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A neural network model of Borderline Personality Disorder

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ABSTRACT

The etiology of Borderline Personality Disorder (BPD) is unknown. This paper develops an etiological hypothesis by constructing a neural network with constraints from neuroanatomy, neurophysiology, and behavior. The neural network ascribes roles to the brainstem's periaqueductal gray, the amygdala, and the anterior cingulate/ventromedial prefrontal cortex (ACC/vmPFC). Neural network simulations show how these brain structures might interact during BPD behavior. The simulations suggest that long term depression (LTD) in ACC/vmPFC may explain several BPD symptoms. The network makes testable suggestions. The current work is the first-ever neural network simulation of BPD.

1. Introduction

Borderline Personality Disorder (BPD) consists of a cluster of symptoms characterized by unstable, impulsive behavior. The DSM-IV-TR (Diagnostics and Statistics Manual IV-Text Revised) lists nine BPD symptoms. They are fear of abandonment, unstable interpersonal relationships, identity disturbance, impulsiveness, self-mutilation and/or suicide, affective instability, empty feelings, inappropriate anger, and dissociation. An individual must have at least five of these symptoms to receive a diagnosis of BPD (American Psychiatric Association, 2000).

In recent years, researchers have used functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to gain some insight into how the BPD brain works (Brendel, Stern, & Silbersweig, 2005). Results vary substantially between different studies due perhaps to methodological issues in study design and difficulties in identifying a homogeneous patient population for study. Nevertheless, the studies do converge on the general impression that the BPD brain has some sort of dysfunction in limbic and prefrontal areas (Brendel et al., 2005).

Structural imaging work appears consistent with the functional imaging work. Structural imaging has found evidence for decreased gray matter in the anterior cingulate cortex (ACC). Two studies found a more substantial decrease in the right ACC (Hazlett et al., 2005; Tebartz van Elst et al., 2003). Another study found no difference (Rüsch et al., 2003).

Neuropsychological testing provides yet another line of investigation into the characteristics of individuals with BPD. This work has found evidence of deficits in visual perception and visual memory (O'Leary, 2000). The reason for these deficits is unclear.

Finally, neuroanatomical work has produced a great deal of information about the limbic system in normal rat, monkey, and human brains (Öngür & Price, 2000; Price, 2003; Stefanacci & Amaral, 2002). The prominence of limbic features in the diagnostic criteria for BPD and in the functional and structural imaging data suggest some sort of change or damage to the limbic system. Thus, a careful examination of a normal limbic system might generate ideas about how a normal brain acquires a BPD phenotype.

These different approaches have generated a large amount of data relevant to BPD, but their success in collecting data has created an important need for a theory that would help researchers weave these different data into a coherent whole. This paper attempts to contribute toward building such a theory. It does so using a novel technique, the construction of a neural network model of BPD.

2. BPD neural network construction

2.1. BPD anger and the dlPAG

One way to begin construction of a BPD neural network is to focus on a specific BPD behavior and consult the literature for ideas about which brain structures might contribute to this behavior. Anger offers a convenient place to start. The DSM-IV-TR defines BPD anger as "…inappropriate intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights)" (American Psychiatric Association, 2000).

This type of anger resembles the defensive aggression discussed in animal research (Gregg & Siegel, 2001). Like animal defensive aggression, BPD anger can be accompanied by angry vocalizations,

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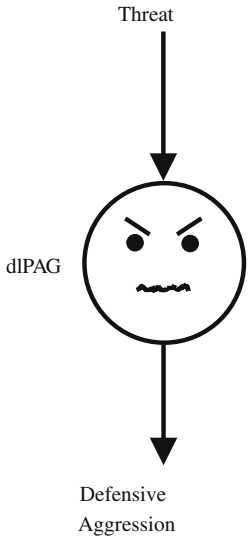

Fig. 1. dlPAG mediates defensive aggression.

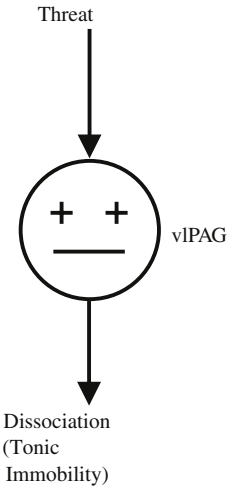

Fig. 2. vlPAG mediates dissociation.

facial expressions, and physical attack. A defensive aggression interpretation of BPD anger appears consistent with the high incidence of childhood abuse associated with the development of BPD (Skodol et al., 2002). Thus, in this line of thinking, the abuser activates brain structures in the abused child that mediate defensive aggression.

Stimulation studies in the cat have implicated a number of brain structures in defensive aggression. For example, certain parts of the periaqueductal gray (PAG), hypothalamus, amygdala, bed nucleus of the stria terminalis (BNST), and septal nuclei have elicited defensive aggression (Gregg & Siegel, 2001). In addition, aggressive outbursts have been reported in human cingulate cortex epilepsy (reviewed in Devinsky, Morrell, and Vogt (1995)).

Lesion studies suggest that the PAG appears near the bottom of the hierarchy of structures that participate in defensive aggression. Lesions of the PAG abolish the aggression elicited by stimulation of other structures that project down to the PAG, but lesions of other structures do not eliminate the defensive aggression elicited by stimulating the PAG (Gregg & Siegel, 2001; Keay & Bandler, 2001).

This hierarchy provides a useful constraint on a BPD neural network. Inclusion of the PAG in a BPD neural network not only provides a structure that can release defensive aggression but also narrows the list of other brain structures that might participate in BPD behavior. We can simply limit the initial list to structures that have known anatomical connections with the PAG.

One part of the PAG, the dorsolateral PAG (dlPAG), participates in a particularly important way in defensive aggression. Stimulation studies in rat and cat implicate the dlPAG in defensive aggression (Gregg & Siegel, 2001; Keay & Bandler, 2001).

We come, then, to the first component of a BPD neural network, the dlPAG. During BPD anger, the dlPAG is presumed activated. The brain structure or structures that activate the dlPAG are left unspecified at this point. However, we can draw a simple network (Fig. 1) which expresses the notion that a threat signal activates the dlPAG and releases defensive aggression. The angry face icon represents populations of neurons in the dlPAG that coordinate defensive aggression.

2.2. BPD dissociation and the vlPAG

Dissociation, another BPD behavior, appears to complement anger as a primitive defense mechanism. The DSM-IV-TR lists the dissociative symptom of BPD as "transient, stress-related paranoid ideation or severe dissociative symptoms" (American Psychiatric Association, 2000). Dissociation has been described as an alteration of perception of physical sensation, time, memory, sense of self, and reality (Scaer, 2001). In a study of 61 people exposed to life-threatening danger (e.g. automobile accidents, near-drownings, falls), study participants reported a variety of experiences including slowing of the passage of time, a detached calm or peacefulness, a sense of unreality, a dreamlike state, a detachment of self in which they viewed themselves from about 50 ft away, a feeling of emptiness, and a feeling that movements or thoughts were mechanical or automatic (Noyes & Kletti, 1977). These experiences are thought to be an adaptive mechanism in response to fear.

Dissociation in humans resembles "tonic immobility" (TI) in animals (Nijenhuis, Vanderlinden, & Spinhoven, 1998). This assertion stems from data on sexual and physical abuse vis-à-vis predator attack. Victims typically have extreme fear and feel that they have no possibility of escape. Victims often report analgesia and insensitivity to touch. Consistent with this view, a study of childhood sexual abuse victims (Heidt, Marx, & Forsyth, 2005) found that 37% of rape victims experienced complete immobility. Furthermore, tonic immobility during the rape correlated with peritraumatic dissociation. A high percentage (52% to 71%) of BPD patients have experienced sexual abuse as children (Schmahl, Vermetten, Elzinga, & Bremner, 2003a).

