**Behavioural, autonomic, and neural responsivity in depersonalisation-derealisation disorder: A systematic review of experimental evidence**

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**Funding:** SP and LSMM have been funded by an MRC Career Development Award to SP (2021-2026 [MR/V032771/1]).

**Disclosure statement:** All authors declared no competing interests.

**Author contributions (CRediT):** Conceptualisation: SP; Funding acquisition: SP; Design/methodology: SP, LSMM, XH; Data curation: XH, LSMM, SW; Writing: LSMM, XH, SP, NM; Supervision: SP, LSMM. All authors reviewed and approved the final version of the manuscript.

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**Abstract**

Depersonalisation-derealisation disorder (DDD) is characterised by distressing experiences of separation from oneself and/or one’s surroundings, potentially resulting from alterations in affective, cognitive, and physiological functions. This systematic review aimed to synthesise current experimental evidence of relevance to proposed mechanisms underlying DDD, to appraise existing theoretical models, and to inform future research and theoretical developments. Studies were included if they tested explicit hypotheses in DDD samples, with experimental manipulations of at least one independent variable, alongside behavioural, subjective, neurological, affective and/or physiological dependent variables. Some evidence for diminished subjective responsivity to aversive images and sounds, and hyperactivation in neurocircuits associated with emotional regulation when viewing aversive images emerged, corroborating neurobiological models of DDD. Inconsistencies were present regarding behavioural and autonomic responsivity to facial expressions, emotional memory, and self-referential processing. Common confounds included small sample sizes, medication, and comorbidities. Alterations in affective reactivity and regulation appear to be present in DDD; however, further research employing more rigorous research designs is required to provide stronger evidence for these possible mechanisms.

**Keywords:** depersonalisation-derealisation disorder; dissociation; experimental; neurobiological; autonomic; behavioural; emotional regulation

**Introduction**

Depersonalisation-derealisation disorder (DDD) is a dissociative disorder affecting approximately 1% of the general population (Yang et al., 2023), characterised by persistent or recurring episodes of detachment from oneself (depersonalisation, DP) and one's surroundings (derealisation, DR) (APA, 2013). Despite these disruptions of self-awareness and feelings of unreality, individuals with DDD have intact reality testing (APA, 2013), differentiating this condition from psychotic disorders. DDD can encompass a multiplicity of symptoms including sensory impairments, feeling as if one is in a dream, emotional numbing, visual perceptual distortions, feelings of detachment, and an unreal or absent sense of self (Simeon & Abugel, 2006). The disorder overlaps with both anxiety and other dissociative disorders (Baker et al., 2003; Millman et al., 2022; Hunter et al., 2003), and symptoms of DP and DR can be seen across psychiatric conditions including post-traumatic stress disorder (PTSD), schizophrenia, functional neurological disorder, depression and panic disorder (Campbell et al., 2023; Hunter, Sierra & David, 2004; Lyssenko et al., 2018), as well as neuropsychiatric disorders including functional neurological disorder and epilepsy (Campbell et al., 2023; Heydrich et al., 2019), although the underlying mechanisms may differ in the latter population (Medford, 2014).

Theoretical models point towards a range of pathways that may lead to the experience of DDD. In their neurobiological model, Sierra and Berrios (1998) proposed that hyperactivation in the left and right prefrontal cortices paired with reciprocal inhibition of limbic and paralimbic structures (e.g., amygdala, anterior cingulate cortex [ACC]) may contribute to flattened autonomic responsivity, hypoemotionality, and simultaneously elevated vigilance in DDD. This proposed corticolimbic interaction has been observed in some DDD samples, with specifically elevated activity seen within the right ventrolateral prefrontal cortex when viewing affective stimuli (Lemche et al., 2007; Medford et al., 2016; Phillips et al., 2001), the same cortical regions reported as key in the deliberate suppression of emotional responses or attempts to control emotional experiences evoked by affective stimuli in healthy individuals (Ochsner, Bunge, Gross, & Gabrieli, 2002; Phan et al., 2005), suggesting emotional processing difficulties in DDD (Jay et al., 2014; Monde et al., 2013; Murphy, 2023). Autonomic dysregulation (Schoenberg et al., 2012; Simeon et al., 2001) and differing temporal patterns of autonomic response (Giesbrecht et al., 2010) have also been seen in some previous studies, although the findings are not always consistent.

