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Depersonalisation Disorder
A Contemporary Overview

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Contents

Abstract

Depersonalisation disorder is characterised by prominent depersonalisation and often derealisation, without clinically notable memory or identity disturbances. The disorder has an approximately 1 **:** 1 gender ratio with onset at around 16 years of age. The course of the disorder is typically long term and often continuous. Mood, anxiety and personality disorders are often comorbid with depersonalisation disorder but none predict symptom severity.

The most common immediate precipitants of the disorder are severe stress, depression and panic, and marijuana and hallucinogen ingestion. Depersonalisation disorder has also been associated with childhood interpersonal trauma, in particular emotional maltreatment.

Neurochemical findings have suggested possible involvement of serotonergic, endogenous opioid and glutamatergic NMDA pathways. Brain imaging studies in depersonalisation disorder have revealed widespread alterations in metabolic activity in the sensory association cortex, as well as prefrontal hyperactivation and limbic inhibition in response to aversive stimuli. Depersonalisation disorder has also been associated with autonomic blunting and hypothalamic-pituitary-adrenal axis dysregulation.

To date, treatment recommendations and guidelines for depersonalisation disorder have not been established. There are few studies assessing the use of pharmacotherapy in this disorder. Medication options that have been reported include clomipramine, fluoxetine, lamotrigine and opioid antagonists. However, it does not appear that any of these agents have a potent anti-dissociative effect. A variety of psychotherapeutic techniques has been used to treat depersonalisation disorder (including trauma-focused therapy and cognitive-behavioural techniques), although again none of these have established efficacy to date. Overall,

novel therapeutic approaches are clearly needed to help individuals experiencing this refractory disorder.

1. Definition and Prevalence

Dissociation is a fascinating psychological phenomenon, and one of the least explored frontiers in psychiatric neurobiology. Dissociation is defined as a disruption in the usually integrated functions of consciousness, memory, identity and perception, leading to a fragmentation of the coherence, unity and continuity of the sense of self. Depersonalisation is a particular type of dissociation involving a disrupted integration of self-perceptions with the sense of self, so that individuals experiencing depersonalisation are in a subjective state of feeling estranged, detached or disconnected from their own being.

The following are common descriptions of depersonalisation experiences: watching oneself from a distance (similar to watching a movie); candid out-of-body experiences; a sense of just going through the motions; one part of the self acting/participating while the other part is observing; feeling like you are in a dream or fog; looking in the mirror and feeling detached from one's image; feeling detached from body parts or the whole body; not feeling in control of one's speech or physical movements; feeling disconnected from one's own thoughts; and feeling detached from one's emotions (numbed or blunted). Depersonalisation is frequently accompanied by derealisation (i.e. a sense of unfamiliarity or detachment from one's own surroundings [people and objects]).

Short-lived experiences of depersonalisation are very common in the general population, with an estimated annual prevalence of 23%.[1] Transient depersonalisation is also a common experience under severe or life-threatening stress, such as accidents or assault, and comprises a prominent diagnostic criterion for acute stress disorder, a condition that can occur in the first month after a traumatic event. However, when depersonalisation becomes persistent or recurrent, and is associated with significant distress and/or impairment, the diagnosis of depersonalisation disorder needs to be entertained. According to the DSM-IV, arriving at this diagnosis requires the presence of intact reality testing, i.e. an awareness on behalf of the individual that the depersonalisation is an 'as if' experience.[2] In addition, psychiatric and medical conditions need to be identified to understand in what context depersonalisation may be occurring. For example, depersonalisation occurring simply in the context of a major depressive episode, a panic attack or a more severe dissociative disorder (e.g. dissociative identity disorder) should be diagnosed as such. Similarly, depersonalisation due to a medical condition or substance, such as temporal lobe epilepsy or ongoing substance abuse should not be diagnosed as depersonalisation disorder.