Both fear and tactile input play a role in triggering TI (Leite-Panissi, Monassi, & Menescal-de-Oliveira, 1999). According to this line of thinking, during predator attack, an animal becomes afraid. Then, the predator makes physical contact, biting the animal and turning it on its back. This triggers TI as a terminal defense behavior. It is tempting to speculate that an individual with BPD may have such a strongly dysphoric brain that simply scratching one's arm provides the necessary tactile input to trigger TI. If true, this might explain the prevalence of "cutting" or self-mutilation in BPD. Cutting may provide some relief from the dysphoria.

It is important to note that "tonic immobility" is not the same as "freezing" (Walker & Carrive, 2003). In both behaviors, an animal does not move. However, while freezing, an animal has increased muscle tone and appears ready to jump. While in tonic immobility, an animal has little muscle tone and appears unresponsive.

Interestingly, in animal experiments, stimulation of the ventrolateral periaqueductal gray (vlPAG), a structure near the dlPAG, elicits tonic immobility. When stimulated, the vlPAG causes "…a passive coping reaction of quiescence/immobility, decreased vigilance and hyporeactivity, the animal neither responding, nor orienting to its external environment…" (Keay & Bandler, 2001).

We can now draw a simple neural network describing how the vlPAG becomes active (Fig. 2). The face icon represents populations of neurons in the vlPAG that coordinate dissociation (tonic immobility).

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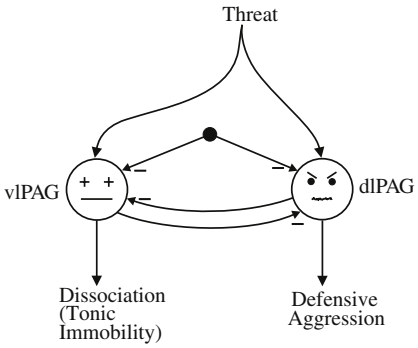

Fig. 3. dlPAG–vlPAG interaction.

2.3. The dlPAG and vlPAG interact

The curious appearance of both anger and dissociation as diagnostic criteria for BPD appears consistent with notions from the animal literature that two fear-related pathways become active when an animal is threatened (Walker & Carrive, 2003). The two pathways compete so that one pathway eventually suppresses the other. The active pathway then organizes the animal's defensive response (i.e. defensive aggression or tonic immobility).

A variety of data supports the idea that the two fear-related pathways course through the dlPAG and vlPAG and, furthermore, engage in an inhibitory interaction. First, when a cat is brought near to a rat, the rat's dlPAG and vlPAG both later show signs of having been active (Canteras & Goto, 1999; Comoli, Ribeiro-Barbosa, & Canteras, 2003). Second, each of the four PAG columns (dorsomedial, dorsolateral, lateral, and ventrolateral) projects to each of the other columns (Jansen, Farkas, Sams, & Loewy, 1998). Third, stimulation of the vlPAG can suppress the tachycardia and pressor response normally evoked by stimulating the dorsal PAG (Lovick, 1992), suggesting an inhibitory interaction. Fourth, in PAG slices, stimulation of the dorsal PAG inhibits ventral PAG neurons (Behbehani, 1995).

The dlPAG and vlPAG neural networks can now be joined (Fig. 3). The black dot represents populations of tonically active inhibitory interneurons, an important component of PAG circuitry (Behbehani, 1995; Chiou & Chou, 2000; Gioia, Tredici, & Bianchi, 1985). The minus signs denote inhibition. In addition to tonic inhibition, active neurons in the dlPAG and vlPAG send inhibitory input to each other, presumably through inhibitory interneurons.

The simple depiction in Fig. 3 shows dlPAG and vlPAG receiving the same threat signal, but Section 3 of the paper will show that dlPAG and vlPAG actually each receive their own versions of this signal. Differences in these threat signals will determine whether dlPAG or vlPAG wins the competition in a given situation.

2.4. The amygdala tells the PAG about threat

Fig. 3 describes PAG circuitry that is presumed activated in the BPD brain, but what brain structure notifies the PAG of a threat? One attractive candidate is the amygdala. The amygdala plays an important role in activating a fear response when an animal confronts a threat (Davis & Whalen, 2001; Sah, Faber, Lopez De Armentia, & Power, 2003). Two nuclei within the amygdala, the basal amygdala (BA) and the central nucleus of the amygdala (CeA), seem particularly important in a fear response.

BA has several characteristics that associate it with defensive aggression. First, stimulation of BA elicits defensive aggression (Gregg & Siegel, 2001). Second, BA's projection to the PAG preferentially targets the dlPAG (An, Bandler, Öngür, & Price, 1998). Third, lesion of BA prevents active coping (Amorapanth, LeDoux, & Nader, 2000).

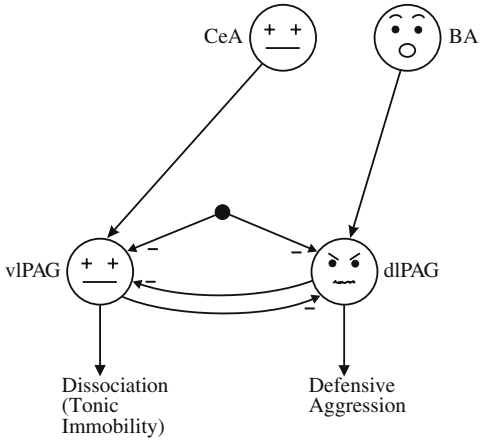

Fig. 4. Amygdala projects to the PAG.

CeA has several characteristics that associate it with dissociation. First, reducing inhibition in CeA by blocking $GABA_A$ (γ-aminobutyric acid) receptors lengthens the duration of tonic immobility (Leite-Panissi & Menescal-de-Oliveira, 2002). Second, CeA's projection to the PAG avoids the dlPAG and instead targets the vlPAG and other areas of the PAG (An et al., 1998; Price & Amaral, 1981; Rizvi, Ennis, Behbehani, & Shipley, 1991). Third, blockade of the medial part of CeA or blockade of the ventral amygdalofugal pathway with lidocaine reduces fear-induced activity in the vlPAG as measured by Fos expression (Carrive, Lee, & Su, 2000).

A question naturally arises from this discussion. The brain has two amygdalae, one in each hemisphere. Do both amygdalae participate equally in recruiting brain structures to deal with a threat? The answer appears complicated. In a review of this amygdalar laterality issue (Zald, 2003), various models of amygdalar laterality did not fit well with some of the lesion and fMRI data. The left and right amygdalae show some degree of functional redundancy, although data support the idea that the two amygdalae may have quantitative or qualitative differences in certain functions.

Several examples illustrate this point. In humans, experientially learned fear requires an intact right amygdala, while cognitively learned fear requires an intact left amygdala (Zald, 2003). Also, the right amygdala habituates more quickly in response to fearful faces than does the left amygdala (Zald, 2003). In rats, predator stress potentiates the right amygdalo-PAG pathway (Adamec, Blundell, & Collins, 2001). Interestingly, predator stress also depotentiates the left amygdalo-PAG pathway. Predator stress appears to change multiple systems.

The current modeling approach assumes that the right amygdala has a privileged role in processing threats relevant to BPD. This assumption permits construction of a simpler neural network model that captures the essential features of BPD while remaining consistent with much of the amygdala data and also with ventromedial prefrontal cortex (vmPFC) data presented later in the paper. It is possible that later BPD models may need to incorporate the left amygdala to provide a more complete accounting of the BPD brain's function.

