Connectomics: A pharmacologic viewpoint

Drug discovery process in medicine, biotechnology and pharmacology, takes a huge time and resource. Therefore, nowadays, several “omics” helps the drug discovery process short and specific so that this process gets quicker for the translational value and society may get benefited namely genomics, proteomics, metabolomics, and other advanced techniques. However, neuroscientists are continuous in search of new scope to discover new drugs for neurological disorders. “Connectomics” as a new scope to the neuroscientist gives an option to understand the “Brain Connections,” including branches of the neurons and their beautiful interconnection. Connectomics is the field of neuroscience studying comprehensive mapping of extraordinary complex and highly organized networks of neurons at cellular and synaptic level. This field began in the 1970s with mapping of the entire nervous system of tiny roundworm *Caenorhabditis elegans*. Using powerful microscopes, scientists created wiring diagram of 302 neurons with 7000 synapses/connections between neurons of *C. elegans*. In the late 1980s, scientists published the entire connectome diagram of *C. elegans*.

**Contextual of Neuroscience**

If we see history, 1700 BC documents on neuroscience dating stated that Egyptians had knowledge on signs and symptoms of some of the brain disorders. Studies on brain became enlarged in the late 18th century after invention of microscope and development of staining techniques to stain brain cells. During the 19th century, neuroscientists pioneered in conducting live experiments in animals to study the behavior and loss of functionality of particular organ due to localized lesions in certain areas of the brain. The principle of “neuron doctrine” was formed in this period which hypothesized that neuron is the functional unit of the brain. Neuroscience got distinct academic status in the 20th century and recognized as a separate academic specialization. Hodgkin–Huxley model for transmission of electrical signals, generation, and propagation of action potential was also established in this period. The 21st century is the golden era for neuroscience; extensive studies on understanding the brain connections known as connectomics became glorified.

In human body, nervous system is the most complex system with brain, spinal cord, and peripheral nerves. Brain is the most complex organ and is the key to evolutionary success of humans and which makes us distinct from other species. It is made up of around one hundred billion neurons with more than one hundred trillion synapses and a very complex wiring which helps in exchange of information among different brain areas. This remarkable feature is one of the main reasons for difficulty in understanding the structure of nervous system unlike other organ systems. Therefore, the need of Neuroscience originated which deals with scientifically studying and understanding nervous system. Today, neuroscience is a discipline which seems to be focal point, where all disciplines of biological sciences converge in and diverge out with innovations. The current status of neuroscience became broaden by collaborating with other allied fields such as cognitive sciences, computational neuroscience, neuroinformatics, neuro-robotics, developmental neuroscience, neuroanatomy, neuromorphic computing, neuro-imaging, systems neuroscience, and other interdisciplinary fields such as physics, chemistry, engineering, and computer science.

Nervous system occupies the first place, which associated with long list of incurable diseases. Till today, there are many nervous system illnesses without known cause and even know which part of the nervous system got affected? Knowing what can go wrong with different nervous illnesses is primary approach to find the solution for treatment. Neuro-anatomic methods cannot be able to scale up the complex networking and pattern of neural connectivity. Now, neuroscientists are interested in how different parts of the brain are connected and how information gets stored in the brain. Connectomics is such a beautiful platform which can help in better understanding of structural and functional connectivity of the brain.

**Connectomics, the Connections of the Brain**

Development of new technology brings novel and big connectome data into neuroscience which provides us clear picture of structural organization of the nervous system and its functions. It also wipes off the poorly understood aspects of connections of the neurons. Neuroscientists are showing keen interest in how memories are physically stored in brain? How brain connectivity will change with age? How behavior and cognition vary from person to person? How the connectivity of psychiatric patients differs from normal? How healthy brain works and how to fix when it can go wrong? Connectomics is such an interesting area which
Connectomics, which based on the remarkable research progress of these imaging technologies, would show broad prospects.[10]

fMRI is a widely used technique in connectomics analysis.[11] In a study by Dandash et al., 2018, disturbance in functional connectomics is evident in mood disturbance associated with mania. Compared to healthy controls, patients with the first episode of mania showed reduced connectivity in corticostriatal systems in fMRI and increased connectivity in a circuit linking the ventral striatal system, cerebellum, and thalamus. Lithium and quetiapine normalized these abnormal increased connectivities at 3 and 12 months of follow-up. Action of lithium was noted to be more rapid compared to quetiapine.[12] Dopamine is widely implicated in molecular pathways affecting cognition, but the mechanism of this large-scale modulation of cognition by dopamine is still unknown. Using a connectomics-based approach, Alavash et al., 2018 found that enhanced dopaminergic signaling modulates the two potentially interrelated aspects of large-scale cortical dynamics during cognitive performance and the degree of these modulations is able to explain inter-individual differences in l-dopa-induced behavioral benefits and thus established the dynamic role of dopamine in maintaining communication between cortical systems at connectomics level and the degree of these inter-individual differences could explain the inter-individual difference in response to levodopa.[13] Liu et al., 2017 evaluated the effects of propofol on brain connectomes.[14]

