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Disconnection Syndromes

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ABSTRACT

In this review, the history and current status of the topic of disconnection syndromes, which was introduced to the discipline of Behavioral Neurology by the founding father Norman Geschwind and that has become the dominant paradigm for the explanation of neuropsychiatric disorders with new developments, like network connectivity imaging in the living human brain are discussed.

Keywords: Disconnection syndromes, Geschwind, intrinsic connectivity networks, neural networks

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INTRODUCTION

We watched a 15-minute video of M-Marsel Mesulam at the 14th Neuropsychiatry Days in December 2021. The Turkish title of the speech was "Norman Geschwind, 60 Years of Disconnection Syndromes and Neurocognitive Networks". Dr. Mesulam based this speech on an article published in Brain journal in 2015 (1). This article was written by Dr. Mesulam, upon the invitation of the editors of Brain, to commemorate the 50th anniversary of Norman Geschwind's gigantic 116-page article titled "Disconnexion syndromes in animals and man", which was published in two parts in the same journal in 1965 (2,3).

Dr. Mesulam mentions the opening statement of the protagonist (Osman) in Orhan Pamuk's novel "New Life" at the beginning of the article: "I read a book one day and my whole life changed". He expresses the change in his life that reading this unique monograph, which can be considered the founding manifesto of the modern times of the discipline of Behavioral Neurology, caused. As a matter of fact, one of the authors of this article (HG) always used the same expression to his close circle about Mesulam's book "Principles of Behavioral Neurology", which he read in 1987 after encountering this sentence in "New Life" in 1994. Following Geschwind's text, Mesulam's book would be an indispensable guide for new generations of Behavioral Neurology after its publication (4). Like M-Marsel Mesulam, Geschwind's students, such as Antonio Damasio, Albert Galaburda, Frank Benson, Kenneth Heilman, Elliott Ross, and David N. Caplan, constitute the first-generation founding fathers of Behavioral Neurology.

HISTORY

Mesulam likens Geschwind's founding intervention for modern Behavioral Neurology to Mendeleev's founding in chemistry with the periodic table. Both ushered in the modern era of their discipline with a unique synthesis of their predecessors. In this respect, it can be said that his interventions correspond to the "aufhebung" (raising , sublimation) in Hegel's dialectical parlance. It can also be argued that this Hegelian "aufhebung" created by the Geschwind monograph corresponds to a Thomas Kuhn-style paradigm shift in the field of Behavioral Neurology (5). The necessary foundation has now been laid for the replacement of the old localizationist paradigm with new large-scale neural networks in understanding brain-behavior relationships. To understand and conceptualize a new paradigm of neural networks, it was necessary to abandon the view of vertically organized, autonomous cerebral centers with those centers at the top of the hierarchy engaged in different aspects of mental functioning and, instead, to design large-scale neural networks with cortical and subcortical components spread over the topography in the brain, using the computational strategy of parallel distributed processing, relative specialized nodes and their interconnections with each other by analogy from non-human primate neuroanatomy (6).

Highlights

- **In the Geschwind disconnection approach, the emphasis is on the cortico-fugal feedforward pathways.**
- **Mesulam added the simultaneous functionality of cortico-petal feedback pathways to the first concept in the disconnection approach.**
- **"Intrinsic connectivity networks" interact positively or negatively with each other.**

Mesulam says that Geschwind chose to use the myelogenetic map of the axon fibers connecting the cortical areas instead of the widely used cytoarchitectonic topological center maps based on the horizontal laminar and vertical columnar organization of the cerebral cortex to design such a connectivity map. Among the many cytoarchitectonic maps, including the one in which Exner distinguished 500 different areas, the best known and still widely used is Brodmann's map (7–10). Myelogenetic mapping, which can be considered the origin of hodological connectivity

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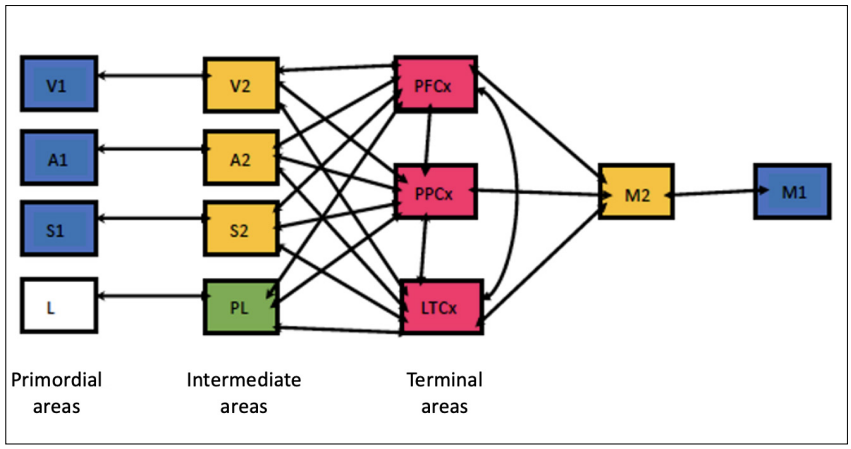

