The Spectrum of Organic Depersonalization: A Review Plus Four New Cases

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Depersonalization and derealization are commonly reported in the general population as a response to stress. The symptoms have also been described in patients with a primary psychiatric or organic diagnosis, where their secondary status precludes a DSM-IV diagnosis of depersonalization disorder. The authors present 4 new cases of depersonalization in patients with an underlying organic condition, along with 47 cases from the literature in which the available information permits diagnosis of organic depersonalization. Information from case series documenting depersonalization in the context of medical illnesses is also presented and the underlying etiology discussed. Epilepsy and migraine appear to be the disorders most commonly associated with depersonalization. Left-sided temporal lobe dysfunction and anxiety are suggested as factors in the development of depersonalization; however, further studies are needed to determine the relationship. The introduction to the DSM-IV of an organic subtype of depersonalization disorder would facilitate research in this area.

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The symptom of depersonalization (DP) has been defined in DSM-IV as an experience of feeling detached from and as if an outside observer of one's mental processes or body, while maintaining intact reality testing; derealization (DR) has been defined as the sensation that the external world is strange or unreal.[1] Although these symptoms are classified separately under dissociative disorders in the DSM-IV, they often coexist,[2] and both consist of altered perceptions of the self and the environment.[1] DP and DR are commonly reported in the general population[3–5] and in patients with a variety of psychiatric disorders.[6–11] The symptoms tend to be transient and of short duration; however, they may persist and develop into the syndrome of depersonalization disorder, which can be diagnosed when persistent or recurrent episodes of DP cause distress and occur in the presence of intact reality testing.[1] The diagnostic criteria are similar in ICD-10; however, in this system, derealization is included along with DP,[12] whereas it is classified separately as a variant of "dissociative disorder not otherwise specified" in DSM-IV.[1] The syndrome tends to begin in adolescence and characteristically has a chronic course, although the intensity of the symptoms may vary. According to the diagnostic criteria, however, the disorder must not occur exclusively during the course of another mental disorder and must not be due to the effects of a drug (prescribed or illicit). Further-

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more, a preexisting diagnosis of an organic disorder precludes the diagnosis.[1,12] However, the validity of this construct has been argued.[13]

This article reviews the English-language literature documenting depersonalization and/or derealization in patients with an underlying organic condition (not attributable to substance abuse or intoxication) and presents four new cases of organic depersonalization. The relevance of the concept of organic depersonalization for determining the underlying mechanism of its development and for understanding its neural correlates is discussed.

METHODS

A computerized literature search was performed (using the PsychLit and MEDLINE databases), employing the following terms: depersonalization, derealization, dissociation, multiple personality disorder, autoscopy, and "Alice in Wonderland" syndrome, combined with the following: organic, neurological, epilepsy, migraine, cerebral tumors, delirium, encephalitis, head injury, and traumatic brain injury. In addition, articles reviewing the psychiatric and neuropsychiatric comorbidity of organic disorders were searched for cases of DP. Similarly, depersonalization case series were searched for patients with a coexistent organic disorder. Reports of acute stress and cases of posttraumatic stress disorder were also reviewed and included if symptoms of DP/DR occurred in the context of an underlying organic disorder. Articles were included only if there were reasonable grounds given for a diagnosis of DP. These methods resulted in over 60 case reports and series, from which enough information was documented in 47 cases to merit detailed tabulation. Case reports are summarized in Table 1 and studies in Table 2.

LITERATURE REVIEW

It has long been thought that DP may have an organic etiology. Mayer-Gross[14] regarded it as resulting from a "preformed functional response of the brain," and Ackner[15] as "the result of a cerebral dysfunction, which itself is specific, but which may be set in motion by a number of different causes." Ackner[15] asserted that DP occurs in a variety of conditions, including epilepsy, head injury, encephalitis, tumor, chorea, intoxication, carbon monoxide poisoning, and toxic and delirious states. Despite this extensive list, most subsequent studies have focused on the first two conditions.

It is difficult to determine with certainty that depersonalization is occurring secondary to an organic disorder rather than a psychiatric disease, because in most medical and neurological conditions, psychiatric disorders coexist. In fact, Ackner himself maintained that "depersonalization symptoms can never be entirely organic in origin for, being concerned with changes in experience, they are indivisibly related to the mental functioning of the individual . . . their occurrence will be related to periods of emotional stress which make manifest a latent deficiency in the biological substrate for integration."[15] Cohen[16] linked these two concepts with the hypothesis that all depersonalization and derealization was "organic" in nature, the result of the changes in metabolism and cerebral blood flow produced by hyperventilation.

RESULTS

Traumatic Brain Injury (TBI)

Depersonalization commonly accompanies acute stress[9,17–19] and is thought to play an important role as a psychological defense mechanism protecting against the long-term sequelae of trauma. Thus, it is difficult to determine whether depersonalization following TBI is secondary to the physical or the psychological effects of the injury. Additional complications include evaluating the role of comorbid psychiatric problems such as depression, anxiety, and posttraumatic stress disorder (PTSD).

The literature on the development of depersonalization following TBI is surprisingly sparse and mainly consists of single case reports. Thivierge and Julien[20] described a patient who developed headaches, blurred vision, and depersonalization following a minor head injury with no or minimal loss of consciousness and no reported posttraumatic amnesia (PTA). All neurological investigations were normal except for a marked asymmetry of the late cortical auditory evoked response, which persisted for 2 years and then normalized within months of clinical improvement. Recently, Cantagallo et al.[21] described the case of a 32-year-old man who developed transient episodes of DP (as well as one episode of "multiple personality") 6 weeks following a mild brain injury (PTA <1 hour). He had not previously suffered episodes of dissociation, and episodes of DP ceased within 1 year of the accident. The CT scan was normal, but left temporal and biparietal hypoperfusion was visible on a [^{99m}Tc]HMPAO SPECT scan. Grigsby[22] reported a case of a patient who developed DP (an "out-of-body" experience) at the scene of a car accident but then went on to suffer from both DP and DR for several months following the mild closed head injury.

