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The Neural Correlates of Depersonalization: A Disorder of Self-Awareness

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Depersonalization can be understood, at least in part, as a disorder involving disruptions of self-awareness. Recent neuroimaging evidence indicates that the right hemisphere is likely essential to self-related processing, such as self-recognition, autobiographical retrieval, self-evaluation, and autonoetic consciousness. Disorders of self-awareness caused by focal lesions, such as asomatognosia and mirror sign, have also implicated the right hemisphere (see Chapter 8, Feinberg, this volume and Chapter 9, Postal, this volume). Although early studies were inconclusive, we review the most recent literature and suggest that as imaging techniques improve, right hemisphere dysfunction may be implicated in dissociative processing and particularly in depersonalization.

The Self and the Right Hemisphere

For centuries philosophers have considered the concept of self-awareness as central to human existence. Many attempts have been made to elucidate the nature of self-awareness, most recently by cognitive neuroscientists seeking to identify possible neural correlates of this most fundamental of human capabilities (for a review, see Keenan, Gallup, & Falk, 2003). Over the past few years the rise of modern neuroimaging techniques has led a number of researchers independently to speculate that the right hemisphere, particularly in prefrontal areas, may be dominant for self-related processing. Such self-related processing includes self-recognition, self-face recognition, self-voice recognition, autobiographical/episodic retrieval, self-evaluation, first-person perspective, and autonoetic consciousness (Keenan et al., 2001; Sugiura et al., 2000; Breen, Caine & Coltheart, 2001; Nakamura, Kawashima, Sugiura, Kato, Nakamura et al., 2001; Markowitsch, 1995; Miller et al.,

2001; Spangenberg, Wagner & Bachmnan, 1998; Fink et al., 1996; Levine et al., 1998; Craik et al., 1999; Vogeley et al., 2001; Stuss, 1991; Wheeler, Stuss, & Tulving 1997), as both self-related processing and self-recognition may be considered markers of self-awareness (Keenan et al., 2003).

Over the past few years many studies have found greater right-hemisphere involvement in tasks involving self-face recognition, especially in prefrontal areas. Whereas the fusiform gyrus has been implicated in general face recognition (Kanwisher, Stanley, & Harris, 1999; Kanwisher, McDermott, & Chun, 1997), investigations examining self-face versus other face recognition have found that recognition of the self-face is often correlated with greater activity in the right hemisphere. For example, in a neuroimaging study employing functional magnetic resonance imaging (fMRI), Keenan, McCutcheon, and Pascual-Leone (2001) contrasted subjects' brain activity when they viewed their own faces with the activity when they viewed the face of another individual (Bill Clinton). The results showed that when subjects viewed their own faces there was significantly more activation within the right inferior frontal gyrus than when they viewed the nonself face. In a different study Keenan and coworkers (2001) employed the WADA test to further investigate the role of the right hemisphere in self-face recognition. In this procedure, (named after the neurologist Juhn A. Wada) typically used to find the language-dominant hemisphere before surgery, one hemisphere at a time is anesthetized following administration of amobarbital (a strong barbiturate) to the intracarotid artery. Keenan and colleagues used a morphing procedure to create pictures that were a combination of patients' own faces and that of a famous person. While anesthetized, the patients were shown a picture of the morphed face and were instructed to remember it. After recovery from the anesthesia, the patients were asked to choose the picture they saw while anesthetized, from the two original pictures used to construct the morphed face. Following anesthesia to the left hemisphere, all five patients selected the self-face, suggesting that self-recognition does not depend on the left hemisphere. In contrast, following anesthesia to the right hemisphere, four of the five patients selected the famous face, suggesting that the right hemisphere is essential for self-face recognition. To ensure that this effect was not due to a simple biasing of naming (i.e., the left hemisphere is needed to name famous faces), 10 normal subjects were presented with similar morphed images. The authors used transcranial magnetic stimulation (TMS) to determine the cortical excitability of the left and right hemispheres and found that excitability in the left hemisphere did not differ significantly between self- and other morphs. This suggests that the level of cortical activation in the left hemisphere was similar for self- and other processing. Interestingly, however, there was significantly greater activation of the right hemisphere for self-morphs compared to familiar morphs. Consistent with these findings, Keenan and colleagues (2003) have recently found evidence in split-brain patients for a right-hemisphere bias in self-related processing. In addition, when peripheral physiological data are collected (e.g., skin resistance), it has been found that the right hemisphere of split-brain patients is significantly more active in response to the self-face even when emotionality is controlled for (Preilowski, 1977). Again, the left hemisphere shows no

such differentiation between self and other (but see Turk et al., 2002, for contradictory evidence).

