have been strong and consistent findings that maternal/prenatal exposure to *Toxoplasma gondii* is associated with increased risk of developing schizophrenia [21,22]. Indeed, exposure to this parasite has been reported as the most significant single risk factor for development of schizophrenia ("Although the OR of 2.73 is modest, it exceeds that for genetic or other environmental factors identified to date" [21]). Subsequent research has found more significant associations and expanded the link between infectious agents and schizophrenia to include Human Herpesvirus 2, Endogenous Retrovirus, Chlamydophila pneumoniae and others [23]. The heterogeneity of these infectious agents suggests that downstream effects may be the true cause of the observed association--a theme that will observed multiple times as etiological factors are considered. In light of these findings, it appears that the immune system may play a role in the development of schizophrenia.

Given that prenatal exposure to any one of a number of biological pathogens has been associated with later development of schizophrenia, it may be the case that a malfunctioning of the immune system may be the mechanistic pathway for realizing these observed associations. Conceivably, it could even be the result of an interaction between normal functioning immune systems, pathogens, and other processes. The immune system has been theorized by many to

play a major etiological role in schizophrenia [24–26]. It is instantiated by an extraordinarily complex set of biological processes, and studying their role in schizophrenia is made even more challenging due to the apparent need contextualize their effects within prenatal development. Nonetheless, several major insights have been made. For example, previous research has implicated a role for glial cells [26–28], finding abnormalities in all subtypes. Neuroinflammation, a natural reaction to infections pathogens by microglia, has also been noted to be associated with schizophrenia [29–31], although the time course for this, and thus mechanistic implications, are less well understood. Inflammation has also been associated with ischemic insult and hypoxia [32,33], processes which have themselves been associated schizophrenia. It has even been found that head trauma in childhood is associated with the development of schizophrenia [34]. Once more, this suggests that systems beyond inflammation and immune system response are involved.

In addition to well established findings relating to the immune system and inflammation, there is an extensive body of literature linking obstetric complications to schizophrenia as well [18,19,35–38]. Interestingly, the range of prenatal developmental insults is quite broad and includes pre-eclampsia, long labor, low birthweight, hypoxia, maternal diabetes, rhesus incompatibility, malnutrition, and many other issues. These risk-factors are manifestly heterogeneous, admitting of no obvious underlying pathology which might link them. As such, whatever underpins these risk-factors' relation to schizophrenia is likely downstream, though it is also worth noting that the damage caused by these issues is also heterogeneous. This diversity of contributors is interesting as it not only has temporal implications (in that something occuring *after* these insults is probably fostering schizophrenia), but also implications for the level at which the shared etiological factor is occuring. Because the structural or systemic damage caused by obstetric complications is so diverse it is unlikely that the specifics of the damage (i.e. location, contributing mechanism, etc) are particularly pertinent schizophrenia. Rather, it is more likely that a shared (higher order) *consequence* of the damage is the relevant factor.

Admittedly, there are other potential explanations. For example, previous research has indicated that there may be genetic factors that are linked with both obstetric complications and schizophrenia [36]. However, the previous inferences regarding unique, non-inherited etiological contributions made by obstetric complications are bolstered by FTA studies in discordant monozygotic twins [19,35,36,38]. That being said, it has been known for some time that heritable and genetic factors play a major role in schizophrenia.

Foundational Etiologies - Genetic factors

One of the most long standing observations in the study of schizophrenia is that there is a significantly heritable component to the disorder [39,40]. Indeed, as noted by Kendler, FTA studies have indicated a major role for heritable factors for many mental disorders [9,40,41]. Studies of monozygotic twins (ostensibly genetically identical individuals that shared the same natal environment) consistently find a concordance rate (probability that if one twin develops the disorder the other will as well) which approaches 50% [40]. As many have noted, if schizophrenia was ground solely in genetic factors we would expect this to be 100%, as would be the case in a mendelian disorder, indicating an influence of environmental factors as well. Regardless, even in the absence of clinically diagnosed manifestation of the disorder, traits associated with schizotypy are consistently observed in close relatives [42–45]. This has led to efforts to identify specific genetic risk factors, which have returned a wide array of candidate genes, though replicability is often a concern [9,40,41]. Of central importance to this paper's proposal is the claim that there are two dimensions of genetic risk factors, one of which is active early in brain development (**Genetic factor set 1**), the other of which is active later (**Genetic factor set 2**). The former of these is discussed next, while the latter will be discussed later.