The cognitive-behavioural model put forward by Hunter et al. (2003) builds on the proposed elevated vigilance in DDD, placing a specific emphasis on the link between DDD and anxiety disorders (i.e., panic) and suggesting the involvement of an excess monitoring or hyperawareness and catastrophic misinterpretation of DP/DR symptoms which leads to the maintenance and chronicity of the disorder, although it does not explain how these initial DP/DR experiences arise (Hunter et al., 2014). A more recent theory chimes with this, suggesting an inability to attenuate somatosensory signals, wherein individuals with DDD may “overthink” and exert a heightened focus on interoceptive or exteroceptive signals, contributing to the symptomatology and experience of DDD (Ciaunica, Seth, Limanowski, & Friston, 2022). This overthinking and self-objectification was proposed to result in feelings of detachment from the self and impaired implicit self-processing (Ciaunica et al., 2022; Sierra & David, 2011), seen in preliminary studies (Ketay et al., 2014; Liu et al., 2022). The individual may feel as though they are “trapped” in their head but separated from their body (Ciaunica et al., 2021), hyperaware of the split of consciousness between experience/action and observation (Simeon & Abugel, 2006).

Predictive coding models implicate “interoceptive silencing” or the systematic suppression of bodily signals in DDD, which may play a role in the feelings of disembodiment or physiological numbing seen in the disorder (Gatus, Jamieson, & Stevenson, 2022; Gerrans, 2019; Saini et al., 2022). Studies revealing reduced activation in the insula and ACC, key areas involved in interoception and body representation (Seth, 2013; Medford, 2012, 2016; Michal et al., 2014; Schulz et al., 2016), lower interoceptive accuracy, awareness and/or sensibility (Millman, Hunter et al., 2023), and different cortical representations of bodily signals (Schulz & Vogele, 2015; Sedeno et al., 2014) further suggest altered integration of, or disconnection between, physiological and cognitive functions in this disorder.

DDD is a highly complex condition, with underpinnings and alterations spanning behavioural, subjective, and physiological dimensions. Although the prevalence of DDD is comparable to other mental health conditions (i.e., schizophrenia, PTSD), there is a relative paucity of experimental research and limited understanding of the mechanisms underlying DP/DR symptoms, as well as how best to treat them (Salami, Andreu-Perez, & Gillmeister, 2020; Wang et al., 2023). A systematic review of experimental psychological and neuroscientific studies in DDD is required to comprehensively understand the evidence base for altered functioning and responsivity in DDD and to examine the evidence for the models outlined above. A better understanding of the evidence base will allow for an assessment of which domains, in particular, are in need of further research, and the best way forward in terms of methodological rigour in this research area.

***1.1 Aims***

The primary aim of this review was to synthesise and critically evaluate previous experimental findings on behavioural, subjective, and physiological functioning in DDD, to appraise the current evidence for existing theoretical models, and to explore possible relationships between experimental outcomes and clinical features (i.e., DDD symptom severity, depression, adverse event exposure).

**2. Methods**

**2.1 *Search Strategy***

This systematic review protocol was registered on PROSPERO (CRD42023434906) and developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2020). Searches were conducted across Embase, MEDLINE, and PsycINFO, from inception to 19th June 2023. Search terms are included in Box 1. A manual search of the reference lists of relevant articles (primary studies and reviews) was conducted to extract further relevant published literature.

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| **Box 1. Database search terms** |
| *Searched in title, abstract, subject heading, and keyword fields:* “depersonali\* OR “dereali\*”AND “disorder” OR “diagnos\*”AND “neuroimag\*” OR “MRI” OR “magnetic resonance imag\*”OR “MRS” OR “magnetic resonance spectroscopy” OR “PET” OR “positron emission tomography” OR “EEG” OR “electroencephalograph\*” OR “CT” OR “tomograph\*” OR “structur\*” OR “paradigm” OR “theor\*” OR “sympathetic” OR “autonomic” OR “process\*” OR “memor\*” OR “attention\*” OR “mood” OR “cardiovascular” OR “respiratory” OR “endocrine” OR “immun\*” OR “metabolic” OR “behavio?r\*” OR “cognit\*” OR “affect\*” OR “emotion\*” OR “physiolog\*” OR “skin conduct\*” OR “experiment\*” OR “intervent\*” OR “control\*” OR “research” OR “task” OR “test” OR “measur\*”truncation (“\*” or “?”) was used to capture words with both UK and US spellings |

To be included, articles were required to be original research, published in peer-reviewed academic journals, with an explicit experimental research design as follows:

1. The investigators intentionally manipulated one or more independent (predictor) variables to assess the effect on at least one dependent (outcome) variable.
2. Experimental hypotheses were explicitly stated.
3. The studies included at least one dependent variable quantifying behavioural, subjective, or physiological responsivity.
4. At least one participant group consisted of participants clinically diagnosed with DDD according to DSM-5 (APA, 2013) or ICD-11 (WHO, 2019) criteria.
5. At least one control group or condition was included.

Unpublished sources (i.e., theses, preprints), conference abstracts, publications not in English, and reviews/meta-analyses were excluded. Any studies that did not meet the aforementioned inclusion criteria were excluded, as were studies of mixed samples without the presentation of DDD-specific data.