In addition to the experimental evidence suggesting a right-hemisphere dominance for tasks involving self-recognition, there is also considerable evidence for a right-lateralized bias from clinical studies examining deficits in self-recognition, known as "mirror sign" (see Chapters 8 and 9, this volume).

Other deficits in self-awareness have also been linked to right-hemisphere dysfunction (Feinberg, 2000; Stuss 1991). Feinberg in Chapter 8 in this volume details a number of delusional misidentifications, all of which which seem to involve right-hemisphere disorders. Further support for the preferential involvement of the right hemisphere compared to the left in delusional misidentification comes from the WADA test. In a study by Meador et al., 2000, the right hemispheres of 32 patients were anesthetized, and it was found that only 8 of these patients were able to correctly recognize their own hands, while the other 24 patients claimed their hands were someone else's. This study clearly suggests that the right hemisphere is important for self-related processing and that this processing is not limited to self-face recognition but extends to other aspects of self-identity.

Drawing another link between self-processing and right-lateralized activation, Ruby and Decety (2003) recently used PET to investigate the neural correlates of first-person perspective-taking versus third-person perspective-taking. In the experiment participants were asked to answer questions from both their own perspectives and from the perspective of a third person. The authors concluded that the right inferior parietal lobe was critical for distinguishing self and other, along with frontopolar and somatosensory regions. These results confirmed previous results reported in the motor domain in which activation in the right somatosensory cortex was associated with a "preservation of the sense of self" (Iacoboni et al., 1999). In a recent review article Decety and Sommerville (2003) argued that the inferior parietal cortex and the prefrontal cortex in the right hemisphere play a special role in interpersonal awareness, such that they are critical for understanding and separating self from other. In addition, Decety and coworkers have suggested that the right parietal cortex is important for self-representation (Decety et al., 2002).

The experimental studies and clinical cases reviewed thus far seem to suggest a dominant role for areas in the right hemisphere in self-awareness and self-related processing. If this is indeed the case, then it is reasonable to suppose that other disorders of self-awareness and self-related processing may involve dysfunction in similar or related areas. Thus, findings from previous studies can be used as a platform from which to investigate and interpret data concerning the neural mechanisms of other self-related disorders, such as dissociative disorders and particularly depersonalization disorder (DPD). The dissociative disorders, of which DPD is an example, are characterized by two main deficits: a disruption in the usually integrated sense of self or identity, and a dissociation of mental processes (DSM IV, APA). By their very nature these disorders are concerned with the experience of self and with the mechanisms of self-awareness. Indeed, it has been argued that depersonalization is always associated with altered levels of awareness (Mayer-Gross, 1935). Despite great interest and decades of research, the neural correlates and biological mechanisms underlying these disorders remain poorly understood.

Many factors complicate the study of such disorders as well as the interpretation of results. Among these complicating factors are the dynamic nature of the symptoms, differential diagnoses, presence of medication in many patient populations, insufficient sample sizes, poor controls, and the frequent presence of comorbid disorders. As might be expected, these problems are especially evident in earlier studies.

Due to the overwhelming complexity of each of the dissociative disorders and the variation among different disorders within the dissociative cluster, only DPD and the depersonalized states will be considered here.

Depersonalization

As the name suggests, depersonalization disorder (DPD) is characterized by persistent or recurrent episodes of depersonalization, a state that is, in itself, characterized by a distortion in self-awareness. Depersonalization often includes an altered, detached, or estranged subjective experience of one's self, one's mental processes, and one's surroundings while reality testing remains intact. Transient experiences of depersonalization have been reported by nearly 50% of college students (Dixon, 1963), and such states can be induced in normal individuals following temporal lobe stimulation (Penfield & Rasmussen, 1950), or administration of tetrahydrocannabinol (THC; Mathew et al., 1999; Mathew et al., 1993; Johnson, 1990; Melges et al., 1970b; Moran 1986; Herman & Szymanski 1981), alcohol (Raimo et al., 1999), amphetamines (Vollenweider et al., 1998), the partial serotonin agonist m-CPP (Simeon et al., 1995), and the 5-HT1a and 5-HT2a receptor agonist Psilocybin (Vollenweider et al., 1999; see also Chapter 5, this volume).

