Neurological disorders of COVID-19 can be explained in terms of both "loss and gain of function" states of a solution for the nervous system

To understand the mechanism of a seemingly complex biological function, first, it is necessary to make a large number of observations followed by using constraints offered by them to arrive at a solution that can provide inter-connectable explanations for all the findings. Once a solution is obtained, either a specific lesion of a keystone location of the mechanism that can generate "loss of function" state of the system or addition of excess number of unitary mechanisms (if there is a possibility for their presence) that can generate a "gain of function" state of the system can be carried out to examine whether they can provide expected disease outcomes. A classical example is the observation of "inborn errors of metabolism" by Archibald Garrod[1] that indicated genetic material must be present in pairs, supporting earlier discoveries made by Gregor Mendel regarding gene segregation.[2] Another example is the derivation of a model for the structure of DNA[3] that can explain several findings from different levels such as Chargaff's rule, X-ray crystallographic features, hydrogen bonds between bases, and coiling and super-coiling abilities of DNA, in an interconnected manner. This was followed by identification of a specific sequences of DNA, called genes, which led to several "loss or gain of function" studies in *Drosophila*.

The nervous system has different features at multiple levels of its organization and it was difficult to find a solution that allows explaining these features in an interconnected manner. The most important reason for this is the inaccessible nature of first-person inner sensations of several brain functions that are referred to as constituting the "mind." By using inference from logical arguments made by Marvin Minsky that a mechanism for memory can be discovered by searching for properties that can generate cue-specific hallucinations (internal sensation of items and events in the absence of arrival of sensory stimuli from them),[4] it was possible to derive a mechanism that can generate the first-person internal sensation of memory. This is the basis of the semblance hypothesis,[5] which was able to provide interconnected explanations for different features of the system from multiple levels.[6] Further verification of the derived mechanism can be carried out by (1) artificially generating a defect in a key location of the derived mechanism and examining whether it causes expected changes in the functioning of the system, (2) searching for pathological conditions that specifically target a structural change responsible for the mechanism, and (3) examining effects of addition of an excess number of operating units (if any), either generated by natural events or created by artificial means. Examining whether features arising from such alterations match with the anticipated properties of disorders of the system can be used as a method to verify the derived mechanism. The rationale for the present work is to examine whether any COVID-19 viral factors can specifically cause "loss and/or gain of function" changes of the proposed mechanism of brain functions that in turn may explain specific set of neurological findings in COVID-19 infection.

The Specific Set of Clinical Features of COVID-19

An ongoing outbreak due to severe acute respiratory syndrome coronavirus 2 or COVID-19 is associated with neurological symptoms of anosmia,[7] seizures,[8] delirium,[9] encephalopathy,[10] and eventually respiratory failure.[11] All the above clinical features have been observed as independent disorders in individuals during the pre-COVID-19 era. Moreover, a person having seizure disorder due to non-COVID pathology can have few or all the remaining neurological features of COVID-19 listed above. This indicates that either a defect or an excess number of the operating unitary mechanisms of the system (if any) at different locations and in various degrees can lead to different clinical manifestations. In this context, if it becomes possible to explain all the clinical features of COVID-19 in terms of "loss and/or gain of function" changes of a linchpin mechanism of the nervous system, then it can serve as an opportunity to understand both pathophysiology of COVID-19 neurological disorders and normal mechanism of nervous system functions. An additional verification can be carried out by identifying a specific reason why the mechanism in a subgroup of aged population causes increased mortality due to COVID-19.[12] It should also be possible to explain why a subset of young individuals suffers neurological disorders from COVID-19.