**2.2 *Data extraction***

All articles were uploaded to Rayyan (Ouzzani et al., 2016) and duplicates were removed. Initial title and abstract screening to exclude duplicates and studies that were clearly not relevant was first done by XH. Following this initial screening, the remaining titles, abstracts and/or full texts were screened independently by two authors (XH and SW). Any disparities were resolved by discussion with LSMM and SP. Reasons for exclusion were noted and are recorded in the PRISMA flow diagram (Figure 1).

The following data were extracted by XH and LSMM and checked for accuracy by SW: authors, year, geographical location, study design, study population/s, sample size, experimental task/s, outcome variables, scores on the specified outcome variables, between-group comparisons.

<insert Figure 1 around here>

**2.3 *Risk of bias (quality) assessment***

Quality and risk of bias assessment was completed for each full text to be included using the Newcastle-Ottawa Case-Control Scale (Wells et al., 2000), independently by two authors (XH and SW). In case of any discrepancies, SP and LSMM were consulted. Study quality was assessed with three items: selection, comparability, and outcome. The selection category is rated out of four and includes determining the adequacy of how cases (in this case, individuals with DDD) were defined, how representative the cases are, and how controls were both defined and selected. Comparability is rated out of a maximum of two points, and assesses how comparable the cases and controls are, as defined by the design or analysis of the study (i.e., do the authors control for what would be considered the most important factor between groups within the study [age, sex, education, medication, etc.]). The outcome category is rated out of three, and assesses how cases were determined (i.e., secure record, structured interview, etc.), if the same method was used for both cases and controls, and the non-response rate for the included groups. Thresholds for risk of bias were 7-9 (high quality), 4-6 (high risk), and 0-3 (very high risk of bias) (Wells et al., 2000). Overall risk of bias as measured with the NOS for each included study is reported in Supplementary Table 1.

**2.4 *Data synthesis***

Data from included studies were integrated in a narrative synthesis according to domain of functioning. Statistical values such as central tendency (e.g., mean, median) and measures of dispersion (e.g., standard deviation, interquartile range) were extracted/calculated and tabulated where possible.

**3. Results**

**3.1 *Study characteristics***

Thirty studies met our inclusion criteria (Table 1). Included articles were published between 2000-2023 with geographical locations including the USA (k=7), Germany (k=5), UK (k=17), and China (k=1). Two studies implemented a mixed between- and within-subjects design (Medford et al., 2016; Schonenberg et al. 2012), and the remaining 28 involved case-control comparisons. Sample sizes of DDD participants ranged from six (Phillips et al., 2001) to 32 (Schoenberg et al., 2012; Simeon & Knutelska, 2023), with a mean and median sample size across studies of 16 and 15, respectively.

Mean age across DDD samples ranged from from 25.8 years (Liu et al., 2022) to 37.1 years (Jay et al., 2014). Five studies by Lemche et al. (2007, 2008, 2013, 2016a, 2016b), two studies by Lawrence et al. (2007, 2012), and three studies by Schulz et al. (2015, 2016) and Michal et al. (2014) assessed different outcomes but reported on the same or largely overlapping DDD samples. Six studies included control participants with psychiatric diagnoses besides DDD as a separate group alongside healthy controls (HCs) (Hedrick & Berlin, 2012; Hunter et al., 2014; Lawrence et al., 2012; Phillips et al., 2001; Sierra et al., 2002; Sierra et al., 2006), and one study included psychiatric controls only (Michal et al., 2013).

<insert Figure 2 and Table 1 around here>

**3.2 *Risk-of-bias***

Overall, five studies were rated as high quality, 23 as high RoB, and two as very high RoB (Supplementary Table 1). Most studies matched demographic characteristics, including age and gender, between groups.

The majority of studies excluded potential DDD participants if they reported current or lifetime psychotic disorder/psychosis, neurological disease, psychoactive substance abuse, history of head injury/trauma, schizophrenia, or current PTSD, with a minority also specifying that they ensured DDD was not secondary to another disorder (i.e., anxiety, panic). Even though these exclusion criteria were regularly implemented, many comorbid diagnoses still emerged across DDD samples in 12 studies including major depression, dysthymia, panic disorder, agoraphobia, generalised anxiety disorder, obsessive-compulsive disorder, body dysmorphic disorder, and personality disorders, and 15 studies did not report on current comorbid diagnoses.

The description of recruitment was another recurrent weakness, particularly a lack of specification of whether recruitment was continuous, and the strategy for participant selection. Future studies should aim towards more transparency regarding the recruitment and selection of both patient and control samples. Further, there was inconsistent reporting regarding the absence of a history of DDD in HCs, and minimal information regarding mental health characteristics of HCs in general. Current medication use in DDD samples was reported in 15 studies (including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, lamotrigine, clonazepam, olanzapine,), five studies reported their DDD samples to not be taking any current medication, and 10 studies failed to report on medication use.

