THE IMBALANCED BRAIN: FROM NORMAL BEHAVIOR TO SCHIZOPHRENIA

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ABSTRACT

An outstanding problem in psychiatry concerns how to link discoveries about the pharmacological, neurophysiological, and neuroanatomical substrates of mental disorders to the abnormal behaviors that they control. A related problem concerns how to understand abnormal behaviors on a continuum with normal behaviors. During the past few decades, neural models have been 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. The present article models 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 this 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. 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. The negative symptoms are due to the way in which the depressed opponent process interacts with other circuits throughout the brain.

METHODS AND MATERIALS

1. Introduction: Attention, Affect, and Volition in Schizophrenia

It is well known 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).

These introductory remarks underscore the importance of understanding how brain mechanisms of attention, affect, and volition interact during both normal behavior and schizophrenia. More generally, they raise the fundamental problem of how to link brain to behavior. During the past thirty years, neural models of behavior have been making such a linkage with ever greater precision. These models have typically been derived to explain behavioral data about normal learning and memory. The present article proposes how these normal brain processes can break down to give rise to negative symptoms of schizophrenia. How positive symptoms may arise has been described elsewhere (Grossberg, 1999a).

2. Attentional Modulation of Learning

It is well-known that animals and humans learn to attend to the most reliable non-redundant stimuli in their environment (e.g., Grossberg, 1982b; Kamin, 1969, Staddon, 1983). Attention is controlled by sensory and cognitive expectations, which are matched against sensory inputs. Attention is also controlled by emotional and motivational expectations, which are regulated by learned feedback between cognitive representations and reward and punishment centers. The present article briefly reviews neural models of normal learning during cognitive-emotional interactions to set the stage for suggesting how clinical symptoms may arise when modulatory arousal signals within these models become imbalanced.

For example, Figure 1 summarizes the hypothesis that some symptoms of schizophrenia, Parkinson's disease, attention deficit disorder, and depression are influenced by a type of opponent processing circuit whose net arousal level may be too large or too small in sensory, cognitive, and/or motor circuits, where the particular circuits involved can depend on the disorder. Such opponent processing circuits exhibit a Golden Mean of optimal behavior at an intermediate arousal level (Grossberg, 1972b, 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 (Grossberg, 1972b, 1984a). 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 arise during normal behavior will now be described.

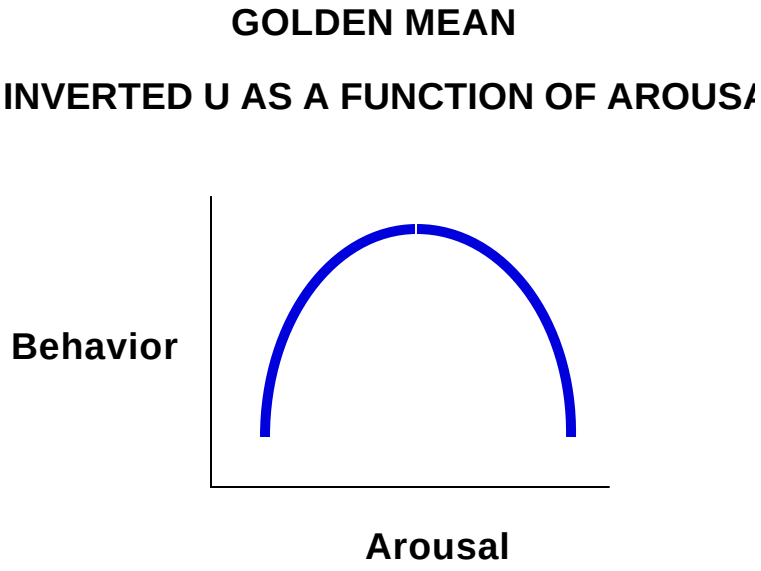

Figure 1. Gated dipole opponent processes exhibit an Inverted-U behavioral response as a function of arousal level, with underaroused and overaroused depressive syndromes occurring at the two ends of the Inverted-U. See text for details.

3. Cognitive-Emotional Interactions and Classical Conditioning

We begin by reviewing data and models concerning the simplest type of associative learning; namely, classical or Pavlovian conditioning (Pavlov, 1927). As shown below, classical conditioning is far more subtle and relevant to complex human cognitive-emotional behavior than one might first realize. During classical conditioning an unconditioned stimulus (US), such as a shock, can elicit an unconditioned response (UR), such as fear. Before conditioning, a conditioned stimulus (CS), such as a bell, does not elicit fear. However, pairing the CS with the US on a number of learning trials enables the CS to acquire some of the reinforcing properties of the shock. It can then elicit a conditioned response (CR), including fear, on its own. When this happens, the CS is called a *conditioned reinforcer*, because it has acquired reinforcing properties through conditioning.

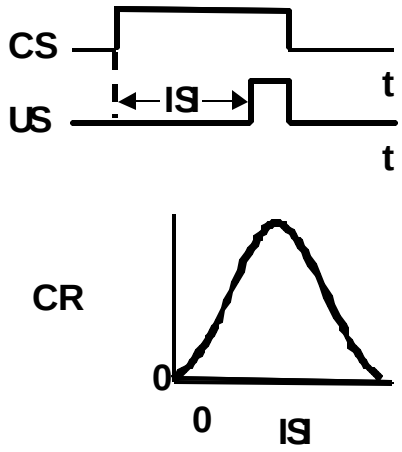

Figure 2. The Interstimulus Interval Effect: The conditioned response (CR) is strongest at a positive value of the Interstimulus Interval, or ISI. It deteriorates at smaller and larger values of this optimal interval.

Several properties of classical conditioning that are relevant to abnormal behaviors are now summarized. The first is the Interstimulus (ISI) Effect (Figure 2): When one varies the ISI between the CS and US and plots the strength of the learned CR, one often finds an Inverted-U curve, which shows that there exists an optimal, non-zero ISI for classical conditioning. Why learning becomes poor at very large ISIs is obvious. But why learning also becomes poor at the zero ISI, where the simultaneous CS and US are "perfectly correlated" is not so obvious. We will come back to this point in a moment.

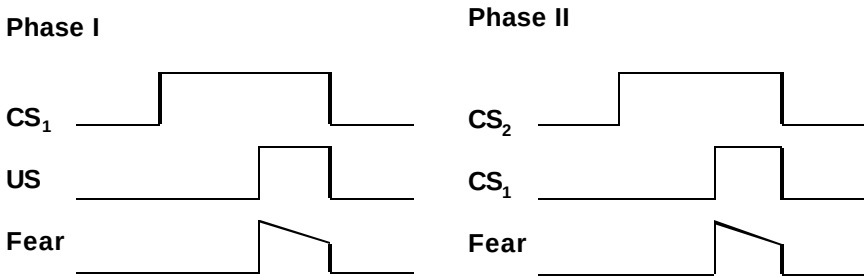

Figure 3. Secondary conditioning: After conditioning CS_1 to become a conditioned reinforcer by pairing it with a US, CS_1 can be used to condition a new CS_2 to become a conditioned reinforcer.

A second important property of classical conditioning is Secondary Conditioning (Figure 3), which is the process whereby conditioned reinforcers can be used as rewards in their own right. Secondary conditioning involves at least two learning phases. In the first phase, a first CS (CS_1) is associated with a US, say shock, until it becomes a conditioned reinforcer that is capable of eliciting fear. In the second learning phase, a new conditioned stimulus (call it CS_2) is paired with the conditioned reinforcer CS_1 until CS_2 also becomes a conditioned reinforcer.