Figure 1. Flechsig's schematic myelogenetic map: Primordial areas are primary sensory (visual [V1], auditory [A1], and somatosensory [S1]), primary motor (M1), and limbic (L) cortices. Primordial areas are interconnected with unimodal association areas in their modalities (V2, A2, S2, and M2) located in the intermediate areas in the next step without connecting with each other; this connectivity is with paralimbic areas (PL) for L. Finally, each of the intermediate areas is interconnected with each of the heteromodal association cortices (prefrontal cortex [PFCx], posterior parietal cortex [PPCx], and lateral temporal cortex [LTCx]) located in terminal areas. Cortico-fugal feedforward is mostly from primordial areas to terminal areas, whereas cortical-petal feedforward is from terminal areas to primordial areas. Interconnections between different cortices belonging to the same area exist only for the terminal area. Color codes are adapted from the Principles of Behavioral Neurology (4). According to this codification, primary sensorimotor cortices are shown in blue, unimodal association cortices in yellow, paralimbic cortices in green, and heteromodal association cortices in magenta. The limbic areas are not colored as they cannot be seen in the lateral and midsagittal medial sections of the brain.

maps (or "connectomics") instead of topological center maps, is based on Paul Flechsig (11). What Flechsig means by myelogenesis is the spatio-temporal myelination of axonal fibers in the human brain during ontogenetic development. Accordingly, the fibers that complete their earliest myelination in ontogenesis originate from the primary sensory-motor and limbic cortex, and Flechsig calls these areas "primordial". In the second place are the unimodal association and paralimbic areas surrounding these areas, which are called "intermediate areas". Finally, in the last place are the prefrontal, posterior parietal, and lateral temporal heteromodal association cortices, and are called the "terminal areas". The basic principle of the myelogenetic map on which Geschwind explains the disconnection syndromes is the absence of connections between the primordial areas, the fact that the congenital connections between the intermediate areas are truncated in the adult cerebral architecture with the effect of developmental neuroplasticity (e.g., synesthesia is the result of an "abnormal" intermodal connection that persists in adult brain architecture as a result of the absence of such truncation) and large-scale neural networks formed by rich interconnections between terminal domains. In the first two steps, modality-specific cortico-fugal information processed in parallel is combined transmodally in terminal areas. Since the phenomenal experience of man consists of holistic elements (faces and objects) in a temporal-spatial context, it can be said that the first two steps correspond to the cognitive unconscious, while the conscious awareness required by the phenomenal experience is realized in the last step. While human's perception of phenomenal experience is like an uninterrupted flow in time, to mention Libet and Mesulam together, in fact, according to the principles of this cortico-fugal flow that goes from sensation to cognition, the perception that corresponds to the conscious awareness of the contextual features of the perception takes place 500 ms after the mapping of sensation in primordial areas (12,13). A schematic version of Flechsig's myelogenetic map is shown in Figure 1, with color codes representing the different cortical areas that Mesulam used in his Principles of Behavioral Neurology.

Mesulam cites Wernicke, Déjérine, Charcot, Lichtheim, and Liepmann as inspirations for Geschwind. of these five, three (Wernicke, Déjérine, and Liepman) were also mentioned by Catani and ffytche in the 40th Anniversary commemorative article of the Geschwind monograph (14). The following brief history has been reviewed based on these two commemorative articles.

In 1874, 9 years after Paul Broca said, "we are talking with our left hemisphere", Karl Wernicke defined Wernicke's sensory aphasia, which contrasts with "motor" Broca's aphasia and would have been named after him in his doctoral thesis titled "Aphasia Symptom Complex" (15,16). Wernicke, who was only 26 at the time of writing his thesis, defined "sensory" aphasia with the case reports he had seen and, with great vision, predicted conduction aphasia, which he had never seen before. He based this prediction on history's first cerebral connectivist model. In this drawing, he suggested that the motor Broca's area, located in the inferior frontal gyrus, and the sensory Wernicke's area, located posterior to the superior temporal gyrus, must be interconnected. In the next step, he envisioned the first disconnection syndrome disconnecting these two centers. Alfred Kussmaul made the second prediction with this originary connectivist model (or hodological map) and defined auditory agnostic patients who cannot understand spoken language like Wernicke's aphasics but have no problem understanding written language as the disconnection between auditory cortices and Wernicke's area However, the connections between the visual areas and Wernicke's are intact for a preserved reading comprehension (17). Eleven years after Wernicke, this time Lichtheim made an addition to the Wernicke's model with two aphasic patients, one of whom was motor and the other was sensory aphasic, whose standard features were the preservation of repetition abilities, and defined transcortical aphasias as disconnections of this added structure from perisylvian Broca's and Wernicke's areas (18). Since this addition resembles a model house when drawn to resemble a roof, this model would later be referred to as the Wernicke-Lichtheim House (see Figure 2). Such models were ridiculed as "diagram makers" by the British neurologist Henry Head, who was the prominent representative of the holistic movement in which basic paradigms of brain-behavior

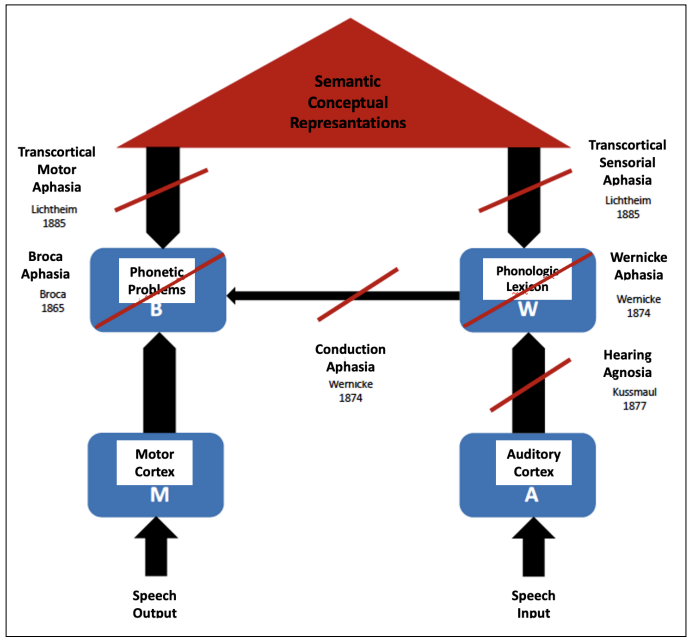

Figure 2. Wernicke-Lichtheim house.