BA and CeA can now be added to the BPD neural network (Fig. 4). BA projects to the dlPAG. CeA projects to the vlPAG. The BA and CeA nuclei here are assumed to be in the right hemisphere's amygdala. The frightened face icon represents populations of neurons in BA that fire in response to threat. CeA uses the same face icon that vlPAG uses to indicate that CeA participates with vlPAG in mediating dissociation.

2.5. The LA–ICM switch in the amygdala

With the dlPAG and vlPAG both presumably receiving excitatory input in response to threat, how does the brain know how

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to choose defensive aggression, say, over dissociation? The answer seems to involve the brain's judgment about how "escapable" the threat is (Keay & Bandler, 2001; Walker & Carrive, 2003). The amygdala may participate in this judgment, because, as discussed in the dissociation section above, both fear and tactile input play a role in triggering TI.

In one proposal (Royer, Martina, & Paré, 1999), the lateral nucleus of the amygdala (LA) and the intercalated cell mass (ICM) work together to enable BA neurons to excite CeA neurons. Sensory information suggestive of threat arrives at BA. BA then commands dlPAG to initiate defensive aggression so as to counter the threat. Simultaneously, BA attempts to excite CeA with this threat information. However, CeA does not become active, because CeA receives inhibition from inhibitory interneurons excited by BA input (labeled "1" in Fig. 5) and other tonically-active inhibitory interneurons. The inhibitory interneurons ("1") excited by BA are situated in the ICM.

Input from LA, a major site of sensory input to the amygdala (Carmichael & Price, 1995), then acts to "throw the switch" to enable BA to excite CeA. LA neurons do this by exciting certain ICM inhibitory interneurons (labeled "2" in Fig. 5) that then laterally inhibit the inhibitory interneurons ("1") that were inhibiting CeA neurons. The newly active CeA neurons then activate vlPAG neurons that mediate dissociation. These highly active vlPAG neurons inhibit dlPAG neurons that had been coordinating defensive aggression.

2.6. BA may drive the BPD brain's strong responses

Fig. 5 shows essentially normal brain circuitry. A normal brain will express defensive aggression when appropriately threatened. A normal brain will also dissociate when strongly threatened with no possibility of escape.

A BPD brain, though, will respond with aggression or dissociation more readily than a normal brain will. For example, the DSM-IV-TR lists "…*inappropriate* intense anger…" and "…*severe* dissociative symptoms…" (italicized by the author for emphasis).

Fig. 5 suggests that BA could drive this stronger response in a BPD brain. BA sits at a key point in the network. Greater activity in BA would more strongly drive activity in dlPAG and the CeA–vlPAG circuit if switched by LA and ICM. Thus, some type of defect in the right hemisphere's BA or in a brain structure that projects to BA, could account for the greater defensive aggression and dissociation seen in the BPD brain.

2.7. Dysfunction in the right vmPFC/ACC

The neural network described so far (Fig. 5) provides one hypothesis for how a BPD brain generates aspects of defensive aggression and dissociation. However, additional lines of evidence suggest the involvement of another brain area, the right ventromedial prefrontal cortex (vmPFC) and/or anterior cingulate cortex (ACC).

One line of evidence involves deficits or distortions in Theory Of Mind (TOM) reasoning, the ability to reason about another person's motivations or intentions (Frith & Frith, 1999; Stuss, Gallup, & Alexander, 2001). In BPD, these TOM deficits manifest themselves in various ways. First, people with BPD can have a strong fear of abandonment even though another person does not intend to leave them. Second, people with BPD may alternately strongly idealize another person and then, a few minutes later, strongly devalue them even though the other person may have done nothing to evoke these strong feelings. Third, people with BPD may also suffer deficits in reasoning about their own motivations or intentions. This deficit appears to manifest itself in an identity disturbance that the DSM-IV-TR describes as "…markedly and persistently unstable self-image or sense of self" (American Psychiatric Association, 2000).

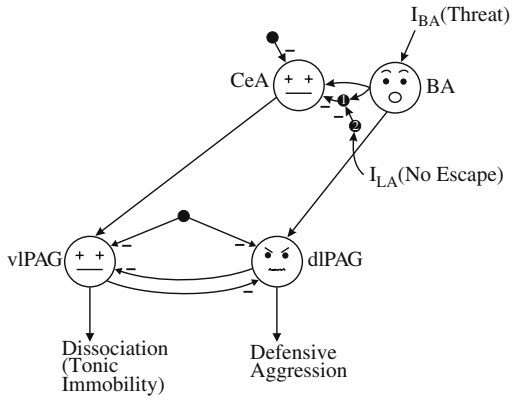

Fig. 5. The LA–ICM Switch in the amygdala.

These TOM deficits in BPD may actually stem from a particular subtype of TOM that has been called "affective TOM" (Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005). Affective TOM gives one the ability to understand another person's feelings. In interpreting their results, Shamay-Tsoory and colleagues distinguished "affective TOM" from "cognitive TOM" (Shamay-Tsoory et al., 2005). As they put it, "To understand irony and even more so to detect faux pas, one is required not only to understand the knowledge of the others but also to have empathic understanding of their feelings" (Shamay-Tsoory et al., 2005).

This distinction between affective TOM and cognitive TOM carries important implications for the current discussion about TOM deficits in BPD. People with BPD are widely seen as manipulative (Potter, 2006). Manipulation most likely requires a good deal of cognitive TOM reasoning. However, people with BPD have also been found to have deficits in empathy (O'Leary, 2000). Thus, one could understand the TOM deficit in BPD as an affective TOM deficit that leaves cognitive TOM largely intact.

This pattern of TOM deficit in BPD suggests impairment in the right vmPFC. Lesion data in humans motivates this assertion (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Shamay-Tsoory et al., 2005). When the right vmPFC is damaged, a person "…may understand a social interaction but might fail to comprehend the emotional outcome of this interaction…" (Shamay-Tsoory et al., 2003).

BPD impulsiveness also suggests a role for the right vmPFC. The DSM-IV-TR describes this BPD symptom as "Impulsiveness in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, and binge eating)" (American Psychiatric Association, 2000). Lesion and brain imaging studies indicate that the right vmPFC participates in evaluating the emotional consequences of proposed actions (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, & Damasio, 2000, 2003; Tranel, Bechara, & Denburg, 2002 but see also Tranel, Damasio, Denburg, & Bechara, 2005 for a possible influence of gender). Thus, a dysfunctional right vmPFC could enable impulsive behavior.

It is useful to pause here and point out that impulsivity can be defined in different ways (Fellows & Farah, 2005). Sometimes, impulsivity is defined as response inhibition, a phenomenon typically measured in Go/No–Go tasks or perseverative errors as seen in the Wisconsin Card Sorting Task (Bechara et al., 2000). This type of response inhibition depends on the right inferior frontal cortex (also known as the right ventrolateral prefrontal cortex) (Aron, Robbins, & Poldrack, 2004). Interestingly, vmPFC patients are not impaired in tests of this type of response inhibition (Bechara et al., 2000).

Another way to define impulsivity is what Bechara and colleagues have called a "myopia for the future" (Bechara et al.,

1994). Patients with right vmPFC damage have this type of myopia (Bechara et al., 2003). When presented with "…a large immediate reward, even if it can cost a large loss in the future, the patients seem unable to delay the gratification of the reward…" (Bechara et al., 2000). This inability to delay gratification holds true even though these patients know the consequences of their actions. Their central deficit seems to be their inability to activate an emotion bound to the imagined consequence. BPD may involve this type of impulsivity. In fact, a recent study of 20 patients with BPD found deficits in their performance on the Iowa Gambling Task (IGT), a test of impulsive behavior (Haaland & Landrø, 2007).

