A Theoretical Model to Explain the Symptoms and Progression of Schizophrenia

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Abstract

Through the use of a simplified model of consciousness this paper illustrates the symptoms of schizophrenia linked to neocortical structures and functions. It makes the case that the bewildering and varied presentation of symptoms in schizophrenia can be analyzed and explained using such models. The model is used to illustrate the central thesis of the paper, that schizophrenia is a disorder of neurogenesis which leads to progressive neurochemical, functional and neurophysiological changes that create the characteristic behaviors of the disease.

Keywords: Schizophrenia | Incomplete neurogenesis | Sleep-Wake Cycle | Non-REM Sleep

A Simplified Large-Structure Model of Human Consciousness

Recent function MRI studies lead to the discovery that the basal ganglia, the cerebellum and the cerebral cortex form an integrated, topographically organized network that interconnects sensory motor and cognitive functions in the human brain. [1] Synaptic activity from most of the cortical regions was found to loop through the cerebellum back to the prefrontal cortex (PFC). These findings are the basis for a model of consciousness presented here.

The term "stream of consciousness" is often used to characterize the self-referential duality of the conscious mind. Consciousness is modeled here not as a stream, but rather as a "cognitive loop". Further, neuroscientists have theorized that the cerebellum may be responsible for **predicting** or automating rules for social and emotional interactions, and most significantly, cognition. [2]

In the loop theory of consciousness, each loop is a recorded "moment". Each moment the waking human brain receives sensory input which stimulates a cascade of synaptic patterns that arrive in the cerebellum, hippocampus and neocortex, stimulating secondary synaptic patterns through the cerebellum, neocortex, and back to the hippocampus. The initial sensory input becomes a short-term memory of a simple sensory event followed by layers of association, emotion and thought that arrive in the cerebellum in a

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predictable order that was determined by chance and by choice in early childhood, and familiar to the higher reasoning and planning regions of the neocortex. This set of remembered sense and stimulated responses supply the temporal context for the next loop/moment and successive moments. This allows the PFC and cerebellum to stitch discreet samples together into a consistent internal narrative of external reality, consciousness and continuous time.

That is not to assert that cognitive loops are strictly consecutive. Cognitive loops follow long and complex neural pathways resulting in long propagation times relative to the speed of sensory stimulus. Consecutive sensory samples arrive to start each new cognitive loop long before the previous loop has completed. Multiple cognitive loops of incremental maturity propagate simultaneously through the cognitive loop to temporary storage in the hippocampus. Thus the interval between successive cognitive loops is determined by the by the arrival of successive sensory samples. Each cognitive loop is fixed to its sensory moment, and the moments perceived in order by the reasoning conscious elements of the neocortex creating an orderly and progressive temporal context.

Theoretically, in the early stage of schizophrenia, the temporal context is occasionally disordered. Sensory events may trigger visual, emotional or cognitive associations in varying order, or from an earlier time that diverges from the internal rules formatted in childhood and adolescence. The executive PFC functions are forced to filter out-of-context information, possibly providing training in analysis of conflicting or disjointed stimuli. However, as the condition progresses the temporal context becomes increasingly noisy and disordered causing the narrative of reality and continuity of time to become increasingly unreliable. In psychotic episodes the noise overwhelms the capacity of the neocortex to filter it into a consistent conscious narrative connected with current (real) sensory events.

A Theory of Initial Cause

Theoretically the neurochemical initiator of schizophrenia is present in early life, and could be detected in childhood as early as by six years of age. It is no coincidence that schizophrenia usually presents in

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adolescence or early adulthood. That is roughly coincident-with or shortly after cessation of skeletal growth and levels of Growth Hormone (GH) drop. Normally, after adolescence GH continues to be released during Non-REM sleep by the pituitary, neurons in the hippocampus and possibly other neocortical regions in gradually decreasing amounts through adulthood. Hypothetically, in an adolescent or young adult with schizophrenia, the NREM release of GH is well below normal, at a level consistent with that seen in geriatric adults. In theory GH mediates synaptic growth in the formation of permanent memory and cognitive cortical connections during NREM sleep. In persons with schizophrenia the pituitary and/or neocortical neurons fail to release GH in normal amounts during NREM sleep. Through childhood and adolescence there would be sufficient GH circulating to facilitate musculoskeletal growth to allow efficient synaptic growth to proceed. Theoretically once this source of GH is lost the synaptic consolidation of long-term synaptic memory and cortical cognitive connections would be compromised. This could lead to episodic deficits in working memory, and cognitive difficulties that become chronic as the disease progresses.