Present work was motivated by certain unusual combination of findings in COVID-19 infection. Even though it is possible to find superficial explanations for the following findings, they are not sufficient at a deep level. First, anosmia can be explained in terms of congestion of mucous membranes over the cribriform plate region where olfactory nerve terminals are present. Since the loss of smell with COVID-19 persists in a subgroup of patients even after the disappearance of nasal congestion, it is most likely that the brain mechanism for the perception of smell is affected. Second, breathing difficulties can be explained in terms of inflammatory exudates formed in the alveoli. However, ventilator dependency of a subset of patients indicates loss of trigger from the respiratory centers in the brainstem, which cannot be explained in terms of alveolar pathology alone. Third, several comorbidities associated with old age can explain increased mortality in this age group. However, no specific reasons such as immunodeficiency were found contributing to the increased death rate among these individuals. This brings the question, "Are there any factors predisposing the old age population to increased mortality by this virus?" Finally, it is necessary to explain altered consciousness observed in some of the COVID-19-infected people in terms of an alteration of the normal mechanism of consciousness. All the above features prompt one to ask, "Is there anything unique in this viral infection that predisposes people to get specific set of neurological disorders, and can the symptoms be explained in terms of "loss and/or gain of function" states of the normal mechanism of the system in an interconnected manner?"

COVID-19 Spike Protein is a Fusion Protein

COVID-19 viral entry is mediated by its spike protein, which is responsible for receptor binding and fusion between viral and host cell membranes.[13] Even though the main function of spike protein is to promote fusion between viral and host cells, it also facilitates inter-cellular fusion between host cells.[14,15] Several cell lines show fusion between cells after co-incubation with COVID-19-infected cells to form syncytia,[16] supporting inter-cellular fusion by COVID-19 virus. Fusion between membranes is a very common finding observed in biological systems during exocytosis, endocytosis, and actions of some of the intracellular organelles. The fusion process takes place through multiple steps that involve membrane contact, reversible partial, and complete hemifusion stages followed by the final stage of formation of a fusion pore.[17] Fusion pore formation across an IPL is expected to take place by one or more of the many ways cells can fuse.[18] If the normal operating mechanism of the nervous system involves any one of the steps of fusion process or even factors that control fusion process, and if inter-cellular fusion property of COVID-19 spike protein can affect normal mechanism of the system, then details of this relationship will be of substantial value in understanding the pathophysiology of COVID-19.

The Linchpin of a Proposed Mechanism of Brain Functions Involves Early Stages of Fusion

Based on the semblance hypothesis, associative learning events and perception lead to the formation of inter-postsynaptic (inter-spine) functional LINKs (IPLs) by the interaction between dendritic spines (spines or postsynaptic terminals) that belong to different dendrites usually of different neurons and rarely of the same neuron.[5,19] Structural changes of IPL formation range from close contact between spines that belong to different dendrites to reversible partial and complete hemifusion stages of fusion[5] [Figure 1a]. Depolarization can propagate across the IPLs to induce units of internal sensation at the inter-LINKed spines. Internal sensation of memory is generated as a cue-induced hallucination[4] of the associatively learned item[5] and is summarized in Figure 1b. Inter-LINKed spine (and in fact all the spines) is heavily depolarized by volleys of release of neurotransmitter molecules when signals from environmental stimuli arrive at the presynaptic terminal as action potentials. Furthermore, all the spine head regions are continuously being depolarized by quantal release of neurotransmitter molecules from their presynaptic terminals even during sleep.

In the above dominant background state of continuous depolarization of spines by neurotransmitter molecules from their presynaptic terminals along with intermittent strong depolarization of spines during arrival of signals from the environmental stimuli, any artificial strong depolarization of a spine is expected to trick that spine to hallucinate that it is receiving signals from certain environmental stimuli as a system property. This matches with the observations that artificial stimulation of specific sensory cortices produces corresponding sensory hallucinations.[20] This leads to an inference that any arrival of depolarization from a lateral direction through the IPL that depolarizes an inter-LINKed spine generates a hallucination that the latter is receiving sensory inputs from the environment though its presynaptic terminal, contents of which are expected to constitute units of first-person internal sensation.[5] Potentials (depolarization) propagating through the IPL toward the axon hillock of the inter-LINKed spine's neuron may trigger firing of that neuron, provided that neuron is held at a subthreshold activation state short of those potentials for firing by the action of