***3.3 Behavioural/subjective outcomes***

Eighteen studies measured behavioural/subjective functioning or responsivity in DDD (Table 1; Supplementary Table 2), including measures of reaction time, recall, subjective arousal, and emotion reactivity. Sample sizes ranged from six to 32 (M=16.61, SD=6.56), including a total of 283 individuals with DDD. The mean age across DDD samples was 31.47 (SD=7.50) and 32.27 (SD=7.57) in controls. For every 1.02 females there were 2 males on average in the DDD group. Eleven studies included HCs only, one included psychiatric controls only, and six included both.

***3.3.1 Cognitive processing***

Across four studies examining the influence of emotional or unexpected material/events on attention in DDD, mixed results were present. Two studies found no significant interference of emotional/negative stimuli on selective attention in DDD and HCs (Guralnik et al., 2000; Lemche, Sierra-Siegert et al., 2016), although one reported elevated distraction and reduced response consistency in DDD when presented with negative stimuli (Lemche, Sierra-Siegert et al., 2016). Hunter et al. (2014) found momentary DP/DR symptom reductions when participants focused their attention on irrelevant, cognitively demanding tasks, and symptom elevations when attention was oriented towards the symptoms. Adler et al. (2014) found that those with DDD displayed a smaller total attention directing effect than HCs on a task with high attentional demand.

 One study examined conditional reasoning in a DDD sample and found impairments in cognitive flexibility in the DDD group compared to HCs (Lawrence et al., 2012). Further, although HCs were more likely to endorse emotional fallacies than neutral fallacies, this was not seen in DDD (Lawrence et al., 2012).

***3.3.2 Emotional memory***

Five studies examined memory for emotional stimuli in DDD samples, who exhibited normal memory enhancement for peripheral emotional material (Montagne et al., 2007), elevated objective and subjective memory fragmentation compared to HCs (Giesbrecht et al., 2010), better recall/recognition of depersonalisation-related/emotional words (Guralnik et al., 2000; Medford et al., 2006), and reduced forgetting of negative words (Simeon & Knutelska, 2023). Memory for neutral words was not enhanced when they were encoded under emotional conditions in DDD, in contrast to HCs (Medford et al., 2006).

***3.3.3 Responses to facial expressions***

Two studies assessed responsivity to facial emotion in DDD using variants of facial expression processing tasks. DDD samples showed reduced sensitivity in identification of both angry and disgusted faces compared to HCs (Montagne et al., 2007), and rated facial expressions of disgust as significantly less intense than both HCs and individuals with anxiety (Sierra et al., 2006). In contrast, Lawrence, et al. (2007) found no significant difference between DDD and HCs groups on the ‘Reading the Mind in the Eyes’ test (Baron-Cohen et al., 2001), and when controlling for demographic variables, the DDD group outperformed HCs on the task (Lawrence et al., 2007).

***3.3.4 Responses to affective stimuli***

In two studies examining responsivity to affective images, both reported no significant differences in valence of emotional responses in DDD (Phillips et al., 2001; Sierra et al., 2002), although Sierra et al. (2002) found lower subjective arousal in response to unpleasant images in DDD compared to HCs and clinical controls. Michal et al. (2013) examined responses to emotional sounds in a DDD sample and reported significantly reduced ratings of unpleasantness for aversive sounds compared to clinical controls and normative ratings.

***3.3.5 Self-referential processing***

Three studies examined self-referential processing in DDD. Ketay et al. (2014) found no difference between DDD and HCs in reaction times (RTs) or response accuracy when viewing self or stranger’s faces. However, Liu et al. (2022) found significantly faster RTs for subliminal self-face processing compared to famous or stranger’s faces in HCs, which was not observed in the DDD group. Perhaps contrastingly, another study revealed significantly higher implicit self-esteem in DDD compared to both HCs and individuals with borderline personality disorder (Hedrick & Berlin, 2012).

***3.3.6 Interoception***

One study examined aspects of interoception, with no differences in interoceptive accuracy seen between DDD and HCs, as well as no relationship between DP/DR symptom severity and interoceptive accuracy in DDD (Michal et al., 2014).

***3.4 Physiological outcomes***

Fifteen studies measured autonomic dependent variables (Table 1; Supplementary Table 3), encompassing skin conductance responses (SCR), heart rate (HR), and blood pressure. Sample sizes ranged from 9 to 32 (M=16.4, SD=6.21), with a total of 215 individuals with DDD. Individuals with DDD were 31.68 years old on average (SD=7.92) and controls were 30.92 (SD=7.61). For every 1.02 females there were 1.73 males across the DDD samples. Twelve studies included HCs only, one included psychiatric controls only, and two included both.