This notion of right vmPFC involvement in BPD impulsive behavior suggests an interesting experiment. Research in altruistic punishment (Schadenfreude, that is, taking delight in someone else's suffering) indicates that the strong desire to punish another person correlates with activity in the striatum, a structure associated with pleasurable feelings (de Quervain et al., 2004). However, when confronted with a personal cost associated with inflicting punishment, test subjects showed activity in the vmPFC and medial orbital frontal cortex (OFC) while weighing the costs and benefits of punishing the other person. It seems plausible that the BPD brain would have difficulty activating the vmPFC in the de Quervain et al. (2004) experimental protocol. Thus, an individual with BPD would enjoy inflicting pain on other people, because they do not have the normal "brake" that healthy individuals have.

Neuropsychological deficits also support the idea that the right mPFC/ACC is impaired in the BPD brain. Although not a diagnostic criterion for BPD, neuropsychological testing has found substantial impairment in tests of visual memory and visual perception (Dinn et al., 2004; O'Leary, 2000; Ruocco, 2005). For example, studies of patients with BPD have found significant impairment in the Digit Symbol Substitution, Block Design, and Rey Osterrieth Copy Figure tests (Dinn et al., 2004; O'Leary, 2000; Ruocco, 2005). A study of conflict resolution using a flanker task with incongruent arrows found slowed reaction time in individuals with BPD compared to controls (Posner et al., 2002).

This pattern of neuropsychological impairment suggests damage or alteration in the right hemisphere. Such an impression stems in part from lesion studies that have demonstrated substantial degradation in performance on the Digit Symbol Substitution and Block Design tests after right hemisphere damage (Glosser, Butters, & Kaplan, 1977; Uzzell, Zimmerman, Dolinskas, & Obrist, 1979; Warrington, James, & Maciejewski, 1986). Researchers studying neuropsychological impairment in BPD have voiced similar impressions of right hemisphere involvement in BPD (Dinn et al., 2004; Ruocco, 2005).

The apparent right hemisphere impairment in BPD needs further investigation to more precisely describe which right hemisphere structures might be compromised. However, one could speculate that damage or alteration to the right hemisphere's ACC could explain this impairment. The right ACC exerts cognitive control in a variety of tasks by recruiting other brain structures while completing a task (Stephan et al., 2003). In fact, ACC's cognitive control appears lateralized in such a way that the right ACC increases its influence on right hemisphere structures during visuospatial decisions while the left ACC increases its influence on left hemisphere structures during linguistic decisions (Stephan et al., 2003). Thus, a damaged right ACC might not be capable of recruiting the right hemisphere structures necessary to efficiently complete tasks such as the Digit Symbol Substitution or Block Design tests.

Posner et al. (2002) has previously suggested that an impaired ACC could explain the slowed reaction time in individuals with BPD while completing a flanker task. The current work differs slightly from the Posner et al. (2002) work by also suggesting a role for the ACC in impairments on the Digit Symbol Substitution, Block Design, and Rey Osterrieth Copy Figure tests. Additionally, the current work asserts an especially important role for the *right* ACC in explaining these impairments.

The general term, "Anterior Cingulate Cortex", requires some unpacking. ACC does not consist of one monolithic area of cortex but instead has a number of subregions (Carmichael & Price, 1994; Öngür, Ferry, & Price, 2003; Öngür & Price, 2000; Peterson et al., 1999). One or more of these subregions, if impaired, could degrade performance on a visuospatial task, because several attentional subsystems activate simultaneously during certain tasks. For example, in an fMRI study of the Stroop task, factor analyses identified seven attentional subsystems activated while completing the task (Peterson et al., 1999). Every one of these subsystems involved portions of the ACC or nearby cortex. One of the factors (their "Factor 3") appears to fall in ventral ACC or vmPFC.

Structural imaging data also lend some support to the idea of a compromised ACC in BPD although the literature is not in complete agreement on this point. A magnetic resonance imaging (MRI) study of 50 patients with BPD reported reduced gray matter volume in ACC (BA 24) compared to healthy controls (Hazlett et al., 2005). The right ACC had a more substantial gray matter reduction than did the left ACC. A second study with eight patients also found reduced gray matter volume in the right ACC (Tebartz van Elst et al., 2003). A third study with 21 patients found no difference in the right ACC (Rüsch et al., 2003).

Finally, functional imaging studies also provide a small amount of support for the notion that the right ACC may not function normally in the BPD brain. In two symptom provocation studies using positron emission tomography (PET), women with BPD listened to scripts describing personal stories of childhood abuse and abandonment (Schmahl et al., 2003a, 2003b). These women either had a decrease in blood flow in the right ACC compared to normal controls or failed to activate the right ACC.

These functional imaging data should be considered with caution, though, because the functional imaging literature has not converged on one precise pattern of brain activity in the BPD brain (Brendel et al., 2005). This lack of consensus may stem from methodological issues in different study designs. Nevertheless, the functional imaging literature could perhaps safely say at this point that some sort of dysfunction exists in the BPD brain's limbic system and prefrontal areas (Brendel et al., 2005).

2.8. Amygdala inhibits vmPFC/ACC

It turns out that the right vmPFC and ACC fit well into the BPD neural network. In the macaque monkey, the vmPFC and ACC project heavily to BA. BA returns a robust projection to the vmPFC and ACC (Amaral & Price, 1984; Carmichael & Price, 1995; Porrino, Crane, & Goldman-Rakic, 1981; Price, 2003; Stefanacci & Amaral, 2002). This BA projection to vmPFC and ACC heavily targets areas 25, 32, 24, and 14 (Amaral & Price, 1984). Rat and cat brains use a similar wiring scheme (Price, 2003). Presumably, the wiring in human brains follows the same basic pattern.

In the rat, Pérez-Jaranay and Vives (1991) found that the basolateral amygdala (BLA) largely inhibits mPFC neurons. A single, small amplitude stimulation of the BLA inhibited 63.5% of mPFC neurons for a lengthy time and with no post-inhibitory rebound. Interestingly, 8.5% of neurons had a short excitatory response followed always by a silent period. The other neurons (28%) in their study did not respond to BLA stimulation.

The authors suggested that BLA inputs to the mPFC might activate inhibitory interneurons that then suppress mPFC activity. This explanation seems plausible, because BLA pyramidal cells that project to mPFC use glutamate and aspartate, excitatory neurotransmitters (McDonald, 1996).

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Lesion work also supports the idea that the BLA inhibits mPFC activity. After fear conditioning to a tone, rat mPFC neurons decreased their activity when the tone sounded. However, after lesioning an amygdala in one hemisphere, ipsilateral mPFC neurons no longer decreased their activity in response to the tone (Garcia, Vouimba, Baudry, & Thompson, 1999).

In a PET study of anticipatory anxiety, participants suppressed activity in two regions of vmPFC while awaiting a painful shock to their hands (Simpson, Drevets, Snyder, Gusnard, & Raichle, 2001). The authors suggest that this suppression may have come from the amygdala, but they did not see any amygdalar activity in the PET data. They mention, though, that PET may have missed activity in one of the amygdala's component nuclei because of PET's limited resolution.

This suppression of vmPFC activity in the PET data creates a paradox, though. If the amygdala activates a network of inhibitory interneurons in mPFC as suggested by Pérez-Jaranay and Vives (1991), then the PET data would have shown an *increase* in blood flow, because active inhibitory interneurons consume metabolic resources (Simpson et al., 2001). Simpson et al. (2001) suggest that dopamine release in vmPFC might directly inhibit neuronal activity in vmPFC without the need to activate inhibitory interneurons. However, another explanation appears possible.