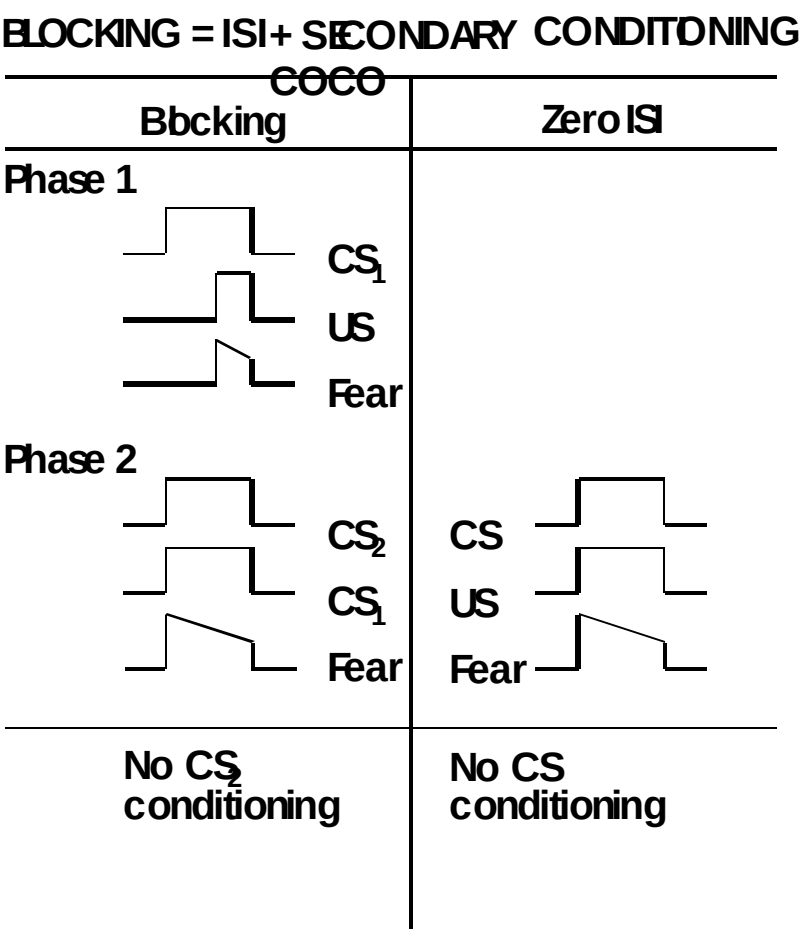

Figure 4: Blocking may be explained by a combin-ation of the mechanisms that explain secondary conditioning and why no conditioning occurs with a zero ISI. See text for details.

When the ISI Effect and Secondary Conditioning are combined, it is possible to understand how classical conditioning is related to processes of selective attention. This linkage is illustrated by the process of Attentional Blocking (Kamin, 1968, 1969; Pavlov, 1927) whereby sensory events that do not predict new rewarding events are not attended. The Blocking paradigm is illustrated in Figure 4. It also involves two phases. Phase I involves the usual classical conditioning whereby a CS (call it CS_1) becomes a conditioned reinforcer by being paired with a US. Phase II presents CS_1 *simultaneously* with a second conditioned reinforcer (call is CS_2) that has not yet been associated with a reinforcer. This simultaneous presentation of cues is followed by the same US as in Phase I. The result is that CS_2 does not become a conditioned reinforcer. For example, in the case where the US is a shock, the learning subject does not respond to CS_2 with fear. Much evidence suggests that this is true because CS_2 is predictively irrelevant; it does not predict anything more than the previously conditioned CS_1 already predicted. This interpretation is supported by the Unblocking paradigm, in which the US in Phase II does not equal the US in Phase I. For example, the shock in Phase II may be chosen much more intense than the shock in Phase I. Under these conditions, CS_2 does become a conditioned reinforcer of fear, because it predicts an increase in shock level.

Figure 4 shows how Attentional Blocking may be understood as the combined effect of the ISI Effect and Secondary Conditioning acting together. The left hand column of Figure 4 summarizes the Blocking paradigm, wherein CS_2 is not conditioned. The right hand column

depicts the zero ISI condition wherein CS is not conditioned. Note that both Blocking and the zero ISI condition involve a simultaneous presentation of an unconditioned CS (CS_2 in the left column, and CS in the right column) and a reinforcer (the conditioned reinforcer CS_1 in the left column, and the primary reinforcer US in the right column). The only difference between these cases is due to the Secondary Conditioning that converts CS_1 into a conditioned reinforcer in the Blocking paradigm. Thus, if we can understand how Secondary Conditioning and the zero ISI effect occur, then we can also understand key properties of Attentional Blocking, and from that, as suggested below, how attentional regulation of learning may break down during schizophrenia.

RESULTS

4. A Neural Model of Cognitive-Emotional Learning

The ISI Effect, Secondary Conditioning, and Attentional Blocking can all be explained, among many other data, using the model summarized in Figure 5. Such a model is called a CogEM model because it explains, perhaps in the simplest possible way, data about interacting Cognitive, Emotional, and Motor learning properties. It was first introduced in Grossberg (1971) and has since undergone substantial development (Grossberg, 1972a, 1972b, 1975, 1982a, 1982b, 1984b; Grossberg and Gutowski, 1987; Grossberg and Levine, 1987; Grossberg and Merrill, 1992, 1996; Grossberg and Schmajuk, 1987). Variants of this model have also been proposed to explain data about learning in invertebrates like *Aplysia* (e.g., Buonomano, Baxter, and Byrne, 1990) and on data about vertebrate thalamocortical substrates of emotional conditioning (e.g., Aggleton, 1993; Davis, 1994; LeDoux, 1993).

Figure 5 summarizes the hypothesis that (at least) three types of internal representation interact during reinforcement learning: sensory and cognitive representations S, drive representations D, and motor representations M. The S representations are thalamocortical representations of external events, including the object recognition categories that are learned by inferotemporal and prefrontal cortical interactions (Desimone, 1991; Gochin, Miller, Gross, and Gerstein, 1991; Harries and Perrett, 1991; Ungerleider and Mishkin, 1982). The D representations include hypothalamic and amygdala circuits at which homeostatic and reinforcing cues converge to generate emotional reactions and motivational decisions (Aggleton, 1993; Bower, 1981; Davis, 1994; Gloor *et al.*, 1982; Halgren *et al.*, 1978; LeDoux, 1993). The M representations include cortical and cerebellar circuits that control discrete adaptive responses (Evarts, 1973; Ito, 1984; Kalaska *et al.*, 1989; Thompson, 1988). More complete models of the internal structure of these several types of representations have been developed elsewhere (e.g., Bullock, Cisek, and Grossberg, 1998; Carpenter and Grossberg, 1994; Contreras-Vidal, Grossberg, and Bullock, 1997; Fiala, Grossberg, and Bullock, 1996; Grossberg, 1987b; Grossberg and Merrill, 1996; Grossberg and Schmajuk, 1987).

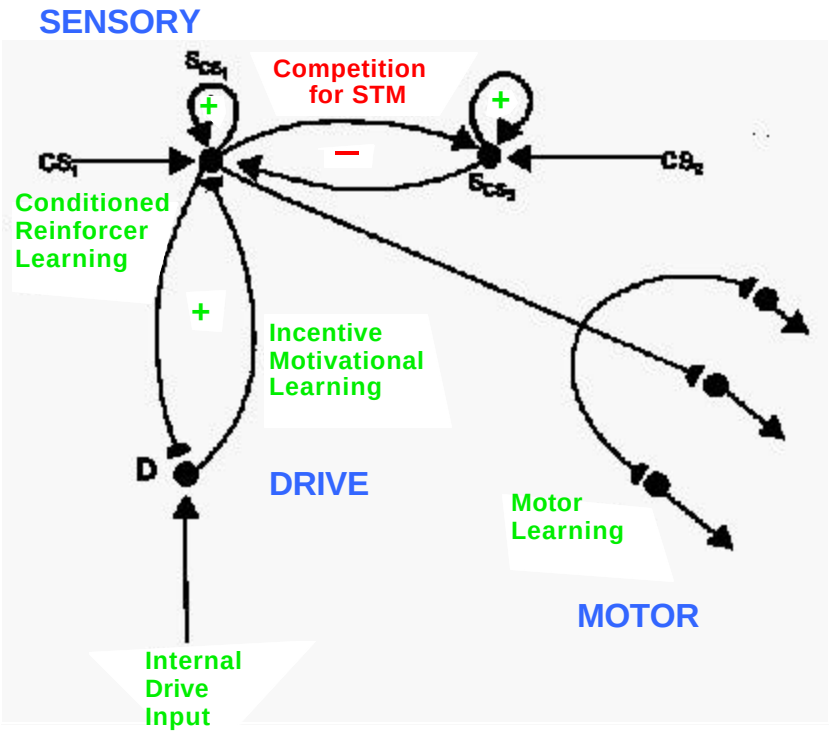

Figure 5: The simplest CogEM model: Three types of interacting representations (sensory, drive, and motor) that control three types of learning (conditioned reinforcer, incentive motivational, and motor) may be used to explain many conditioning data.