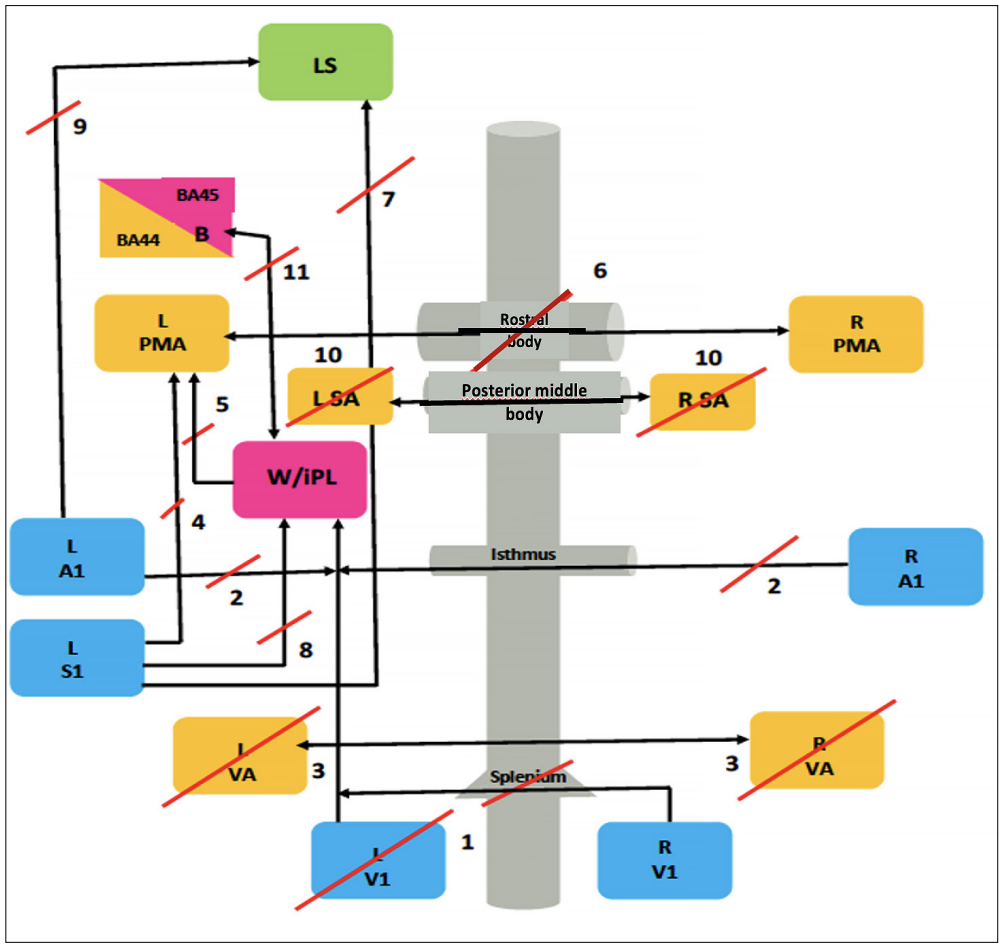

Figure 3. Modified Geschwind disconnection syndromes (1: Pure alexia [combined damage to left V1 + CC splenium]; 2: Pure word deafness [bilateral auditory-linguistic disconnection]; 3: Visual agnosia [bilateral damage to ventral visual association areas]; 4: Tactile apraxia [somatomotor disconnection]; 5: Bilateral ideomotor apraxia [left inferior parieto-premotor disconnection]; 6: Left ideomotor apraxia [interhemispheric premotor disconnection due to CC rostral trunk injury; 7: Pain asymbolism [somato-limbic disconnection]; 8: Tactile aphasia [somato-linguistic disconnection]; 9: Auditory amnesia [auditory-limbic disconnection]; 10: Tactile agnosia [bilateral damage to somatosensory association areas]; 11: Conduction aphasia [left arcuate fasciculus damage];A1: primary auditory cortex; B: Broca's area; BA: Brodmann area; CC: corpus callosum; iPL: inferior parietal lobule; L: left; LS: limbic system; PMA: premotor area; R: right; S1: primary somatosensory cortex; SA: somatosensory association cortex; V1: primary visual cortex; VA: visual association cortex; W: Wernicke's area).

functions can be summarized as "mental functions are not localized in the brain, and the mind is a holistic function of the brain". Mesulam states that Geschwind's massive 116-page monograph lacks any figures to avoid being labeled a "diagram-maker". However, 40 years after Geschwind, Kenneth Heilman will transform the Wernicke-Lichtheim House into a mansion with the addition of complex new aphasic disconnections (19).

Visual agnosia, another classical disconnection syndrome from the same period, was first reported verbally by Wernicke and then published by his assistant Heinrich Lissauer in Breslau (20). Wernicke and Lissauer defined visual agnosia as a disconnection between visual and linguistic domains. They divided visual agnosia into two as "apperceptive" as a result of the involvement of the extrastriate visual fields and as "associative" in the case of involvement of the association fibers connecting the visual cortices to the linguistic areas. According to this distinction, which is still used today, subjects with associative visual agnosia can draw objects that they cannot visually name, while subjects with apperceptive visual agnosia can neither draw objects norvisually name them.