Glutamate from amygdalar neurons might directly inhibit mPFC neurons. There is precedent for this glutamatergic suppression of neuronal activity in the mammalian brain. Morikawa, Khodakhah, and Williams (2003) found that stimulation of glutamatergic inputs to dopamine neurons in the rat ventral tegmental area (VTA) caused a brief burst of action potentials followed by a pause (silent period). The burst was mediated by NMDA (N-methyl D-aspartate) receptors. The pause was mediated by metabotropic glutamate receptors (mGluR's). This burst-pause behavior appears similar in some respects to the burst-pause behavior seen in mPFC neurons responding to amygdalar input (Pérez-Jaranay & Vives, 1991).

Interestingly, mGluR's participate in many more functions in many areas of the brain than just transient suppression of neuronal activity in the VTA (Ferraguti & Shigemoto, 2006). Some of these functions include induction of long-term depression (LTD) (Otani, Daniel, Takita, & Crépel, 2002), apoptosis (Borodezt & D'Mello, 1998), and protection from excitotoxic neuronal death (Risterucci et al., 2006).

Because many mGluR subtypes exist (Ferraguti & Shigemoto, 2006), it seems possible that genetically susceptible individuals may have mGluR subtypes that make them vulnerable to vmPFC damage. Thus, according to this thinking, trauma activates the right amygdala. The right amygdala then activates mGluR's in the right vmPFC that subsequently damage the right vmPFC. The damaged right vmPFC then plays an important role in the behavioral characteristics of Borderline Personality Disorder.

This is all just informed speculation, of course. Still, because the amygdala plays an important role in fear and the vmPFC plays an important role in inhibitory self-control, it would be very helpful to learn just exactly how the amygdala to vmPFC projection works. For now, the BPD neural network assumes simply that the amygdala inhibits vmPFC activity and that this inhibition leads to LTD of other input to the vmPFC.

2.9. vmPFC/ACC suppresses the amygdala

Human fMRI studies support the view that control systems in PFC, ACC, and OFC can modulate activity in the amygdala (Ochsner & Gross, 2005). The particular control system that becomes active depends on the cognitive strategy used. For example, during self-focused reappraisal of an aversive photograph, participants engaged the right mPFC (BA 32) while suppressing negative emotion. Suppression of negative emotion correlated with a decrease in amygdalar activity (Ochsner et al., 2004), suggesting that BA 32 played a role in decreasing amygdalar activity.

In a more direct test of this idea, an analysis of an emotional Stroop task (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006) revealed "…a specific enhancement of a top-down inhibitory pathway from the rostral cingulate to the amygdala". Etkin and colleagues used a dynamic causal modeling analysis of the fMRI data to show this enhancement. Furthermore, they conducted a psychophysiological interaction (PPI) analysis, measured reaction time (RT), and recorded skin conductance response (SCR). The PPI, RT, and SCR data all agreed with the dynamic causal modeling analysis. Subsequent work confirmed that the rostral cingulate can inhibit activity in the amygdala (Egner, Etkin, Gale, & Hirsch, 2008).

These human fMRI studies correspond well with electrophysiological work in rats. Stimulation of the rat mPFC (prelimbic and infralimbic PFC) causes a "…potent inhibition of projection neuron activity within the BLA…" (Basolateral Amygdala) (Grace & Rosenkranz, 2002).

While the Grace and Rosenkranz data offer a useful starting point from which to understand how the mPFC may modulate the amygdala, three sets of data suggest that this modulation carries substantially more complexity than one might at first think. First, recent work has identified a number of architectonic subdivisions within the human mPFC (Öngür et al., 2003). Thus, the broad term, vmPFC, could include some or all of areas 25, 32pl, 32ac, 24, 10m, 10r, 14c, 14r, and 11m by Öngür et al.'s 2003 naming scheme.

Second, anatomical studies in the macaque monkey provide evidence that different subdivisions within mPFC project to different subdivisions within the amygdala (Stefanacci & Amaral, 2002). For example, an anterograde tracer injection into area 24 heavily labels BA with only very light label appearing elsewhere. Another injection into area 25 labels not only BA but also a number of other subnuclei within the amygdala.

Third, fear extinction work has highlighted the importance of considering the roles that different subnuclei play within the amygdala (Sotres-Bayon, Bush, & LeDoux, 2004). "An important issue that is emphasized by our finding is that researchers interested in extinction or other functions mediated by the amygdala should, when possible, use the known detailed anatomical partitioning of the amygdala into subnuclei…rather than rely on less precise concepts, such as the basolateral complex" (Sotres-Bayon et al., 2004).

While acknowledging the complexity of the vmPFC to amygdala projection, the current work reduces this complexity to a single inhibitory projection from vmPFC to BA. This single projection expresses the intuition that vmPFC can modulate activity in BA. Fig. 6 shows how vmPFC fits into the BPD neural network. BA inhibits vmPFC, and vmPFC inhibits BA. I_{vmPFC} provides a driving input to vmPFC through a synapse (black semicircle). The synapse gates the input to vmPFC and can vary in strength according to a learning rule that tracks the activity in vmPFC. I_{vmPFCo} also excites vmPFC but without the synaptic plasticity present in the I_{vmPFC} projection.

The use of the term, "vmPFC", in Fig. 6 requires some clarification. The term, "vmPFC", here means not only vmPFC but also portions of ACC ventral to the genu of the corpus callosum.

3. BPD neural network simulations

3.1. BPD neural network equations

With the BPD neural network architecture in hand, a shunting equation (Grossberg, 1973) provides a way to simulate the activity of each node in the network. The shunting equation states that the rate of change of a node's activity, x, depends on three terms: passive decay, excitation, and inhibition. For example, Eq. (1) describes the time rate of change of vmPFC's activity, x_{vmPFC}.

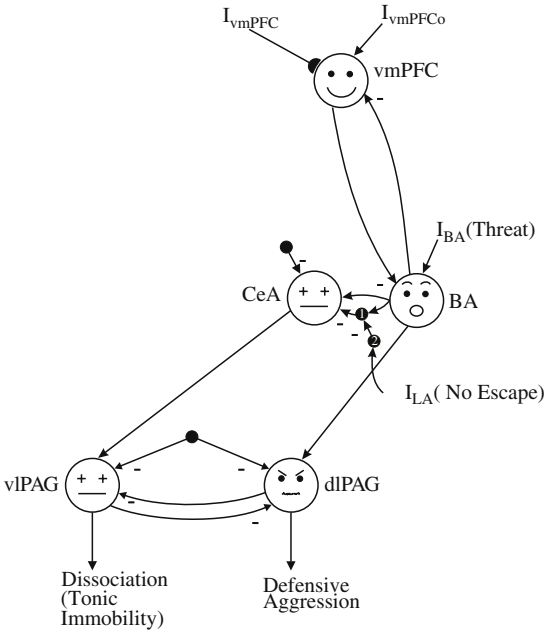

Fig. 6. The BPD neural network.

If vmPFC receives no excitation or inhibition, then x_{vmPFC} will decay to zero according to the passive decay term, $-A_{vmPFC}x_{vmPFC}$.

In the current network, vmPFC receives excitatory input, though. A tonic excitatory input, I_{vmPFCo}, remains on at all times. A second excitatory input, I_{vmPFC}, acts through the synaptic weight, z_{vmPFC}, to drive vmPFC. These two inputs work together in the excitation term, $(B_{vmPFC} - x_{vmPFC})[I_{vmPFC}z_{vmPFC} + I_{vmPFCo}]$, to push vmPFC toward higher activity.

B_{vmPFC} enforces an upper, shunting limit on x_{vmPFC}. As x_{vmPFC} approaches B_{vmPFC}, the difference, $B_{vmPFC} - x_{vmPFC}$, approaches zero. In this case, no matter how much larger the input becomes, x_{vmPFC} will not exceed B_{vmPFC}.