The prevalence of depersonalisation disorder in the general population is unknown, but it is probably more common than its typical label as a 'rare' disorder that most clinicians have never encountered. One study suggested a 2.4% prevalence,[3] not unlike schizophrenia or bipolar disorder, yet depersonalisation disorder is rarely diagnosed. There are likely to be several factors that account for the infrequent diagnosis of depersonalisation disorder: (i) limited familiarity on the part of many clinicians regarding the entity and its typical presentation; (ii) reluctance on the part of many patients to disclose their symptoms because of an expectation that they will not be understood, that they may sound crazy or are unable to describe their depersonalisation experiences; and (iii) a trend to diagnose depersonalisation as just a variant of depression or anxiety, even when the diagnosis of a distinct condition is clearly warranted. As is typical with various poorly recognised and under-treated disorders, patients can feel tremendous relief from contact with a clinician who is able to recognise their symptoms for what they are, is familiar with the basic presenting features of the disorder and is able to give this elusive condition a name and to let the patient know that he

or she is not alone in this disorder. Patients frequently feel as if they are the only person experiencing this disorder, when in fact they are not.

2. Clinical Presentation

How does a typical case of depersonalisation disorder present?[4,5] The average age of onset is around the age of 16 years, although some may have experienced depersonalisation disorder as far back as they can remember, and others may have had onset in their 20s, 30s or even 40s.[5] Large studies have recently confirmed that the gender ratio in depersonalisation disorder is 1 : 1.[5,6]

The onset of the condition is sometimes acute and sometimes insidious. With acute onset, individuals may recall the exact moment, setting and circumstance when they had their first depersonalisation experience. This can be after a prolonged period of severe stress and adjustment efforts; after a traumatic event, with the initial episode of another mental condition such as panic disorder or depression (however; when these resolve, the depersonalisation continues); with the intake of various drugs such as marijuana or, less commonly, a hallucinogen, ecstasy or ketamine; or seemingly out-of-the-blue with no identifiable triggers. When the onset is insidious, it may either be so far back in time that there is no clear memory, or it may begin with limited episodes of lesser severity and gradually become more pronounced.

An interesting historical review of the disorder[7] has revealed that the phenomenology of depersonalisation has remained stable over the past century, as reflected in the core symptoms of emotional numbing, visual derealisation and altered body experience. Another study has shown that the disorder presentation and symptom severity are the same, whether triggered by illicit drugs or psychological triggers.[8]

The disorder is episodic in about one-third of individuals,[5,6] and each episode may last hours, days, weeks or months at a time. In a sizeable proportion of people, depersonalisation may start episodically for months or even years, and subsequently become continuous, i.e. depersonalisation is always present, either at constant intensity or with varying intensity, according to various environmental or emotional factors that alleviate or exacerbate symptoms.[5] The distress associated with depersonalisation disorder can be profound. Many people experiencing it find the robotic, detached state analogous to the 'walking dead', and deeply question the meaning of being alive if they do not feel alive and real. Fears of going crazy, losing control and having permanent brain damage are also common. Cognitive complaints are frequent, specifically a decline in ability to focus on tasks, especially complex ones, increased forgetfulness in their daily lives and difficulty in vividly evoking past memories. Accordingly, specific attention and memory deficits have been demonstrated with neuropsychiatric testing.[9] As a result of these deficits, complaints of occupational impairment are very common and many individuals feel they are working at well below their previous capacity, some are even unable to work. Interpersonally as well, people experiencing depersonalisation disorder are often troubled by the intense sense of emotional disconnection from those they care about.

3. Psychiatric Comorbidity and History of Trauma

There is frequent comorbidity with Axis I mood and anxiety disorders in depersonalisation disorder, as we have found in our initial series of 30 patients[4] and similarly in our expanded series of 117 patients to date.[5] However, none of these disorders have been found to have an onset prior to depersonalisation disorder, and none predict the severity of symptoms. Similarly, there is extensive comorbidity with Axis II personality disorders, found in about 60% of patients.[5] The most common are borderline, avoidant and obsessive-compulsive disorder; however, all personality disorders are represented. As with Axis I, no Axis II disorder emerges as uniquely related to the presence or severity of depersonalisation disorder.[4] Thus, these findings support the conceptualisation of depersonalisation disorder as a distinct disorder with its own standing, rather than a

depressive or anxious equivalent as some clinicians are still prone to thinking.

