Testable predictions from semblance hypothesis

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Testable predictions are indispensable elements of any theoretical work. In this regard, semblance hypothesis has put forward the following predictions. If these are found wrong, then the hypothesis should be rejected.

1. Inter-postsynaptic LINK formation is expected to occur by rapid removal of water of hydration between the abutted spines at which converging stimuli arrive simultaneously. Since this is a high energy requiring process, rapid reversal of this change is expected. This mechanism is expected at locations responsible for perception and working memory (Vadakkan 2015, 2017).

2. Inter-postsynaptic LINKs are expected to get stabilized for different duration of time by reversible membrane hemifusion. Further stabilization is expected to occur by insertion of certain trans-membrane proteins (Vadakkan, 2016).

3. Artificially changing the frequency of oscillating potentials in the olfactory glomerulus in *Drosophila* will lead to changes in the net semblance for olfactory perception that will alter olfactory perception (Vadakkan, 2015).

4. Blocking large number of inter-postsynaptic functional LINKs either in the visual cortex of mammals or in the glomerulus of olfactory path in *Drosophila* is expected to alter the horizontal component of oscillating potentials, which will alter the frequency of oscillating potentials and disrupt visual or olfactory perception respectively (Vadakkan, 2015).

5. Inter-postsynaptic membrane hemifusion that physically separates the postsynaptic cytoplasmic compartments can be observed using microscopes of high resolution. The average surface area of a dendritic spine ranges from 0.61 to 3.14 μm^2 (Wilson et al., 1983). Inter-spine LINKs spanning only a few nanometers are similar to the observed inter-membrane interaction occurring at comparable lengths by using artificial membranes (Leikin et al., 1987). IPLs of this length can serve the expected functions. Therefore, dedicated high-resolution microscopic examination to view the lipid bilayers (Kuwajima et al., 2013) from locations of convergence such as the hippocampus, amygdala is expected to show the presence of inter-spine inter-membrane LINKs. By using high-resolution microscopic techniques that can resolve real-time changes at nanometer scales (Chen et al., 2014; Balagopalan et al., 2018), it is expected to visualize inter-spine membrane hemifusion changes *in vivo* (Vadakkan, 2016).

6. Injecting different neurons, within one neuronal order, using different lipophilic fluorophores to stain their membranes (Floyd et al., 2008) followed by associative learning is expected to show hemifusion process (Vadakkan, 2016).

7. A robust checkpoint mechanism of specific SNARE proteins such as Q-SNARE possibly by interacting with complexin, syntaxin-3, or other postsynaptic proteins is expected to arrest membrane hemifusion (Vadakkan, 2016).

8. A spectrum of inter-spine LINKs are expected to take place during LTP induction. A reversal of this process is expected to occur during the reversal phase after LTP induction (Vadakkan, 2015, 2016).

9. The strength of LTP induced at different locations of the nervous system for a given distance between the stimulating and recording electrodes will depend on the number of inter-spine LINKs formed during the delay time after stimulation and the peak potentiated effect. This in turn depends on the number of converging inputs, their density, inter-spine extracellular matrix properties and lipid composition of the spine membranes at different locations (Vadakkan, 2017).

10. Kindling induced at the Schaffer collateral area is expected to produce more inter-spine fusion than produced by LTP induction at the same location. Following kindling, the fused areas are expected to be large and are expected to remain irreversible when compared to mostly small and reversible fused inter-spine areas induced by LTP (Vadakkan, 2017).

11. It should be possible to carry out the gold standard test of replication of the mechanism in engineered systems (Vadakkan, 2016).

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