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Linking Brain to Behavior in Normals and Schizophrenics

An outstanding problem in psychology and neuroscience concerns how to link discoveries about brain mechanisms to the behaviors that they control. A related problem in psychiatry is to understand how abnormal behaviors arise from breakdowns in the brain mechanisms that govern normal behaviors. During the past few decades, neural models have been getting developed of how normal cognitive and emotional processes learn from the environment, focus attention and act upon motivationally important events, and cope with unexpected events. When arousal or volitional signals in these models are suitably altered, they give rise to symptoms that strikingly resemble negative and positive symptoms of schizophrenia, including flat affect, impoverishment of will, attentional problems, loss of a theory of mind, thought derailment, hallucinations, and delusions. These models thus suggest how an *imbalance* that is created in otherwise normal brain mechanisms can ramify throughout the brain to create the clinical symptoms that are observed.

Another key theme in these models is that constraints on brain development and learning greatly constrain the kinds of information processing that govern both normal and abnormal behaviors. For example, one of these models is called a CogEM model, because it joins together Cognitive, Emotional, and Motor processes (Grossberg, 1982, 1984b). The CogEM model tries to explain how emotional centers of the brain, such as the amygdala, interact with sensory and prefrontal cortices (notably ventral, or orbital, prefrontal cortex) to generate affective states, attend to motivationally salient sensory events, and elicit motivated behaviors. Closing the feedback loop between cognitive and emotional centers is predicted to generate a cognitive-emotional resonance that can support conscious awareness. When such emotional centers become depressed, negative symptoms of schizophrenia emerge in the model (Grossberg, 1984a, 2000b), as summarized below. Such emotional centers are modeled as opponent affective processes, such as fear and relief, whose response amplitude and sensitivity are calibrated by an arousal level and chemical transmitters that slowly inactivate, or habituate, in an activity-dependent way. These opponent processes exhibit an Inverted-U whereby behavior become depressed if the arousal level is chosen too large or too small. Underaroused and overaroused depression can be distinguished clinically by their parametric properties. Negative symptoms are proposed to be due to the way in which depressed affective opponent processes interact with other circuits, notably cognitive and motor circuits, throughout the brain.

A related model suggests how brain mechanisms of cognitive learning, attention, and volition work, and may give rise to positive symptoms like hallucinations during schizophrenia and other mental disorders. This Adaptive Resonance theory, or ART, model (Grossberg, 1980, 1999b) proposes an answer to the "stability-plasticity dilemma;" namely, how the brain can learn quickly throughout life without being forced to forget previously learned memories just as quickly. ART proposes how normal learning and memory may be stabilized through the use of learned top-down expectations. In other words, we are "intentional" beings so that we can learn quickly without suffering

catastrophic forgetting. These expectations learn prototypes that are capable of focusing attention upon the combinations of features that comprise conscious perceptual experiences. When top-down expectations are active in a priming situation in the absence of bottom-up information, they can modulate or sensitize their target cells to respond more effectively to future bottom-up information that matches the prototype. Such expectations cannot, however, fully activate these target cells under most circumstances. When bottom-up inputs do occur, an active top-down expectation selects the cells whose input features are consistent with the active prototype, and suppresses those that are not. This matching process can synchronize and amplify the activities of selected cells. Such a matching process has been mathematically proved to be necessary to stabilize the memory of learned representations in response to a complex input environment (e.g., Carpenter and Grossberg, 1991). In order to realize these matching properties, top-down expectations and attention were predicted to be controlled by top-down on-center off-surround networks. A balance between top-down excitation and inhibition in the on-center of this network leads to the modulatory effect in the on-center on its target cells, even while cells that are in the off-surround may be strongly inhibited. Recent psychophysical and neurophysiological data have supported this prediction; see Raizada and Grossberg (2003) for a review.