The network also has an inhibition term, $(x_{vmPFC} + C_{vmPFC})[x_{BA}]$. BA provides the inhibitory input to this term through the activity, x_{BA}. C_{vmPFC} provides a lower, shunting limit analogous to B_{vmPFC}.

Eq. (1) uses the following parameters.

$A_{vmPFC} = 0.7 \quad B_{vmPFC} = 3 \quad C_{vmPFC} = 0.5$

$I_{vmPFC} = 0.5 \quad I_{vmPFCo} = 0.5$

$Z_{vmPFC} = 1.0$ (Normal Brain) or 0.1 (BPD Brain)

$$\frac{dx_{vmPFC}}{dt} = -A_{vmPFC}x_{vmPFC} + (B_{vmPFC} - x_{vmPFC})\,[I_{vmPFC}z_{vmPFC} + I_{vmPFCo}] - (x_{vmPFC} + C_{vmPFC})\,[x_{BA}]\,. \quad (1)$$

Eq. (2) describes the activity of BA. BA receives an excitatory input, I_{BA}. BA also receives inhibitory input from vmPFC's activity, x_{vmPFC}.

Eq. (2) uses the following parameters.

$A_{BA} = 0.2 \quad B_{BA} = 3 \quad C_{BA} = 1.2$

$I_{BA} = 1.0$ (Normal Brain and BPD Brain simulations) or 2.0 (z_{vmPFC} change simulation)

$$\frac{dx_{BA}}{dt} = -A_{BA}x_{BA} + (B_{BA} - x_{BA})\,[I_{BA}] - (x_{BA} + C_{BA})\,[x_{vmPFC}]\,. \quad (2)$$

Eq. (3) describes the activity of the inhibitory neuron, ICM1, situated between BA and CeA. ICM1 gets excitatory input from BA's activity, x_{BA}. ICM1 receives inhibitory input from ICM2, a laterally-placed inhibitory neuron.

Eq. (3) uses the following parameters.

$A_{ICM1} = 2 \quad B_{ICM1} = 4 \quad C_{ICM1} = 6.5$

$$\frac{dx_{ICM1}}{dt} = -A_{ICM1}x_{ICM1} + (B_{ICM1} - x_{ICM1})\,[x_{BA}] - (x_{ICM1} + C_{ICM1})\,[x_{ICM2}]\,. \quad (3)$$

Eq. (4) describes the activity of ICM2. This neuron receives excitatory sensory input, I_{LA}, that indicates an inescapable threat. For example, a predator that has bitten an animal's leg and not let go would provide tactile input indicating that no escape is possible. ICM2 acts simply to shut down ICM1, so ICM2 does not need inhibition that would facilitate a graded response to I_{LA} in the current simulations.

Eq. (4) uses the following parameters.

$A_{ICM2} = 1.5 \quad B_{ICM2} = 3$

$I_{LA} = 1.0$

$$\frac{dx_{ICM2}}{dt} = -A_{ICM2}x_{ICM2} + (B_{ICM2} - x_{ICM2})\,[I_{LA}]\,. \quad (4)$$

Eq. (5) describes CeA's activity. CeA receives excitatory input from BA. CeA receives inhibitory input from ICM1 and a tonically-active inhibitory neuron, I_{CeAi}. When I_{LA} switches on, ICM2 becomes active and shuts down ICM1. When ICM1 shuts down, the inhibitory term in Eq. (5) drops far enough that BA begins to excite CeA.

Eq. (5) uses the following parameters.

$A_{CeA} = 4 \quad B_{CeA} = 8 \quad C_{CeA} = 7$

$I_{CeAi} = 0.3$

$$\frac{dx_{CeA}}{dt} = -A_{CeA}x_{CeA} + (B_{CeA} - x_{CeA})\,[x_{BA}] - (x_{CeA} + C_{CeA})\,[x_{ICM1} + I_{CeAi}]\,. \quad (5)$$

Eq. (6) describes vlPAG's activity. CeA excites vlPAG. Inhibitory input comes from dlPAG's activity and input from tonically-active inhibitory interneurons, I_{PAGi}.

Eq. (6) uses the following parameters.

$A_{vlPAG} = 2 \quad B_{vlPAG} = 5 \quad C_{vlPAG} = 2.7$

$I_{PAGi} = 0.3$

$$\frac{dx_{vlPAG}}{dt} = -A_{vlPAG}x_{vlPAG} + (B_{vlPAG} - x_{vlPAG})\,[x_{CeA}] - (x_{vlPAG} + C_{vlPAG})\,[x_{dlPAG} + I_{PAGi}]\,. \quad (6)$$

Eq. (7) describes dlPAG's activity. BA excites dlPAG. Inhibitory input comes from vlPAG and tonically-active inhibitory interneurons.

Eq. (7) uses the following parameters.

$A_{dlPAG} = 1.8 \quad B_{dlPAG} = 5 \quad C_{dlPAG} = 4$

$I_{PAGi} = 0.3$

$$\frac{dx_{dlPAG}}{dt} = -A_{dlPAG}x_{dlPAG} + (B_{dlPAG} - x_{dlPAG})\,[x_{BA}] - (x_{dlPAG} + C_{dlPAG})\,[x_{vlPAG} + I_{PAGi}]\,. \quad (7)$$

Eq. (8) describes the way in which the synaptic weight, z_{vmPFC}, changes (Grossberg, 1980). This equation differs from the shunting equations used so far. In Eq. (8), the synaptic weight changes only if two conditions are met. First, I_{vmPFC} must be greater than 0. Second, κ must be greater than 0. In the synaptic weight change simulation, $\kappa = 0.1$ if x_{BA} exceeds a critical value ($x_{BA} > 1.0$). Otherwise, $\kappa = 0$. This rule for κ says that only high levels of fear (high x_{BA}) will induce LTD in some vmPFC synapses. Consequently, if $I_{vmPFC} > 0$ and $\kappa = 0.1$, then z_{vmPFC} will begin to track x_{vmPFC}. At a sufficiently long time, z_{vmPFC} will essentially become equal to x_{vmPFC}. At this

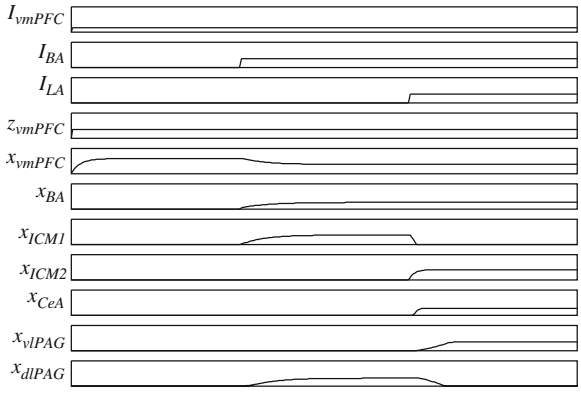

Fig. 7. Normal brain.

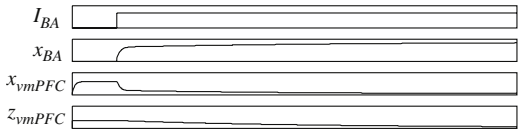

Fig. 8. Long term depression of z_{vmPFC} in a high fear state.

point, $x_{vmPFC} - z_{vmPFC}$ becomes zero, and no further weight change occurs.

Eq. (8) uses the following parameters.