The relationship of depersonalisation disorder to trauma is also an interesting one. Hundreds of studies to date (see van Ijzendoorn and Schuengel[10] for a meta-analysis) have confirmed a relationship between dissociation and traumatic stress, such as the dissociation occurring in more complex dissociative disorders, e.g. dissociative identity disorder or peritraumatic dissociation. However, until recently the relationship of depersonalisation disorder to trauma was less clear. In a recent study, Simeon et al.[11] showed that compared with healthy controls, patients with depersonalisation disorder experienced significantly more childhood trauma, especially emotional abuse, as well as physical and sexual abuse. This did not appear to be a non-specific finding, as depersonalisation severity, but not overall dissociation severity, was uniquely predicted by a total emotional abuse score. One could thus speculate that there is a severity spectrum of dissociative disorders, represented at the milder end by depersonalisation disorder and mediated in part by long-term and moderate abuse or neglect; whereas, more severe dissociative disorders, such as dissociative identity disorder, are mediated by more extreme forms of early abuse, such as sexual and physical abuse. Furthermore, later-life traumatic stress factors such as the traumatic death or suicide of a close family friend or relative can trigger depersonalisation disorder, as well as prolonged forms of subacute stress, such as severe interpersonal or role adjustment conflicts.

This discussion naturally leads us into the next issue of a dissociative diathesis in a proportion of the population, which may be partly genetically determined and becomes expressed phenotypically in the face of later adversity. Such stress-diathesis models of dissociation have been put forth, some claiming that certain inheritable traits such as suggestibility, ability to be hypnotised or absorption may lead to more pathological forms of dissociation if notable environmental stress factors occur over the course of a lifetime, childhood or adulthood.[12] There is still considerable debate in the literature as to whether dissociation is a heterogeneous entity consisting of various components that may be more or less related to each other. In regards to genetic predisposition, the only research to date consists of two twin studies with conflicting findings. One study found no evidence for a genetic component,[13] while another study found 48% genetic influence.[14]

In addition, the interesting cases of an acute onset of depersonalisation disorder with specific chemical intoxications, albeit sporadic compared with the overall incidence of substance use in the population, suggest that chemical triggers of a specific nature can initiate long-standing depersonalisation disorder (in the absence of continued substance use). Such drugs are marijuana, hallucinogens, ecstasy and ketamine, even at times in the absence of co-occurring traumatic stress.[5,6,8] Two explanations might exist for such a phenomenon. One is that these drugs, in dissociation-susceptible individuals, may induce a profound alteration in self-state that is perceived as highly destabilising, in effect traumatic, thus triggering a depersonalisation reaction. The other possibility is that these drugs act as highly specific triggers that dysregulate already vulnerable neurochemical systems that may underlie the neurobiology of depersonalisation disorder. The two models, of course, are not mutually exclusive.

4. Neurobiology

Several neurotransmitter systems have been implicated in depersonalisation disorder, although evidence for each is scant and partly indirect. The four classes of chemicals implicated in inducing depersonalisation in healthy controls are glutamate NMDA receptor antagonists, cannabinoids, hallucinogens and opioid receptor agonists. These drugs and related neurotransmitter systems are discussed below.

The NMDA antagonist ketamine, also known as the ‘dissociative anaesthetic’ and as the street drug Special K, induces a profound dissociative state in healthy individuals that has been likened to the negative symptoms of schizophrenia.[15] The dissociative, but not the psychotogenic, effect of ketamine can be blocked in healthy individuals by pre-

treatment with the anticonvulsant lamotrigine.[16] 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 receptors). NMDA receptors are widely distributed in the cortex, as well as in the hippocampus and the amygdala, and are thought to mediate associative functioning and long-term potentiation of memory, which, in turn, facilitates new learning. It is thus plausible that diminished NMDA-related neurotransmission may be related to dissociative states.

Cannabinoids, such as marijuana, have been consistently shown to induce depersonalisation, with a pronounced component of temporal disintegration, in both naturalistic and experimental paradigms in healthy individuals. In addition to their action at cannabinoid receptors, whose natural function is largely unknown, cannabinoids have been shown to block NMDA receptors at sites distinct from other noncompetitive NMDA antagonists.[17] Thus, their dissociative effect might in fact be mediated via the NMDA receptor. There are case reports in the literature of chronic depersonalisation induced by short-term cannabis ingestion[18,19] and in a series of 117 individuals with depersonalisation disorder, about 13% reported the short-term triggering of chronic depersonalisation by marijuana smoking.[5]