In keeping with findings that prenatal neurodevelopmental abnormalities--however manifested--are associated with schizophrenia, the proposed class of genetic risk factors corresponding to **Genetic factor set 1** are those that ultimately result in an aberrant neuro-informational regime, as manifested in **Pathology "token" 1**. Thus, these would be

genes associated with either (1) neurodevelopment or (2) neurotransmitter activity and active prior to the adolescent pruning event. Downstream of either of these processes is the establishment of "normal" neural signaling motifs (which will be discussed later relative to **Pathology "token" 1** and **Genetic factor set 2**). Disruption of processes involved with initial brain structuring would result in abnormal brain architecture which could be manifested through abnormal variations of any number of genes. For example, 22q11 deletion has been associated with structural abnormalities of various body parts including the head, indicating altered brain structure [19]. Other candidates for genes associated with early neurodevelopmental disruption would be those that result in abnormal axonal growth or initial myelination. Early neurotransmitter dysregulation could be associated with specific genes (e.g. COMT, GRM3, RGS4, PPP1R1B, and AKT-1[46]) or systems more generally (i.e. dopamine [47,48]). Interestingly, an implication of the proposed model is that these genetic factors are almost certainly *not* specific to schizophrenia--it would actually be evidence against the model if they were. This is in keeping findings that many genetic risk factors associated with schizophrenia are also associated with other disorders like autism, bipolar disorder, and depression [27,49–53]. Overall, what unifies the genetic factors in this category is that they (1) are necessarily in place *before* the major neural pruning event typically associated with adolescence[54–62] and (2) necessarily result in a disruption of standard neuro-informational systems (i.e. via abnormal structure or signaling) [63]. The combination of these two states of affairs (which are also observed in **Environmental factor set 1**) are what eventually instantiate **Pathology "token" 1**.

<u>Shared etiological midpoint: abnormal information transmission</u>

The previously discussed initial etiological factors (**Environmental factor set 1 and Genetic factor set 1**) eventually give rise to a state of affairs in which there is are chronically (as opposed to transiently) abnormal patterns of information transfer, which is here referred to as **Pathology "token" 1**. The use of the term "token" is to emphasize that this state can be

achieved via a diverse range of precursor states (as seen above). However, to reiterate points made above, there are three characteristics that these initial etiological factors (i.e. Level 1 in **Figure 2**) must share:

1. They must be in place or otherwise "active" *before* the onset of the neural pruning cascades typically associated with adolescence[54–62].
2. They must result in a disruption of the standard activity patterns of neuro-informational systems[64–67].
3. They are *not* specific to schizophrenia[68–70]

In a certain sense, the state specification of **Pathology "token" 1** is admittedly vague ("disrupted activity patterns of neuro-informational systems"). However, this is the state that all established, pre-onset etiological factors result in--it is the single point of overlap and, as we shall see, the substrate for the true onset of the disorder. Explicitly: obstetric complications directly damage the brain's architecture and permanently disrupt neural development; inflammation and immune responses disrupt the standard activities of glial cells and impact normal myelination processes; disruption of myelination processes themselves (either via metabolic or genetic pathways) alter rates of information transfer (see "Computational Models of White Matter Structure & Related Biological Characteristics"); and finally, genetic abnormalities can alter a range of processes including neurodevelopment, immune responses, and neurotransmitter systems. Given the practical challenges with directly measuring "disrupted activity patterns of neuro-informational systems", assessing whether or not this state is in effect may seem daunting. Fortunately for investigators, there is a single feature which has the effect of all of these phenomena etched onto it: the white matter of the brain.