Subsequently, Grigsby and Kaye[17] assessed 70 patients who had been referred for neuropsychological assessment on average 22.3 months following a head injury (Table 2). Half reported feelings of unreality following the head injury, mostly occurring at the time of the injury. Patients with the most minor head injuries (no loss of consciousness or unconsciousness <30 min) were more likely to develop DP/DR (67%, compared with 11% of those with loss of consciousness ≥30 min). Only 6% experienced an isolated episode of unreality at the time of the injury, whereas the majority described frequent recurring and remitting episodes of DP/DR. There was no association with any neuropsychological or personality measures or with ongoing litigation. Their sample was atypical, however, in that although most head injuries occur in men, their sample contained more women. Furthermore, most patients do not require referral for neuropsychological assessment following TBI, with an estimate of only 20% continuing to have problems 6 weeks after an injury.[23] Grigsby and Kaye[17] extrapolated from these figures and estimated that a minimum of 13% of patients would develop depersonalization following a head injury. Half of the patients with symptoms of DP met DSM-III-R criteria for PTSD, and in fact only 5 patients with PTSD did not also experience DP. Thus, it could be argued that DP in patients with mild TBI was merely an expression of a psychogenic disorder.

Epilepsy

The association between DP and epilepsy has long been reported. Jackson and Colman in 1898[24] described the "dreamy state" in a patient with temporal lobe epilepsy (TLE) secondary to a lesion in the left uncinate gyrus. However, it is not always clear from the published literature whether the DP is occurring interictally or as part of the seizure. In patients with frequent seizures, this differentiation may be difficult without video-EEG telemetry. Furthermore, the patients often had other comorbidity, whether organic (previous head injury, migraine) or psychiatric (concomitant depression, anxiety, substance misuse). Thus it is difficult to determine the relationship between DP and epilepsy. For example, Langs et al.[25] reported a case of a man who developed episodes of derealization the day after alcohol and cannabis ingestion. However, he was also sleep-deprived and had experienced a generalized tonic-clonic seizure 15 minutes after the onset of the DR (which thus may have been prodromal). Following the index episode he experienced further episodes of DR along with a fear of having another seizure (whether or not he had ingested cannabis). Determining whether it was the alcohol, cannabis, anxiety, or seizure activity that was responsible for the episodes of DR is impossible.

Case Reports: Greenberg et al.[26] described 4 patients suffering from complex partial seizures secondary to malignant disease. Three developed episodes of an altered perception of reality accompanied by fear, which they interpreted as indicating that they had died or were about to die. Anticonvulsant medication appeared to terminate these experiences, which were believed to be ictal or para-ictal in origin.

One single case report by Kanemoto[27] describes periictal depersonalization. Following clusters of simple partial seizures experienced as ictal fear, the patient developed episodes, lasting up to several weeks, of the Capgras syndrome (the delusion that a person close to the patient had been replaced by an imposter) along with depersonalization. Concurrent depth electrode EEG recordings revealed epileptiform discharges originating from the left amygdalohippocampal region.

Davison[28] described episodic depersonalization in 3 patients who had been diagnosed as having temporal lobe epilepsy; however, the EEG during attacks did not clearly demonstrate ictal activity. In one patient, who also suffered from migraine, the DP lasted for up to two hours and was accompanied by a sensation of fear. It ended abruptly and was followed by exhaustion. The EEG during the episode revealed irregular theta rhythm over the right posterior temporal region. Another patient, who also suffered from migraine, experienced an unpleasant smell for approximately five minutes during the episodes of DP. During an episode, EEG recording revealed bilateral theta activity during overbreathing. In the final case, the episodes followed consumption of alcohol. Although they were reported as being modified by the anticonvulsant phenytoin, there is little evidence to support a diagnosis of epilepsy; therefore only the first two cases are included in Table 1.

Several other case reports have documented DP and DR along with symptoms of panic, which were relieved by anticonvulsant medication.[29–31] EEG studies revealed temporal lobe[29,30] or frontotemporal abnormalities.[31]

Case Series: Most series have found symptoms of DP to be more commonly associated with TLE than other forms of epilepsy.[32] Mullan and Penfield[33] reported ictal phenomena in patients undergoing presurgical evaluation for TLE. Ictal feelings of unreality were described in 3 patients with epilepsy originating from the left temporal lobe, which in all cases was dominant for speech. Depersonalization, but not derealization, was reported in 36.7% of a series of patients with TLE.[34] The DP

TABLE 1. Summary of case reports of patients with organic depersonalization, with investigation results where available