Three types of learning take place among these representations: *Conditioned reinforcer learning* strengthens the adaptive weights, or long-term memory traces, in a S → D pathway when a CS activates its sensory representation S just before the drive representation D is activated by an unconditioned stimulus (US), or other previously conditioned reinforcer CSs. The ability of the CS to subsequently activate D via this learned pathway is one of its key properties as a conditioned reinforcer. As these S → D associations are being formed, D → S *incentive motivational learning* also occurs, due to the same pairing of CS and US. Incentive motivational learning enables an activated drive representation D to prime, or modulate, the sensory representations S of all cues, including the CSs, that have consistently been correlated with it. Activating D hereby generates a "motivational set" by priming all of the sensory and cognitive representations that have been associated with that drive's emotion in the past. These incentive motivational signals are a type of motivationally-biased attention. The S → M *motor*, or *habit*, *learning* enables the sensorimotor maps, vectors, and gains that are involved in sensory-motor control to be adaptively calibrated, thereby enabling a CS to read-out correctly calibrated movements.

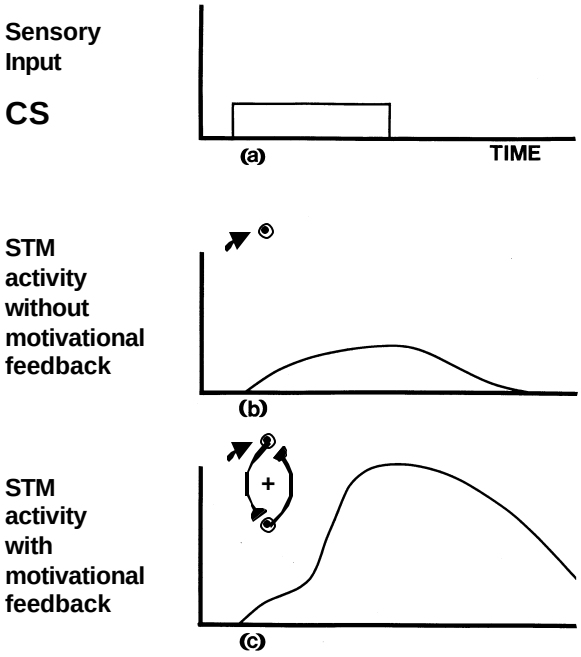

Figure 6. A CS that is not a conditioned reinforcer (row 2) activates its sensory representation less than after it becomes a conditioned reinforcer (row 3) and can use positive feedback from a drive representation to draw attention to itself.

5. Attentional Blocking

The CogEM model explains attentional blocking as a result of three properties interacting together:

1. Conditioned reinforcer CSs can amplify the activation of their sensory representations S via positive feedback from the drive representations D to which they are conditioned.

2. The sensory representations S compete among themselves for a limited capacity short term memory (STM) activation.

3. Other, non-CS, cues lose activation via competition within the limited capacity STM, and can thereby learn slowly if at all.

Property (1) is realized as follows: The combination of learned S $\rightarrow$ D conditioned reinforcer learning and D $\rightarrow$ S incentive motivational learning form a positive feedback loop S $\rightarrow$ D $\rightarrow$ S that is activated when S is turned on by its conditioned reinforcer CS. This positive feedback quickly draws attention to CS by amplifying the activation of its sensory representations (see Figure 6). Said in another way, the conditioned reinforcer uses motivational feedback to drawn attention to itself.

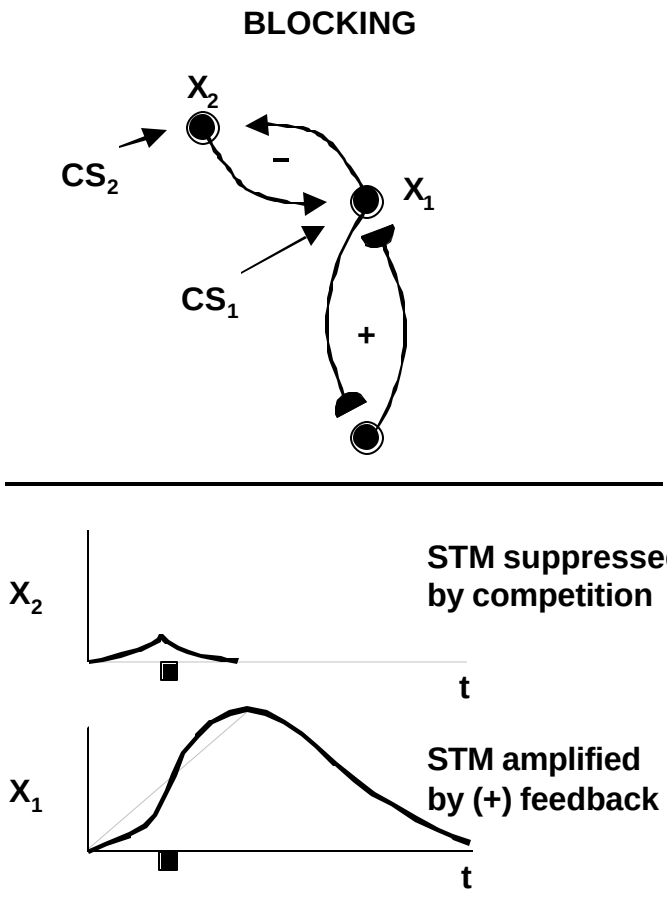

Figure 7: Amplification of a conditioned reinforcer's activa-tion via positive feedback from a drive representation enables it to block competing CSs using lateral inhibition, and thereby prevent them from being attended or generating large output signals.

Property (2) follows from the fact that the sensory representations use recurrent, or feedback, interactions among themselves to store their activities in short-term memory (Baddeley, 1986). This is accomplished by linking the sensory representations by a recurrent on-center off-surround network, whereby cells excite themselves and possibly their immediate neighbors, and inhibit a wider range of cells, possibly including themselves (Figure 5). Such a network enables the sensory representations to store activities that retain their sensitivity to the relative sizes of their inputs, while also tending to conserve, or normalize, the total activity among the active representations (Bradski, Carpenter, and Grossberg, 1994; Grossberg, 1973, 1978a, 1978b; Grossberg and Stone, 1986). This activity normalization property realizes the *limited capacity* of short-term memory, since when one sensory representation gets very active, the representations with which it competes are forced to become much less active. As a result, there is a finite upper bound on how many sensory representations can retain suprathreshold levels of activity at the same time.

The combination of properties (1) and (2) imply property (3), as described in Figure 7. When unattended sensory representations S lose activation due to competition from attended representations, their output signals are correspondingly reduced or eliminated. As a result, any learning that is contingent upon their activation proceeds slowly if at all.

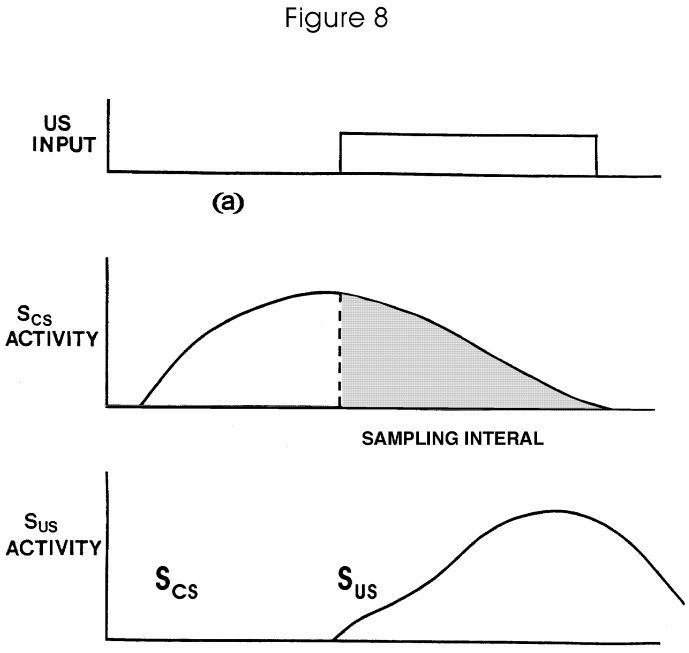

Figure 8. When a CS occurs before a US, it can activate its sensory representation before the US starts to compete with it. Then there is an interval during which the sensory representation of the CS is active, and can be associated with other events, before it is inhibited.