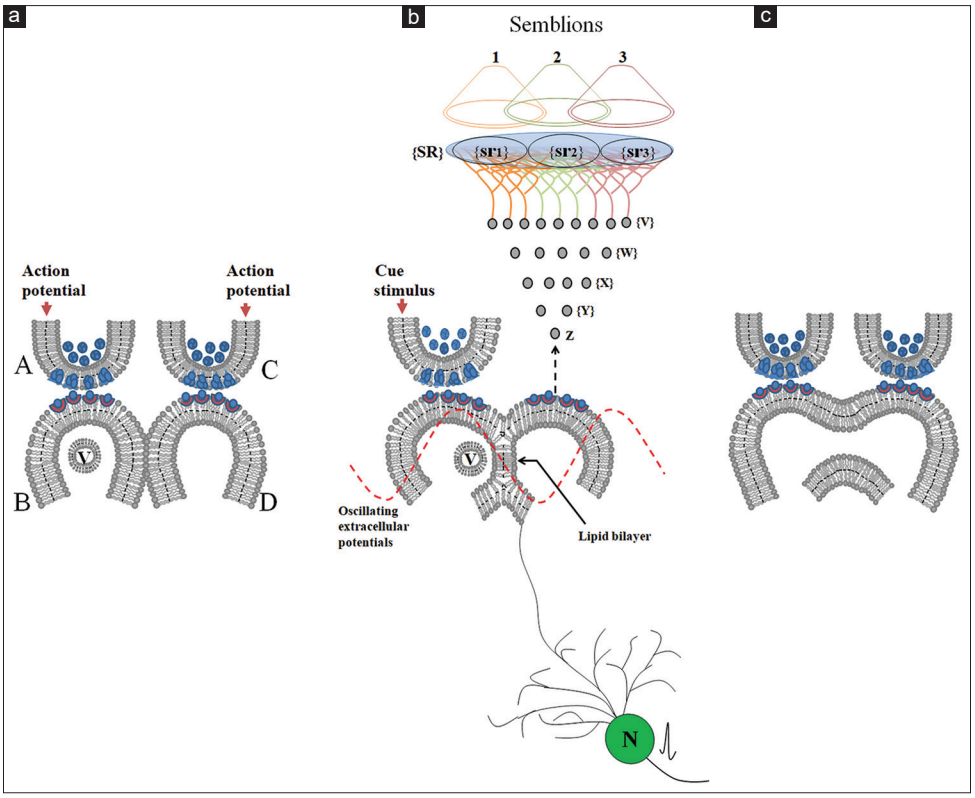

Figure 1: Inter-postsynaptic functional LINK that aids to generate first-person internal sensation and formation of fusion pores across it by COVID-19. (a) Inter-postsynaptic functional LINK formed by inter-spine interactions ranging from close contact to partial hemifusion between Spines B and D that belong to two different neurons. A and C are presynaptic terminals. Inside Spine B, there is one vesicle marked V containing COVID-19 virus, which is ready for exocytosis. (b) Structure of inter-postsynaptic functional LINK formed by transition of partial hemifusion to complete hemifusion between spines consists of a lipid bilayer similar to that of cell membranes. When a signal from a cue stimulus arrives at presynaptic Terminal A, it depolarizes its Spine B and the resulting postsynaptic potentials can propagate across the inter-postsynaptic functional LINK to inter-LINKed Spine D and spark units of internal sensation, namely semblions (for details[5]). There are two possible fates for COVID-19 virus residing inside the Vesicle V in Spine B during vesicle exocytosis. It can allow the virus either to cross the lipid bilayer of cell membrane to reach extracellular matrix space or to cross the lipid bilayer of inter-postsynaptic functional LINK to reach Spine D. Waveform: Both learning and retrieval of memory take place in a narrow range of oscillating extracellular potentials. (c) Fusion pore generated through the lipid bilayer region of hemifused inter-postsynaptic functional LINK following viral exit through it by vesicle exocytosis. This leads to mixing of cytoplasmic contents between Spines B and D as evidenced by dye transfer between COVID-19-infected cells.[16] N: Postsynaptic neuron of the inter-LINKed spine. Figure modified from[5]

inhibitory neurons that form an inhibitory blanket in the cortex.[21] Thus, instantly following generation of internal sensations, potentials arriving toward the inter-LINKed spine's neuron can lead to concurrent motor responses responsible for behavior. Electroencephalographic recordings of surface extracellular potentials[22] indicate that both learning and retrieval of memories take place only when the frequency of oscillating extracellular potentials is maintained in a narrow range.[23,24] Beyond this range, system does not maintain normal consciousness. Synaptic transmission and propagation of potentials across the IPLs are expected to provide vector components for the oscillating extracellular potentials.