Author	Sex, Age at Onset/ (Report)	Organic Diagnosis	Psychiatric Symptoms	DP	DR	EEG	Neuroimaging	Pathology: Focal/Diffuse and Laterality
Todd 1955[67]	F, 17	Migraine Vertigo	Anxiety	√ AWS	AWS	Temporal (paroxysmal dysrhythmia)	N/K	Focal (T) B
	F, 30	Migraine Vertigo	Anxiety Panic attacks	√ AWS	AWS	Anterior temporal (dysrhythmia)	Normal (air encephalography)	Focal (T) B
Mullan & Penfield 1959[33]	M, (16)	Penetrating wound of L temporal lobe TLE	N/K	√	—	N/K	X-ray: bone defect on lateral wall of the left middle fossa	Focal (T) L
	M, (41)	Depressed skull fracture TLE	N/K	√	√	N/K	N/K	Focal (T) L
	M, (42)	Victim of plane crash TLE	N/K	—	√	N/K	N/K	Focal (T) L
Davison 1964[28]	M, 26	Migraine Déjà vu and fear ? TLE	Anxiety OCD Autoscopy	√	—	Posterior temporal (irregular theta during episode)	N/K	Focal (T) R
	M, 13	Migraine ? TLE	Anxiety OCD	√	?[a]	Widespread (theta) during episode	N/K	Diffuse B
Malamud 1967[81]	F, (43)	Cerebral tumor involving 3rd ventricle Epilepsy	Suicide attempts	√	—	N/K	Pneumoencephalography: normal	Focal B
Cutler & Reed 1975[64]	F, 24	Left-sided migraine	MPD Conversion/dissociative episodes Depression Anxiety	—	√	Nonspecific generalized abnormality	N/K	Diffuse B
Copperman 1977[69]	F, (18)	Infectious mononucleosis ? encephalitis	Anxiety	√ AWS	AWS	Anterior and mid-temporal (slow waves)	N/K	Focal (T) L
Mesulam 1981[53]	F, (21)	TLE	MPD Fugue states	√	—	Temporal (spikes)	CT: normal	Focal (T) B; R>L
	F, (27)	TLE	MPD Ictal fear	√	—	Temporal (spikes)	CT: normal	Focal (T) B; R>L
	F, (33)	TLE	MPD Anxiety	√	—	Midtemporal (spikes)	N/K	Focal (T) B; L>R
	F, (26)	TLE	Panic Delusion of possession	√	—	Anterior temporal (spikes)	CT: normal	Focal (T) B
	M, (38)	Right parieto-occipital lobe abscess excision TLE	Ictal fear Delusion of possession	√	—	Midtemporal (sharp wave and spike)	CT: low density in right parieto-occipital region	Focal (T) B; R>L
	F, (29)	TLE	MPD Delusion of possession	√	—	Temporal (dysrhythmia)	N/K	Focal (T) L
	F, (44)	TLE	Grandiose delusions	√	—	Temporal (spikes)	N/K	Focal (T) B
Schenk & Bear 1981[37]	F, (N/K)	TLE	Ictal panic MPD Depression	√ Ictal	—	Temporal (spikes)	N/K	Focal (T) B
	F, (35)	TLE	Borderline LD Aggression MPD	√	—	Temporal (spikes)	N/K	Focal (T) L
Kamiya & Okamoto 1982[49]	F, 30	TLE	Anxiety Autoscopy	√	—	Temporal and central (spikes and slow waves)	N/K	Focal (T, C) R
	M, 21	TLE Ictal sensation of "separation of head and body"	Internal hallucination of his "other self"	√	—	Temporal, frontal, and central (spikes and slow waves)	N/K	Focal (T, F, C) R

	F, 13	TLE	Invisible double Critical internal hallucinations of "other self"	√	—	Frontotemporal (spikes)	CT: normal	Focal (F, T) R
	F, 31	TLE	Invisible double "Good" and "evil" self	√	—	Temporal Central (spikes and slow waves)	N/K	Focal (T, C) R
Sanguinetti et al 1983[70]	M, 32	Infectious mononucleosis	N/K (but treated with BDZ)	√ AWS	AWS	Normal	CT: normal	Normal
Greenberg et al 1984[26]	M, 37	Right frontal cerebral tumor Epilepsy	Anxiety Fear of dying	√	—	Frontotemporal (slowing and spike/wave)	CT: right frontal tumor with surrounding edema	Focal (F, T) R
	F, (36)	Astrocytoma of left temporal lobe Epilepsy	Depression Fear of dying	?[c]	—	Temporal (theta)	Arteriography: vascular mass in left temporal lobe and basal ganglia	Focal (T) L
	F, (67)	Breast cancer with cerebral metastases Epilepsy	Rage Confusion	?[d]	—	Temporal (paroxysmal)	CT: metastases in cerebellum, both frontal and right temporal lobes	Focal (T) B
Stern & Murray 1984[29]	F, (36)	TLE	Schizoaffective disorder Panic attacks	√	√	Temporal (theta)	N/K	Focal (T) B; L>R
Wall et al 1985[84]	F, (33)	A/V malformation TLE	Panic attacks	√	√	Central and parietal (slow activity and sharp waves)	Postoperative changes Porencephaly	Focal (T, C, P) R
Ghadirian et al 1986[83]	F, (69)	Temporal lobe meningioma TLE	Panic attacks	√	√	Frontal/frontotemporal Ictal: temporal	CT: right temporal lobe meningioma	Focal (F, T) R
Grigsby 1986[22]	F, 39	Mild HI Headaches post HI	Depression Anxiety Out-of-body experience	√	√	Normal	CT: normal	Normal
Edlund et al 1987[30]	M, 25	Childhood epilepsy	Panic attacks Alcohol abuse	—	√	Temporal (theta and sharp)	MRI: atrophic changes	Focal (T) L
	M, 29	Head injury	Panic attacks	—	√	Temporal (theta)	N/K	Focal (T) B: R>L
	M, 25	Epilepsy	Panic attacks	—	√	Normal*	N/K	Normal
Ardila & Rosseli 1988[82]	M, (31)	TLE Neurocysticercosis	Depression Capgras syndrome	√	√	Temporal (theta)	CT: temporal lobe cysticercum	Focal (T) L
Thivierge & Julien 1988[20]	M, 16	Mild HI	Social withdrawal Irritability	√	?[e]	Normal: 3 One EEG: short generalized discharge on photic stimulation	Neuropsychology and auditory evoked potential implicate left side	? Focal L
Grigsby & Johnston 1989[78]	F, 17	Migraine Ménière's disease	Anxiety	√	√	N/K	N/K	N/K
	F, (N/K)	Ménière's disease	—	√	√	N/K	N/K	N/K
Hollander et al 1992[89]	M, (23)	Virus	Anxiety	√	√	Normal EEG (Evoked potential studies: left temporal dysfunction)	MRI: normal SPECT: ↓ perfusion left caudate; ↑ posterior-frontal	? Focal L
Dantendorfer et al 1995[31]	F, 27	Epilepsy	Panic attacks	—	√	Frontotemporal	MRI: normal	Focal (F, T) L
Ogunyemi 1995[63]	M, 30	Left-sided migraine with aura → a right hemianopia, amnesia, dysphasia and numbness of right hand	—	√	—	During episode: anterior-midtemporal (theta and delta slow waves) Between episodes: normal	CT: normal	Focal (T) B
Pelletier et al 1995[75]	M, 13	Migraine	Anxiety	√	√	Normal (standard and sleep)	MRI: normal SPECT (during DP): ↑ uptake left anterior temporal lobe	? Focal L (SPECT)