Given that a CS can be blocked by simultaneous occurrence of a primary or conditioned reinforcer, how does conditioning occur when the CS precedes the US? Otherwise expressed, how can we explain the ISI Effect? Figure 8 schematized a proposed answer. If the CS occurs before the US, then its sensory representation S can get highly activated before the US occurs. When the US later occurs, it takes awhile for it to inhibit the active CS sensory representation. The interval after the US turns on and before the CS sensory representation is inhibited is a *sampling* or learning interval. During this learning interval, the CS sensory representation can send signals to D which lead to strengthening of the adaptive weights from S to D, thereby converting CS into a conditioned reinforcer. The signals from D to S, in turn, enable the adaptive weights in their paths to learn also, thereby enabling D to motivationally prime these sensory representations. Finally, the active S representation can also learn sensory-motor associations with M.

In order to generate motivationally appropriate behaviors, the circuit in Figure 7 needs to be refined. One such refinement deals with the following problem. In its present form, after a reinforcing cue activates a sensory representation S, then S can activate a motor representation M at the same time that it sends conditioned reinforcer signals to a drive representation D. Thus a motor response can be initiated before the sensory representation receives incentive motivational feedback to determine whether the sensory cue *should* generate a response at that time. For example, eating behavior could be initiated before the network could determine if it was hungry.

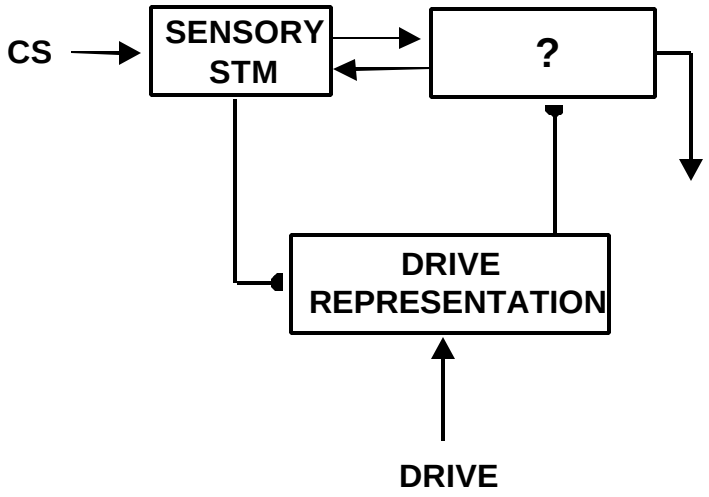

Figure 9. An expanded version of the CogEM model, including at least two stages of sensory representation, is needed to gate commands to motor centers unless they are motivationally appro-priate. The question mark raises the question of what the anatomical locus of the second stage may be.

6. Polyvalent Cortical Cells and Motivational Gating of Attention and Responding

This problem is corrected by using a key property of drive representations D to refine the structure of sensory representations S. In the circuit of Figure 5, each drive representation D obeys a *polyvalent* constraint whereby it can generate incentive motivational output signals to sensory representations only if it gets a sufficiently large primary or conditioned reinforcer input at the same time that it gets a sufficiently large internal drive input. The internal drive input designates whether an internal drive, such as hunger, thirst, sex, etc., is high and in need of satisfaction. Different drive representations exist to represent these distinct internal homeostatic states. Due to the polyvalent constraint at the drive representation, an external reinforcing cue cannot activate strong incentive motivation, and with it action, to satisfy a drive that is already satisfied, because the drive input would be too small to satisfy the drive representation's polyvalent constraint. In contrast, the sensory representations in the circuit of Figure 5 can trigger an action even without incentive motivational support, because these sensory representations do not obey a polyvalent constraint. Imposing such a polyvalent constraint on the sensory representations would prevent them from triggering an action until they get incentive feedback from a motivationally-consistent drive representation. This is done by giving each sensory representation S two successive processing stages, such that the second stage obeys a polyvalent constraint, as in Figure 9.

To see how this polyvalent constraint at S solves the problem, suppose that the first stage of S sends a large reinforcing signal to a drive representation at a time when the drive representation happens also to be receiving a sufficiently large drive input. Then the polyvalent constraint of the drive representation is satisfied and the drive representation can fire. In other words, the drive representation can fire when the drive is not yet satisfied and sensory cues are available that predict drive satisfaction. All the drive representations that are active at that time compete among themselves to allow the most active one---the one that represents the best combination of sensory and drive information at that moment---to fire. Suppose that the winning drive representation delivers a strong incentive motivational signal to the second stage of an active

sensory representation S. Then the polyvalent constraint of the second stage is satisfied, and it can generate output signals. In summary, by making the final stages of both the sensory and the drive representations polyvalent, the S $\rightarrow$ M motor pathways are activated only if the S $\rightarrow$ D $\rightarrow$ S feedback pathway can get sufficiently activated. Then the network generates a strong conditioned response only if it receives enough motivational support. It is worth noting that the second *sensory* stage is also involved in regulating the release of *motor* responses.

The circuit in Figure 9 also shows how positive feedback from the second stage to the first stage of active sensory representations S amplifies only those active first-stage sensory representations whose features are motivationally prepotent in the present context. This amplification of activity enables these sensory representations to attentionally block less salient representations via S $\rightarrow$ S lateral inhibition, as in Figure 7. When this happens, a cognitive-emotional resonance can be established that can support conscious awareness. This resonance is attentionally focused through motivational feedback on emotionally salient information (Grossberg, 1980, 1982b, 1984b; Grossberg and Merrill, 1996)

7. Resonant Interactions between Sensory Cortices, Amygdala, and Orbital Prefrontal Cortex

The circuit in Figure 9 may, in principle, be replicated at multiple stages of thalamocortical and corticocortical processing of sensory events. For example, stage one may be a thalamic stage, and stage two a cortical stage, as in the data of LeDoux (1993). For present purposes, we interpret Figure 9 in terms of the circuit depicted in Figure 10, which shows that many different types of sensory cortex, including visual, somatosensory, auditory, gustatory, and olfactory cortex, are connected to both the amygdala (and other emotional centers) and to the prefrontal cortex, and that the amygdala also sends a strong projection to the prefrontal cortex (Barbas, 1995). This interpretation is given by the model circuit in Figure 11. Here, the various sensory cortices play the role of the first stages of the sensory representations; the ventral, or orbital, prefrontal cortex plays the role of the second stages of the sensory representations; and the amygdala and related structures play the role of the drive representations.

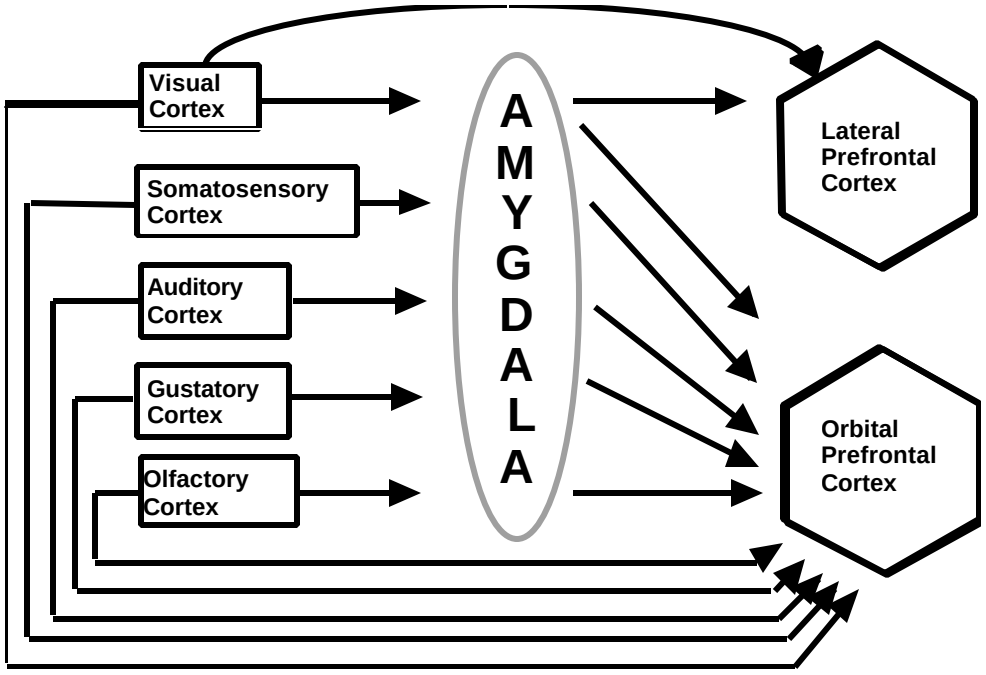

Figure 10. The amygdala receives inputs from many sensory cortices and generates outputs to the prefrontal cortex. The sensory cortices also project to the prefrontal cortex. [Adapted with permission from Barbas (1995).]