***3.4.1 Responses to affective stimuli***

During emotional image exposure, two studies found significantly reduced SCR when viewing aversive/unpleasant images in DDD compared to HCs (Medford et al., 2016; Sierra et al., 2002), with Medford et al. (2016) also reporting reduced SCR to neutral images in the DDD group. In contrast, Michal et al. (2013) observed more pronounced autonomic responses for negative, highly arousing sounds, as well as neutral sounds, in DDD compared to psychiatric controls. Sierra et al. (2002) also reported significantly shorter latency of SCRs in DDD in response to nonspecific physical stimuli (hand clap, sigh), compared to HCs.

Giesbrecht et al. (2010) reported a faster SC mean rise time to peak and no SC recovery in DDD compared to HCs after watching an emotionally provocative movie clip. In another study using speech rate as a measure of physiological arousal, Lawrence et al. (2007) found individuals with DDD exhibited a faster speech after reading a sad vignette relative to HCs.

***3.4.2 Responses to facial expressions***

Two studies reported mixed results regarding autonomic responsivity to facial expressions. In response to facial disgust, Sierra et al. (2006) found individuals with DDD did not experience a significantly greater autonomic response compared to HCs, although individuals with anxiety did (Sierra et al., 2006). In contrast, Lemche et al. (2008) found significantly more variability in SC level and higher SC means across facial expressions compared to HCs.

***3.4.3 Emotion regulation***

Monde et al. (2013) examined emotion regulation in DDD and revealed an impaired ability to enhance emotion alongside a heightened ability to suppress emotion, as measured with HR, compared to HCs (Monde et al., 2013). Further, a positive correlation between HR and enhancement of unpleasant emotion was seen in the DDD group, whereas HCs showed a positive correlation between HR, SCR, and the ability to suppress pleasant emotion.

In a second study testing the Sierra and Berrios (1998) neurobiological model of DDD, administration of repetitive transcranial magnetic stimulation (rTMS) to the ventrolateral prefrontal cortex (VLPFC), but not to the temporoparietal junction (TPJ), increased the capacity for autonomic response in DDD, which was linked with a reduction in subjective DP/DR symptoms (Jay et al., 2014).

***3.4.4 Cognitive processing***

In one study, elevated SCR amplitudes were seen in DDD compared to HCs under negative priming, but not in a neutral condition (Lemche, Sierra-Siegert et al., 2016). Further, positive correlations between cognitive load and autonomic responses were present in the DDD group.

***3.4.5 Interoception/processing of bodily signals***

During completion of an interoceptive accuracy task, Schulz et al. (2015) found no difference in heartbeat evoked potential (HEP) amplitudes during task completion versus at rest in DDD, whereas elevated HEPs during task completion were seen in HCs. Two other studies suggested different patterns of autonomic response and/or the presence of autonomic dysregulation in DDD compared to HCs as measured with HRV and diastolic blood pressure in response to unpleasant images (Owens et al., 2015), and plasma cortisol after oral dexamethasone administration (Simeon et al., 2001). Further, when examining the effects of electrodermal biofeedback on DDD symptomatology, Schoenberg et al. (2012) found that their DDD sample was significantly more labile than HCs, but they exhibited reduced SC levels (relative to baseline) and increased HRV in the real-time condition (in the moment SCL increases moved a videogame character through a maze on screen) compared to the sham (prerecorded SCL sequence moved the videogame character) condition, alongside a reduction in state DP/DR symptoms. Schulz et al. (2016) also reported no difference in startle response magnitudes across the cardiac cycle in DDD, although these differences were present in HCs.

***3.5 Neuroimaging***

Nine studies measured brain activity with neuroimaging in DDD samples (Table 1; Supplementary Table 4). Sample sizes ranged from 9 to 14 (M=9.33, SD=2.06) and included a total of 48 individuals with DDD across all studies. The average age across DDD samples was 34.10 (SD=7.67) and 29.05 (SD=5.88) in controls. For every 1 female there were 2.99 males included on average in the DDD group across the nine studies. Eight studies included HCs only, and one included both.

***3.5.1 Self-face processing***

Ketay et al. (2014) reported elevated activation in in the right ACC, bilateral medial prefrontal cortex, and left middle frontal gyrus in a DDD sample compared to HCs, when viewing faces of themselves versus strangers (Ketay et al., 2014). In this sample, DDD symptoms were positively associated with activation in the left middle frontal gyrus and bilateral medial prefrontal cortex to self versus stranger’s faces (Ketay et al., 2014).

***3.5.2 Responses to facial expressions***

Four studies examined neural responses to facial expressions in DDD. Increasingly intense emotional expressions were associated with reduced sub-cortical limbic activity (hypothalamus, amygdala) (Lemche et al., 2007) and decreased whole brain Blood Oxygen Level Dependent (BOLD) signals (Lemche et al., 2008) in DDD, with HCs exhibiting the opposite pattern of results. In the DDD group, negative correlations between neural and autonomic responses in the right and left and dorsomedial prefrontal cortices were seen (Lemche et al., 2007), and they peaked in haemodynamic response significantly earlier post-stimulus than HCs (Lemche et al., 2008).