$I_{vmPFC} = 0.5 \qquad \kappa = 0.1 \quad \text{if } x_{BA} > 1.0, \text{ otherwise } \kappa = 0.$

The initial value of z_{vmPFC} is 1.0.

$$\frac{dz_{vmPFC}}{dt} = I_{vmPFC}\,(x_{vmPFC} - z_{vmPFC})\,\kappa. \tag{8}$$

3.2. Simulation of normal brain

Fig. 7 shows a simulation of a normal brain. The simulation used Euler integration with 300 time steps. Each time step was 0.1. The length of each plot box is 300 time steps. The height of each plot box ranges from 0 to 3. Each activity is thresholded to zero so that negative activities are not passed on to other neurons in the network (i.e. a neuron cannot fire negative action potentials). I_{vmPFC} turns on at the beginning of the simulation. I_{BA} turns on after 100 time steps. I_{LA} turns on after 200 time steps. The synaptic weight, z_{vmPFC}, remains constant through this simulation.

At the beginning of the simulation, I_{vmPFC} excites x_{vmPFC} through the synaptic weight, z_{vmPFC}. The tonic input, I_{vmPFCo}, is not shown in Fig. 7 but remains on during the entire simulation. When I_{BA} turns on and excites x_{BA}, x_{BA} begins to inhibit x_{vmPFC}. At the same time, x_{BA} excites x_{dlPAG}. This causes a release of defensive aggression. CeA does not become active, because the strong inhibitory input from ICM1 overpowers the excitatory influence of x_{BA}.

At 200 time steps, I_{LA} switches on. This input excites ICM2. ICM2 then inhibits ICM1. Consequently, CeA becomes active because of the excitatory input from BA and the loss of inhibition from ICM1. CeA then excites vlPAG, and vlPAG inhibits dlPAG. The activity in vlPAG releases tonic immobility (dissociation).

3.3. Simulation of LTD in vmPFC

Fig. 8 shows how the synaptic weight, z_{vmPFC}, decreases during a high fear state. When I_{BA} is switched on, it is set at 2.0, double the value used in the normal brain simulation of Fig. 7. This high I_{BA} drives x_{BA} to a high value. BA's high activity strongly inhibits x_{vmPFC}. At high x_{BA}, z_{vmPFC} begins to track x_{vmPFC}, so z_{vmPFC} decreases. Eventually, z_{vmPFC} decays to about 0.1. This simulation used 1000 time steps (the length of the plot box).

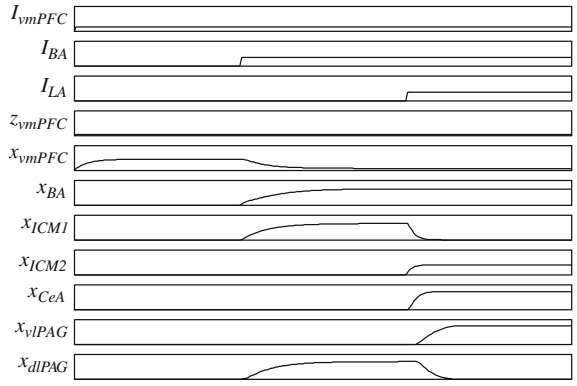

Fig. 9. BPD brain.

3.4. Simulation of BPD brain

The next simulation (Fig. 9) shows a BPD brain's response to the same inputs used in the normal brain simulation (Fig. 7). The only difference between the normal brain network and the BPD brain network is the decrease in z_{vmPFC} from 1.0 to 0.1 due to the LTD induced by high fear (Fig. 8). With the decrease in z_{vmPFC}, I_{vmPFC} has a reduced ability to excite vmPFC. This reduction in x_{vmPFC} releases x_{BA} to rise to a much higher value than in the normal brain. The higher x_{BA}, then, more strongly drives x_{dlPAG}. Then, when switched by I_{LA}, x_{vlPAG} rises to a much higher level than it did in the normal brain. Thus, one "single point of failure", the LTD in z_{vmPFC}, causes the BPD brain to respond with higher defensive aggression and dissociation than does a normal brain. Also, the diminished ability to activate vmPFC in the BPD brain presumably contributes to some of the other behavioral features seen in BPD as discussed earlier in the paper.

4. Discussion

The current neural network provides a novel way to think about BPD by building a computational sketch of how certain brain structures may interact in the BPD brain. The network captures core features of BPD such as defensive aggression, dissociation, switching between these states, TOM deficits, impulsiveness, neuropsychological deficits, and some structural and functional magnetic resonance imaging data. The BPD neural network appears consistent with other data, as well.

For example, 50% of BPD patients also have post-traumatic stress disorder (PTSD) (Schmahl et al., 2003a). This high comorbidity suggests that BPD and PTSD may engage some of the same brain structures. The current BPD neural network could account for this finding in the following way. While in a fear mode, the right amygdala would damage the right vmPFC/ACC, causing the brain to take on a BPD phenotype. However, in addition, the right amygdala in some individuals remains hypersensitive to stimuli that resemble the original trauma. This hypersensitive right amygdala would then recruit other brain structures (e.g. visual association cortex) in an inappropriate way so as to produce flashbacks to the original trauma as seen in PTSD.

The BPD neural network also appears consistent with recent PET work exploring the idea that the amygdala and PFC become "disconnected" in BPD (New et al., 2007). This study measured resting metabolic rate correlations between various prefrontal areas and the amygdala in impulsive–aggressive BPD patients. The study found no significant correlations between OFC and the amygdala in patients. This lack of correlation supports the view that prefrontal areas in BPD patients have a degraded ability to modulate amygdala activity. The study also found significant

group differences between controls and BPD patients in BA 10, 11, 12, 32, 44, 45, and 46. BA 10, 11, 12, 32, and 46 all fall in the "medial prefrontal network" (Carmichael & Price, 1996). The BPD network would explain these PET data by asserting that the amygdala induces LTD and/or apoptosis in cortical areas of the medial prefrontal network. Consequently, as New et al. (2007) put it, these data "…suggest that the primary abnormality in BPD relates to the failure of the PFC to 'come on line' in response to amygdala activation".

Success in treating BPD dissociative symptoms with Naltrexone, an opioid receptor antagonist, provides another example of other data that appears consistent with the BPD neural network (Bohus et al., 1999; Bolm & Piegler, 2001). Both CeA and vlPAG, structures identified in the BPD neural network as important in dissociation, contain opioid system circuitry (Keay & Bandler, 2001; Manning, 1998). Consequently, they could provide a means whereby Naltrexone suppresses dissociation.

In addition to incorporating the PTSD, PET, and Naltrexone data, the BPD neural network may suggest ways that a person could develop BPD without being exposed to trauma. Between 20% and 40% of BPD patients have not been abused or neglected (Graybar & Boutilier, 2002). Also, some research supports the view that BPD has an important genetic component (Torgersen, 2000).

Genetic anomalies that disrupt normal development of vmPFC and/or ACC might create a BPD-like brain. Sonic Hedge Hog (Shh) and genes coding for Bone Morphogenetic Proteins (BMPs) play an especially important role in brain midline formation (Bertrand & Dahmane, 2006; Furuta, Piston, & Hogan, 1997). Shh and BMPs also play a role in the normal development of left–right body asymmetry (Monsoro-Burq & Le Douarin, 2001), a potentially useful finding given the current BPD neural network's emphasis on involvement of the right ACC/vmPFC. Interestingly, many non-neural tissues such as teeth, bone, tendon, skin, kidney, and heart also use Shh and BMPs to guide development (Ducy & Karsenty, 2000). If mutations in these genes do exist, then some of these tissues may develop in an abnormal way as well. These putative pleiotropic mutations might aid in identifying BPD subtypes.

Genetic variation in mGluR's might also promote the development of BPD behavior. If the amygdala to vmPFC/ACC projection does use mGluR's, then variations in the type of mGluR present in a particular individual might increase the likelihood that the right amygdala in that individual will damage the right vmPFC and/or ACC. Many splice variants of mGluR's exist (Ferraguti & Shigemoto, 2006).