The following properties of Figure 11 are consistent with this anatomical interpretation: 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). The feedback between the second and first sensory stages may be interpreted as an example of the ubiquitous positive feedback that 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. Finally, the model is also consistent with data suggesting that 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.

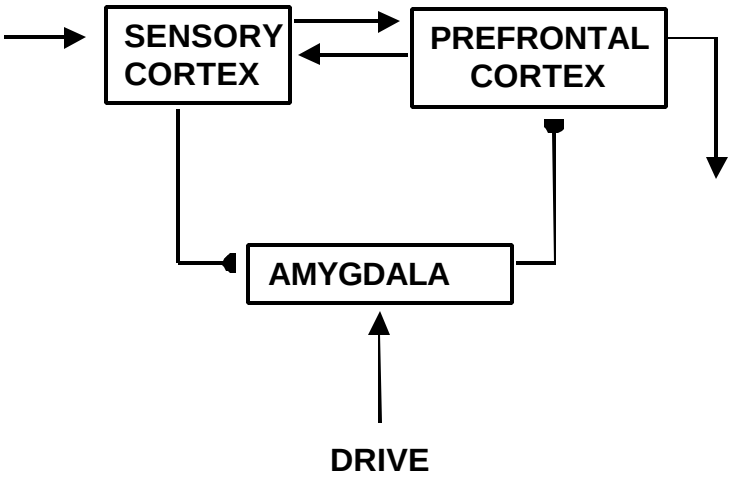

Figure 11. One anatom-ical interpretation of the CogEM model in Figure 9 in terms of the anatomical connections in Figure 10. Multiple copies of CogEM-style connections may occur in other thalamo-cortical and corticocortical circuits.

Interestingly, Damasio (1999, p. 178, Figure 6.1) has proposed a circuit that is very similar to the CogEm circuits in Figures 9-11 to explain how "core consciousness" arises. In his proposal, the first sensory stage is called the "map of object x" and the second sensory stage is called the "second-order map". The drive representation is called the "proto-self". As in the CogEM model, conjoint inputs from the "map of object" and "proto-self" activate the "second-order map" which, in turn, attentionally enhances the "map of object" via top-down feedback. Damasio also notes that these structures bring together the very processes of homeostasis, emotion, attention, and learning (see pp. 272-273) that the CogEM model has been predicting for almost thirty years. The subsequent discussions of schizophrenia can thus be viewed as predictions about how prescribed brain mechanisms may influence core consciousness in schizophrenic patients.

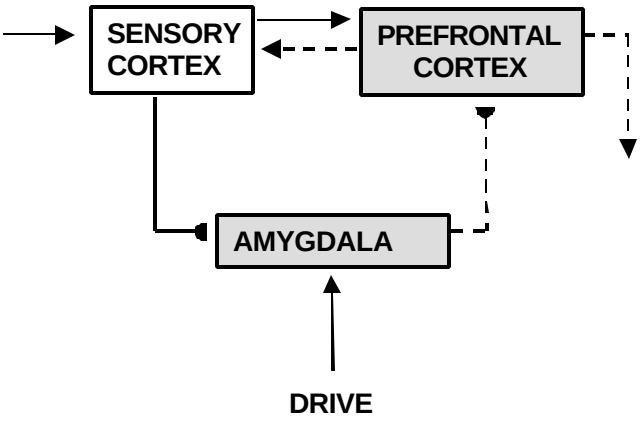

Figure 12. When a drive representation like the amygdala gets depressed, its diminished activation by sensory events prevents normal interpretation of emotionally important events, and also attenuates motivationally-appropriate signals to and from the prefrontal cortex.

8. Depression of the Amygdala and Negative Schizophrenic Symptoms

Suppose that a drive representation, such as the amygdala, generates depressed responses to its inputs, for any of several possible reasons. Such a local imbalance in the model circuit of Figure 11 can generate many negative symptoms that are characteristic of schizophrenia, including the loss of a Theory of Mind (Frith, 1992, 1994), and the impoverishment of will that a Theory of Mind does not explain.

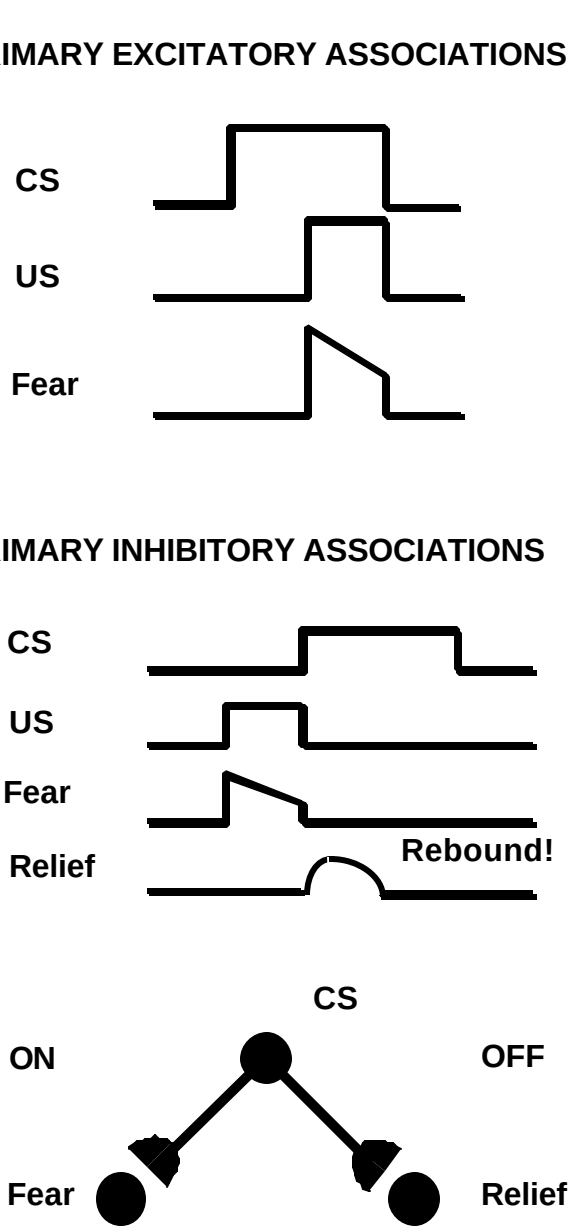

Figure 13. Opponent proces-sing: A given CS can become conditioned both to the onset of a reinforcing event, as well as to its offset. The offset response may be due to an antagonistic rebound of activation within a drive representation that codes an opponent emotional response to the one caused by onset of the reinforcing event.

The most immediate effect of such a depressed response in emotion-representing areas is flat affect. 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 model, as indicated in Figure 12, 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 in the amygdala and related emotion-representing circuits. As a result, photos of people would necessarily be described physically, rather than in terms of emotionally relevant mental states (Pilowsky and Bassett, 1980).

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 circuit of Figure 12 because the depressed

response of the drive representation also depresses the incentive motivational signals that would normally activate the prefrontal cortex in response to motivationally salient events. 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 (see Figure 12). 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."