 Two later studies explored correlations between BOLD responses to increasingly intense facial expressions and a range of psychological traits. Brain regions associated with group-level differences in alexithymia included left globus pallidus externus, insula, left dorsal anterior cingulate, left paracingulate gyrus, left posterior cingulate and right orbital gyrus (Lemche et al., 2013). Further, as facial expressions became more intense, the DDD sample displayed reduced functional connectivity in the regions discriminating them from HCs. In their later study investigating cerebral correlates of self-reported dissociation, anxiety, depression and somatisation in response to emotional expressions, brain regions discriminating DDD from HCs encompassed the amygdala and left pulvinar nucleus of the thalamus (depression, state anxiety), right temporal operculum and bilateral ventral striatum adjacent to the subgenual cortices (trait somatisation), right supramarginal gyrus and left inferior temporal gyrus (dissociative experiences), and left inferior frontal gyrus, left parahippocampal gyrus, right caput of the caudate nucleus and right superior temporal gyrus (state and trait anxiety) (Lemche, Surguladze et al., 2016).

***3.5.3 Cognitive processing***

During completion of a combined Stroop/negative priming task, DDD and HC groups differed in activation of the left dorsomedial prefrontal cortex (hyper-activated in DDD) and dorsal posterior cingulate cortex (hypo-activated in DDD) (Lemche, Sierra-Siegert et al., 2016).

***3.5.4 Emotional memory***

No significant group differences (DDD versus HC) were seen in neural activation during encoding on an emotional verbal memory task (Medford et al., 2006). During target word recognition, significantly greater activation in bilateral frontal areas, bilateral precuneus, and cerebellum was seen in HCs, whereas during embedded word recognition, significantly greater activation in the cerebellum and primary visual cortex was seen in DDD during both neutral and emotional phases.

***3.5.5 Responses to affective stimuli***

Presentation of aversive images revealed different patterns of neural responsivity in DDD across two studies. Phillips et al. (2001) found their DDD sample displayed elevated activation in the right ventral prefrontal cortex and hypo-activation of the insula when viewing aversive images compared to HCs and individuals with OCD (Phillips et al., 2001). Further, elevated overall neural response, as well as activity in the insula, was only present in DDD when viewing neutral scenes (Phillips et al., 2001). Medford et al. (2016) found aversive images to be associated with hyper-activation of the right dorsolateral prefrontal cortex and bilateral anterior cingulate cortex in DDD compared to HCs, whereas bilateral secondary visual cortex was activated to a greater degree in HCs. After pharmacological treatment, participants whose DDD symptoms had improved displayed elevated activity in the insula (Medford et al., 2016).

**4. Discussion**

This review synthesised experimental psychological and neuroscientific studies of behavioural, subjective and physiological functioning/responsivity in DDD. Reduced subjective responsivity to aversive images or sounds, and inhibited neural responses to emotional images, were seen in some studies. Mixed evidence was found for atypical autonomic responses to affective stimuli, differences in facial expression processing, and emotional memory. In the interpretation of these results, important methodological limitations must be considered.

***4.1 Cognitive processing***

Two studies aligned with the proposed cognitive-behavioural model of DDD (Hunter et al., 2003). One suggested enhanced orientation or responsiveness to unexpected events (Adler et al., 2014), though these results could have been influenced by current medication use, and the other indicated modulation of self-reported DP/DR symptoms by manipulations of attention towards or away from the symptoms (Hunter et al., 2014). Redirecting attention away from symptoms and/or potentially threatening stimuli or events and towards the completion of practical and cognitively challenging tasks may be a useful strategy in the management of DP/DR. Other studies contrastingly found no significant interference of general emotional/negative stimuli on selective attention (Guralnik et al., 2000; Lemche, Sierra-Siegert et al., 2016), but impairments in cognitive flexibility (Lawrence et al., 2012). The small number of experimental studies, three of which were at high risk of bias, assessing cognitive processing in DDD leaves much to be explored, and uncertainty with regards to the role of cognitive functions including attention and mental flexibility in DDD symptomatology.