The ART model proposes how the brain has exploited the modulatory property of expectations and attention to enable fantasy, imagery, and planning activities to occur. In particular, phasic volitional signals can shift the balance between excitation and inhibition to favor net excitatory activation when a top-down expectation is active. Such a volitionally-mediated shift enables top-down expectations, in the absence of supportive bottom-up inputs, to cause conscious experiences of imagery and inner speech, and thereby to enable fantasy and planning activities to occur. If, however, these volitional signals become tonically hyperactive during a mental disorder, the top-down expectations can give rise to conscious experiences in the absence of bottom-up inputs and volition. Many data about schizophrenic hallucinations can be clarified by these model properties (Grossberg, 2000a). Related work has predicted the detailed laminar circuits within the visual cortex wherein these top-down expectations and volitional signals may act, and by extension in other sensory and cognitive neocortical areas (Grossberg, 1999a, Grossberg and Raizada, 2000; Raizada and Grossberg, 2003). ART also predicts that the contents and level of abstractness of learned prototypes may determine the contents and abstractness of hallucinations. A similar breakdown of volition may lead to delusions of control in the motor system.

Attention, Affect, and Volition in Schizophrenia

This CogEM and ART models bring a new perspective to thinking about the well-known fact that schizophrenia involves a loss of attentional control, motivational defects, and disorganized behavior. Kraepelin (1913/1919) early noted that "This behavior is without doubt clearly related to the disorder of attention which we very frequently find conspicuously developed in our patients. It is quite common for them to loss both inclination and ability on their own initiative to keep their attention fixed for any length

of time" (pp. 5-6). Attentional deficits in schizophrenia have also been emphasized by a number of other workers; e.g., Bleuler (1911/1950), Braff (1985) and Mirsky (1969).

Since the time of Kraepelin, many efforts have been made to classify schizophrenic symptoms across distinct patient populations, including the basic classifications into negative and positive symptoms, or deficit and nondeficit symptoms (Buchanan *et al.*, 1997; Bustillo *et al.*, 1997). Liddle (1994) has segregated schizophrenic symptoms into "three distinguishable syndromes: (1) psychomotor poverty (poverty of speech, flat affect, decreased spontaneous movement); (2) disorganisation (disorders of the form of thought, inappropriate affect); and (3) reality distortion (delusions and hallucinations)" (p. 43), which have been supported by several studies (Arndt *et al.*, 1991; Pantelis *et al.*, 1991; Sauer *et al.*, 1991). Liddle suggested that two of these syndromes "reflect volitional disorders: psychomotor poverty reflects a difficulty initiating activity and disorganisation reflects a difficulty in the selection of appropriate activity" (p, 43). Both of these problems are, moreover, associated with impairment in neuropsychological tests of frontal lobe function.

In a different direction, Frith (1992, 1994) has interpreted schizophrenic symptoms as impairments in the processes that underlie a "theory of mind", including the ability to represent beliefs and intentions. For example, when asked to describe photographs of people, schizophrenics described their physical appearance, rather than their mental states (Pilowsky and Bassett, 1980). Frith noted, however, that the theory of mind approach "does not explain the other major feature of negative schizophrenia: their impoverishment of will." (Frith, 1994, p. 150). He also wrote that "mental states include not only affects and emotions, but also goals and intentions. A person who was unaware of their goals could, on the one hand, be a slave to every environmental influence or, on the other hand, be prone to perseverative or stereotyped behaviour, because they would not have the insight to recognize that certain goals were unobtainable or inappropriate" (Frith, 1994, p. 151).

All of these properties have explanations using CogEM and ART. In particular, these models analyze how attention is regulated during normal cognitive and cognitive-emotional interactions, and how it breaks down when these normal processes experience some sort of imbalance. Such models point to processes that have not been as actively considered as they might be towards explaining schizophrenic behavioral symptoms.

Gated Dipole Opponent Processing

One such process is *opponent processing*, whether of opponent emotions, like fear and relief, or of opponent perceptual features, like red and green. Opponent processing plays a key role in controlling the dynamical reset and rebalancing of sensory, cognitive, emotional, and motoric representations in response to rapidly changing environmental inputs. Such opponent processing circuits exhibit a Golden Mean of optimal behavior at an intermediate arousal level (Grossberg, 1972, 1980, 1984a, 1984b). For larger or smaller levels of arousal, behavior deteriorates in different ways, thereby giving rise to an