9. How Drive Representations Get Depressed: Opponent Processing, Antagonistic Rebound, and Arousal

The above theoretical considerations suggest that a depressed drive representation, as in the amygdala, may be one cause of hypofrontality in schizophrenia. This conclusion is complicated by the fact that there are reciprocal connections between the amygdala and the prefrontal cortex (Amaral and Price, 1984; Turner *et al.*, 1980), so questions of cause and effect are hard to disentangle. Let us take the hypothesis at face value in order to explore its implications. In particular, such a hypothesis raises the question of how can a drive representation become depressed? In order to answer this question, we need to ask how drive representations are designed. Such an analysis has undergone several stages of theoretical development. Here only concepts that are crucial for our purposes will be described.

This refinement can be motivated as follows. Up to the present, we have discussed how the *onset* of a rewarding event like a shock acts like a negative reward. It is, however, also well known that the *offset* of a shock can be positively rewarding, and may be used for escape and avoidance learning. For example, as noted in Figure 13, a CS that occurs before a shock US begins can be conditioned to a negatively reinforcing fear response (Estes and Skinner, 1941), but a CS that occurs after a shock US terminates can be conditioned to a positively reinforcing relief response (Denny, 1971). The model proposes that offset of a shock input to cells whose activation subserves fear causes an *antagonistic rebound* of activation at cells that subserve relief. Similar rebound properties occur during instrumental, or operant, conditioning (Reynolds, 1968). The cells at which fear and relief are represented form an opponent processing circuit. Each CS can potentially get conditioned either to the fear channel or to the relief channel of such an opponent processing circuit.

Opponent processing circuits are ubiquitous in the brain. In addition to their role in controlling emotional conditioning, they also influence perceptual processing, where they are used to

represent opponent colors such as red and green, or perpendicular orientations such as vertical and horizontal, or opposite directions such as up or down (Brown, 1965; Helmholtz, 1866, 1962; Sekuler, 1975). In all of these situations, offset of the ON channel in an opponent process can lead to an antagonistic rebound in the OFF channel. For example, after sustained viewing of a red image, its offset can lead to a negative aftereffect of green. After sustained viewing of water flowing downwards, its offset can lead to a negative aftereffect of upward motion. Motor behaviors may also have an opponent organization, as illustrated by the existence of GO and STOP signals for gating the onset or offset of motor actions in the basal ganglia (Horak and Anderson, 1984a, 1984b), and the opponent organization and control of flexor and extensor muscle groups.

Why is opponent processing so ubiquitous in the nervous system? I have proposed that opponent processing helps the brain to self-organize its neural circuits in a *self-stabilizing* way, both during childhood development and adult learning; that is, it helps to dynamically buffer brain development and learning against catastrophic reorganization by irrelevant environmental fluctuations (e.g., Grossberg, 1980). Antagonistic rebounds within these opponent processes help to *reset* cell activations in response to rapidly changing events, and thereby to help drive a search process for better representations of the world.

Antagonistic rebounds can be triggered within an opponent process in at least two ways: a sudden decrease of a phasic input to one channel of the opponent circuit, and an unexpected event. A sudden decrease of input to one channel (say, the "fear" channel, or the "red" channel) can lead to a transient activation, or antagonistic rebound of activity, in the opponent channel (say, the "relief" channel, or the "green" channel). For example, when there is a sudden decrease of fearful cues in a given situation, then the relief rebound can supply positive motivation with which to learn the sensory-motor contingencies that led to the reduction of fear, or to extinguish a previously fearful memory of a situation that is no longer fearful (cf., Denny, 1971; Grossberg, 1982b, 1984b, 1987b; Masterson, 1970; McAllister and McAllister, 1971a, 1971b; Reynierse and Rizley, 1970). A neural analog is found after electrical stimulation of the hypothalamus: If hypothalamic stimulation elicits a given behavior, then its offset can transiently elicit an opposite behavior (Cox, Kakolewski, and Valenstein, 1969; Valenstein, Cox, and Kakolewski, 1969).

How does offset of an input to the ON channel of an opponent process cause an antagonistic rebound of activation in the OFF channel? In order for this to happen, at least two properties are needed: First, prior activity in the ON channel biases a process in that channel which changes on a slower time scale than the rate with which the input to the ON channel can change. The slower time scale of this process determines how long the ON input needs to be kept on before a strong antagonistic rebound can be elicited. When the ON input shuts off, this slowly varying process biases the response of the opponent circuit to favor activation in the OFF channel. Second, there must be some type of internal input source, or tonically active arousal, that can energize the antagonistic rebound when the phasic ON input shuts off. When these concepts are rigorously implemented in an opponent processing circuit, it follows as a

mathematical consequence that the circuit gets depressed in the manner summarized in Figure 1 when its arousal level becomes too small or too large.

10. Habituative Transmitter Gates as Unbiased Transducers

What is the slowly varying process that calibrates an antagonistic rebound? I suggest that it is a habituative chemical transmitter that multiplicatively gates, or multiplies, signals within the opponent processing channels. A simple derivation of such a transmitter law clarifies how it operates as an *unbiased* transducer of neural signals. Suppose that the input signal is S and the output signal is T. Then the simplest unbiased law is a linear law: T = SB, where B is a constant that determines the gain of the response by T to the input S. Suppose that T is due to release of a chemical transmitter y at a synapse. In this situation, the unbiased law can be rewritten as T = Sy, where y approximately equals B in order to preserve the gain, or sensitivity, of the transduction process. The law T = Sy can be interpreted as a mass action law for the rate which transmitter is released in response to input S and available transmitter y. This law says that y multiplicatively *gates* the input S to produce the output T. The constraint that y approximates B means that y accumulates until it reaches the target level B.

Transmitter y cannot maintain the target level B at all times if it is being released, or inactivated, at rate T, unless the accumulation rate is infinite. No biological process occurs at an infinite rate. The simplest differential equation whereby y can attempt to satisfy both constraints at a finite rate is given in Figure 14. This is the simplest law for a habituative transmitter gate (Grossberg, 1968, 1969, 1980, 1984a, 1984b). It is also called a law for synaptic depression, and has recently attracted a great deal of renewed interest through the experimental and modeling work of Larry Abbott, Henry Markram, and their colleagues (Abbott *et al.*, 1997; Markram *et al.*, 1997; Markram and Tsodkyks, 1996; Tsodyks *et al.*, 1998), which has provided neurophysiological evidence for properties of depressing synapses that had previously been used to model many types of psychophysical data, notably data about visual perception (e.g., Carpenter and Grossberg, 1981; Francis and Grossberg, 1996a, 1996b; Francis, Grossberg, and Mingolla, 1994; Grossberg, 1980, 1987a; Ögmen, 1993; Ögmen and Gagné, 1990).

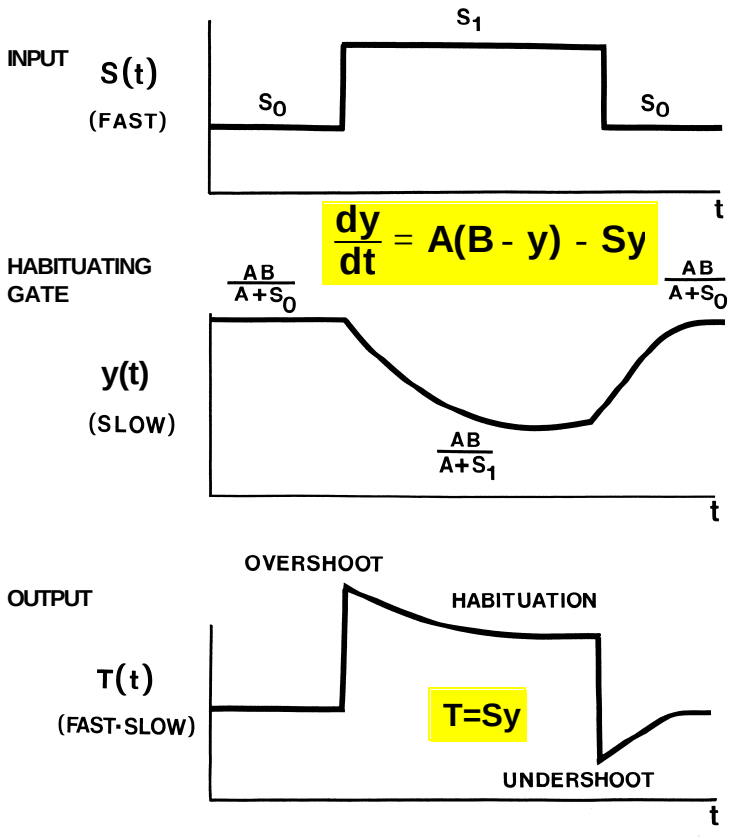

Figure 14. How the output T(t), which is a product of the rapidly varying input S(t) and the more slowing habituating, or depressing, transmitter y(t), generates overshoots and undershoots in response to input steps.

