Comment on “Psychiatric Disorders and Neural Mechanisms: How are They Connected?” By William Bechtel

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- A bold topic. There is a large graveyard full of “neural” theories of major psychiatric disorders.
- I want to focus on what I might term the typology of possible “mechanistic accounts” that Bechtel outlined.
- He suggests three possibilities:
- 1. “A collection of components whose operation produces the symptoms of a disease as a **disease mechanism**.”
- 2. “A broken mechanism that when **operating normally** performs a function in the healthy organism.”

- 3. “altered functioning of a network of control mechanisms.”
- For the last form of network dysfunction, he uses the example of cancer cells. From their own perspective, it is possible to be a “good cancer cell” purring away. From the organism’s perspective of course, it is working with an entirely perverted mechanism.
- He then develops this ideas as applied to major depression (MD) and analyzes in some detail the case of serotonin and circadian rhythms.
- He favors the third model and writes, in his conclusion: “The focus should not be on specific mechanisms but on network of control mechanisms that is altered and then has widespread consequences including psychopathologies. “
- I was intrigued by this typology and decided to take it for a test drive – to try applying it to three “neural” theories of psychiatric disorders – two for schizophrenia and one for panic disorder.

Neuropsychology of schizophrenia

What are the implications of intellectual and experiential abnormalities for the neurobiology of schizophrenia?

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Frith, C. (1996). Neuropsychology of schizophrenia: What are the implications of intellectual and experimental abnormalities for the neurobiology of schizophrenia?. *British medical bulletin*, *52*(3), 618-626.

The diagnosis of schizophrenia is largely based on reports of bizarre experiences such as having alien thoughts inserted into one's mind. Many patients with this diagnosis show a marked intellectual decline and particular problems with tasks involving certain kinds of memory or requiring mental flexibility. Similar patterns of performance can be seen in patients with damage in the prefrontal cortex. However, patients with schizophrenia show a very varied pattern of impairments relating to their current mental state. Chronic patients with negative features, such as poverty of speech, are most likely to show poor test performance, while the presence of severe hallucinations and delusions need not be associated with any impairment. A cognitive approach suggests that hallucinations and delusions result from the patient attributing his own actions to an external agency. This error is due to an inability to distinguish between external events and perceptual changes caused by his own actions. The basis of this failure could be a functional disconnection between frontal brain areas concerned with action and posterior areas concerned with perception.

- Phenomenon of “made actions” in schizophrenia – a “Schneiderian” symptom
- Normal function to be able to complete complex movements flawlessly:
  - Decision to move arm → send signal to spinal cord and hence to muscles and efferent copy to “feed-forward center” in prefrontal cortex.
- Test of “mineness” → inquire from feed-forward center “Is it one of ours?”
- In schizophrenia, signal to spinal cord transmits well but efferent copy to “feed-forward center” degrades.
- So, the movement fails the test of “mineness” and is attributed to outside agency.
- Decision to move arm → signal to spinal cord and arm moves but efferent copy to “feed-forward center” does not arrive → inquire from feed-forward center “Is it one of ours?” → Answer “No” so perceived as a “Made action.”

False Suffocation Alarms, Spontaneous Panics, and Related Conditions

An Integrative Hypothesis

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• A carbon dioxide hypersensitivity theory of panic has been posited. We hypothesize more broadly that a physiologic misinterpretation by a suffocation monitor misfires an evolved suffocation alarm system. This produces sudden respiratory distress followed swiftly by a brief hyperventilation, panic, and the urge to flee. Carbon dioxide hypersensitivity is seen as due to the deranged suffocation alarm monitor. If other indicators of potential suffocation provoke panic, this theoretical extension is supported. We broadly pursue this theory by examining Ondine's curse as the physiologic and pharmacologic converse of panic disorder, splitting panic in terms of symptomatology and challenge studies, reevaluating the role of hyperventilation, and reinterpreting the contagiousness of sighing and yawning, as well as mass hysteria. Further, the phenomena of panic during relaxation and sleep, late luteal phase dysphoric disorder, pregnancy, childbirth, pulmonary disease, separation anxiety, and treatment are used to test and illuminate the suffocation false alarm theory.

(*Arch Gen Psychiatry*. 1993;50:306-317)

common fear reported by many normal subjects,[6] indicating a common adaptation. Claustrophobia and panic disorder overlap since many claustrophobes also panic in nonenclosed spaces. In the study of S. J. Rachman, PhD (written communication, April 18, 1991), almost half of the claustrophobic subjects also reported panics in nonenclosed places, although these were not classifed as "spontaneous" or "situational."