The evidence that a disorder of neurogenesis is involved in the development of schizophrenia is subtle, but can be found in brain imaging studies from the last 30 years. There is ample evidence from brain imaging studies of schizophrenics that have shown significant gray matter loss and reduced cortical volume following onset of the disease. [3] This has been recently been ascribed to glutamatergic neurotoxicity in what has been called the “glutamate hypothesis”. [4] However, the glutamate hypothesis does not specify a cause of glutamate dysregulation nor does it completely explain the degenerative changes in the schizophrenic neocortex. [5] For example excitotoxicity would be responsible for neuronal loss through apoptosis but this is not prominent as the disease progresses. Excitotoxicity can explain the “positive” symptoms of psychosis, agitation, mania and hallucinations, but not the “negative” symptoms of psychosis, the loss of initiative, cognitive deficits, and diminished social and emotional responsiveness.

In this theory glutamate excitotoxicity is an important contributor to the symptoms of schizophrenia and neuronal death but it is the disruption of the fundamental process of neurogenesis that is the primary

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cause of the disease. In this view, the pruning of synaptic connections that is a normal part of neuronal plasticity continues unabated in schizophrenics. But because neurogenesis is compromised new connections are not formed to replace them. The primary driver of the reduction in cortical volume and negative symptoms of schizophrenia are primarily due to the net loss of synaptic connections.

Disruption of the Sleep-Wake Cycle

Accepting that long-term synaptic connections are formed during NREM sleep begs the question, "Which connections?" While it is widely believed that memory consolidation and memory-cortical connection occurs during NREM sleep, in this theory is memory consolidation is a two stage process with discrete contributions during REM and NREM sleep. In theory the function of REM sleep is triage.

To explain the REM triage function we define "strongly stimulatory" memories as short-term or temporary memories that provoke strong synaptic responses from the neocortex. During REM the neocortex and hippocampus potentiate strongly stimulatory memories for preservation through neurogenesis during NREM, and by omission designate weakly stimulatory memories for removal during the NREM cycle. In theory, cognitive loop processing during REM would be used to prepare the connections for neurogenesis while current sensory input and voluntary motor functions are switched off. The hippocampus would present short-term memories to the executive functions of the PFC which would assemble them into a reprised narrative of the memories to be preserved. But during REM sleep the cognitive loop is not constrained to preserve temporal context. The original sensory event and the corresponding stimulated responses are already recorded. All of the sensory/cognitive loop could be sent through the PFC and hippocampus in random order without the propagation delays in the original acquisition. The executive functions would then attempt to assemble this into a consistent narrative that we call a dream. The distinctive rapid eye movement of REM sleep is a consequence part of the integration of spatial memory. In the theory that there is survival value in remembering the precise spatial context of strongly stimulatory visual memories, particularly with respect to social interaction, the

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eye movement preserves a positional context relative to the head. The eye movement is rapid because during REM sleep visual memories can fire in any order disconnected from the temporal context and order in which they were acquired.

Depending upon its severity schizophrenia very much resembles a waking dream, or a waking nightmare. In theory, the disconnection of temporal context typical of REM sleep becomes episodic during the wake cycle. It is no coincidence that the symptoms of schizophrenia mimic those of sleep deprivation. The reason is that efficient memory consolidation through neurogenesis is a function that is essential to cognition, the health of the neocortex, and particularly the health of the hippocampus. Once memories are potentiated for long-term synaptic preservation a neurochemical process is initiated to perform it. But because the neurogenic process is disrupted it does not complete. One explanation would that that insufficient GH is available during NREM to complete neurogenesis. The normal mix of the neurochemicals required to create permanent synaptic connections goes unused and persists in the neocortex and hippocampus potentially until the wake cycle resumes. Also, potentiated memories would persist in the hippocampus without new synapses. Therefore in theory, schizophrenia has the same root cause as Alzheimer's dementia. That is, it is caused by incomplete or ineffective neurogenesis. The differential presentation could be due to the relatively lower bioenergetic potential and general chronic metabolic distress of cortical neurons in Alzheimer's patients. [6]

The memory consolidation neurochemistry of sleep would then be combined with waking neurochemistry. Theoretically this neurochemical dysregulation becomes syndromic. Repeated incomplete synaptic formation would cause memory consolidation neurochemicals to be up-regulated. The heightened levels of the sleep cycle memory consolidation neurochemicals during waking hours would force up-regulation of waking neurochemical release. Repeated cycles of dysregulation and increased synaptic activity put the hippocampus and neocortex under metabolic stress. [7]

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The function of Non-REM Sleep is not merely to facilitate synaptic growth, but to allow the hippocampus and executive neocortex to perform essential maintenance and repair functions free of most of the energy demands of synaptic activity. However theory suggests that the neurochemical environments the sleep-wake cycle would be increasingly similar. The process by which neurochemical memories get converted into synaptic memories would be incomplete so synaptic potentiation would proceed without new synaptic connections. The neurochemical primers for memory potentiation and consolidation would be present while awake and waking neurochemistry would be present during sleep. The low metabolic benefits of NREM sleep would diminish or vanish. The metabolic demands of consciousness could persist throughout the wake-sleep cycle placing the neocortex and particularly the hippocampus under continuous metabolic stress.