(continued)

TABLE 1. *(continued)*

Author	Sex, Age at Onset/ (Report)	Organic Diagnosis	Psychiatric Symptoms	DP	DR	EEG	Neuroimaging	Pathology: Focal/ Diffuse and Laterality
Kanemoto 1997[27]	F, (24)	TLE	Capgras syndrome	√	—	(Ictal: depth electrode)	MRI: left hippocampus	Focal (T) L
		Ictal fear		Perictal		Amygdalohippocampal	<right	
Lilja & Salford 1997[80]	F, (26)	Astrocytoma (grade II)	Panic attacks	√	?[b]	N/K	CT: hypodense area in	? Focal R (CT)
		Epilepsy	Anxiety				right orbitofrontal area	
	F, (66)	Astrocytoma (grade III – IV)	Panic attacks	√	√	"Abnormal"	CT: right temporoparietal mass with edema and	? Focal R
		Epilepsy	Anxiety				midline shift	
Morioka et al 1997[85]	F, 36	Infarction: inferior ventral pons	Depression	√	—	N/K	MRI: infarction of right side of pons	Focal R (MRI)
			Anxiety					
Cantagallo et al 1999[21]	M, 32	Mild HI	DID (MPD)	√	—	Normal	CT: normal	? Focal L (SPECT)
			Trance states				SPECT: ↓ perfusion left temporal and biparietal	

Note: Age at report (shown in parentheses) is age of patient when report was written (used when age of symptom onset is not known). AWS = cases of "Alice in Wonderland" syndrome with DP/DR; BDZ = benzodiazepines; DID (MPD) = dissociative identity disorder (MPD = multiple personality disorder); DP = depersonalization; DR = derealization; LD = learning disability; HI = head injury; OCD = obsessive-compulsive disorder; TLE = temporal lobe epilepsy; N/K = not known; B = bilateral; L = left-sided; R = right-sided; C = central; F = frontal; P = parietal; T = temporal; ↑ = increased; ↓ = decreased; √ = present; — = absent.

[a]"Like being in another world"; [b]"Feelings of unreality"; [c]"Am I dead yet?"; [d]"Near death/out-of body experiences"; [e]"Living in another world."

*Normal EEG with both standard and nasopharyngeal leads.

tended to be of abrupt onset and short duration and was often accompanied by a sensation of fear.

Kenna and Sedman[35] reported DP in 11 of 32 patients with epilepsy who had been referred to the psychiatric services. These 11 patients suffered from psychomotor or multiple types of seizure, were predominantly female, and tended to be slightly older than patients without DP. No clear laterality effects were noted on routine EEG studies. There was, however, an association of DP with current depression and an "insecure" personality.

Smirnov[36] described the ictal experiences in 39 patients with temporal lobe tumors. In patients with right-sided lesions, the main symptoms were the emotions of fear or grief, usually accompanied by viscero-autonomic disturbances, along with both derealization and depersonalization. Also experienced were olfactory and auditory hallucinations, déjà vu, and jamais vu. Patients with left-sided tumors tended to experience anxiety accompanied by speech disturbances, along with auditory hallucinations, automatisms, and compulsive thoughts and reminiscences.

Schenk and Bear[37] reported recurrent dissociative experiences in one-third of their patients with TLE, mostly occurring in the female patients. The episodes always followed the onset of seizures, usually by months to years. The authors presented 7 cases of multiple personality disorder (MPD) in patients with TLE, 2 of whom also experienced episodic depersonalization. The authors were confident that these episodes occurred interictally.

Several studies have documented the frequency with which symptoms of depersonalization occur in patients with epilepsy and compared this with experiences encountered in the general and psychiatric populations. Silberman et al.[38] showed that patients with epilepsy (PWE) suffering from complex partial seizures, as well as patients with affective disorders, had more experiential phenomena than control subjects and tended to experience them more during episodes of illness. Derealization was reported by 16% of PWE, 18% of patients with affective disorders, and 3% of control subjects. Other dissociative symptoms reported by patients, but by none of the control subjects, included altered body size (11% of PWE, 9% of patients with affective disorders); body part dissociation (19% of PWE, 7% of affective-disorder patients); and autoscopic states, which were experienced more by patients with affective disorders (14%) than PWE (5%). Interestingly, there were no group differences for "depersonalization," which was experienced by 19% of PWE, 14% of patients with affective disorders, and 10% of control subjects.

Devinsky et al.[39] compared scores on the Dissociative Experiences Scale (DES)[40] between normal control sub-

TABLE 2. Summary of studies of depersonalization in groups of medically and psychiatrically ill patients

Author	Patient Group: % with DP/DR (if known)	EEG in Patients with DP	Control Group: % with DP (if known)	Comment
Harper & Roth 1962[34]	TLE; $n=30$ DP: 36.7%; DR: none	Abnormal in 29/30 EEG in those with DP: N/K	PADS; $n=30$ DP: 56.7%; DR: 36.7%	PWE; DP: sudden onset, brief duration, and associated with feelings of fear PADS group: DP lasts minutes to hours
Kenna & Sedman 1965[35]	TLE; $n=32$; 34.4%	Focal changes: 7; (R: 3; L: 4) NS abnormal: 4	N/A	Premorbid "insecure personality" and depression related to DP
	Acute/subacute organic psychosis; $n=15$; 13.3%	Normal: 3 Dysrhythmia: 1; N/K: 1	N/A	
	Chronic organic psychosis; $n=49$; 6.1%		N/A	
Devinsky et al 1989[39]	Epilepsy: $n=71$ Mean DES: 8.75	N/K	MPD; $n=42$; mean DES: 52.8 Age-matched normal control subjects; $n=34$; mean DES: 4.37	PWE with dominant hemisphere seizure foci had higher DP/DR subscale scores than those with nondominant foci
Ross et al 1989[52]	CPS; $n=20$ Mean DES: 6.75 Neurological disorders; $n=28$ Mean DES: 5.2	Temporal: (L: 6; R: 5; B: 1) Frontal lobe: 2 N/K	MPD; $n=20$; 65% Mean DES: 38.3	
Devinsky et al 1991[43]	CPS; $n=128$ DP: ictal, 15%; interictal, 10% DR: ictal, 18%; interictal, 14% PGE; $n=20$ DP: ictal, none; interictal, none DR: ictal, none; interictal, 5%	N/K	Non-neuropsychiatric control subjects ($n=58$) DP: 3%; DR: 12%	
Grigsby & Kaye 1993[17]	HI (total): $n=70$; 50% Mild HI: (LOC <30 min); $n=48$; 67% Moderate-severe HI; $n=18$; 11%	N/K	None	Coexistent: Anxiety: 60%; PTSD: 51%