Another widely used technique is EEG connectomics. EEG connectomics is also widely used in the evaluation of different neuropharmacological agents. EEG parameters such as oscillation and amplitude are used as potential biomarkers for drug response. Researcher gets out that in the resting stage (persons do not do any brain-related task) of EEG, when increased, the percentage of theta power is correlated with depressive symptom of person. EEG checks the neuronal activity of brain; therefore, EEG and clinical symptom make relationship to predict the drug effect.

EEG and MEG give good temporal resolution as compared to fMRI.[15] Quantitative techniques based on EEG measures can be used as biomarkers. EEG biomarkers are comparable to Alzheimer’s disease (AD) severity. Theta power exhibits a correlation with AD. Further study says that QEEG is a clinical method which is used to convert the electrical signals of brain into digital form. The delta bend power percentage of QEEG is also used as an indicator because EEG pattern can be influenced by ketamine which acts as a biomarker to help in the treatment of refractory status epilepticus patients. Levetiracetam shows the cognitive effect in
epilepsy patients which is evaluated by EEG frequency and observe the depth of anesthesia.[15]

Consequently, connectomics-based approach is being widely incorporated in both basic research as well as evaluation of efficacy and safety of drugs.

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**References**

1. Alivisatos AP, Chun M, Church GM, Greenspan RJ, Roukes ML, Yuste R, et al. The brain activity map project and the challenge of functional connectomics. Neuron 2012;74:970-4.
2. Behrens TE, Sporns O. Human connectomics. Curr Opin Neurobiol 2012;22:144-53.
3. Plaza SM, Scheffer LK, Chklovskii DB. Toward large-scale connectome reconstructions. Curr Opin Neurobiol 2014;25:201-10.
4. Mikula S. Progress towards mammalian whole-brain cellular connectomics. Front Neuroanat 2016;10:62.
5. Sebastian S. Connectome: How the Brain’s Wiring Makes Us Who We Are. Boston: Houghton Mifflin Harcourt; 2012. p. 359
6. Sporns O. The human connectome: A complex network. Ann N Y Acad Sci 2011;1224:109-25.
7. Morgan JL, Lichtman JW. Why not connectomics? Nat Methods 2013;10:494-500.
8. Lichtman JW, Pfister H, Shavit N. The big data challenges of connectomics. Nat Neurosci 2014;17:1448-54.
9. Macey PM, Rieken NS, Kumar R, Ogren JA, Middlekauff HR, Wu P, et al. Sex differences in insular cortex gyrri responses to the Valsalva maneuver. Front Neurol 2016;7:87.
10. Smith SM, Vidaurre D, Beckmann CF, Glasser MF, Jenkinson M, Miller KL, et al. Functional connectomics from resting-state fMRI. Trends Cogn Sci 2013;17:666-82.
11. Wang X, Zhang Y, Long Z, Zheng J, Zhang Y, Han S, et al. Frequency-specific alteration of functional connectivity density in antipsychotic-naive adolescents with early-onset schizophrenia. J Psychiatr Res 2017;95:68-75.
12. Dandash O, Yücel M, Daglas R, Pantelis C, McGorry P, Berk M, et al. Differential effect of quetiapine and lithium on functional connectivity of the striatum in first episode mania. Transl Psychiatry 2018;8:99.
13. Alavash M, Lim SJ, Thiel C, Sehm B, Deserno L, Oleser J, et al. Dopaminergic modulation of hemodynamic signal variability and the functional connectome during cognitive performance. Neuroimage 2018;172:341-56.
14. Liu X, Lauer KK, Ward BD, Roberts CJ, Liu S, Gollapudy S, et al. Fine-grained parcellation of brain connectivity improves differentiation of states of consciousness during graded propofol sedation. Brain Connect 2017;7:373-81.
15. Tian Y, Yang L, Xu W, Zhang H, Wang Z, Zhang H, et al. Predictors for drug effects with brain disease: Shed new light from EEG parameters to brain connectomics. Eur J Pharm Sci 2017;110:26-36.