Development can become impaired not just through genetic mutations but also through environmental teratogens. For example, the corn lily (*Veratrum Californicum*) contains cyclopamine, an antagonist of Shh (James, 1999). Because of Shh's importance in the network of genes that regulate normal development of the brain's midline, antagonizing Shh alters brain midline development. Perhaps factors in the environment could induce development of a BPD-like brain in some individuals.

Although apparently successful in explaining some BPD data, it is worth noting that the BPD neural network just presents a computational sketch of how certain brain structures may interact in a BPD brain. Other structures and connections might participate in BPD behavior. The following discussion mentions some of these in order to highlight potential limitations of the BPD neural network and also to provide ideas for future research into a more sophisticated BPD neural network.

The BPD neural network emphasizes the right amygdala's role in activating the PAG, but vmPFC/ACC can activate the PAG as well. The vmPFC/ACC has direct, monosynaptic access to the PAG (An et al., 1998). In stimulation studies, though, forebrain sites must receive strong input to elicit a response in PAG neurons (Behbehani, 1995). Does the vmPFC/ACC to PAG projection influence BPD behavior?

The BPD neural network asserts an important role for the amygdala and PAG in BPD anger (defensive aggression) and BPD dissociation (tonic immobility), but the hypothalamus can also participate in these behaviors. Stimulation of the medial hypothalamus in cats evokes defensive aggression (Gregg & Siegel, 2001). Stimulation of the anterior lateral hypothalamus in guinea pigs increases the duration of tonic immobility (de Oliveira, Hoffman, & Menescal-de-Oliveira, 1997). The hypothalamus has connections with vmPFC/ACC, the amygdala, and the PAG (Öngür, An, & Price, 1998) (all the components of the current BPD neural network). Does the hypothalamus contribute to BPD behavior?

Remarkably, all of the brain structures identified here (vmPFC/ACC, amygdala, hypothalamus, and PAG) map onto elements associated with the "medial prefrontal network" (Carmichael & Price, 1996; Öngür et al., 1998). The medial prefrontal network consists of cortical areas that have robust connections with each other and very little if any connections with other orbital frontal areas. Components of the medial prefrontal network project in a predictable way to subdivisions within the amygdala, hypothalamus, and PAG. Figure 19 of Öngür et al. (1998) provides a very clear summary of these projections. The tight mapping of the current BPD neural network onto brain structures associated with the medial prefrontal network suggests that BPD might be considered primarily as a disorder of the medial prefrontal network.

Representing the components of the medial prefrontal network in greater detail seems likely to improve the biophysical fidelity of BPD simulations. For example, the current BPD neural network represents vmPFC/ACC as a single node, but several cortical areas together comprise vmPFC/ACC (Öngür et al., 2003). Similarly, the BPD neural network represents the amygdala as having two nodes (BA and CeA) with a small amount of additional circuitry, but the amygdala actually has a number of subnuclei with complex intra- and inter-nuclear connections (Pitkänen, Savander, & LeDoux, 1997).

The BPD neural network models structures in the right hemisphere. Do left hemisphere structures also participate in BPD behavior? Structural MRI work found reduced gray matter in the right ACC (Hazlett et al., 2005), but this same work also found reduced gray matter in the left ACC. The right ACC had a more *substantial* reduction than did the left ACC, but the presence of gray matter reduction in the left ACC suggests that the left hemisphere may also influence BPD behavior.

The BPD neural network makes no distinction between a female brain and a male brain, but gender seems important in BPD. Approximately 75% of individuals with BPD are female (American Psychiatric Association, 2000). In a small study of four men and four women, men who had damage to the right vmPFC had substantial impairments in social conduct and decision-making (Tranel et al., 2005) while women had only mild impairment or no impairment at all. Women who had damage to the left vmPFC or, in one case, bilateral damage to the vmPFC had severe impairments in social conduct and decision-making. Finally, in a study of acute and chronic foot shock stress, male and female rats showed marked differences in gene expression in medial prefrontal cortex (Trentani et al., 2003). The authors speculate that the differences may reflect different coping strategies between male and female rats in response to aversive conditions.

5. Suggested work

The process of building the BPD neural network has produced several ideas for future work. First, we need to figure out *precisely* how the amygdala to vmPFC/ACC projection works. The neural network claims that this projection modulates and perhaps damages the vmPFC/ACC. Repeating the experiment of Pérez-Jaranay and

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Vives (1991) but this time using mGluR antagonists might show that mGluR's participate in the amygdala to vmPFC/ACC projection.

Second, an fMRI study of the BPD brain's processing during the Digit Symbol Substitution Test (DSST) may demonstrate impaired cognitive control by the ACC. The factor analysis approach (Peterson et al., 1999) used in a study of the Stroop test might provide a useful way to understand the fMRI data.

Third, studying the BPD brain's processing of altruistic punishment (Schadenfreude) may also yield an insight into vmPFC impairment. In a normal brain, vmPFC becomes active while considering the personal cost of punishing another person. The BPD brain may fail to activate vmPFC. The PET experimental protocol of de Quervain et al. (2004) offers a convenient way to study this Schadenfreude question. Follow-on work in this area might also include a healthy person in one scanner interacting real-time with a BPD patient in another scanner. This arrangement could provide data on how a person with BPD affects other people.

Fourth, test TOM competence in people with BPD. Do people with BPD perform normally on a particularly demanding type of TOM test such as the social faux pas? The social faux pas test requires empathic understanding of another person's feelings. Individuals with damage to the right vmPFC perform poorly on social faux pas tests (Shamay-Tsoory et al., 2005).

Fifth, study the incidence of pleiotropic mutations in non-abused BPD patients. If non-abused patients have a higher than normal incidence of these mutations (e.g. skeletal, skin, heart), then this might identify genetic mutations that alter brain structure in some way that causes BPD-like behavior.

Sixth, capture epidemiological data (e.g. place of birth) to assess teratogen exposure. Does BPD in non-abused patients occur at a higher frequency in certain locations?

Seventh, begin construction of a limbic system simulator. Construction will take ten to twenty years and produce several simulators of increasingly greater biophysical fidelity. Eventually, the simulator should model subpopulations of neurons including their dendritic trees, axonal arbors, ion channels, receptors, and ligands. Validated experimental data will aid this modeling work. In time, this work should also generate male and female versions of the limbic system simulator.

Construction of the simulator offers several benefits. The simulator will aid in teasing out the individual contributions of different brain structures and projections in BPD. Perhaps BPD patients present with somewhat different symptoms, because these brain structures participate to varying degrees in different individuals. The simulator should also improve the understanding of other mental disorders that have a prominent limbic system component. The simulator will facilitate drug development by offering a way to test how drugs targeted at one subpopulation of neurons in the amygdala, for example, affect operation of the entire limbic system. Finally, building the simulator will identify technology gaps that will provide ideas for experimental work. For example, building the current BPD neural network identified a lack of data about the amygdala to vmPFC/ACC projection. Does this projection use mGluR's?

6. Conclusion

This paper presents a neural network model of Borderline Personality Disorder. The model identifies the periaqueductal gray, the right amygdala, and the right ACC/vmPFC as important structures in the development and expression of BPD behavior. The model's architecture and function appear consistent with much of the available neuroanatomical, neurophysiological, and behavioral data. Simulation results suggest that the right amygdala changes or damages the right vmPFC and/or ACC in a way that degrades the BPD brain's ability to anticipate the emotional consequences of proposed behaviors, to engage cognitive control circuits for some visual tasks, and to suppress amygdalar activity. The model suggests impairment in the DSST and altruistic punishment tasks. The model also suggests that the right amygdala will change or damage the right ACC/vmPFC through mGluR's that induce long term depression or perhaps even apoptosis in ACC/vmPFC neurons. Future BPD modeling work would benefit from construction of a limbic system simulator.

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