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Commentary

Dissynchronization Syndromes in Animals and Man: What would Norman Geschwind say in the 21stcentury?

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Perhaps the most remarkable feature of the human brain is its ability to process an infinite number of unique "events" to produce an infinite number of possible unique behavioral outcomes, and do this almost instantly. No wiring diagram can account for the complexity, variety and especially the speed of these processes, nor of the capacity to learn and remember. The concept of neural networks arose to clarify the needed qualities, including parallel and distributed computation and plasticity, but there has not been a reasonable proposal for how these networks communicate, and how they communicate in a almost instantaneous fashion.

The discovery of neural networks is changing how we think about brain organization. Research revealing the location and function of networks has increased exponentially during the past 25 years. A PubMed search for neural, brain, or central nervous system networks found two articles in 1950, 140 in 1990 and 1,909 in 2015. Although we have not read all of these articles, none, to our knowledge addresses how these networks communicate.

In 2012, Sepulcre et al., [1] added another tool for defining neural networks and their connections. In an elegant study developed Stepwise Functional Connectivity Analysis (SFC) to infer directional connectivity in neural networks. Through this method they defined the step-wise transitions from primary sensory cortices to higher-order brain systems, thus to cortical hubs wherein it is proposed that perceptual integration occurs. This work builds on the many functional imaging, neurophysiological and anatomical studies done over the past decade or so.

Kenneth Heilman and his colleagues have studied the neglect syndrome for more than forty years. During those years they proposed a network underlying the neglect syndrome, both the attentional and intentional components [2,3]. In 1994 they also described neglect in non-human primates following lesions of both banks of the superior temporal sulcus, but not following lesions of the inferior parietal lobule. In that paper Watson et al., [2] proposed specific attentional and intentional networks that relied partly on the seminal study done by Jones and Powell [4]. Sepulcre et al., [1] paper also references the 1970 study by Jones and Powell [4] and comments on how their SFC and Jones and Powell's anatomical tracing studies arrived at similar conclusions. Fleichsig's [5] study of myelinization predicted the findings of Jones and Powell and Sepulcre et al. In his remarkable study studied the development of myelinization in humans. He described three chronological groups based on the age at which myelin was present: primordial zones, intermediary zones and terminal zones.

"I find it useful to denote the areas simply by numbers (1 to 36) corresponding to their respective places in order of development, and therefore wholly chronological. In order to present a comprehensive view, and having regard to differences of a general nature, I have classified them in the three following chronological groups: (1) regions of early development (primordial zones); (2) regions of intermediate development (intermediate zones); regions of late development (terminal zones)."

If one overlays the zones of Flechsig onto the technicolor voxels of Sepulcre the similarity between the three zones of Flechsig and the initial (unimodal), intermediate (multimodal) and terminal (cortical hubs) of Sepulcre et al., [1] is striking.

Even before Fleichsig, such luminaries as Karl Wernicke, Paul Broca, Hugo Liepman, Joseph Dejerine and others localized the higher cortical functions in "modules". Their remarkable conclusions, based on the careful study of patients, were based on these "modules" and their connections. This viewpoint was challenged during the first half of the 20th century by those who thought the brain functioned in a holistic fashion, rather than by modules and their connections. A chief proponent of this view, Karl Lashley, who studied behavior in lesioned rats, concluded that the brain worked by mass action and that all parts of the cortex were equipotential.

In 1965 Dr. Norman Geschwind published "Disconnexion Syndromes in Animals and Man" [6]. This was pivotal in furthering interest in the behavior of non-human primates and man. In his 1965 articles Geschwind discussed the findings of his predecessors, including the anatomical work of Flechsig. Geschwind's [7] articles renewed interest in the localization of higher cortical functions, both specific cortical areas and their connections, and returned thinking about higher cortical functions more to the concepts of the late 19th century. Dr. Geschwind emphasized association cortex, the phylogeny of the highest cortices in humans, the "association of association cortex", and how injury to association cortex or to the white matter tracts between association cortices could explain many disorders of higher cortical function. He might now be criticized for overly focusing on language and for trying to explain too many findings based on disconnection, criticisms Geschwind anticipated. Nevertheless, later studies have confirmed that the human brain functions via networks, rather than by the direct connections between isolated modules or between association corticies. We are certain that Geschwind would have quoted Jones and Powell if they had published before him and equally certain that the newer imaging and neurophysiological studies would have been of great interest to him; and for the most part, support his 1965 conclusions.