The Glutamate Hypothesis

Neural plasticity is crucial for the normal development of brain circuits. Neurogenesis is the essential function that enables neural plasticity throughout the neocortex. However, while individual neurons bear the metabolic burden of neurogenesis, the requirement for new connections is imposed collectively by dispersed cliques of neurons throughout the neocortex. In theory, the bulk of neurogenesis normally occurs during NREM sleep when the metabolic load of conscious synaptic activity is absent. At that time glutamate uptake and energy production can be devoted to neurogenesis, repair and maintenance functions.

However, if the neurogenic process is interrupted such that the metabolic potential is not utilized, the glutamate taken up to support neurogenesis becomes a temporarily dysregulated waste product. The consequence is a heightened metabolic potential during the wake-sleep cycle and theoretically, a lower threshold to excite a synaptic response to stimulus. Affected neurons would respond to stimuli that would normally be inhibited therefore potentially producing synaptic responses that are inconsistent with the cognitive temporal context when awake, and disruptive to NREM processes.

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Any increased synaptic activity of isolated cliques of neurons would propagate through the entire cognitive loop. This would increase the metabolic requirement to support greater synaptic activity through the entire neocortical network. Theoretically glutamate uptake would generally increase and glutamatergic neurons would increase glutamate output to compensate. Repeated cycles of interrupted neurogenesis, glutamate dysregulation, increased synaptic activity leading to increased glutamate production could create metabolic stress due to what has been termed "glutamate toxicity" in a syndromic process.

Conclusion

Neurogenesis is a fundamental process that is essential for neural plasticity in a healthy brain. In theory a disruption of neurogenesis is the root cause of schizophrenia and Alzheimer's disease. In both cases theory asserts that the process of neurogenesis is mediated by the timely release of GH principally during NREM sleep and that reduced levels of GH are principally responsible for interruptions in the neurogenic process. This results in glutamate dysregulation, disruption of NREM processes and increasing levels of neural metabolic stress and dementia. Treatments that reduce glutamate uptake or response have therapeutic benefit in schizophrenia, but do not treat the root cause.

In theory, the presence or absence of GH release during NREM sleep could be a reliable predictor of the development of schizophrenia and Alzheimer's disease. However, regardless of whether GH levels are a primary cause of disruptions of neurogenesis, in theory a treatment that restores normal sleep-wake neurochemistry and neurogenesis will short-circuit the glutamate dysregulation syndrome, correct the decimation of synaptic connections and produce better outcomes for schizophrenia and Alzheimer's patients.

References

1. Bostan, Strick. "The basal ganglia and the cerebellum: nodes in an integrated network", *Nature Reviews Neuroscience* volume 19, pages338–350 (2018)
2. Koziol, Budding, Andreasen, D'Arrigo, Bulgheroni, et al. "Consensus paper: the cerebellum's role in movement and cognition", *Cerebellum* 2014 Feb;13(1):151-77
3. Anderson, Voineskos, Mulsant, George, McKenzie. "The Role of Untreated Psychosis in Neurodegeneration: A Review of Hypothesized Mechanisms of Neurotoxicity in First-Episode Psychosis." *Canadian Journal of Psychiatry, 2014. Revue Canadienne de Psychiatrie*, *59*(10), 513–517.
4. Moghaddam, Javitt,. "From Revolution to Evolution: The Glutamate Hypothesis of Schizophrenia and its Implication for Treatment." *Neuropsychopharmacology*, 2012, *37*(1), 4–15.
5. Iritani. "WHAT HAPPENS IN THE BRAIN OF SCHIZOPHRENIA PATIENTS?: AN INVESTIGATION FROM THE VIEWPOINT OF NEUROPATHOLOGY." *Nagoya Journal of Medical Science*, 2013, *75*(1-2), 11–28.
6. Overholt, M. Metabolic and Hormonal Contributors to Neuronal Necrosis in Alzheimer's Dementia. Preprints 2018, 2018050335 (doi: 10.20944/preprints201805.0335.v2).
7. Camandola, Mattson. "Review: Brain metabolism in health, aging,and neurodegeneration". *Embo Journal* 2017, 201695810