Note: CPS = complex partial epilepsy; DES = Dissociative Experiences Scale; DP = depersonalization; DR = derealization; HI = head injury; LOC = loss of consciousness; MPD = multiple personality disorder; PADS = phobic anxiety depersonalization syndrome; PGE = primary generalized epilepsy; PTSD = posttraumatic stress disorder; PWE = people with epilepsy; TLE = temporal lobe epilepsy; L = left; R = right; N/A = not applicable; N/K = not known; NS = nonspecific.

jects ($n = 34$), patients with multiple personality disorder ($n = 42$), and 71 PWE (12 with generalized and 59 with complex partial seizures). A cutoff score of 15–20 on the DES has been thought to detect dissociative disorders.[41] The DES has three subscales: amnesia/dissociation, absorption/imaginative involvement, and depersonalization/derealization.[42] Devinsky et al.[39] found that PWE had DES scores between those of MPD patients and normal subjects. Patients with partial seizures had higher scores than those with generalized seizures on the dissociation subscale only. Furthermore, patients with dominant hemisphere foci had higher DP subscale scores than those with nondominant foci. Overall, they found that one-fifth of PWE had significant dissociative experiences.

They also reported the findings of resting EEGs and prolonged video-EEG telemetry on 6 of these patients during dissociative episodes. All were originally suspected of having a diagnosis of epilepsy, but the telemetry refuted this and all were found to suffer from MPD with depersonalization. The EEGs both between and during episodes were abnormal in 5 of the patients; however, the features were nonspecific variants such as intermittent temporal theta activity or occasional spikes, with no clear epileptiform activity during the episodes.

In a later study, Devinsky and co-workers[43] compared the experience of dissociative symptoms in patients with focal and primary generalized epilepsy and non-neuropsychiatric control subjects. Ictal depersonalization was reported by 15% of patients with partial seizures, occurring interictally in 10%. This symptom was reported by 3% of control subjects but by none of the patients with primary generalized epilepsy. Derealization was more common: it occurred ictally in 18% with complex partial seizures, and interictally in 14% with partial seizures, 5% with primary generalized epilepsy, and 12% of control subjects. Related symptoms such as distortion of size/shape and distance were not experienced by the control group, but occurred interictally in both groups with epilepsy and also ictally in those with partial seizures.

The same group[44] administered the DES to 169 PWE and 132 patients with conversion nonepileptic seizures (NES). The mean DES score for PWE was 12.7, and the investigators commented that this might be elevated because of items that may reflect memory and attention. Patients suffering NES had a mean DES score of 15.1 and scored significantly higher than PWE on the DP/DR subscale. Patients who had histories of childhood physical or sexual abuse scored highest on the absorption-imaginative involvement subscale regardless of the origin of their seizures.

A recent study by Kuyk et al.[45] assessed psychological and somatoform dissociation in 94 patients with TLE, 40 with extratemporal and generalized epilepsy, and 65 with NES. They found higher psychological dissociation in patients with TLE and NES compared with nonclinical control subjects. Furthermore, patients with NES also showed somatoform dissociation compared with the other groups.

Persinger and Makarec[46] compared patients suffering from PTSD, anxiety-depersonalization, or complex partial seizures with a control group. All of the patient groups had elevated depersonalization scores, the highest being in those with epilepsy, and the authors concluded that such symptoms should be viewed as occurring along a continuum from "normal" individuals to people with epilepsy.

Toni et al.,[47] using a semistructured interview, found features of depersonalization and derealization in 61% of a sample of 41 patients with complex partial seizures. The symptoms were similar to those experienced by patients with phobic-anxiety depersonalization, comprising mainly feelings of detachment from the environment (DR), feelings that the external world is unfamiliar (DR), and feelings of losing self-control (DP).

Autoscopy (or heautoscopy), the visual experience of seeing an image of oneself in external space viewed from within one's body,[48] and out-of-body experiences, in which there is a sensation of leaving one's body and viewing the image from outside, are associated with dissociation and depersonalization. A meta-analysis in 1994[48] of 56 published cases of autoscopy revealed that 59% of the patients had a neurological illness and 32% had epilepsy (predominantly TLE). There were no significant laterality effects; however, in cases with focal pathology, the images tended to appear in the contralateral field. DP occurred in 18% of the 56 cases, the commonest coexisting psychiatric disorders being depression, anxiety, and panic. Kamiya and Okamoto[49] described 9 cases of "double consciousness" in patients with epilepsy. Three had episodes of autoscopy, 2 had a sensation of an invisible double outside their body (often referred to as Doppelgänger), and 4 had a sensation of a double identity (often good versus bad) inside their body. Four (all with right-sided EEG abnormalities) also experienced depersonalization, and these tended to belong to the latter group (invisible double identity within the body).