The newer approaches have been instrumental in developing a better understanding of these networks and their interconnections. Functional imaging, tractography, mathematically driven EEG studies, and magnetoencephalography have led to thousands of publications that largely agree that the brain has networks and that there are both anatomical and functional connections between and among networks. For example, a "Default Mode Network" (DMN), one of several resting state networks, has been extensively studied. In 2012

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Sepulcre, et al., [1] concluded that their "hubs" are much the same as the DMN. Resting networks are active when we are not attending to or interacting with objects in extrapersonal space. Both hypofunctioning and hyperfunctioning networks have been proposed to underlie many disorders, including depression, autism and schizophrenia.

The question arises as to the relationship of a metabolically active network to behavior, and whether it is the active network that is critical or the one less active. An important observation is that even though a network may be "inactive", it is never turned off. It seems apparent that all networks are active to lesser or greater degrees and remain primed to immediately guide many, if not all, human behaviors, other than reflex behaviors. The questions must be asked: How do the resting state networks, e.g. the DMN, and activation networks interface? How is attention directed to and allocated between intrapersonal activities and extrapersonal space? How does it happen instantaneously? Seemingly instantaneous changes in behavior or the online rapidity seen in a simple conversation can't be explained by the relatively slow conduction along white matter tracts and the millions or billions of synapses that would need recruitment.

Sepulcre et al., [1] imply that SFC explains "how" these interactions occur. But the further demonstration of connectivity doesn't answer how the interfaces occur, only more precisely where they might occur. "Connectome mappers" have replaced "diagram makers", but they have much in common in clarifying the "where", rather than the "how". We think neurophysiologists will discover how the brain utilizes its networks and their connections to allow the remarkable human cognitive capacity. Specifically, neurophysiologists will discover how oscillations occur and how they are synchronized. When that understanding is reached the universe of prevention and treatment will change dramatically. In the future it may be possible to map "normal" patterns of brain oscillations and their synchrony, and to study how these differ in disorders like autism, schizophrenia, addiction and other disorders. Understanding these oscillations and their

synchrony might also provide an entirely novel way of studying brain plasticity.

Stevenson [8] provided an insightful Journal Club review of the paper by Sepulcre et al., [1] in which he wrote, "Individual differences in how the flow of information is disrupted within the network may help explain the differences between the distinct endophenotypes seen in autism spectrum disorders". Perhaps understanding how the flow of information is disrupted can lead to treatment to correct the abnormal flow in autism and other disorders.

One of the problems with disconnection syndromes is the speed with which human behavior can change, e.g. from rest to focused attention, as if there are a multitude of "on-off" switches, that can't be easily explained by the speed of conduction in white matter pathways and the recruitment of millions or billions of synapses. On the other hand, a specific neuronal firing pattern can be altered in a "split-second" to change mice from depression resiliency to depression-like behavior. In humans during electrode placement for DBS, a striking tremor can disappear instantly with the correct placement of the electrode. Parkinson's patients who have been treated long-term for Parkinson's disease have "on-off" behavior, switching instantaneously from akinesia to uncontrolled movements. There are many such examples and such observations must lead to asking how the functional networks in the brain communicate, and do so with extraordinary speed?

In an email conversation Emmanuelle Tognoli [9] proposed several crucial possibilities. In response to whether oscillators at a distance from each other in the brain can synchronize he replied, "Theoretical evidence on coupled oscillators and empirical facts in the neuroscience unambiguously show that oscillators do "synchronize" at short and long distances. Your question about time factors has several meanings. A lot of the empirical work is about the process of being synchronized, not the fact of establishing synchronization. It is likely that oscillators maintain a level of coupling at all times through metastability, and that what an "event" does is to alter the parameters of this coupling." In response to the question, "Are the known anatomical tracts necessary but not sufficient for synchrony?" he replied, "It is possible to conceive of a system where the coupling would not be based on this wiring but that could still communicate information efficiently, and maybe in a functionally meaningful manner. There is also mounting evidence of the influence of extracellular waves. We are currently working on a hypothesis based on this form of coupling here." And finally, in response to my question asking about the speed of human behaviors, such as conversation, that can't be easily explained by the relatively slow transmission along white matter pathways, he replied, "If there is a superposition of two coupling systems (wires and extracellular waves for instance), those massive tracts would be very good instruments to carry an important concept from dynamical systems which is symmetry (symmetry is responsible for synchronization tendencies, symmetry breaking helps in segregation and complexity, both are important for the systems)."