Depersonalisation states in healthy individuals are also transiently induced by the use of hallucinogens, such as lysergide (LSD), psilocybine (psilocybin) and dimethyltrytamine (DMT), in both naturalistic and experimental settings. In Simeon et al.'s[5] series of 117 patients with depersonalisation disorder, 6% reported the induction of chronic depersonalisation by short-term hallucinogen use. These substances act as agonists of serotonin 5-HT_{2A} and 5-HT_{2C} receptors, suggesting a possible mediating role for serotonin in depersonalisation. Such a relationship is indirectly and anecdotally supported by the prominent obsessional phenomenology in at least a subgroup of patients with depersonalisation disorder.[20] Neurochemical challenge studies with the 5-HT_{2C} receptor agonist meta-chlorophenylpiperazine (m-CPP) have demonstrated the induction of depersonalisation in patients with various diagnoses such as social phobia, borderline personality disorder and obsessive compulsive disorder,[21] as well as the induction of flashbacks and dissociative symptoms in a subgroup of patients with post-traumatic stress syndrome (PTSD).[22]

Stress-induced analgesia is known to be mediated by the endogenous opioid system,[23] and the post-traumatic stress analgesic response to combat stimuli can be blocked by pre-treatment with the opioid antagonist naloxone.[24] In healthy individuals, the κ-opioid agonist enadoline induced a depersonalisation-like syndrome (with perceptual disturbances and a sense of detachment), compared with placebo.[25] Along these lines, opioid antagonists such as high-dose naltrexone (in patients with borderline personality disorder[26]) and intravenous naloxone (in patients with chronic depersonalisation[27]) have been reported to reduce dissociation (see section 5.1). The opioid antagonist nalmefene has been reported to decrease emotional numbing in veterans with PTSD.[28] Selective κ-opioid antagonists for use in humans have not yet been developed.

The autonomic system is also of particular interest in dissociation. While there is extensive evidence for autonomic hyper-reactivity in PTSD, there is limited evidence for autonomic blunting in dissociation, such as the finding of decreased heart rate and galvanic skin response in women who have been raped and present with high dissociation.[29] Specifically in depersonalisation disorder, there is some limited but compelling evidence for autonomic hypo-reactivity. Sierra et al.[30] showed that compared with healthy individuals and patients with anxiety disorders, patients with depersonalisation disorder exhibited reduced magnitude and increased latency of skin conductance response to unpleasant stimuli, but not to non-specific stimuli; this suggests that patients with depersonalisation disorder demonstrate a selective inhibition of emotional processing. Noradrenaline (norepinephrine) is a neurotransmitter central to facilitating alertness, selective attention and enhanced memory encoding under stressful conditions[31] and, therefore, may play a role in this

inhibition. Indeed, in a preliminary report,[32] 24-hour urine noradrenaline was found to be strongly inversely correlated ($r = -0.88$) to depersonalisation severity in nine patients with depersonalisation disorder.

Finally, 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 sensitisation in PTSD.[33] The HPA axis has been preliminarily investigated in depersonalisation disorder, and the results of the two studies reported to date are conflicting.[34,35] While one study reported non-significantly lower basal salivary cortisol levels in patients with depersonalisation disorder compared with healthy controls,[35] the other study reported a tendency for elevated basal urinary and plasma cortisol levels in patients with depersonalisation disorder compared with healthy controls, with a definite resistance to low-dose dexamethasone suppression[34] suggestive of diminished HPA axis sensitivity. Larger studies are needed to definitively delineate the function of the HPA axis in depersonalisation.

There are a few hypotheses regarding the brain circuitry that may underlie depersonalisation in the literature. As far back as 1950, Penfield and Rasmussen[36] 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. These researchers 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[37] put forth the 'corticolimbic disconnection hypothesis'. This model is theoretically extrapolated from experiential narratives of depersonalised patients, the neurological literature and cognitive neuroscience. It proposes bilateral corticolimbic disconnection with prefrontal activation and limbic inhibition, resulting in hypoemotionality (via amygdala inhibition) as well as attentional difficulties (via cingulate inhibition). Sierra et al.[38] have proposed two distinct components of the depersonalisation experience subsumed by distinct neurocircuitry: visual derealisation associated with occipita-temporal dysfunction, and body alienation associated with parietal dysfunction. Lambert et al.[39] have highlighted the organic aetiologies that sometimes underlie chronic depersonalisation and have proposed consideration of an organic subtype of the condition.