A similar phenomenon is that of "multiple personality disorder" (MPD)—now referred to as dissociative identity disorder (DID)—which is defined as a dissociative disorder characterized by the existence of two or more distinct personal identities within a single individual, which recurrently take control of the person's behavior.[1] Depersonalization has been reported in 38% to 65% of patients with MPD.[50–52]

MPD was first described in a patient with epilepsy in 1898.[24] Since then, several studies have explored this re-

lationship. Mesulam[53] noted MPD in 7 of 61 patients with TLE seen in a behavioral neurology unit over a period of 1 year. In 4 patients, symptoms of depersonalization were also present. He also described a further 3 cases of patients with epilepsy, depersonalization, and a delusion of possession (by evil or God). In all cases, the EEG was abnormal (Table 1). Benson et al.[54] reported 2 PWE with dual personality and Capgras syndrome who shifted between personalities on recovery from seizures. However, the accuracy of diagnosis of MPD in the latter two studies has been questioned.[52] Drake[55] also described 5 patients who exhibited different personalities while in the postictal state. Attempts have been made to compare EEGs recorded during different personalities in an individual patient, but in most cases changes have been confined to those associated with alteration in concentration and mood.[56,57] Coons et al.[51] found a 10% incidence of epilepsy in 50 patients with MPD, and abnormal EEGs (not associated with medication) in 14% (usually mild, nonspecific slowing, but also spikes affecting the frontal, temporal, and parasagittal areas). Ross et al.,[52] however, did not find cases of MPD or of raised DES scores in a series of 30 PWE.

Stimulation Studies: The "dream-like" state has been elicited by electrically stimulating the medial temporal lobe in patients undergoing assessment for epilepsy surgery.[58–60] However, the specific anatomical site or even the hemisphere that would habitually produce particular experiential sensations when stimulated has not been identified. Gloor et al.[60] concluded that it was the personal characteristics and memory bank of the patient that were the major factors in determining the mental phenomena evoked.

Migraine

Shorvon et al.[61] found that 38% of patients with DP also suffered from migraine. Since this early study, several others have documented this association. (Tables 1 and 2).[9,28,34,62] Ogunyemi[63] performed EEG studies in a patient at the time he was suffering from a prolonged (>1 hour) migrainous aura accompanied by depersonalization, "as if he was outside his body." His EEG showed intermittent, asynchronous, focal theta and delta slow waves in the anterior-midtemporal regions bilaterally, which resolved when he was symptom free. Derealization accompanying MPD has also been reported in a patient with migraine.[64] Furthermore, headaches were commonly reported when patients with MPD were assessed by clinicians,[50] and in one study, 26% of patients described their headaches occurring either just before or during the transition from one personality to another.[51]

Other experiences related to DP and DR, such as autoscopy, have also been described accompanying migraine.[65,66] The patients experienced a sensation of being two people—the secondary body being the more real, thinking, feeling and controlling all movements, the original body being devoid of feelings. The sensation lasted only seconds but tended to occur either as the migraine aura, with the headache, or immediately afterwards. In some cases, the autoscopy preceded the onset of migrainous headaches by several years. Todd[67] reported 5 patients (4 female) who suffered from migraine or migraine equivalent (migraine symptoms such as nausea, giddiness but without headache) and had recurrent episodes (occurring over many years, in some cases), which he described as the syndrome of "Alice in Wonderland" (AWS). The patients described objects or their own body (or isolated parts) as changing in size. These experiences were accompanied by transient depersonalization in 2 cases. In 2 patients, the attacks were accompanied by an alteration in the perception of time, and in 2 other patients autoscopy occurred (again with the sensation that the secondary body contained the mind). All of the patients also suffered episodes of vertigo or giddiness, and all had a psychiatric comorbidity—predominantly of anxiety.

Since Todd's series was published, further, similar cases of AWS have been reported in both adults and children, either associated with migraine[62,68] or infections.[69–74] These case reports of body image distortion, often in association with depersonalization and/or derealization, suggest parietal lobe pathology. However, the frequent accompanying symptoms of fear,[62] anxiety, and panic implicate the temporal lobe. In most cases, neuroimaging and EEG studies were normal; however, nonspecific findings have been reported, including temporal lobe dysrhythmia,[67] left anterior and midtemporal slow waves,[69] and parieto-occipital sharp waves.[72] [^{99m}Tc]HMPAO SPECT brain imaging in a patient with migraine and DP demonstrated an increase in uptake in the left anterior temporal lobe when symptomatic. Between episodes, there was a decreased uptake in the left temporal lobe.[75]

Vertigo

DP and DR have been reported in patients suffering from vertigo,[39,67,76,77] either due to Ménière's disease[78] or following head injury.[17] Fewtrell and O'Connor[79] reviewed the association between depersonalization and dizziness per se. They concluded that either these were identical experiences described in different ways or they were distinct experiences lying on opposite ends of a continuum of a disturbance in "self–world" relations.

TABLE 3. Demographic and psychometric data and results of investigations on four new cases of organic depersonalization

Case No.	Sex, Age	Hand.	Organic Diagnosis	Psychiatry	DP	DR	EEG	MRI	Pathology and Laterality	BDI	BAI	DES	DES-DP/DR Subscale
1	F, 42	N/K	Acute intermittent porphyria	Capgras syndrome Depression	√	√	Nonlocalized nonspecific changes	Normal	Diffuse	30	N/K	25	69
2	F, 48	R	Brain stem infarction	Depression	√	√	N/K	Multiple areas of increased signal affecting the cerebellum, brainstem, posterior part of the thalamus, and the L occipital lobe	Diffuse	10	N/K	N/K	N/K
3	F, 22	R	TLE L temporal lobectomy Rasmussen's encephalitis	Ictal panic	√	√	Ictal activity arising from L suprasylvian fissure	L temporal lobectomy Atrophic tissue extending to the left occipital pole	Focal: L	9	39	20.7	15
4	F, 32	R	Occipital lobe fracture Occipital and temporal lobe epilepsy Temporal lobe meningioma	Depression Generalized anxiety Panic attacks PTSD	√	–	Ictal activity arising from left posterior quadrant and left temporal areas	Meningioma of left sylvian region	Focal: L	39	15	4.3	3.3

Note: Hand. = handedness; DP = depersonalization; DR = derealization; BDI = Beck Depression inventory; BAI = Beck Anxiety Inventory; DES = Dissociative Experiences Scale; DES-DP/DR subscale = DES items 7,11,12,13,27,28; TLE = temporal lobe epilepsy; PTSD = posttraumatic stress disorder; √ = present; – = absent; N/K = not known.