One of the central claims of this paper is that **Pathology "token" 1** can be observed in the white matter of the brain, either via *post mortem* dissection or *in vivo* structural neuroimaging. Indeed, white matter has increasingly become a focus of study in schizophrenia [68,71–77], with some even proposing white matter as being the locus of disruption [60,78]. In some cases it is easy to see how a given etiological process would mechanistically come to

involve the white matter and thus and be subsequently observed. In cases of obstetric complications there are well established findings of disruptions of brain structure (white and grey matter) and increases in ventricle volume [35,38], which is also a general feature of schizophrenia even when obstetric complications are not explicitly indicated [79,80]. Likewise, neuroinflammation has been linked to oligodendrocyte disruption [28,29,77,81] and demyelination[82–84] and can be measured in studies of schizophrenia using *in vivo* neuroimaging techniques [30,31]. Direct disruption of white matter structure and myelination (irrespective of etiology) can be measured using diffusion imaging and tractographic methods[74–76,85–87]. However, it is somewhat less obvious how disruptions to synaptic transmission and neurotransmitter systems might be manifested in the white matter. As we shall see there is good reason to believe that schizophrenia etiologies associated with these factors would be observable there as well.

In paper 2 of this series, “Computational Models of White Matter Structure & Related Biological Characteristics”, the relationship between axonal properties and information transfer rates was discussed extensively. There it was shown that properties like axon diameter and myelination determine informational properties like conduction delay and maximum firing rate [88]. Interestingly, this is a bidirectional relationship--increased information transfer drives processes which promote changes in the aforementioned structural properties. It has been shown that neural activity can drive myelination [89–92], and that axon diameter (a parameter in computations of neuron information transfer rates) is associated with synaptic bouton size [93]. This, in turn would be associated with strength or frequency of activation in postsynaptic neurons as greater quantities would neurotransmitters would be dumped into the synapse[94]. Given that presynaptic neurons are shaped by the activity of their postsynaptic targets [95–97], serve to reinforce larger or more active neurons. Thus there is a reciprocal relationship between axon properties (i.e. axon diameter and myelination) and information transfer rates. Explicitly, increased axon diameter and myelination decreases conduction speed and increases

maximum firing rate (thus increasing information transfer rates), while alteration information transfer rates promotes modification of these structural properties. If neurotransmitter dysregulation would ultimately impact myelination, how would this impact a model of schizophrenia?

Although many studies have found an association between schizophrenia and neurotransmitter systems [47,48,98–100], fewer have extrapolated these findings to consider the link between neurotransmitter activity and white matter. Mirnics et al. [63] present a model of schizophrenia which holds that schizophrenia arises from synaptic dysregulation which is then complicated by the adolescent pruning cascade. Given that, as we have seen, essentially all etiological pathways would result in altered synaptic dynamics this is true in some sense. However, it is here suggested that this is too vague of a claim in that *any* neurological disorder will result in a disruption of synaptic dynamics, simply in virtue of it being a neurological disorder. Within the context of Kendler[9], this would be the wrong level of analysis[4] to try and understand schizophrenia at. Moreover, a closer reading of Mirnics et al.'s model reveals that it is necessarily predicated on the presence of genetic factors which result "in altered function of proteins that control the 'mechanics' of synaptic transmission." This is despite there being a whole class of non-genetic etiological routes which can lead to disrupted information dynamics in the brain, once again emphasizing that the synapse is the wrong level to try and understand schizophrenia at. The overarching point here is that *aberrant activity leads to aberrant structure*. It is this aberrant structure--which *is not* unique to individuals with schizophrenia--that is acted upon by a factor that *is* uniquely associated with schizophrenia and schizotypy, **Genetic factor set 2**.

Schizophrenia as a neurodevelopmental process

Although indicators of schizophrenia risk can be observed and measured in children, they are not taken to be part of the "true" schizophrenia complex under this model. This is in virtue of their being either contributors to or consequences of **Pathology "token" 1**, which is a

different pathological process. Such indicators include developmental delays, motor abnormalities, social abnormalities, and intellectual performance/achievement [19,101]--all of which are noted to be present in other disorders as well [62,69]. This is also reflected in the shared genetic risk factors between schizophrenia and other disorders [102]. Instead, the hallmark of schizophrenia (temporally and behaviorally) is the presentation of abnormal behavior and cognition patterns associated with schizotypy [45,103,104] in mid to late adolescence [54,55]. Given the temporal character of this onset, as well as the differential timings of presentation and predicted course of disorder in males and females (thus reinforcing the importance of timing due to differences in onset of puberty) [105,106], this suggests that a biological process that is uniquely engaged during this period may be the culprit. Indeed, this is the central tenet of the "Feinberg hypothesis" [55,61] which posits that a malfunctioning of the normal pruning that occurs during adolescence [54–62] leads to a pervasively disrupted neuro-archetecture. This has led many to propose a recategorization of schizophrenia as a neurodevelopmental disorder[60,69,101,107], a move which is entirely consistent with (if not required by) the model of this paper. What is the nature of this pruning event though, and how does it go awry in schizophrenia?