***4.2 Emotional memory***

Results across three studies (Guralnik et al., 2000; Montagne et al., 2007; Simeon & Knutelska, 2023) suggested intact/enhanced memory for emotional material as well as a reduced ability to disengage attention from emotional material, potentially aligning again with the cognitive-behavioural model of DDD (Hunter et al., 2003). It is important to note that two of three studies (Montagne et al., 2007; Simeon & Knutelska, 2023) were at high risk of bias, weakening the strength of the evidence for a suggested attentional focus on or bias towards emotional material in DDD. In contrast, two other studies reported different results suggesting elevated memory fragmentation (Giesbrecht et al., 2010) which ties in with subjective symptom reports in DDD, no memory enhancement when words were encoded under emotional conditions, and no differences in neural response between neutral and emotional material, results which were not explainable by medication use (Medford et al., 2006). However, both of these studies were at high risk of bias, again making it difficult to draw strong conclusions regarding emotional memory and the processing of emotional material in DDD. The mixed and relatively weak evidence in this area requires further investigation with higher quality studies.

***4.3 Responses to affective stimuli***

Some studies revealed reduced behavioural/subjective (Michal et al., 2013; Sierra et al., 2002; Phillips et al., 2001) and autonomic responsivity (Medford et al., 2016; Sierra et al., 2002) to unpleasant/aversive images or sounds compared to controls, and mixed evidence for reduced responsivity to neutral or pleasant images (Medford et al., 2016; Sierra et al., 2002). In the interpretation of these results, it is important to note that the possible influence of medication use was not tested in two studies (Michal et al., 2013; Phillips et al., 2001), though Michal et al. (2013) suggested that comorbid conditions were unlikely to confound results given the comparable anxiety and depression scores between groups. Although two of these studies were rated as high quality (Phillips et al., 2001; Sierra et al., 2002), the others were at high risk of bias (Medford et al., 2016; Michal et al., 2013), mainly due to a lack of reporting on the selection of and definition of controls and information regarding how study groups were determined. Therefore, although these reduced subjective and autonomic responses suggest that there may be a specific impairment in processing emotional or threatening stimuli, corresponding to symptoms of emotional and physiological numbing in DDD (Sierra et al., 2006), considerations of study quality are important in the interpretation of these results.

In contrast, elevated autonomic responsivity in DDD was present in two other studies, both of which were at high risk of bias (Giesbrecht et al., 2010; Michal et al., 2013), and even though autonomic activity was dampened in response to affective stimuli in one study previously mentioned, a shorter latency of response with the presentation of nonspecific physical stimuli was seen in both individuals with DDD and anxiety (Sierra et al., 2002). These results suggest a possible cognitive and physiological uncoupling in response to emotional stimuli (Michal et al., 2013), and present a role for elevated state/trait anxiety in DDD which may lead to a heightened state of alertness in general (Howard & Ford, 1992; Hunter et al., 2014; Sierra et al., 2002). As proposed by Sierra and Berrios (1998), an excitatory mechanism, possibly driven by anxiety, may lead to heightened responses to general stimuli/alertness in DDD, and an inhibitory mechanism, possibly driven by DDD symptomatology, may lead to diminished or inhibited responses to affective stimuli (Lawrence et al., 2007), but this is not clear cut across all included studies (Sierra et al., 2002, 2006; Hunter et al., 2014).

Aligning with the Sierra and Berrios (1998) model, different patterns of neural responsivity were seen in response to affective images, with DDD samples displaying elevated activity in networks associated with emotional regulation (Medford et al., 2016; Phillips et al., 2001) and no activity in emotional processing circuits when presented with aversive images, though current medication (Phillips et al., 2001) may have influenced these results. Interestingly, after lamotrigine treatment, increased insular activity was linked with reduced symptoms of DDD (Medford et al., 2016). The reduction in DP/DR symptoms linked with elevated activity in the insula highlights the importance of this region for emotional responsivity and bodily processing. Interventions that aim to increase limbic activity and enhance one’s ability to experience emotional and bodily feelings may be of use in the reduction of DP/DR symptoms, including emotional/physiological numbing and anomalous body experiences (Millman, Hunter et al., 2023).

***4.4 Emotion regulation***

Individuals with DDD exhibited a diminished ability to enhance emotion paired with a heightened ability to suppress emotion compared to HCs, a result which remained after controlling for anxiety and depression (Monde et al., 2013), and experimental disinhibition of the VLPFC via rTMS appeared to increase physiological arousal capacity in DDD (Jay et al., 2014), though neither study explored the possible influence of medication use. Further, both studies were at high risk of bias, either due to the lack of comparability between participant groups (Jay et al., 2014) or a lack of reporting on the selection and exposure criteria in HCs. Bearing this in mind, the results of these two studies do support the hypothesis that there may be a specific reduction or impairment in the processing of affective stimuli in DDD, potentially caused by a heightened ability to suppress emotional responses, linked to hyperactivation in the left and right prefrontal cortices, with reciprocal inhibition of limbic and paralimbic areas (Sierra & Berrios, 1998). Further high-quality investigations of emotional regulation in DDD, implementing subjective/behavioural and neuroimaging outcomes, is required to better tease apart the ways in which emotional/aversive material is interpreted and processed in this group.