Cerebral Tumors and Cerebrovascular Disease

Lilja and Salford[80] compared the presenting symptoms in patients with high-grade and low-grade gliomas. Panic attacks with prominent experiences of DP and DR tended to occur early in the course of low-grade frontal lobe tumors. Epilepsy tended to occur more frequently in patients with low-grade tumors. Several single case reports also document DP in patients with cerebral tumors (Table 1); however, in all cases, concomitant epilepsy[81,82] and psychiatric symptoms[83] complicate evaluating the etiological significance of the tumor in the development of DP.

Similarly, DP has been reported in patients with cerebrovascular disease, again in association with panic[84] and depression.[85] (Table 1).

NEW CASE HISTORIES

Demographic and psychometric data and investigative results on four new cases seen by the authors are summarized in Table 3.

Case 1. A 42-year-old woman with no personal or family history of any neuropsychiatric disorder was diagnosed with acute intermittent porphyria at the age of 39. Her attacks tended to occur monthly, generally premenstrually, and consisted of intense abdominal pain radiating to both legs, accompanied by headache, nausea, and occasionally vomiting. During severe attacks she would become mute, later stating that she tried to talk but "the words would not come out." Following a severe episode, she became comatose for 2 weeks and on regaining consciousness, was found to be delirious. After 1 month, the delirium cleared, revealing a Capgras syndrome with reduplicative paramnesia. Although she could recognize her husband, her children, and her house, she believed that there was "something different about them." She thought that either everything had been duplicated or that she had been "taken by aliens to another planet where things were similar." She also experienced intense symptoms of depersonalization. She stated that her body felt strange, as though it did not belong to her, and that she did not know whether she existed or not. She also felt that she was not in control of her behavior. She believed that either she had changed and everything else had remained the same or that she was real and everything else had changed. On noticing a familiar birthmark, she decided on the latter explanation. Neuropsychological assessment revealed sensory aphasia, color blindness, visual agnosia, and both episodic and semantic memory impairment. MRI and SPECT were unremarkable, and her EEG revealed nonlocalized nonspecific changes. Her overall DES score was 25; however, she scored 69 on the DP/DR subscale. The Capgras syndrome and the symptoms of DP and DR lasted 6 months, gradually resolving.

Case 2. A 48-year-old right-handed woman with no personal or family neuropsychiatric history suffered a brainstem infarct. MRI revealed multiple areas of increased signal affecting the cerebellum, brainstem, posterior part of the thalamus

bilaterally, and the left occipital lobe, consistent with ischemic lesions in the vertebrobasilar territory. Six months following the infarct, she developed low mood accompanied by both DP and DR. She referred to herself as the "old" and "new" selves. She described the "new self" as if "part of me is not me" and "something's missing." She was anxious that the "new self" might take over. She experienced a reality distortion of objects and unfamiliar people in the outside world, which she described as "I know that it's there . . . but it's not the same," and "I know that you're there . . . but you're not." She also found that she had to concentrate much harder to understand details of conversation and to register details of other objects and people. Paroxetine relieved the depressive ideation but not the DP and DR, which persisted for several months.

Case 3. A 22-year-old right-handed woman with a family history of depression developed partial epilepsy at the age of 17. The seizures were medically intractable, and thus she underwent a left-sided temporal lobectomy at the age of 18. Pathological examination of the resected temporal lobe revealed Rasmussen's encephalitis. Neuroimaging confirmed the complete removal of all the medial temporal structures. Eighteen months later, her seizures recurred, consisting of a "thumping" sensation in her head, along with fear and the feeling of someone being behind her. They were accompanied by symptoms typical of a panic attack, with palpitations, overbreathing, a dry mouth, a sense of the world closing in on her, and a fear of dying. She also experienced marked symptoms of depersonalization and derealization. She felt that she "wasn't there," that she was not real, and that she was in a dream. She also felt that the surroundings and other people were not real, as though she were watching television. A video-EEG revealed frequent runs of epileptiform activity originating in the left suprasylvian region and rapidly becoming generalized. The EEG changes were accompanied by her symptoms of panic and depersonalization, confirming the ictal nature of the episodes. She scored highly on measures of anxiety and dissociation while having these frequent seizures (Table 3). The episodes ceased on increasing her anticonvulsant medication.

Case 4. A 32-year-old right-handed woman with no personal or family psychiatric history developed medically intractable posttraumatic epilepsy of occipital lobe origin at the age of 25, 9 months after suffering an assault. The seizures consisted of flashing lights in the right hemifield, which at times would generalize into a tonic-clonic seizure. In addition, she experienced complex partial seizures consisting of a feeling of depersonalization during which she lost the "sense of herself" and episodes in which she felt she went "outside herself" and during which she "observed herself." During these episodes she was unaware of her surroundings, and they were accompanied by automatisms consisting of plucking actions involving her right hand, along with chewing movements. These seizures also had a tendency to generalize. Neuroimaging revealed a meningioma arising from the left temporal lobe. Following the assault she suffered from PTSD and developed a depressive illness, which was treated with cognitive-behavioral therapy. The seizures, and thus the ictal depersonalization, developed several months after the depression had shown some improvement with therapy. Interictally, her overall score on the DES was 4.3, with a DP/DR subscale rating of 3.3. A left temporal lobectomy relieved the episodes of ictal depersonalization and temporal lobe automatisms, but the occipital seizures remained.

DISCUSSION

The literature reveals a large body of published cases of organic DP. However, in many cases it is not clear whether the DP is fleeting, episodic, or chronic as part of a depersonalization disorder. In addition, many cases of DP developed alongside other psychiatric symptoms. However, literature review is complicated by absent or incomplete information. The presence of DP and/or DR as shown in Table 1 was determined from the case descriptions in the individual reports. However, in some cases only terms such as "depersonalization," "derealization," "dreamy state," or "feelings of unreality" were documented, and thus the accuracy of diagnostic classification cannot be assured.