Reactions to psychosocial indicators of suffocation broaden our perspective beyond carbon dioxide to other releasing stimuli. During World War I, "gas hysteria" caused entire army units to break ranks and run without objective provocation.[7]

Modern, cocoonlike full protective gear caused three of 70 to panic immediately after donning the protective mask.[7] They manifested hyperventilation, shaking, confusion, and fear of dying. Eleven others had marked anxiety and hyperventilation within the first 10 minutes, which came under control only after removal of all protective gear.

- The Suffocation false-alarm theory of panic disorder. Interestingly, in his 1993 paper, Klein writes that his model infers a failure “of a particular evolved adaptive system.”
- Facts
  - Presence in the brain and periphery of sensitive measures of arterial CO_2
  - Rising CO_2 suggests that suffocation may be imminent, e.g. in a cave-in or forced underwater for a prolonged period. This is an extremely aversive stimulus. Getting to oxygen is vital for survival. Evolution would favor a system where all physical and hormonal resources are put to getting to air.
  - Indirect evidence that such a CO_2 detection system might be over-sensitive in a subgroup of individuals with panic disorder.

- So, hypothesized mechanism is very simple
- Modest “blip” upward in arterial CO_2 → suffocation alarm systems fires (inappropriately) → panic attack.

ARTICLE

doi:10.1038/nature16549

Schizophrenia risk from complex variation of complement component 4

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Schizophrenia is a heritable brain illness with unknown pathogenic mechanisms. Schizophrenia's strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus, but the genes and molecular mechanisms accounting for this have been challenging to identify. Here we show that this association arises in part from many structurally diverse alleles of the complement component 4 (*C4*) genes. We found that these alleles generated widely varying levels of *C4A* and *C4B* expression in the brain, with each common *C4* allele associating with schizophrenia in proportion to its tendency to generate greater expression of *C4A*. Human C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

- Facts :
  - Presence of C4A risk variants on Chromosome 6 → increased risk for schizophrenia
  - Presence of C4A risk variants on Chromosome 6 → increased C4A expression in brain in mice
  - Presence of C4A risk variants on Chromosome 6 → increased C4A expression in post-mortem brain samples in schizophrenics versus controls
  - Increased C4A expression in brain in mice → increased synaptic pruning.
  - Evidence that individuals with schizophrenia, compared to controls, have experienced excess synaptic pruning.

- So, presence of C4A risk variants on Chromosome 6 → increased C4A expression in brain → increased synaptic pruning → schizophrenia.

- How would our three “toy” etiologic models fit into Bechtel’s typology?

Made Actions

- “Made actions” – This has some features of his model 2
  - A broken mechanism that when operating normally performs a function in the healthy organism, where the broken mechanism is the feed-forward system.
- But, as we understand how “mineness” for other aspects of mental functioning, especially thoughts and “our “inner voice”, we would hope to learn more about the broader control mechanisms of which the made action would be one example. So perhaps, his third model (“altered functioning of a network of control mechanisms”) would provide a better and more comprehensive explanation for this class of clinical phenomenon in schizophrenia giving us a more generalized model.

Panic Attacks

- Panic attacks seem to fit best his model 2:
- A broken mechanism that when operating normally performs a function in the healthy organism.
- But perhaps as we know more of a broader account of how the organism responds to changing CO_2 levels, we could apply his model 3. But maybe not.

Complement 4a and Schizophrenia

- Harder. Likely that C4a is part of a finely tuned system that, which working properly, produces an optimal level of synaptic pruning that produces a maximally efficient CNS. There are surely a range of control mechanisms that influence this and the genetic variants that up-regulates C4a is one of many.
- At our current understanding, this simple story looks more like model 2. Levels of C4a normally produce and optimal synaptic pruning but with these variants, the system goes into overdrive producing disease.
- But, we could predict that there are likely other ways that excess pruning could occur which would also predispose to schizophrenia.

Complement 4a and Schizophrenia

- So where we would like to get to scientifically, is to understand the entire system that governs levels of pruning. Then our goal would be to apply Bechtel's model 3 – to understand the network of control mechanisms – thereby clarifying the multiple lines of disturbances that could predispose to schizophrenia.