Inverted-U as a function of arousal level. In particular, when arousal is too small, such an opponent process causes an elevated behavioral threshold, since there is not enough arousal to support a more normal threshold. Paradoxically, it also gives rise to behavioral *hyper*excitability when this elevated threshold is exceeded. When arousal is too small, the opponent process causes a low behavioral threshold. Paradoxically, it also gives rise to behavioral *hypo*excitability when this reduced threshold is exceeded. Due to these properties, an *in*crease in arousal can *de*crease the sensitivity of an underaroused opponent process of this kind, and can bring it into the normal behavioral range. The model proposes that, in this way, a pharmacological "up" like amphetamine can reduce the hypersensitivity of attention deficit disorder children. These properties emerge through interactions across the entire opponent processing circuit. They cannot be understood just by looking at the pharmacology or neurophysiology of individual cells within the circuit. How such opponent processes work during normal behavior and schizophrenia is described in Grossberg (1984a, 1984b, 2000b). When their output signals become depressed, such opponent processes are predicted to lead to various symptoms of flat affect. When their effects ramify throughout the sensory and prefrontal cortices with which they interact, they can lead to all the negative symptoms that are summarized above.

Negative Symptoms as Emergent Properties of System-Wide Interactions

The most immediate effect of a depressed response in the outputs of emotion-representing areas is flat affect, although how this is understood must be carefully evaluated; see below. This defect, in turn, causes an inability to represent others' beliefs and intentions, in the sense that all mental states that depend upon interpreting one's own emotional state, or the emotional states of others, will be diminished. This happens in the CogEM model because emotionally charged sensory inputs, such as the emotional expressions on other people's faces, will activate the appropriate part of inferotemporal cortex but will not elicit an appropriate emotional response from the amygdala and related emotion-representing circuits; see Figure 1. As a result, photos of people would necessarily be described physically, rather than in terms of emotionally relevant mental states (Pilowsky and Bassett, 1980).

Figure 1

A problem with impoverishment of will, as well as with the setting of goals and intentions, will then indirectly arise. This happens in the model because the depressed response of the emotional representations depresses the incentive motivational signals that would normally activate the prefrontal cortex in response to motivationally salient events (Figure 1). As a result, the prefrontal cortex will not be adequately activated, and a hypofrontal condition will emerge (Weinberger, 1988). Due to this hypofrontality, the working memory representations and plans that are ordinarily formed within the prefrontal cortex will be degraded, so goals will not form in a normal fashion.

Given a hypofrontal response, top-down signals from the prefrontal cortex to the sensory cortices will also be reduced or eliminated (Figure 1). As a result, the sensory representations will not be able to use these top-down signals to organize information-processing according to its emotional meaning or motivational goals. Said in another way, motivationally irrelevant information will not be blocked from attention, so it will be able to continually intrude, leading to distractability. Or, in Kraepelin's words, schizophrenics "lose both inclination and ability on their own initiative to keep their attention fixed for any length of time."

Neurobiological Correlates

The CogEM model also clarifies the following types of anatomical, neurophysiological, and biochemical data. The amygdala, and related structures, has been identified in both animals and humans to be a brain region that is involved in learning and eliciting memories of experiences with strong emotional significance (Aggleton, 1993; Davis, 1994; Gloor *et al.*, 1982; Halgren *et al.*, 1978; LeDoux, 1993). The orbitofrontal cortex is known to be a major projection area of the ventral, or object-processing, cortical visual stream (Barbas, 1995; Fulton, 1950; Fuster, 1989; Rolls, 1998; Wilson *et al.*, 1993), and cells in the orbitofrontal cortex are sensitive to the reward associations of sensory cues, as well as to how satiated the corresponding drive is at any time (e.g., Mishkin and Aggleton, 1981; Rolls, 1998). Ubiquitous positive feedback occurs between cortical regions (Felleman and Van Essen, 1991; Macchi and Rinvik, 1976; Sillito *et al.*, 1994; Tsumoto, Creutzfeldt, and Legéndy, 1978), including prefrontal and sensory cortices. In addition, the ventral prefrontal cortex and the amygdala are involved in the process by which responses are selected on the basis of their emotional valence and success in achieving rewards (Damasio *et al.*, 1991; Passingham, 1997). In particular, Fuster (1989) has concluded from studies of monkeys that the orbital prefrontal cortex helps to suppress inappropriate responses. These monkey data are consistent with clinical evidence that patients with injury to orbital prefrontal cortex tend to behave in an inappropriate manner (Blumer and Benson, 1975; Liddle, 1994). Other research has suggested that schizophrenia may involve a chronic deficiency in striatal glutamate transmission due to decreased activity in those regions of the prefrontal cortex that project to the striatum (Andreasen, 1990; Carlsson, 1988; Grace, 1991; Lynch, 1992). The CogEM model suggests that one possible cause of decreased prefrontal activity may be a reduction in incentive motivational signals from depressed amygdala circuits that project to the prefrontal cortex.