Although we may think of brain development being completed in infancy or early childhood, it actually continues for quite some time. Indeed, it has been shown that the structure of the brain continues to develop into the third decade of life[108,109]. This process exhibits a stereotyped progression, though there can be slight individual differences in rates of progress, especially in cases of disease or disorder. Additionally, there is a punctuated period of pruning which occurs during this process, typically during early to mid adolescence [54–62]. Given that synapse and axon modeling would be done in response to activity motifs [97,110,111], the aberrant information dynamics of **Pathology "token" 1** would serve as the substrate for this process. However, in the case of schizophrenia this process goes awry, leading to severe degradation of neural architecture [55,59,61,112]. This model holds that this

is the result of genetic abnormalities which cause this process to run out of control. Importantly this is a separate dimension of genetic risk factors from **Genetic factor set 1**, and would likely include factors like NRG1, MIR 137, C4, and OLIG1[40,46,113]. These genes are associated with neurodevelopmental processes, but would only be included in **Genetic factor set 2** if they are particularly involved with the pruning process. With respect to shared genetic risk with other disorders, it is expected that these genetic risk factors are unique to schizophrenia.

Consequences of the model

There are a number of consequences of the model. First and foremost are the empirical aspects of the proposal itself. The model presumes that a number of processes exist and interact with one another in the specified fashion. If these processes were found to be irrelevant, non-existant or sequenced in a different fashion this would undermine if not falsify the model. As such there are distinct aspects of the model that can be subjected to experimentation, including: the existence of a non-specific intermediate neurological disruption (**Pathology Token 1**); the presence of two distinct dimensions of genetic risk factors (**Genetic factor set 1** and **Genetic factor set 2**) and; the influence of stress on the pruning mechanism. The ability to falsify this model is taken to be a positive aspect of this proposal. Beyond the falsifiability of this model, there are other implications as well.

If the proposed model is accurate then a number of consequences may follow. Perhaps most troublingly, this model suggests that there is very little that can be done to remediate the disruption caused by the abnormal pruning event and thus little that can be done to restore an individual to normal functioning after adolescence. Instead, this model suggests that prevention or attempted remediation of **Pathology Token 1** would be the most effective in reducing rates of schizophrenia. As such, implementing better prenatal care policies or prenatal medical interventions would likely result in an overall reduction in schizophrenia rates as the prevalence of **Environmental factor set 1** (and thus **Pathology Token 1**) would be decreased**.** As a specific example of an intervention in early childhood, one could consider supplementation of

omega 3, which has been associated with improved outcomes [114]. In accordance with the proposed model this would likely only be effective in individuals for whom **Pathology Token 1** was caused by some disruption of omega 3's disruption relative to myelination processes [115,116]. Furthermore, given **Pathology Token 1**'s hypothesized involvement with a myriad of psychological disorders these palliative effects would be observed in other disorders (and thus not specific to schizophrenia), which is consistent with empirical findings[116,117]. However, these results would *only* be expected in those for whom **Pathology Token 1** was mediated by omega 3 based effects. Such effects would not be expected for the entire population of those exhibiting **Pathology Token 1**. Additionally, based on this model, incidents of early onset schizophrenia [59,76,85,118] may be associated with premature or otherwise abnormal adrenarche [119].

Insofar as the study of schizophrenia is concerned, this model suggests that large data sets of adult schizophrenia patients will be largely informative in trying to understand schizophrenia. Given that this is a developmental process, pre-onset and post-onset datasets are more likely to of use (and moreso if within-subjects). Naturally, these would be difficult to obtain, but it may be necessary. Given how heterogenous **Pathology Token 1** could be, and how various forms of **Genetic factor set 2** may interact with this one would expect the neurological results to be incredibly heterogenous and difficult to tell a coherent story with. Indeed, if schizophrenia is a developmental process then it is the *difference* caused by **Genetic factor set 2** that is of interest rather than the specific form of **Pathology Token 2.** The path forward is thus challenging but not insurmountable.

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