Krystal et al.[40] 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. Thus, dissociation may involve the disruption of corticocortical, thalamocortical, amygdalocortical and hippocampocortical connectivity.

These models are clearly not mutually exclusive, but rather may all contribute towards brain function models for conceptualising depersonalisation. From an evolutionary perspective, acute depersonalisation 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 depersonalisation symptoms that have become autonomous from stressful triggers are clearly maladaptive, and are suggestive of dysregulated brain function that has failed to repair.

The actual evidence for the neurobiological models of depersonalisation disorder is limited but definitely present. Certainly, the neurological literature, when reviewed, is helpful in providing evidence for brain areas that may mediate neurological syndromes that are at least phenomenologically similar to depersonalisation. These all coalesce in suggesting a unique role for the inferior parietal lobule and other transmodal sensory cortical areas in mediating depersonalisation-like experiences. For instance:

- depersonalisation is common in patients with seizures, especially in temporal lobe epilepsy with left-sided foci;[41]

- inferior parietal and angular gyrus tumours can manifest with depersonalisation symptoms;[42]
- structural lesions underlying 'neglect' syndromes have been found to be concentrated in the right inferior parietal lobule;[43]
- in 82 patients with parietal lobe epilepsy, frequent somatosensory aurae, disturbances of body image, vertiginous sensations and visual illusions were reported;[44]
- in a study of the visual recognition of emotion of 108 patients with focal brain lesions, the right somatosensory-related cortex was found to play a critical role, especially the supramarginal gyrus and somatosensory cortex S1;[45]
- 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;[46]
- 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.[47]

A very limited number of studies in healthy volunteers have addressed the induction of depersonalisation symptoms. A positron emission tomography (PET) study using intravenous tetrahydrocannabinol found that depersonalisation severity was correlated with an increase in cerebral blood flow (CBF) in the right frontal cortex and anterior cingulate, and a decrease in subcortical flow in the amygdala, hippocampus, basal ganglia and thalamus.[48] A PET imaging study showed that the hallucinogenic 5-$HT_{1A/2A}$ receptor agonist psilocybine resulted in increased dopamine in the striatum that correlated with depersonalisation, but there was also prominent mood and psychotic symptom induction.[49] A fluorodeoxyglucose-PET study using a high dose amphetamine found increased metabolism in the anterior cingulate, striatum and thalamus; however, mania was more prominent than depersonalisation.[50] It can readily be seen that the findings of these three studies are partly in accord and partly contradictory with the three models previously outlined in this section.

In assessing the neurobiological underpinnings of depersonalisation, identifying its core feature is a helpful approach. The subjective sense of unfamiliarity is central to the depersonalisation experience. That is, if an incoming perception is not processed as familiar, it will be experienced as unreal, strange, detached or unemotional. Therefore, key disturbances may lie in areas of the brain responsible for matching incoming sensory information to pre-existing memory networks of these perceptions, involving both limbic structures and sensory association cortical areas. There are a few recent imaging studies in patients experiencing dissociation. Lanius et al.[51] studied women with PTSD secondary to childhood sexual abuse, using functional magnetic resonance imaging (fMRI) with traumatic script-driven imagery. Of the PTSD patients, 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 with a healthy control group, the dissociative state was associated with increased activation in the medial prefrontal cortex (BA 9, 10), 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 reliving subgroup, but similar to the results of two imaging studies[52,53] in patients with depersonalisation disorder (described in the following paragraph).

In an fMRI study by Phillips et al.,[52] the responses to neutral and aversive visual stimuli were compared across three groups: (i) patients with depersonalisation disorder; (ii) patients with obsessive-compulsive disorder; and (iii) healthy controls. Patients with depersonalisation disorder rated the aversive pictures as less emotive than those with obsessive-compulsive disorder and healthy controls. In addition, in response to the aversive pictures, the insula (part of the limbic system that is the centre for disgust) was not activated in patients with depersonalisation disorder, unlike individuals in the other two groups. Patients with depersonalisation disorder showed heightened activation in the right ventral

prefrontal cortex in response to the aversive pictures. These findings suggest a neural mechanism for emotional detachment that is mediated by prefrontal activation and limbic inhibition.