There are earlier papers that comment on "reverberation" and "modulation". Konorski described the role of reverberation in learning [10] and Beurle [11] wrote about masses of cells regenerating pulses of communication. These studies preceded the modern techniques and technologies, but when reading them from this "look back" perspective, one wonders if scientists like Kornorsky and Beurle understood that there were different modes of neuronal communication than were previously or subsequently studied? It is likely not as important that the DMN is underactive in autism or overactive in schizophrenia, or that ECT down regulates the "hyperconnectiveness" of the left dorsal lateral prefrontal cortex from the limbic system, or whether DBS changes a network from being underactive or overactive, as much as it is to understand how and why a network might have become abnormally active, or is abnormally synchronizing with another network. If we can achieve a better understanding about dissynchronizations within and among networks then perhaps better therapies can be devised and better prevention can be realized.

By virtue of the tools at our disposal, from Meynert to Geschwind to modern technologies, the focus of study has been heavily on neurons and the anatomy of their white matter connections. Perhaps it is time to study in more depth what role white matter pathways actually play, other than being axons transmitting some form of information, and the role of astroglia in relation to neuronal assemblies. Is it possible that one or both of these is responsible for rapid enhancement of synchrony within and among networks? Unless these are considered, we are in danger of too great a focus on where various networks are located, which will continue the rapid rise of newly described networks but do little to explain how complex human behavior happens. We will also see more diagrams linking, at least hypothetically, various networks. We will in effect go back towards an era of becoming too localization oriented and again become "diagram makers". Instead, we should commit ourselves to the newer, albeit, more difficult questions: How do neuronal oscillations synchronize? Do astrocytes have a key role in this process? What are the network function characteristics within white matter tracks and astrocyte-neuron connections? How might these as yet not fully studied properties be the key(s) to instantaneously bringing some networks online and others offline?

What would Norman Geschwind have thought about the DMN, other described networks, and behavior? It does appear that there are many commonalities among studies and that the most highly evolved

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parts of the human cortex are critical in all, including the prefrontal cortex and parietotemporal region, regions that Dr. Geschwind emphasized, although more the latter than the former. More recent studies do make one ask if we are now somewhere between strict localizationists and non-localizationists, beyond critical "modules" or defined networks and their connections to explain disorders of higher function. Have we arrived at a time to focus research on more distributed networks that work in concert or in opposition based on neuronal synchrony? I think Dr. Geschwind would have welcomed the use of these new techniques and technologies and might now think about dissynchronization of the interactions within and among networks, rather than a more anatomically based and relatively static disconnection of these areas. Dissynchronization of these networks might explain many behavioral disorders, including many of the classical disorders of cognitive function about which Dr. Geschwind wrote. Would he think that dissynchronizations might represent an even higher level of disconnection? Would Dr. Geschwind interpret many of the disorders that both the functional imaging and electrophysiological groups emphasize, e.g. autism, schizophrenia, and depression, as dissynchronization syndromes and now reinterpret some of the classical neurological disorders of higher cortical function as cortical dissynchronization within or among networks? Would he now consider functional connections through synchrony of networks that must in some way be dependent on white matter connections or astroglia, but represent more than parallel or sequential processing? He would still characterize paralysis following a spinal cord lesion as a true disconnection, but when considering disorders of higher cortical function it is possible he might describe them as dissynchronies, rather than disconnections.

I think that if Geschwind had written his classic papers in 2013 he might have titled them "Dissynchronization Syndromes in Animals and Man", rather than "Disconnexion Syndromes in Animals and Man". Furthermore, I think that purposeful exploration of the "how" of network communication, specifically by scientists and clinicians - investigating oscillations and their synchrony or dissynchrony, will create a new way of looking at disorders of cortical functions. These discoveries may well lead to new and targeted forms of prevention and treatment.

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