Few of the published reports used rating scales or standardized interviews to assess depersonalization. The DES is used in some of the case series,[39,44,52] but this instrument mainly screens for dissociation.[41] The six-item DP/DR subscale may be more specific for detecting depersonalization,[42,86] but it is rarely reported in the literature. The patient in Case 1 of our series scored much higher on this subscale than on the overall DES (Table 3), suggesting that her dissociation was mostly accounted for by depersonalization. Unfortunately, no cutoff has been established for this subscale. The DES scores for the two cases of ictal depersonalization (Cases 3 and 4) are markedly different. In Case 3 the questionnaire was completed at a time when the patient's EEG studies suggested she was in nonconvulsive status epilepticus, and thus her DES score could be thought of as an ictal assessment. In contrast, in Case 4 the DES was completed during the interictal period, and thus the patient had low scores. Therefore, the DES and its subscales may be useful both for screening and for determining the etiology of depersonalization.

Although DSM-IV cites an equal sex distribution for depersonalization, most studies have found a preponderance of women.[9,14,61] Twenty-nine of the 47 previously published cases described female patients; the addition of our 4 reveals that 64.7% of patients with organic depersonalization are female, a figure very similar to the 63% found by Simeon et al.,[9] and may reflect the well-known bias of women toward seeking assessment and treatment. The phenomena described seem to be similar to those noted in nonorganic cases, although additional symptoms such as reduplication (Case 1) and personification (Case 2) are rather unusual variants on the depersonalization theme.

Summarizing the nature and site of the brain pathology from the EEG and neuroimaging information available on the 47 published and 4 new cases reveals that only 3 patients (6%) had no documented pathology; 4 were reported as having "diffuse" disease, and in 10 cases there was insufficient information to make any inferences. In remaining 34 cases, the pathology was focal, predominantly affecting the temporal lobe (25 cases). There was no clear evidence of lateralization, with 13 cases being left-sided and 8 right-sided, the rest having bilateral pathology. However, 9 patients had focal pathology affecting extratemporal areas (often in addition to the temporal lobe), of which 7 had right-sided pathology. Moreover, only 1 of the 25 cases of "pure" temporal lobe pathology was right-sided, whereas 11 affected the left, the rest having bilateral disease. Thus, left-sided temporal lobe dysfunction may be a risk factor for the development of depersonalization. Furthermore, other psychiatric disorders, such as depression, have been found to be more common in patients with neurological conditions affecting the left hemisphere, including epilepsy, cerebrovascular disorders, and Parkinson's disease.[87] This link suggests that left-sided pathology may facilitate the development of a secondary psychiatric illness.

Epilepsy emerges as the neurological disorder most commonly associated with DP and DR—at least in terms of the number of published articles examining the issue. Migraine appears to be the next. Summarizing the evidence, it seems that focal epilepsy has a stronger link with DP and DR than does primary generalized epilepsy, which Devinsky and colleagues[43] found not to be associated. Devinsky et al.[43] also found that DP rather than DR was associated with focal epilepsy, whereas the opposite pattern was found by Silberman et al.[38] Part of this distinction can be attributed to the baseline rate of the dissociative symptoms in the control groups. It should be noted, too, that people with nonepileptic seizures score highly on DES ratings of DP and DR.[44] Hence, although paroxysmal alterations in consciousness and temporal lobe pathology may alone or in combination provide a potent substrate for DP and DR, such dysfunction is clearly neither necessary nor sufficient to cause them.

In the majority of cases, both in the literature review and our four new reports, there was evidence of other psychiatric comorbidity, most commonly depression or anxiety/panic attacks (although in Case 3 the panic attacks were ictal in origin). In most instances it is not possible to ascertain whether the underlying organic condition resulted in both anxiety and depersonalization or whether the DP/DR was instead secondary to a state of high arousal associated with the anxiety. For example, in the patient with a right-sided temporal lobe meningioma reported by Ghadirian et al.,[83] DP and DR developed after treatment of her depression and anxiety attacks. Following surgery she had no further episodes of anxiety, DP, or DR, despite ongoing depressive symptoms necessitating therapy. In this case, it is particularly difficult to ascertain whether the DP and DR were secondary to the anxiety disorder or to her meningioma. It has been hypothesized that "depersonalization is a hard-wired vestigial response for dealing with extreme anxiety, combining a state of increased alertness with a profound inhibition of the emotional response system."[88] The mechanism proposed was that in response to high anxiety, the medial prefrontal cortex would inhibit emotional processing on the amygdala and related structures, resulting in a dampening of sympathetic output and reduced emotional experiencing.[88] Whether the DP is triggered by an alteration in consciousness/arousal secondary to an organic/toxic state or to a psychological anxiety state remains unclear. Either way, the findings of this review appear to confirm the early belief of Mayer-Gross[14] that DP results from a preformed functional response of the brain.

This review brings together many reports of organic depersonalization. Although in the majority of cases there is neurophysiological or radiological evidence of temporal lobe involvement, there is no clear lateralization, although a left-sided preponderance is suggested. The wide range of organic illnesses associated with DP suggests that nonspecific temporal lobe dysfunction along with anxiety may result in the development of depersonalization. However, further studies are needed to determine the relationship.

The stipulation in the DSM-IV that a diagnosis of DP cannot be made if there is a preexisting organic diagnosis results in the exclusion of many patients from various studies,[87] thus limiting the available information on the association. The introduction of an organic subtype of depersonalization disorder analogous to "mood disorders due to a general medical condition" in the DSM-IV would fulfill a clinical need and facilitate research in this area. Finally, a more systematic and detailed description of the phenomenology of "organic depersonalization," coupled with advanced neuroimaging and neurophysiological investigative techniques, will facilitate comparison with "idiopathic" or "functional" depersonalization. This in turn will enable a finer-grained mapping of the cognitive and behavioral subcomponents of depersonalization experiences to their neural substrates.

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