In a PET study of depersonalisation disorder,[53] eight patients with depersonalisation disorder and 24 age- and sex-matched healthy controls were compared, using a semantic memory task (the California Verbal Learning Test [CVLT]) during 18-fluorodeoxyglucose uptake as a control for mental activity. PET scans were co-registered with MRI scans, and there were no baseline differences between the two groups on a brief neuropsychological battery and on the CVLT. The depersonalisation disorder 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 depersonalisation disorder 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 depersonalisation disorder group had significantly lower activity in the right temporal region (BA 22 and 21), higher activity bilaterally in the parietal region (BA 7B and 39) and higher activity in left occipital region (BA 19). Dissociation scores were very strongly correlated with BA 7B activity ($r = 0.84$, $df = 6.0$, $p = 0.008$). 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, the 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. The results from this study indicate that depersonalisation may be related to disruptions in functioning along hierarchical sensory association areas (unimodal and crossmodal) responsible for the processing of incoming perceptions against pre-existing brain templates.

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

- NMDA, 5-HT_{2A}, 5-HT_{2C} and opioid receptors may be implicated;
- autonomic blunting may be present, as evidenced by physiological measures and baseline noradrenaline levels;
- HPA axis dysregulation may occur, but there is conflicting evidence regarding whether baseline cortisol levels are decreased or increased. There is also pilot evidence for resistance to dexamethasone suppression;
- disruptions in sensory cortex associative functioning may mediate the perceptual disturbances (somatosensory, visual and auditory) and sense of 'unfamiliarity' characteristic of depersonalisation disorder;
- frontal inhibition of limbic structures may mediate the hypoemotionality characteristic of depersonalisation disorder.

5. Treatment

Treatment recommendations and guidelines for depersonalisation disorder are still not established, but both pharmacological and psychotherapeutic efforts are worthwhile. This section provides a summary of what is currently known about the treatment of the condition.

5.1 Pharmacotherapy

With regards to medication, unfortunately none have been shown to be efficacious to date, although research has been limited, and thus no definitive medication treatment guidelines exist. In the past 10 years, a small open series,[54] a small controlled trial,[55] two single case reports[56,57] and retrospectively collected past treatment data,[4,54-57] had suggested a possible role for serotonin reuptake inhibitors in treating primary depersonalisation disorder. Unfortunately though, a more recently completed placebo-controlled trial, failed to show benefit with fluoxetine in 54 patients with depersonalisation disorder.[58]

Recently there has also been a surge of interest in the treatment of depersonalisation disorder with lamotrigine. It has been hypothesised that NMDA antagonists such as ketamine may induce depersonalisation via increased glutamate transmission at non-NMDA glutamate receptors (see section 4). Pre-treatment with lamotrigine, which inhibits glutamate release, attenuates ketamine-induced dissociation.[16] Along these lines, there was a promising preliminary open trial with lamotrigine in chronic depersonalisation,[59] which described an improvement in five patients with depersonalisation disorder. However, a crossover placebo-controlled trial did not find an improvement with lamotrigine in nine patients with the disorder.[60]

Opioid antagonists have also been of some recent interest in the treatment of dissociation and depersonalisation. Naltrexone in dosages of 25–100 mg/day has been reported to decrease dissociative symptoms in borderline personality disorder over a 2-week period.[26] Nuller et al.[27] reported results from a intravenous naloxone trial in 11 patients with chronic depersonalisation disorder, of whom three experienced complete remission and seven had marked improvement. Nalmefene was reported to decrease emotional numbing in eight veterans with PTSD.[28]

There are additional medication options for patients with depersonalisation disorder. Some individuals anecdotally appear to benefit from benzodiazepine treatment (e.g. clonazepam), in particular when they experience comorbid anxiety or panic, which exacerbates depersonalisation.[4,5] Others report that while benzodiazepines may have lessened their anxiety, these drugs did not impact on symptoms of dissociation. Some patients report improvement, at least in attentional and focusing difficulties, and may feel a little 'clearer' with bupropion or stimulant treatment.[4,5] New classes of medications currently in development such as CRF antagonists, NMDA agonists, glucocorticoid receptor antagonists and neuropeptide Y analogues may hold promise for the future treatment of depersonalisation disorder, as it does not appear that any of the currently available agents have a potent anti-dissociative effect.