Some Open Questions and the Need For Quantitative Brain/Behavior Models

A brief verbal summary such as I have just attempted leaves out so many details that it is subject to misinterpretation. In the case of the CogEM and ART models, whatever be their shortcomings, they offer a precise mechanistic explanation of how interactions among model brain mechanisms give rise to normal and abnormal behavioral properties. The same is not true of intuitive and heuristic attempts to explain schizophrenic symptoms which, albeit necessary to advance our understanding, are inherently too weak

to unambiguously bridge the gap between brain and behavior. The discussion above raises a number of questions when it is confronted by various recent data. For example, it has been proposed that some schizophrenics who exhibit symptoms of flat affect may experience more intense emotions than ordinarily supposed, particularly negative emotions, and that flat affect is due to the fact that their observable responses are reduced (e.g., Alpert *et al.* 2000). The essential property for explaining the effects of flat affect in the CogEM model is that a late stage in emotional processing, one that feeds incentive motivational signals to the prefrontal cortex, is depressed and thereby negatively impacts sensory, cognitive, and motoric processing. Earlier stages of emotional processing may be intact without disrupting model predictions. This being said, questions remain about how some of these patients were tested — in particular, using verbal stories about emotional situations is not necessarily a reliable way to assess experienced emotion.

It has been suggested that flat affect may not be a primary symptom of schizophrenia because flat affect and hallucinations to not always covary (Serper *et al.*, 1996). The CogEM and ART models clarify, however, that these two types of symptoms may be due to distinct brain mechanisms. It has also been suggested that the early appearance of flat affect, before schizophrenic symptoms occur, and the fact that it is sometimes not followed by such symptoms (Alpert, 1985), may suggest that it is only a "risk factor" for schizophrenia (Alpert and Angrist, 2003). Given that there are many reasons why an early symptom may not immediately lead to a fully blown syndrome, one might just as well wonder if the early onset does not provide some evidence that it can be a cause. For example, autoreceptors can, in various brain systems, maintain a robust system response until such a large loss is experienced that they can no longer compensate for it. Such compensatory effects may be occurring in, say, the amygdala-to-prefrontal pathways. Experiments to study this and related pathways more closely would be most valuable towards clarifying this issue.

More generally this article points to how well-known psychological processes such as affective opponent processing, top-down expectations, incentive motivation, volitional gating, and attentional blocking may break down in schizophrenics. Neural models like CogEM and ART, by describing these processes clearly and quantitatively, may make it easier to think about and test their implications when they are subjected to one or another kind of imbalance.