Figure 14 illustrates how, in response to a rapidly changing input signal S(t), a habituative transmitter z(t) can more slowly equilibrate to the input's changing amplitudes. Higher input amplitudes inactivate more transmitter and lead to lower levels of available transmitter; note that transmitter has the input intensity S(t) in its denominator. The transmitter z(t) multiplies, or gates, the input S(t) to generate the output signal T(t) = S(t)z(t). Due to this gating process, monotonic changes in input amplitude S(t) cause overshoots and undershoots in the gated output T(t), before the transmitter gradually equilibrates, or habituates, to the new input level. Right after the input S(t) changes to a new level, during the overshoot or undershoot phase, the output T(t) has the new input level S(t) in its numerator, but the old level of S(t) in its denominator due to the slow rate with which the transmitter changes. The new input level is hereby weighted, or normalized, by the old input level. This is called the *Weber Law* property. It occurs during many types of brain processing, for example during adaptation by the retina to varying levels of light (Carpenter and Grossberg, 1981). This Weber Law property plays a key role in determining the Inverted-U with respect to arousal level in an opponent process, as summarized by Figure 1. In other words, this sort of depression can be traced to how general properties of unbiased chemical transmitter gates interact with mechanisms of opponent processing.

11. Gated Dipole Opponent Processes: Arousal, Transmitters, Signals, Competition, and Thresholds

The opponent processes that are modeled here are called *gated dipoles* because they use transmitter gates to regulate the output from the two poles, or channels, of the opponent process. The paradoxical emergent properties of a gated dipole are due to five basic mechanisms acting together (Grossberg, 1972b, 1980, 1984a, 1984b). Figure 15 depicts the simplest example of a circuit that realizes these mechanisms. The ON channel is turned on by a phasic input, denoted by J in Figure 15; the OFF channel registers the antagonistic rebound that occurs when the phasic input to the ON channel shuts off. The five mechanisms are: (1) a source of nonspecific arousal, denoted by I in Figure 15, energizes both channels of the dipole; (2) a nonlinear signal function, denoted by f, transduces the sum of phasic and arousal inputs to each channel; (3) a habituative transmitter substance multiplies, or gates, the nonlinear signals in both channels; (4) the gated signals compete via an on-center off-surround network; and (5) the net signal after competition is half-wave rectified, or thresholded, before generating an output from the network.

How an antagonistic rebound is generated by the gated dipole in Figure 15 can now be described. First, the phasic input J is added to the tonic input I within the ON channel before being transduced by the signal function f. The result is a step input on a positive tonic baseline, denoted by x_1 in Figure 16. This generates a signal that is gated by the habituative transmitter in the ON channel, which is located in the square synaptic knob. Just as in Figure 14, the step input is transformed by the habituative transmitter into overshoots and undershoots of the gated ON channel activity, denoted by x_3. The OFF channel just processes a tonic baseline of activity, denoted by x_4. When x_4 is subtracted from x_3 in the ON channel, the tonic baseline is shifted downwards, as in x_5, to the value zero (at least in this simplified example). The OFF channel generates the same activity pattern as the ON channel, but with opposite sign, as in x_6. Next, these activities are half-wave rectified, or thresholded, in order to generate output signals. The result is a sustained, but habituative, response in the ON channel, and a transient antagonistic rebound in the OFF channel. The antagonistic rebound is energized by the arousal input I, which can activate the OFF channel even after the phasic input J to the ON channel shuts off, due to the slow rate with which the transmitter in the ON channel recovers from the previous phasic input J.

Many variations on this circuit exist, including variations in which the ON response is transient (Baloch *et al.*, 1999; Ögmen and Gagné, 1990), or the dipole includes feedback pathways that can store activities in short-term memory (Grossberg and Schmajuk, 1987) and even generate periodic clock-wise oscillations during circadian rhythms (Carpenter and Grossberg, 1983, 1984, 1985). Other work (e.g., Grossberg, 1972a, 1972b, 1980, 1982b, 1984a, 1984b; Grossberg and Gutowski, 1987) used gated dipoles to explain data about cognitive-emotional learning and decision making. It is because so many data about normal cognitive-emotional behaviors have been clarified by these circuits that their ability to naturally map onto clinical properties takes on such potential significance.

12. The Golden Mean: Inverted-U Opponent Processing as a Function of Arousal

The main point for present purposes is that such an opponent process gets depressed if it receives an arousal level that is either too small or too large (Figure 1). Such Inverted-U properties are well-known to occur in behavior. For example, D-amphetamine sulfate activates feeding in an anorectic cat at the same dose that totally inhibits feeding in a normal cat (Wolgin *et al.*, 1976). In normal cats, smaller amounts of norepinephrine can have effects opposite to those of larger amounts (Leibowitz, 1974). In like manner, amphetamine augments slow behavior and depresses fast behavior (Dews, 1958). In humans, dopamine pharmacological manipulations have shown that the relation of dopamine activity to reaction-time performance is an Inverted-U function (Netter and Rammsayer, 1991; Rammsayer, Netter, and Vogel, 1993; Zuckerman, 1984). Subjects high on extraversion and sensation seeking scales show impaired task performance if a dopamine agonist is applied, and improved performance if an antagonist is applied. The opposite pattern was found in subjects low in these traits. Inverted-U's have also been reported in event-related potentials, such as the Contingent Negative Variation, or CNV (Tecce and Cole, 1974), which is interpreted in terms of the model's incentive motivational pathway from the drive representations (Figure 11).

13. Underaroused and Overaroused Depressive Syndromes

As noted in Figure 1, an underaroused gated dipole generates a syndrome of Underaroused Depression. Here, due to how the small arousal level interacts with the nonlinear signal f and the opponent competition, inputs must be larger than normal in order to generate suprathreshold outputs. Paradoxically, once inputs are chosen large enough to overcome this threshold, then the circuit is *hyperexcitable* above threshold, meaning that the dipole generates abnormally large outputs in response to additional input increments. This is paradoxical because a naive view might conclude that an elevated threshold would make the circuit less, rather than more, excitable. This hyperexcitability is due to the Weber Law property; namely, the abnormally small arousal level creates an abnormally small denominator in the transmitter terms that define

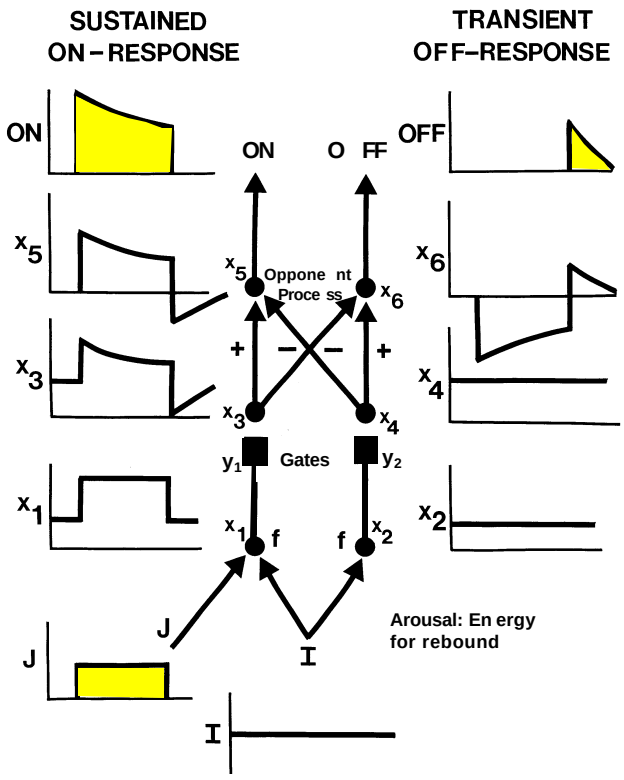

Figure 15. A gated dipole opponent process can generate habituative ON responses and transient OFF responses to the phasic onset and offset, respectively, of an input to its ON channel. See text for details.

dipole outputs. Because such a circuit is hyperexcitable at low arousal levels, its excitability can be brought into the normal range by increasing its arousal level until it reaches the peak of the Inverted-U. Here, the threshold is lower, but the network's excitability is also lower. These properties clarify the paradoxical fact that an arousing drug can make a gated dipole less excitable. This fact suggests how amphetamines may help attention deficit disorder patients (Swanson and Kinsbourne, 1976; Weiss and Hechtmann, 1979) and L-dopa may help Parkinson's patients (Riklan, 1973).