In the presence of symptoms, a diagnosis of DPD is made only if the symptoms are severe enough to cause marked distress or to impair normal functioning. Furthermore, although DPD is diagnosed only when symptoms are not secondary to any other disorder, it is often found in association with other syndromes such as temporal lobe epilepsy and complex partial seizures (Shorvon et al., 1946; Kenna & Sedman, 1965; Greenberg, Hochberg, & Murray, 1984), anxiety disorders and depression (Simeon & Hollander 1993; Nuller, 1982), head trauma (Grigsby & Kaye, 1993; Grigsby, 1986; Ackner, 1954), extreme stress and posttraumatic stress disorder (PTSD) (Bremner & Brett 1997; Lanius et al., 2002), and others.

Early Studies

Early investigations of the neural correlates of depersonalization often did not focus on the disorder per se but rather on depersonalized states, often as part of a comorbid disorder. Moreover, these studies frequently reported mixed or inconsistent results regarding regions of activation and laterality. Shorvon and colleagues (1946) examined records of the electrical activity over the scalp as measured by electroencephalography (EEG). Specifically, the EEGs of 23 patients for whom depersonalization was the leading symptom were examined, and it was found that 13 of

them displayed minor and diffused abnormalities. Only one patient, who reported a history of migraines, had a focal abnormality, but unfortunately the focus of this abnormality was not specified. Although more than 50% of the sample was found to have mildly abnormal EEGs, the authors concluded that EEG abnormalities were not directly related to the mechanism of depersonalization. Similarly, Kenna and Sedman (1965) were unable to show an association between depersonalization and any particular focal disturbance. Of 32 epileptic patients reviewed, 11 patients reported depersonalization, all of whom had abnormal EEGs. The authors reported that no focal activity was found in the EEGs of 4 patients, whereas 4 had a left-sided focus, and 3 had a right-sided focus. In addition, only 5 of 64 patients with organic psychoses reported depersonalization. EEGs were recorded in only 4 of those patients, and 3 of those were found normal. The authors concluded that the data did not implicate any particular brain area, "though the total functioning of the limbic system and/or temporal lobe may be involved" (p. 298). These conclusions regarding possible temporal lobe dysfunction implicated in dissociation have been echoed elsewhere (Penfield & Jasper, 1947; cited in Ackner, 1954).

After the somewhat equivocal findings from early studies, more informative results have been reported in later investigations. For example, Devinsky and colleagues (1989) reviewed cases of 71 epileptic patients and reported that those with left-hemisphere foci had higher depersonalization scores on the Dissociative Experience Scale (DES), although the median score for this group was lower than that of psychiatric patients diagnosed with multiple personality disorder. In a single case study described by Hollander and coworkers (1992), a young male with primary DPD was found to have a normal EEG and a normal MRI scan, although results from brain electrical mapping, evoked potentials, and Single Photon Emission Computed Tomography (SPECT) suggested a left-hemisphere frontotemporal dysfunction. The authors interpreted these findings as suggesting a common neurobiological underpinning for DPD and obsessive-compulsive disorder (OCD), including left-hemisphere lateralization of dysfunction.

Modern Neuroimaging Studies

Recent studies employing advanced functional neuroimaging techniques have attempted to resolve some of the findings that emerged from earlier studies and have directly addressed DPD per se although only with mild success. In a pioneering PET study Simeon and colleagues (2000) attempted to localize abnormalities in eight subjects diagnosed with DPD as they performed a variant of the California Verbal Learning Test. Unfortunately, the comorbidity profiles of the subjects in this study were not reported. Compared to normal controls, those with DPD had significantly lower metabolic rates in the right superior temporal gyrus and right middle temporal gyrus (Brodmann's Areas [BA] 22 and 21, respectively). Conversely, these same subjects showed significantly higher metabolic rates in parietal association areas (BA 7B and 39—the angular gyrus) bilaterally, and in left occipital BA 19. Dissociation and depersonalization ratings on the DES scale correlated positively with activation in area 7B. The authors stated that these findings

may be consistent with the perceptual alterations reported in DPD, as differences in activity were marked in areas whose known function is association and integration, although they are inconsistent with much of the previous literature on temporal lobe epilepsy, for example.