Vesicular Exocytosis during Viral Exit can Lead to Fusion Pore Formation Across the IPL

COVID-19 virus exits from cells by vesicular exocytosis.[25] An exocytosis process allows the virus to cross the lipid bilayer of the host cell membrane to reach the external environment. In the case of a virus within an inter-LINKed spine, it may take one of the two exit routes for crossing the lipid bilayer – either to the extracellular matrix space or to the inter-LINKed spine [Figure 1b and c]. Lateral spine head regions are locations where exocytosis and endocytosis of vesicles containing AMPA receptor subunits take place[26-28] and are suitable locations for IPL formation.[5] It is reasonable to expect that these locations are rich in molecules that can support fusion pore formation across the IPL during vesicle exocytosis. Since complete hemifusion is one end of the spectrum of changes expected of IPLs,[5] and since the location of hemifusion has a bilayer structure, vesicular exocytosis of COVID-19 may utilize the favorable environment at the IPLs to enter into the inter-LINKed spine that usually belongs to another neuron. Creation of a fusion pore between spines of different neurons can lead to mixing of the contents of their cytoplasm that in turn can initiate a homeostatic mechanism within the cells to close the fusion pore. If this fails, mechanisms are expected to trigger changes to remove those spines

from their dendrites. It is to be noted that from the time of early stages of fusion pore formation until spine loss, depolarization can propagate through the membranes around the fusion pores formed across the IPL [Figure 1b], which will continue to maintain IPL function.

"Loss and Gain of Function" States of the Linchpin Mechanism by COVID-19

Fusion pore across the IPL can lead to mixing of the cytoplasmic contents of different neurons. Since transcriptomes of even adjacent neuronal cells of the same type are different,[29,30] fusion pore formation across the IPL by COVID-19 can lead to protein precipitation, loss of spines, and eventual neuronal death responsible for damage in the cortical areas.[31] These changes will prevent both generation of units of internal sensations at the inter-LINKed spines and activation of postsynaptic neurons of the inter-LINKed spines that lead to motor action. Together, these changes can explain cognitive defects. Since it is possible to explain that a modified action of IPLs can generate first-person inner sensation of perception,[19] any loss of this function can explain the loss of perception of smell. Fusion pore across the IPL between spines that belong to different neurons can lead to cellular damage that can result in bulbar edema, which in turn can result in altered consciousness,[32] and coma seen in severe cases of COVID-19.[9]

Subacute neuronal death can explain multiple sclerosis (MS)-like lesions in animal models.[33] Since it was found that MS lesions occur in the cortical regions,[34,35] it matches with the finding that COVID-19 generates MS-like lesions in the cortex. Spine loss and neuronal death in the medullary respiratory center are expected to damage the ability to trigger respiratory effort in response to elevated carbon dioxide levels. This can explain the ventilator dependency of some of the COVID-19 patients, which matches with the expectation of a unique pathology for respiratory failure.[11] Repeated detections of lack of respiratory effort in response to both elevated partial pressure of carbon dioxide above 60 mmHg and a reduction in pH below 7.3 introduced by changing the ventilator settings to patient-triggered mode constitute an accepted standard for determining brain death.[36] As per general standards, brain death is considered "death" even though there are variations in determining death by neurological criteria around the world.[37]

Formation of new IPLs by COVID-19 fusion proteins can lead to "gain of function" effects. For example, formation of nonspecific IPLs can generate nonspecific semblances that can dilute the specificity of net internal sensation of memory and even result in loss of memories. Change in the extracellular ionic properties is expected to lead to the rapid generation of chains of IPLs between large numbers of spines causing seizures.[38] COVID-19 fusion protein can lead to the formation of nonspecific IPLs that can explain hallucinations[5] and altered levels of consciousness due to changes in a proposed mechanism of C-semblance responsible for consciousness.[32,39]