Unlimited increases in arousal do not make a dipole behave more normally. Too much arousal generates a syndrome of Overaroused Depression. Here the extra arousal causes the response threshold to be very low. Paradoxically, however, the circuit is *hypoexcitable* above this low threshold, so that it generates small responses, if any, to inputs of arbitrary size. This is also due to the Weber Law property. Thus "too much of a good thing", such as amphetamine or L-dopa for the patients mentioned above, can create a new, and complementary, problem to the one for which they are being treated.

14. Schizophrenia as an Overaroused Depressive Syndrome

The formal symptoms of the model when its drive representations are overaroused are strikingly reminiscent of negative schizophrenic symptoms. Data consistent with this proposal include the following: Some types of schizophrenia have been ascribed to dopamine hyperactivity of various parts of the limbic system, including increased dopaminergic input to the amygdala (Lloyd, 1978; Reynolds, 1983, 1987). This type of effect may be interpreted as an overaroused condition. This hypothesis is consistent with data showing that dopaminergic agonists, such as L-dopa and amphetamine, can produce a behavioral syndrome that has been compared to schizophrenia (Riklan, 1973; Stevens, 1993; Torrey and Peterson, 1974; Wallach, 1974). In the opposite direction, various antipsychotic drugs block dopamine receptors (Kuhar *et al.*, 1978) and in sufficient quantities can produce a catalepsy that resembles Parkinson's disease (Hornykiewicz, 1975). This latter result, which suggests that schizophrenia and Parkinson's disease are at opposite ends of a dopamine continuum, is consistent with model properties in the underaroused state that resemble Parkinson's disease (Grossberg, 1984a). More generally, the facts that an underaroused syndrome can be transmuted into an overaroused syndrome using a given drug, and that the reverse transformation can be caused by an oppositely acting drug, suggest that the two syndromes may be extremal points on an Inverted-U of a common mechanistic substrate, albeit one that may exist in multiple brain regions for different behavioral purposes.

Because opponent processes like gated dipoles are assumed to exist in many brain regions, too much of a drug that is aimed at correcting a dopaminergic imbalance in one brain region may create an opposite dopaminergic imbalance in other brain regions. In this way, a drug aimed at correcting an emotional imbalance may create a new imbalance in a different system, such as a motor system. Multiple secondary effects, including lateralized effects that are different in

different brain hemispheres, may also occur due to these dopaminergic abnormalities (Early *et al.*, 1994), but these are beyond the scope of the present article.

Because schizophrenia is a heterogeneous disease (Heinrichs, 1993), one issue that needs to be further studied experimentally is whether some schizophrenics who exhibit negative symptoms are overaroused, while other may be underaroused. In either case, flat affect can ensue, but the two types of populations should exhibit different types of sensitivity (hypo versus hyper) to suitably chosen suprathreshold inputs (Figure 1).

15. Weber-Law Models of Mental Disorders

When a drive representation in the brain gets depressed due to underarousal or overarousal of a gated dipole circuit, this may be viewed as a Weber-Law mental disorder. By this is meant that tonic baseline signals determine brain sensitivity to phasic inputs in such a way that low arousal can cause hyperreactive responses to phasic inputs, whereas high arousal can cause hyporeactive responses to phasic inputs. Grace (1991) has suggested a Weber Law model in which low arousal is due to abnormally low prefrontal activity. The discussion above raises the question of whether this is a cause or an effect, or even whether the answer is the same in all patients. The problem is compounded by the fact that there exist multiple feedback loops in the brain regions that are implicated in schizophrenia, including feedback between regions like amygdala and prefrontal cortex. The discussion above suggests how a primary lesion in emotional affect and conditioning centers of the brain can have widespread cognitive and affective indirect effects throughout the brain, including prefrontal cortex.

DISCUSSION

16. Concluding Remarks and Predictions

The above discussion raises a number of issues that may be clarified by further research. One issue concerns the fact that either an underaroused or an overaroused drive representation may become depressed. It is not clear whether just one of these types of depression occurs in all schizophrenics. There are a number of criteria that the CogEM model predicts, however, which may in principle be used to distinguish between patients who differ on this dimension (Grossberg, 1984a). One of these is that underaroused syndromes tend to have elevated behavioral thresholds, but are *hyper*sensitive to increments in phasic inputs after they exceed this threshold. In contrast, overaroused syndromes tend to have low thresholds, but are *hypo*sensitive to suprathreshold phasic inputs. This is a manifestation of the Weber-law properties of such opponent processes.

Another issue is whether depression of a drive representation like the amygdala causes hypofrontal reactions, or whether hypofrontality is a cause of depression in the drive representation. Because the amygdala and prefrontal cortex are reciprocally connected, this may be difficult to determine. This is particularly true because, as noted in Section 11, opponent

processes can exist in sensory and cognitive representations, as well as in drive representations. One role for these opponent processes is to control discriminative behaviors that are contingent upon the offset of events, or to reorganize information processing after unexpected events. For example, if your task is to push a lever when a light shuts off, you need an internal representation to be activated transiently and selectively after the light shuts off with which to activate the level press. Likewise, unexpected events can disconfirm ongoing processing and amplify previously attenuated representations which may be likely to lead to more successful behavior. Thus, the very same arousal source that is depressing a drive representation like the amygdala may also be overarousing or underarousing prefrontal circuits.

This raises the question of what the sources of arousal are that are hypothesized in the model. It is now well recognized that there are several distinct arousal systems in the brain, and that they interact with one another in complicated ways (Marrocco, Witte, and Davidson, 1994; Robbins and Everitt, 1995). These include the locus coeruleous noradrenergic, magnocellular basal forebrain/pedunculopontine cholinergic, substantia nigra/ventral tegmental area dopaminergic, dorsal raphe serotonergic, and tuberomamillary hypothalamic histaminergic sources.

This article discusses one type of arousal: conditioned reinforcer/incentive motivational arousal, and how its depression can lead to negative schizophrenic symptoms. Within the larger Adaptive Resonance Theory (ART) of which the CogEM model forms a part (Grossberg, 1999b), there are also several other types of arousal. These include the type of volitional arousal whereby a learned top-down expectation is converted from a modulator, or prime, of bottom-up information, into a suprathreshold activation that can be used to control internal fantasy, rehearsal, and planning (Grossberg, 1999a). When this type of arousal becomes imbalanced, the model undergoes a type of hallucination with many properties similar to those observed during schizophrenia.

Another type of arousal is activated when bottom-up information mismatches top-down expectations, thereby leading to reset of short-term memory and other reactions that are mediated by a type of orienting arousal. Yet other types of arousal are used to control various action systems. The ART brain models thus predict the need for functionally different types of arousal. It remains to test how well the predicted arousal mechanisms match known brain arousal systems.

One tentative possibility is that the locus coeruleous noradrenergic arousal system is involved in conditioned reinforcer/incentive motivational arousal because of its role in mediating responses to stimuli "that are salient to the animal by virtue of conditioning" (Aston-Jones, 1994). When this source of arousal is finally confirmed, it will have predictable effects on the type of core consciousness that Damasio (1999) has discussed. Within ART, this arousal system is part of an attentional learning system that is complementary to an orienting system for dealing with unexpected events (Grossberg, 1999b). It remains to be determined whether and how this predicted complementarity is realized within the known arousal systems of the brain, and

whether, in fact, it is related to the "complementary roles of the NA and 5-HT systems" that is well-known to exist (Robbins and Everitt, 1995, p. 708).

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