In the first study to employ fMRI in the investigation of DPD, Phillips and colleagues (2001) compared neural responses of patients diagnosed with DPD or OCD and normal control subjects to emotional stimuli (aversive scenes). For this purpose they recruited 6 DPD patients (5 males, 1 female), 10 OCD patients (8 men, 2 women), and 6 normal volunteers (4 men, 2 women). Again, the comorbidity and pharmacological profile of the participants was not specified. Compared to normal control subjects and those with OCD, subjects with DPD failed to show activation of the insula in response to aversive stimuli and showed lower activation in the middle and superior temporal gyri (BA 22 and 37) and inferior parietal regions (BA 40). Both patient groups showed significantly more activation in the right ventral prefrontal cortex (BA 47) in response to the aversive scenes compared to healthy controls subjects, although only DPD patients showed this activation in the absence of insula activation, indicating an inverse functional relationship in DPD between these neural regions during presentation of emotional stimuli potentially reflecting attempts at emotion regulation. The lower activation found in DPD patients in temporal regions is consistent with the findings of Simeon and coworkers (2000), although the activation in the right ventral prefrontal cortex is inconsistent with the same findings, as is the inverse relationship suggested between the insula and the right ventral prefrontal cortex. This latter finding regarding activation in the right ventral prefrontal cortex is consistent, however, with the right lateralization of self-related dysfunction and with findings regarding cerebral blood flow in the THC-induced depersonalization state (see below).

Another recent study that employed fMRI determined the neural activation underlying dissociative responses to traumatic script-driven imagery in sexual abuse–related PTSD patients who were also diagnosed with dissociative disorder, not otherwise specified (but not DPD). In the study Lanius and colleagues (2002) compared 7 female patients who suffered from PTSD as a result of childhood abuse to 10 control subjects who suffered abuse but did not meet the criteria for PTSD. Subjects were scanned while a traumatic script was read and were encouraged to remember any sensations related to the traumatic events. After each script was read to them, they were assessed for dissociative symptoms using the Clinician-Administered Dissociative State Scale (CADSS) and the DES scale. The dissociated PTSD group showed greater bilateral activation in inferior frontal gyrus (BA 47) and greater occipital lobes activation (BA 19) compared to control subjects. However, they also showed greater activation that was right-lateralized in the superior and middle temporal gyri (BA 38), anterior cingulate (BA 24, 32), medial parietal lobe (BA 7), medial frontal gyrus (BA 10), and medial prefrontal cortex (BA 9).

Although the results of Lanius and coworkers (2002) and Phillips and coworkers (2001) lend some support in favor of a greater involvement of right-lateralized circuitry in the dissociative symptoms compared to left-lateralized mechanisms, the interpretation of these results, along with the results of Simeon and coworkers

(2000), is difficult. First, the results from the three studies are somewhat inconsistent. For example, although DPD patients in both Simeon and coworkers (2000), and Phillips and coworkers (2001) showed lower activation in superior and middle temporal regions, patients in Lanius and coworkers (2002), showed greater activation in the same areas during a depersonalized state. These inconsistencies stem from several problems: the patient profile in each study is different, sample sizes are insufficient, comorbid disorders are unspecified, it is unknown whether patients were medicated, each study used entirely different procedures, and in some cases different neuroimaging techniques were used as well. As a result of these serious methodological inequalities and concerns, it is useful to identify alternative approaches to the search for the neural correlates of depersonalization. One example of such an alternative approach is studies that employ temporarily induced states of depersonalization.