Apraxia, another classical disconnection syndrome of the period, was described by Hugo Liepmann, who was another assistant of Wernicke (21). Liepmann's male patient, although unhampered visually and had no problem using gestures and real tools in daily life, but he could not reproduce gestures when requested and could not do so when asked to imitate imaginary tool use. Liepmann suggested that the left parietal lobe was specialized for complex motor behavior, and damage to this area would cause bilateral apraxia, while anterior corpus callosum damage would cause left-hand apraxia by disconnecting the right motor areas and the left parietal praxis area.

Finally, pure alexia should be counted as the French-derived disconnection syndrome of the period. The diagram drawn in France at that time is "Charcot's Bell diagram" and includes a specialized visual vocabulary area (22). However, another Frenchman, Jules Déjérine, was the first to describe pure alexia. He reported a patient with right hemianopsia, and accompanying alexia, despite preserved writing (23).

Catani and ffytche classify Geschwind's disconnection syndromes under three headings: sensory-limbic, sensory-motor, and sensory-Wernicke (14). A diagram that has been adapted and modified from them showing the double lesions that cause pure alexia is presented in Figure 3. In the second edition of Mesulam's book, he separated object-face recognition from language and increased the number of central topics to four (24). A modified version of Mesulam's classification is shown in Table 1.

Mesulam does not hesitate also to criticize the "life-changing" Geschwind monograph. While his implicit criticism is to the priority he gives only to cortico-fugal information processing, the explicit one is the "logocentric bias" of Geschwind, for which he devotes a separate heading (1). Geschwind's logocentrism is due to his attempt to explain all non-limbic disconnections (which Geschwind suggests that limbics are predominantly seen in non-human primates, such as Kluver-Bucy syndrome) in humans as simply the disconnections from the left hemispheric language areas. Mesulam first criticizes Geschwind's classification of agnosias as sensory-linguistic disconnections rather than modality-specific recognition disorders. In the second place, he adds the effort to explain the disorders showing right hemispheric dominance, such as prosopagnosia and contralateral spatial neglect, again with verbal disconnections.

Table 1. Disconnection syndromes

I. Sensory-limbic
a. Pain asymbolism
b. Modality-specific hypoemotionalities
c. Modality-specific amnesias
II. Sensory-motor
a. Modality-specific apraxias
b. Optic ataxia
c. Oculomotor apraxia
III. Sensory-linguistics
a. Modality-specific comprehension disorders (e.g., pure alexia, pure word deafness)
b. Modality-specific anomies
IV. Sensory-temporopolar (object-identification network)
a. Modality-specific recognition disorders (agnosias)
b. Modality-specific identification disorders (prosopagnosia, phonagnosia)

While, in Geschwind, the emphasis is on the cortico-fugal feedforward pathways flowing from sensation to cognition, Mesulam adds to this the simultaneous functionality of cortico-petal feedback pathways flowing from cognition to sensation. During the processing of the phenomenal experience, the flow from sensation to cognition encounters a reverse flow from cognition to sensation, which is loaded with a bias consisting of beliefs and familiarity expectations at every stop. Therefore, the phenomenal contextual experience that emerges into conscious awareness by being transmodally integrated within the heteromodal association areas is how new life elements are perceived by interpreting and blending with these biases. Mesulam gives the example of superstitions shaping subjective experience. In his article, "From Sensation to Cognition", dated 1998, he modified Flechsig's myelogenetic map and placed it in concentric rings (13). In Flechsig's terminology, the primordial areas map sensation in the two outermost rings. Damage to them causes elementary sensory disturbances in the 1st ring (e.g., cortical blindness, cortical deafness) and deficits in sensory attributes in the 2nd ring (e.g., achromatopsia, akinetopsia, astereopsis). Intermediate fields are located in the 3rd and 4th rings. Damage to them causes agnosias (e.g., modality-specific agnosias visual, auditory, or tactile agnosias, prosopagnosia, phonagnosia) as object and identity recognition disorders. Terminal areas in the 5th and 6th rings contain hubs of large-scale neurocognitive networks. Damage to them causes cognitive disorders such as amnesia, aphasia, and contralateral space neglect. Each ring is reciprocally connected to the neighboring ring. Thus, from the outermost 1st ring to the 6th ring in the center, the flow is cortico-fugal from sensation to cognition, while, from the 6th to 1st ring, it is cortico-petal from cognition to sensation to shape it subjectively. One criticism here is that the cortico-petal connections are also designed as synaptic cascades from one ring to the neighboring ring. However, while it is necessary to go through 5 steps to reach the amygdala located in the 6th ring from V1 in the 1st ring, we know that with the direct monosynaptic connection of the amygdala to V1 (amygdalo-calcarine pathway), visual perception can be shaped cortico-petally in a single step (rapidly) (25). In his theoretical contribution ten years later, Mesulam develops his model in a way that eliminates this criticism (26). In the new model, the feedback flow corresponding to the feedforward flow at each synaptic step produces an expectation inference for the incoming flow. Based on past experience records, this inference is coded according to Hebbian simultaneous activation principles and Bayesian empirical prediction theorem. If the expectation inference does not match the input, the previous step notifies the next step, generating an error message that keeps iteration open until a minimum agreement is reached. The innovation beyond this definition already inherent in the theory of concentric rings is the non-Bayesian form of top-down control, a form of non-stepwise, "jumping" control that Mesulam calls "transcendent encoding" and thinks of as "mostly frontal".