Old Age Predisposes IPLs to Undergo Fusion in a Subset of Individuals

Now we can ask, "Are there any factors that predispose the old age population to excessive mortality from COVID-19?" Examination of ontogeny shows that the IPL mechanism has several features of an evolved mechanism.[40] One of the major events during development provides hints about certain possibilities. In the mouse, neuronal precursor cells in the ventricular zone (VZ) undergo cell division. While in the VZ, 100% of the precursors in G2 and S phases of the cell cycle couple together and form clusters.[41] During this stage, dye injected into one cell spreads to the neighboring cells,[41] indicating the formation of fusion pores between these cells. This is followed by death of nearly 70% of these cells and survival of the remaining 30% cells.[42] What inferences can be made from the above findings?

The above findings indicate a high likelihood that an adaptation is triggered in the surviving cells that prevents any future intercellular fusion events. It is also reasonable to infer that maintenance of this adaptation is necessary for continued normal IPL formation by preventing the conversion of a spectrum of IPL structures ranging from close contact between spines to early and intermediate stages of hemifusion to undergo fusion. When factors associated with aging affect this adaptation mechanism, it can lead to gradual inter-spine fusion. The loss of adaptation can also lead to the persistence of newly formed fusion pores across the IPLs,[40] which in turn can continue to cause cytoplasmic content mixing that can lead to protein precipitation, spine loss, and eventually neuronal death. In old age individuals with deteriorating adaptation for preventing the conversion of IPL hemifusion to fusion, this vulnerability can augment the formation of fusion pores at the locations of IPLs [Figure 1c], especially in association with vesicular exocytosis during viral exit from the spines. Since many methods are used by cells to facilitate fusion,[18] COVID-19 is likely allowing IPLs between spines of different dendrites to undergo fusion pore formation across them by one or more of these mechanisms.

It is known that some children suffer from neurological disorders by COVID-19.[43,44] This naturally leads to the questions, "In contract to the loss of adaptation in old age that predisposes them to get fusion pores across the

IPLs, how can brains of young people get affected by COVID-19?" "Are there any factors that predispose IPLs to undergo fusion?" Studies have shown that changes in lipid composition are associated with neurodegenerative diseases such as Alzheimer's disease.[45,46] Hence, it can be tested whether changes in membrane lipid composition are a possible cause that makes a subgroup of young individuals more prone to COVID-19 neurological disorders.

Conclusion

Linchpin of the proposed mechanism of brain functions by semblance hypothesis consists of a spectrum of early stages of inter-membrane changes before the stage of fusion pore formation.[5] Even though abnormalities of such a mechanism for causing neurodegenerative disorders were explained before,[31] recent appearance of COVID-19 highlights that the proposed mechanism of semblance hypothesis has severe vulnerability to viral fusion proteins. Even though it is possible to explain each neurological disorder of COVID-19 by different ways, it becomes possible to explain them in terms of "loss or gain of function" states of a single mechanism (IPL mechanism) by a single factor (COVID-19 fusion protein). This increases the probability that the explained mechanism is theoretically fitting and encourages efforts to undertake its further verification. Since COVID-19 fusion protein can overcome an already fragile adaptation mechanism expected to be present in a subgroup of old age population, it is possible to verify its occurrence and take measures to prevent the adverse effects of viral fusion proteins. It is also possible to analyze membrane lipid composition of red blood cells or platelets of young individuals who suffer from neurological disorders due to COVID-19 to test whether differences in membrane lipids can promote inter-cellular fusion by COVID-19.

Symptoms of fatigue, cognitive disturbances, headache, difficulties to walk, concentrate, and breathe that are observed in the newly emerging post-acute COVID-19 syndrome (long COVID)[47] can also be explained as a spectrum of effects due to "loss and/or gain function" of IPLs in the nervous system. Studies of the effects of fusion pore formation across the IPL may become useful to understand several psychiatric disorders associated with COVID-19.[10,48] Furthermore, inter-cellular fusion events can be explored to understand how COVID-19 affects multiple organs.[47] New fusion inhibitors that prevent animals from COVID-19 infection[16,49,50] offer hope for developing medications to prevent triggering the pathophysiology by this virus. Mechanisms and explanations provided in the present work are testable.

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