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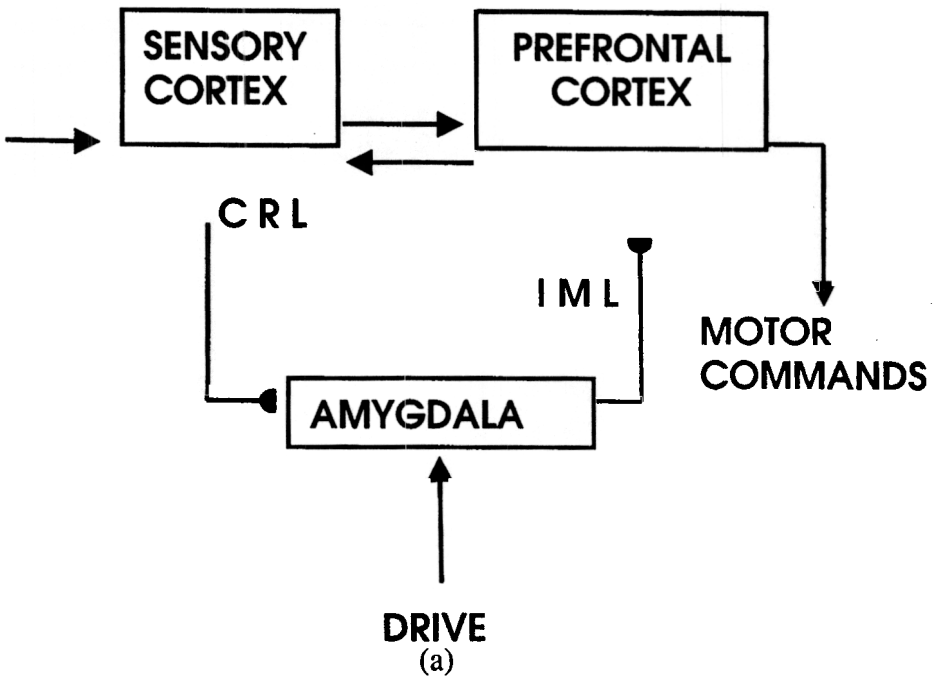
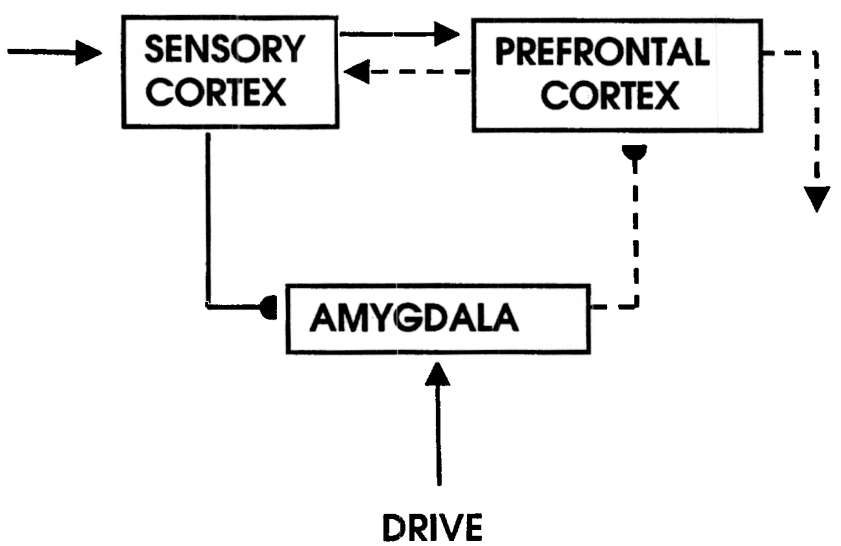


(a)



(b)

1. Figure 1. (a) The simplest CogEM model: Three types of interacting representations (sensory, drive, and motor) that control three types of learning (conditioned reinforcer, incentive motivational, and motor) may be used to explain many learning data. Sensory representations temporarily store internal representations of sensory events. Drive representations are sites where reinforcing and homeostatic, or drive, cues converge to activate emotional responses. Motor representations control the read-out of actions. Conditioned reinforcer learning (CRL) enables sensory events to activate emotional reactions at drive representations. Incentive motivational learning (IML) enables emotions to generate a motivational set that biases the system to process information consistent with that emotion. Motor learning allows sensory and cognitive representations to generate actions. In order to work well, a

sensory representation must have (at least) two successive stages, so that sensory events cannot release actions that are motivationally inappropriate. These stages are interpreted as sensory cortex and prefrontal cortex representations of the sensory event. The prefrontal stage requires motivational support from a drive representation to be fully effective. The amygdala is interpreted as one important part of a drive representation. Amydgala inputs to prefrontal cortex cause feedback to sensory cortex that selectively amplifies and focuses attention upon motivationally relevant sensory events. (b) When a drive representation like the amygdala gets depressed (gray box), diminished activation of its outputs in response to sensory events depresses motivational inputs to the prefrontal cortex in response to emotionally important events, and hereby attenuates motivationally-appropriate signals to and from the prefrontal cortex (dashed lines). As a result, motivationally irrelevant events are not attentionally suppressed, and prefrontally-mediated plans and actions are insufficently activated.