In the last decade of the last century, Antonio Damasio also developed his own theory of cerebral information processing, which he called "time-locked multiregional retroactivation," in parallel with Mesulam (27–29). As the term "retroactivation" suggests, this theory emphasizes cortico-petal processing. According to Damasio, cortical traces of new experience processed according to myelogenetic understanding create a vectorial configuration. Conscious awareness corresponds to the retroactivation of this vectorial configuration. The sensation begins with fragment records. As the phenomenal experience is fragmented into sensory modalities, in each modality, it is processed in parallel by being fragmented into the sub-attributes of that modality. Accordingly, the fragment recording recorded with the V1-V4 connection in the visual modality records the color attributions of the visual features of the experience, and the V1-V5 fragment records the motion attributions. The second term in Damasio's theory is convergence zones (Cz). It defines three distinct Czs, two local and one non-local. Local Czs are located in modality-specific association cortices. Local Czs in upstream areas are specialized with generic entity binding, while those in downstream areas are specialized with specific entity binding. The former provides modality-specific object recognition, and the latter provides identity recognition. Non-local Czs are for event binding. What Damasio means by "event" is the context made up of specific and generic entities. This context formed a vectorial configuration when it came as a parallel flow from the early sensory cortices and was bound as an event. Retroactivation of this vectorial configuration will be required for conscious awareness of the phenomenal experience and subsequent recollection as a contextual memory trace stored in episodic memory. Missing elements during recollection can be conceived as missing vectors in the retroactivated configuration.

Figure 4 shows a superimposed diagram of Mesulam's "concentric rings" and Damasio's "retroactivation" theories.

Intrinsic Connectivity Networks and Neuroimaging

Dr. Mesulam concluded his speech with what could be considered an implicit critique, or in other words, a further advance of the 1990 large-scale understanding of neurocognitive networks. These networks were designed as a result of adapting data obtained from non-human primate neuroanatomy studies to the human brain (6). Although the network approach represents a paradigm shift against localizationism (and its antithesis holism) in brain-behavior relations, designing these networks as autonomous units specialized in a specific cognitive function is a localizationist residue, to speak in Gaston Bachelard's terms, it can be interpreted as an incomplete "epistemological rupture" from the localizationist paradigm (30). Over time, advances in magnetic resonance imaging (MRI) have led to the definition of so-called "intrinsic connectivity networks" (ICNs) in the human literature. Rather than working autonomously, ICNs function by interacting positively or negatively with each other (31). For example, when the default mode network (DMN) is active and self-referential mental activity directed towards endogenous stimuli dominates, if a salient exogenous stimulus is detected by the salience network (SN), the SN may function as a railroad switch and assign the task to the dorsal attention network (DAN) in order to focus attention on the stimulus by suppressing DMN activity, and if the stimulus requires a problem solution, assign the task to the frontoparietal network (FPN) (32). While DAN activity voluntarily focuses attention on an exogenous stimulus by top-down voluntary control, the ventral attention network (VAN) activated simultaneously with it maintains its activity in an anti-correlated manner with DAN, similar

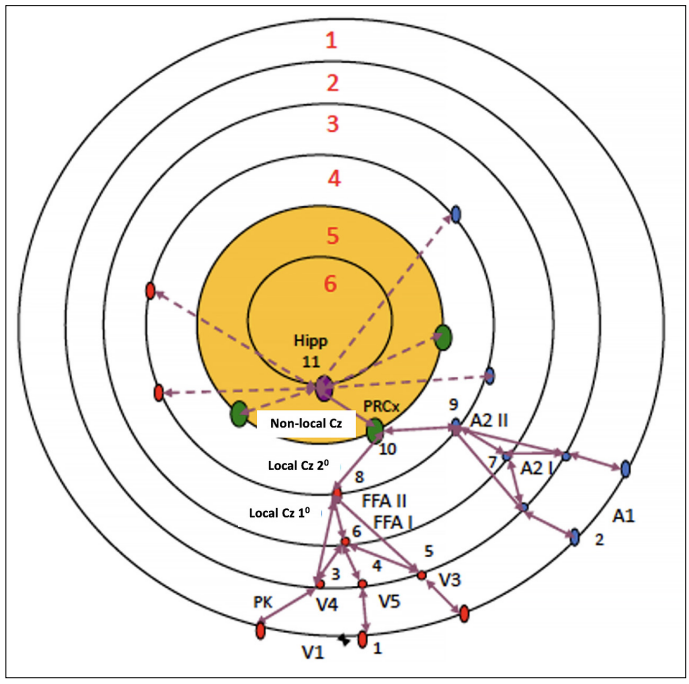

Figure 4. Neuroanatomical concentric loops of information processing and the computational strategy of time-locked multiregional retroactivation (1: Cortical blindness; 2: Cortical deafness; 3: Achromatopsia; 4: Akinetopsia; 5: Astereopsy; 6: Apperceptive prosopagnosia, 7: Auditory agnosia; 8: Associative prosopagnosia; 9: Phonagnosia; 10: Multi-modal prosopagnosia; 11: Contextual amnesia; A1: primary auditory cortex; A2 I: auditory association cortex-upstream; A2 II: auditory association cortex-downstream; Cz: convergence zone; FFA I: fusiform facial area-upstream; FFA II: fusiform facial area - downstream; Hipp: hippocampus; Local Cz 1°: Local junction site for binding to the generic entity; Local Cz 2°: Local junction site for binding to the specific entity; Non-local Cz: Transmodal junction site for event binding; PK: particle records; PRCx: perirhinal cortex).

to the SN, in order to detect the external stimulus that draws attention and focus attention on the new stimulus bottom-down by preventing DAN activity an action also called "circuit-breaking," when necessary (33). If the SN assigns the task to the FPN to solve the problem, the FPN undertakes this task by working in correlation with the cingulo-opercular network (CON) (34). CON, which remains active during the time that FPN needs to solve the problem, takes on the task of error monitoring and inhibition of inappropriate stimuli. Finally, there seems to be hemispheric lateralization of these ICN interactions. The left FPN interacts with the left DMN and language networks, and the right FPN selectively with the right hemispheric attention networks (35). Dr. Mesulam also emphasized network interaction while ending his speech. Using the metaphor of the maestro, he asked whether there is a conductor to direct this interaction between the ICNs, which resembles the instrument groups of a symphony orchestra and left the task of finding it to the younger generation of behavioral neurologists-cognitive neuroscientists.