Manipulating Depersonalization

Studies concerned with induced states of depersonalization provide an alternate line of evidence regarding the possible neural mechanisms of depersonalization. This is especially important in light of the limitations of studies investigating patients suffering from DPD. Although the depersonalization symptoms reported following THC (Delta-9-tetrahydrocannabinol—the main psychoactive ingredient of marijuana) intoxication do not constitute a disorder such as that seen in DPD patients, the phenomenology of the experience is similar, as measured, for example, by the DES scale. Furthermore, these experiences do constitute a disturbance of self-awareness and an alteration in the experience of self as seen in DPD as exemplified by an estranged or detached sense of one's self.

The effects of THC administration on depersonalization have been known for quite some time. Indeed, Melges and colleagues (1970a) first reported that THC induces temporal disintegration, or an impairment of one's ability to plan sequential adjustment during goal pursuit. Melges and colleagues (1970b) reasoned that a fundamental component of one's sense of self is one's sense of subjective time. On this premise they investigated the relationship between temporal disintegration and the possibility of THC-induced depersonalization. Eight subjects were administered oral doses of THC and were asked to perform the Goal-Directed Serial Alteration (GDSA) task and to respond to the Temporal Integration Inventory (TTI) and the Depersonalization Inventory (DPI). The results showed that THC did induce temporal disintegration and that the degree of depersonalization was positively correlated with the degree of temporal disintegration. Hence, Melges and colleagues (1970b) provided the first evidence for a link between THC intoxication and the depersonalized state.

Another early report by Herman and Szymanski (1981) reviewed four cases of prolonged depersonalization following marijuana abuse. Of the four cases, three had normal EEGs, while one showed right-lateralized frontal temporal slowing. Consistent with these findings are those described by Moran (1986), who reported occurrences of depersonalization following marijuana use in six subjects, and by

Mathew and colleagues (1993), who reported similar findings in 35 healthy volunteers during marijuana intoxication. In their study marijuana smoking but not placebo smoking induced significant depersonalization that peaked 30 minutes after administration of the drug.

In an attempt to identify the neural correlates of the administration of THC, Mathew and colleagues (1992) investigated regional cerebral blood flow (rCBF) using the ^{133}Xe inhalation technique. No significant changes were found following placebo administration, whereas THC administration was associated with bilateral CBF increase, with greater increase marked in frontal areas, and in the right hemisphere compared to the left. To extend these findings, Mathew and colleagues (1997) studied brain activation following THC administration using PET. IV infusions of low-dose THC, high-dose THC, or placebo in a double blind procedure were given to 32 subjects. Levels of intoxication reached a peak 30 minutes after administration in the drug groups. CBF significantly increased following THC administration, with more marked increases in the right hemisphere compared to the left, and in anterior regions compared to posterior. In the high-dose group increased activation was found bilaterally in frontal, temporal, and parietal areas and the cingulate, basal ganglia, insula, and thalamus at 30 minutes and at 60 minutes. More specifically, the right hippocampus and amygdala were significantly more active at 30 minutes, but not at 60 minutes. The low-dose group displayed a similar pattern, with activation peaking at 60 minutes post administration. Levels of intoxication were measured using the Analogue Intoxication Scale (AIS), and scores correlated significantly with global CBF, with the strongest correlation marked with levels of activation in the right frontal lobe and left cingulate gyrus. Depersonalization was reported significantly more in the drug groups, but no specific correlations between depersonalization and activation were reported.

In a follow-up study Mathew and colleagues (1999) used PET to directly investigate a possible direct relationship between global CBF and depersonalization during THC intoxication and to further examine the involvement of subcortical structures. CBF was measured before and during intravenous administration of low-dose or high-dose THC or placebo in a paradigm similar to Mathew and colleagues (1997). As predicted, THC infusion induced depersonalization compared to placebo, with ratings reaching a maximum at 30 minutes after infusion. In both dosage groups THC administration was associated with a significant increase in global CBF, most markedly in the right hemisphere, the frontal lobes, and anterior cingulate. In this study depersonalization scores (as measured using the DPI and AIS) were positively correlated with increased CBF in most regions. particularly significant correlations were found between depersonalization and activation of the right frontal lobe and right anterior cingulate. These studies, taken together, may lend support to an account of depersonalization suggestive of right-hemisphere dominance.