5.2 Psychotherapy

A variety of psychotherapeutic techniques can be used to treat depersonalisation disorder, although again none of these have established efficacy to date. The empirical literature is unfortunately very limited, with case reports of psychodynamic or behavioural interventions, and the general outlook has traditionally been that the condition is difficult to treat. Psychodynamic techniques can be helpful, in particular for those patients who have not experienced depersonalisation disorder too chronically or unremittingly, and in whom either the depersonalisation can be linked to particular dynamics, or in which the depersonalisation has acquired secondary meanings that could benefit from exploration.

Frances et al.[61] have described psychodynamic approaches to depersonalisation based on the concept of self-constancy, that is the cohesiveness and stability of self representations (e.g. action, body, feeling, thought). In the proposed framework, depersonalisation is differently linked to various levels of character pathology. In psychotic-spectrum pathology, there is impaired self-object differentiation, which may benefit from boundary strengthening. In borderline pathology, there are unstable and poorly integrated self-representations and their exploration and better integration can lead to greater self-cohesion and potentially diminished depersonalisation. In narcissistic pathology, self-representations remain stable only in the face of object constancy (self-objects) and narcissistic injuries can trigger depersonalisation states. Finally, in neurotic pathology, intrapsychic conflict may underlie depersonalisation and should be worked through.

Trauma-focused therapy may also be very helpful in some patients with depersonalisation disorder; in particular those with histories of poorly processed traumatic experiences that appear to relate to the depersonalisation symptoms and course. It is plausible that individuals with chronic depersonalisation disorder have, from early on, dissociated emotionally overwhelming material and this process may in

part underlie their chronic dissociative state. Indeed, there is rare co-occurrence of PTSD in these patients, suggesting both that the traumatic stress factors may be less severe or life-threatening than those typically associated with PTSD, and possibly that patients with depersonalisation disorder have an innate predisposition to dissociate. Depersonalisation disorder is often encountered in settings of major emotional abuse or neglect, as well as after deaths of loved ones. Depersonalisation may be a response to later prolonged life stress, especially in individuals who experienced it in a helpless and out-of-control fashion. Various trauma treatment approaches might be helpful, such as exposure or cognitive processing, in challenging the chronic dissociation.

Cognitive-behavioural techniques specifically tailored to depersonalisation disorder may also be helpful, and the Institute of Psychiatry in London, UK, has done work in this area and presented preliminary approaches to treatment.[62] They propose two phases to the treatment of depersonalisation disorder. For the initial phase, non-specific interventions are recommended, such as activity scheduling, graded exposure to avoided behaviours and settings, and the challenging of negative automatic thoughts through the use of cognitive diaries. In the second phase of treatment, techniques are recommended to facilitate the controlled re-experiencing of emotions and the refocusing of attention away from the self and the depersonalisation experience.

Finally, some general psychotherapeutic principles can be helpful guides to treating depersonalisation disorder. One of these principles is to help individuals learn to better modulate their level of arousal. Some individuals with depersonalisation disorder seem to be in a constant high arousal and high anxiety state, and these individuals may benefit from techniques focusing on relaxation, breathing exercises and meditation. Other individuals with depersonalisation disorder seem to be in an abnormally low arousal state, such as those who only occasionally feel more real with intense stimulation such as physical pain, exercise or sexual activity. Such individuals may benefit from techniques that heighten their arousal state in a productive fashion. Thought blocking techniques that focus on breaking the obsessional cycle or preoccupation and checking of depersonalisation experiences may be helpful to those with an obsessional layer to their pathology. Grounding techniques, focusing on immediacy of experience and related effects can also be helpful. Finally, keeping a diary may be helpful in assisting individuals become more attuned to even subtle fluctuations in the intensity of their symptoms, thus building on any experiences of feeling more real both in the treatment and in the outside world.

6. Conclusion

Depersonalisation disorder remains an underdiagnosed and poorly treated psychiatric disorder. In this article we have reviewed the most current perspectives on phenomenology, neurobiology and treatment approaches and have delineated directions for future research and clinical practice.

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