Younger generations must master functional and structural connectivity imaging to initiate and maintain this task.

Structural neuroimaging consists of diffusion tensor imaging (DTI) and methods that are derived from and superior to DTI (e.g., tractography, diffusion spectral imaging [DSI]) in problematic situations such as crossing fibers, whereas functional connectivity imaging consists of functional connectivity MRI (fcMRI) which is a task-negative functional MR imaging (fMRI) method. In Figure 5, structural and functional neuroimaging is shown schematically.

The diffusion of free water molecules, confined to axons and myelin sheath in the brain, is quantified in three dimensions with DTI. The resulting diffusion tensor gives both the magnitude of the global diffusivity, expressed as mean diffusivity (MD) and the fractional anisotropy (FA) values of water diffusion, which reflect the arrangement and orientation of the fiber bundles. With the perfection of DTI and the methods derived from it, it has been possible to visualize the connectivity in the living human brain down to the last detail. Highly competent connectivity atlases have been published, so to speak, with this "virtual in vivo dissection" facility (36,37). It has also been possible to redefine neurodegenerative diseases as disconnections from a hodological perspective after structural imaging. Thus, the following diseases could be defined as degenerative disconnections reflected by FA reductions in the mentioned areas: Alzheimer's disease (AD) in the fornix in its earliest stages, behavioral variant frontotemporal dementia (dvFTD), and semantic dementia (SD) in the right and left uncinate fascicles, and logopenic variant primary progressive aphasia (lvPPA) in arcuate fasciculus (38–40). Moreover, decreases in cingulum bundle and uncinate fasciculus FA have been associated with psychopathy, attention deficit hyperactivity disorder, obsessive-compulsive disorder, schizophrenia, autistic spectrum disorders, and post-traumatic stress disorder, and it has been shown that even these complex psychiatric disorders can be considered as disconnection syndromes (41,42). Figure 6 shows the DTI templates obtained from our group's images and some of the interhemispheric callosal and intrahemispheric association fibers.

In neuroscience, functional connectivity in the brain is defined as "temporal correlations between neurophysiological events that are spatially distant from each other" (43). In fcMRI, these are temporal correlations between BOLD signals of anatomical regions. While the two regions may be structurally linked to each other, a monosynaptic structural link is not always necessary. If we look at the history of sequential identification of individual ICNs with fcMRI, we first see that low-frequency (0.01-0.08 Hz) BOLD signal fluctuations that show a high degree of synchronization at rest on the sensory-motor cortex are reportedly identified (44). Then, one after another, visual and emotional (45), auditory (46), language (47), default mode (48), and attention (DAN and VAN) networks (49) were defined. These developments finally enabled the drawing of cortical parcellation maps of ICNs, especially under the leadership of the Computational Brain Imaging Group at the National University of Singapore under the direction of Thomas Yeo (50,51). Following, parcellations of the cerebellar (52) and striatal (53) components were performed using the same color codes initially employed for different cortical ICNs in these parcellation maps. The

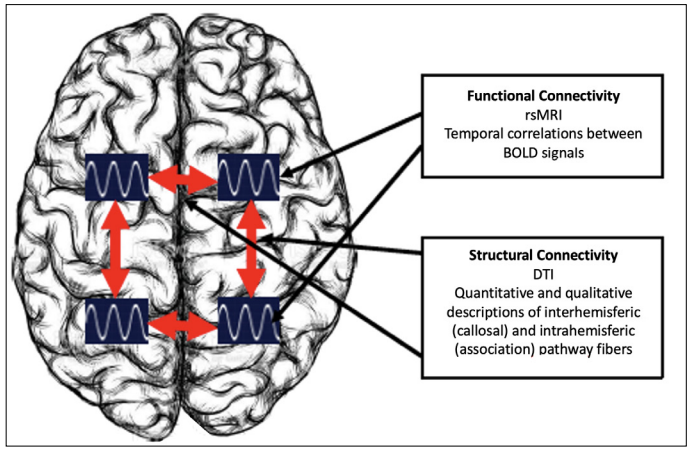

Figure 5. Principles of structural and functional connectivity neuroimaging: In the brain, major nodes in the bilateral frontal eye fields (FEF) and intraparietal sulci (IPS) in the dorsal attention network (DAN), which are detected by high temporal correlations of fcMRI BOLD signals, are intrahemispherically connected to the upper bundle of the superior longitudinal fasciculus (SLF I) with IPS as shown by DTI, whereas the major nodes of both DANs are also connected to each other by interhemispheric callosal fibers (FEFs with transcallosal fibers passing through the rostral body of the corpus callosum and IPSs with transcallosal fibers passing through the isthmus).