Treatment

DPD is considered refractory to most pharmacological treatments (Simeon, Stein, & Hollander, 1998; see also Steinberg, 1991). In recent years a few very prelimi-

nary reports have emerged that suggest a possible role for selective serotonin reuptake inhibitors (SSRIs) in the treatment of DPD, although, to our knowledge, no major clinical trial has been published that could be taken as evidence that such treatment is indeed effective for DPD. For example, Hollander and colleagues (1990) reported substantial improvement in six of eight patients who suffered from either DPD or depersonalization symptoms following treatment with fluoxetine. However, seven of the reported patients suffered from comorbid OCD, obsessive-compulsive symptoms, panic disorder, or panic symptoms, which are known to be ameliorated by SSRI therapy. The one patient who did not suffer from any comorbid disorders, a 26-year-old woman, was one of the two who showed little or no improvement in symptoms following treatment. Similarly, Simeon, Stein, and Hollander (1998) reported on eight adult subjects who entered a double-blind crossover trial of clomipramine versus desipramine. Again, every subject in the study suffered from comorbid disorders such as dysthymia, panic disorder, generalized anxiety disorder, OCD, and social phobia. The authors themselves stated that the small sample size did not lend itself to statistical analysis but described improvement in two of the cases.

Relevant to this discussion, Keenan, Freund, and Fascual-Leone (1999) described a case study of a single woman suffering from DPD, who was treated with administration of inhibitory 1 Hz repetitive transcranial magnetic stimulation (rTMS) to her right prefrontal cortex. After the second day of stimulation, her depersonalization symptoms dramatically subsided. In her posttreatment journal the patient described herself compellingly: "I was me again; awake and feeling what's around me. I was looking through freed eyes. God has reopened my eyes, and not just a little, but wide open. I don't feel unsure and afraid of myself any longer. I feel like_____ [patient's name]."

The patient's reactions noted here occurred within the first two days of a two-week treatment for depression. Over the course of the next two weeks, the patient slipped back into her depersonalized state. For example, in the second week of treatment, the patient indicated, "I'm disappointed about todays [sic] results from the treatment. Although things are appearing clearer and more real to me, I still feel as though I'm on the outside of myself." The patient returned for further treatment, and the initial positive results were never replicated. Again, while these data initially suggested an important role for the right hemisphere, the fact that there was no replication makes it extremely difficult to establish the true role of the right hemisphere in the depersonalized state. That is, it is unclear whether the subjective experience of the patient was a direct result of right-hemisphere TMS specifically or a more general result of experiencing TMS; the initial reaction may have occurred if stimulation was applied to the left frontal region or even if sham TMS had been administered.

Conclusion

Right-hemisphere dysfunction has been implicated in self-related processing and in deficits in the perception or recognition of self, as seen in mirror sign and

asomatognosia. Similarly, several converging lines of investigation provide some support to the notion that the depersonalized state and DPD, characterized by a distorted sense of self, are associated with right-lateralized dysregulation. However, to date there have been very few rigorous and well-designed neuroimaging studies that attempted to identify the neural underpinnings of DPD. It is, however, encouraging that as research continues the limitations of earlier studies are being addressed and amended. Although much progress has been made in recent years compared to earlier periods of investigation, findings are still contradictory, and it is too early to draw bold conclusions regarding the neural circuitry underlying self-related processing. Nevertheless, it is abundantly clear that studies that seek to investigate these phenomena can contribute to our understanding of self-awareness and self-processing in general. In doing do, they will surely help to unravel the exact role of both frontal and parietal regions of the right hemisphere in self-related processing and self-related dysfunction.

However, in order to improve our understanding of, among other things, lateralization of function in self-related processing, several recommendations are in order. Ideally, future research on dissociative conditions and depersonalization should seek to use advanced high-resolution neuroimaging techniques, employ larger sample sizes, and include carefully designed control and experimental conditions in the case of empirical studies, and well-matched control groups in the case of patient studies. Furthermore, more detailed patient profiles would assist in comparing results across different studies. Neuroscientific investigation of DPD and related states is still very much in its infancy, but it promises to aid in not only our understanding of such disorders, but also the development of possible treatments. Finally, there is no doubt that it will also contribute a great deal to the identification of the neural correlates of self-awareness in general.

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