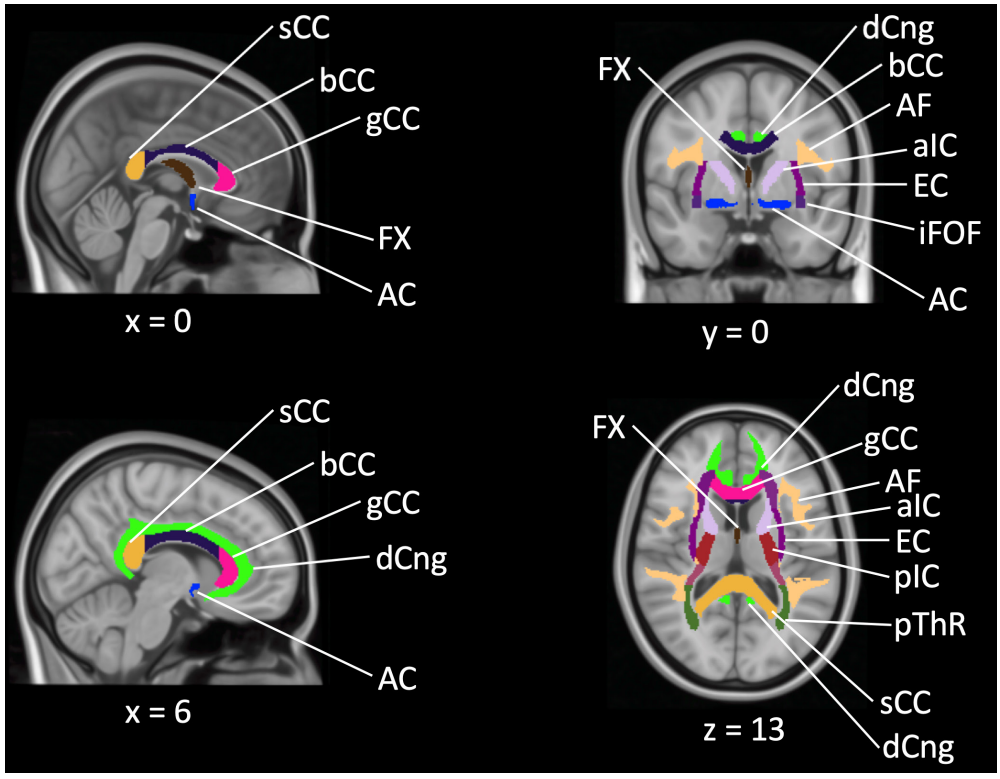

Figure 6. Inter and intrahemispheric connectivity with DTI (From archive of Istanbul Faculty of Medicine, Department of Behavioral Neurology and Movement Disorders, and Istanbul University Hulusi Behçet Life Sciences Laboratory. AC: Anterior commissure; AF: Arcuate fasciculus; aIC: Anterior internal capsule; bCC: Body of corpus callosum; dCng: Dorsal cingulum; EC: External capsule; FX: Fornix; gCC: Genu of the corpus callosum; iFOF: Inferior fronto-occipital fasciculus; pIC: Posterior internal capsule; pThR: Posterior thalamic radiation; sCC: Splenium of the corpus callosum).

structural and functional connectivity of the thalamus was demonstrated by a combined DTI and fcMRI study (54). One of the last steps of this effort was subcortical parcellation in an Australian study, in which the striatum, thalamus, amygdala, and hippocampus were added (55). It looks like the hypothalamus, basal forebrain, and some brainstem nuclei remain to complete the effort.

ICN research in neurodegeneration is also of increasing interest. In one of the early studies, the functional connectivity of the DMN was significantly reduced in AD dementia compared to healthy controls (HC) (56). Although this first study, which did not have very high sensitivity and specificity, could not raise fcMRI to a very prestigious place among the AD diagnostic methods, subsequent studies seem to have given the credit it deserves. In the following study by Sheline et al., three groups consisting of HC and AD dementia patients and amyloid-positive cognitively normal individuals (preclinical AD) were compared (57). This study showed that DMN connectivity was indistinguishable from each other in both AD groups and significantly lower than HC. This time, the same group compared the three groups by forming the third group not as preclinical AD but as amyloid negative but cognitively normal individuals carrying the APOE gene risk allele (ε4) (58). This time, the AD dementia group and the APOE-ε4 groups were not different from each other in terms of DMN connectivity but were found to be significantly lower than the HC group. The fact that PET ligands used for the detection of amyloid positivity can bind to insoluble forms of amyloid such as fibrillar Aβ and plaques shows that even soluble forms that should be present in large amounts in APOE-ε4 carriers but cannot be detected can disrupt DMN connectivity. It has been observed that SN has a selective predisposition to behavioral variant frontotemporal dementia (dvFTD) (59). Moreover, when AD and dvFTD were compared, polar opposition was found in DMN and SN activities: In AD, DMN is hypoactive, and SN is hyperactive, whereas in dvFTD, on the contrary, DMN is hyperactive and SN is hypoactive (60). It has been demonstrated that the susceptibility of these two neurodegenerations to DMN and SN also persists in the cerebellar components of these networks (61). Another study showed that ICN susceptibility did not overlap when five different neurodegenerative disease groups diagnosed with AD, dvFTD, SD, progressive aphasia, and the cortico-basal syndrome were compared with each other (62). Like DTI, fcMRI has been used in neuropsychiatric diseases. It has been shown that interhemispheric functional connectivity decreases in autism (63). It has been found that the functional connectivity of the subgenual cingulate and thalamus with the DMN increases in depression (64). In a schizophrenia study, "dynamic functional connectivity analysis" (DFCA), in which time dimension was added as well as traditional static connectivity analysis, was performed (65). The authors concluded that the subnetworks in the schizophrenia group have a weaker and relatively more rigid connectivity pattern with each other than in the HC group, as the task demands of the HC group change over time, changing connectivity between subnetworks and dynamically navigating between these networks, providing the resources needed for the task faster.

All these results show that the concept of disconnection syndromes can be applied to neurodegenerative and neuropsychiatric diseases with functional connectivity neuroimaging methods. Studies in neurodegenerative diseases give the impression that they can be interpreted in accordance with the classical definition of disconnection, with reduced connectivity in specific ICNs to which they are more prone. However, in the studies mentioned above in neuropsychiatric diseases, not only classical hypoconnectivity was found, but hyperconnectivity and even interconnectivity changes between different networks were reported. These results, of course, indicate that we need to look at the disconnection syndromes from a new perspective: there must be an optimal connectivity pattern in the adult brain, and any deviation from this pattern (whether in the form of hypo-hyperconnectivity or interconnectivity changes) can lead to a disconnection syndrome dan sonra ,and even "misconnection" may be a better term for the new definition. Adding the time dimension to the classical static analysis, DFCA seems to be more sensitive in revealing this optimal pattern.

Recently, efforts have been increasing to combine functional and structural neuroimaging (66). Based on mathematical models derived from graph theory, it has been possible to map the brain's structural (sNET)

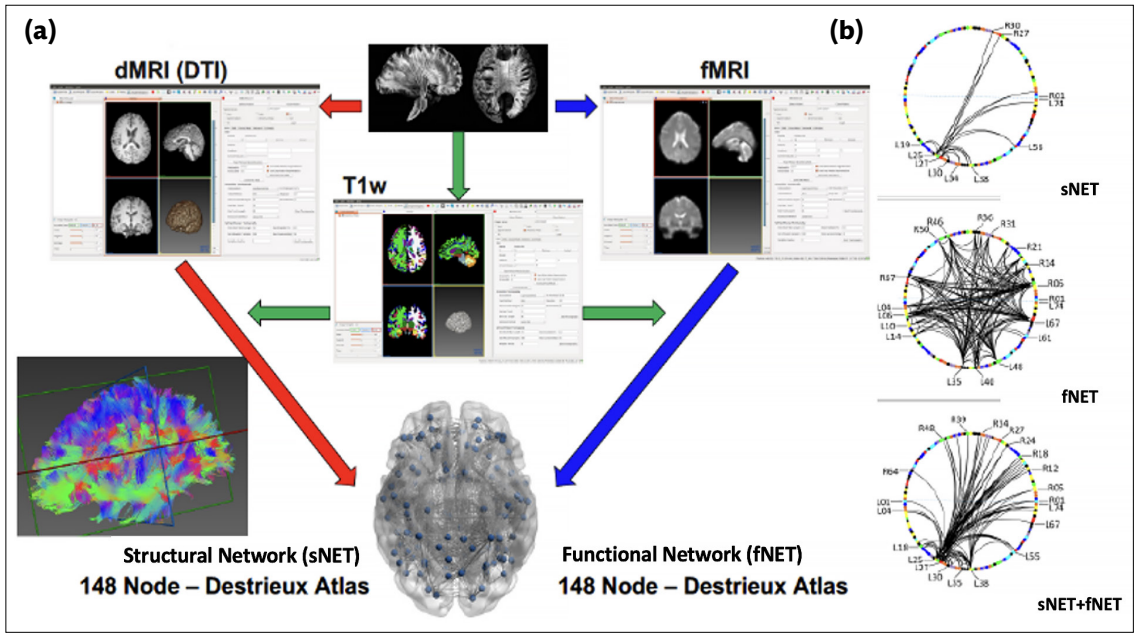

Figure 7. Connectome analysis in neurodegeneration: Multi-modal connectome obtained by superimposing T1-weighted MRI, DTI, and fcMRI data from a total of 148 nodes from Destrieux Atlas (70), the most frequently used parcellation atlas for gyral and sulcal parcellation with FreeSurfer **(a).** Small world representations of sNET, fNET, and multi-modal NET, which are significant in distinguishing SCI, MCI, and AD dementias (connectograms). Letter codes correspond to the positions of 74 nodes in the atlas in the left (L) or right (R) hemisphere. Accordingly, the most prominent regions are the precuneus (L/R30), angular gyrus (L/R25), supramarginal gyrus (L/R26), superior parietal lobule (L/R27), precentral gyrus (L/R29), postcentral gyrus (L/R28), dorsal and ventral posterior cingulate cortex (L/R 9-10) **(b)**.

and functional connectivity (fNET) into connectomes organized into a "small world". Connectomes can be modeled as graphs representing k edges (connections) connecting a series of n nodes (vertexes). In the small world connectome, connectivity consists primarily of k's (short distance) between neighboring n's and a smaller number of k's (long distance) connecting two n's at random locations. The multi-modal sNET-fNET approach has been applied to various clinical situations, including the developmental evolution and connectivity disruption in various developmental and destructive neuroplasticity (neurodegeneration, traumatic brain injury) states. A comprehensive review of the subject can be found in the recent review of Moody et al. (67).

In a study in collaboration with Boğaziçi University, the three groups of subjective cognitive impairment, mild cognitive impairment, and mild Alzheimer's type dementia continuum were obtained with a graph theory method (B-tensor factorization) with an accuracy in the range of 77-100% of the superimposed sNET-fNET connectors (68). Figure 7 shows one of the multi-modal connectomes found in this study.

CONCLUSION

As a result, we live in a time when fascinating developments are expected in the future. These developments will probably not be able to produce a maestro or conductor who is entirely free to comprehend his will and whose geographical boundaries can be determined in the brain. To use Althusserian terms, this maestro probably corresponds to an ensemble of neural networks that is "overdetermined" (69) by mental structure according to the demands of the task at the given moment. Although not a single maestro will emerge, developments in connectomics herald a future subjective connectome that reflects the uniqueness and uniqueness of the human individual, such as fingerprints.

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