***4.5 Responses to facial expressions***

Variable results regarding behavioural/subjective and autonomic responsivity to emotional facial expressions were seen across studies, three of four of which were at high risk of bias (Lawrence et al., 2007; Lemche et al., 2008; Montagne et al., 2007; Sierra et al., 2006), with no clear evidence for altered processing in DDD compared to HCs or clinical controls. However, neuroimaging studies revealed differences in neural responsivity to facial expressions (Lemche et al., 2007, 2008, 2013), including quicker processing of facial emotional signals in DDD (Lemche et al., 2008), and group differences in brain regions associated with interoception and emotion regulation (Lemche et al., 2013; Lemche, Surguladze et al., 2016). The emotional blunting/hypoemotionality reported in DDD could again be a result of the suggested aberrant corticolimbic interactions leading to reduced emotional processing alongside excessive emotion regulation, but inconsistencies across studies prevent clear conclusions from being drawn, particularly in relation to the processing of facial expressions (Phillips et al., 2001; Sierra et al., 2006; Sierra & Berrios, 1998). It is also important to note that the four neuroimaging studies assessing responsivity to facial expressions included in this review are drawn from the same DDD sample, were all at high risk of bias, and the possible impact of diagnosed comorbidities and current medication use were not tested. It is imperative that similar paradigms are tested in future studies with both different and larger samples, as the evidence regarding aberrant facial expression processing in DDD is relatively weak.

***4.6 Interoception/processing of bodily signals***

The finding of intact interoceptive accuracy paired with subjective anomalous bodily experiences, and no significant relationship between these measures, suggests the presence of difficulties in bringing together bodily perceptions and physical sensations in DDD, though this study was at high risk of bias (Michal et al., 2014). Although intact accuracy in the detection of bodily signals does not align with models implicating interoceptive silencing (Gatus, Jamieson, & Stevenson, 2022; Gerrans, 2019; Saini et al., 2022), the presence of subjective anomalous bodily experiences emphasises the importance of continuing to explore the mechanisms that may contribute to this. For example, the presence of autonomic dysregulation (Owens et al., 2015; Schoenberg et al., 2012; Simeon et al., 2001) and differing representation of visceral-afferent neural signals, though effects of current medication use or comorbid diagnoses were not tested in this study (Schulz et al., 2016), suggests physiological alterations in the processing of bodily signals in DDD; however, these results require cautious interpretation due to the high-very high risk of bias across included studies. Further experimental research will elucidate how these alterations impact symptoms, and perhaps what causes them in the first place.

***4.7 Self-referential processing***

There was no advantage in self-face recognition in DDD in one study (Liu et al., 2022), aligning with the detachment from the self and/or potential impairment in implicit self-processing seen in this disorder (Ciaunica et al., 2022; Ketay et al., 2014; Sierra & David, 2011). Although behaviourally, another study reported contrasting results in the form of no group differences in self-face processing, elevated activation in brain regions required for conflict detection was seen in the DDD group which may suggest potentially deficient implicit self-processing (Ketay et al., 2014), linking with the split of consciousness proposed by Simeon and Abugel (2006) wherein the individual consciously recognises their own face, but simultaneously does not know the self. Significantly higher implicit self-esteem (Hedrick & Berlin, 2012), seen in DDD, may be a result of a combination of elevated alertness and reduced limbic/emotional activity acting as a protective mechanism in DDD, dampening potential negative self-associations (Hedrick & Berlin, 2012). The relative lack of experimental research, elevated risk of bias in the included studies, and presence of mixed results in the area of self-referential processing suggests this may be an important area to investigate further, particularly given the presence of detachment and separation from the self, reported in DDD.

***Limitations & future directions***

This review had some limitations. Meta-analysis was not conducted due to the diversity of outcome measures and experimental manipulations. Studies were included if they were published (no grey literature) and in English, which may have limited the scope of our searches. Further, initial title and abstract screening was conducted by one author, which could have resulted in the exclusion of relevant studies. There was a lack of high-quality studies in this review, and the influence of potential selection and response biases should be considered. Some studies from the same research groups reported on either overlapping or identical samples of individuals with DDD and HCs, leading to lower generalisability and an increased risk of bias. Psychological comorbidities and medication use were often not controlled for or specified. Particularly in the context of physiological and neuroimaging studies, medications including benzodiazepines, antipsychotics and antiepileptics may have had an impact on the results presented, and future studies should aim to either limit medication use within samples or incorporate medication into their relevant analyses. Further, the heterogeneity seen across some results could be, at least in part, caused by a diagnosis of DDD being applied to individuals with other primary disorders, but whom also experience significant DP/DR symptoms. Although consistent results were found in some studies involving diverse comorbidities and differential medical histories, which can be justified as better representing the population at hand, it becomes unclear how these differing characteristics play a role in the behavioural, subjective, and physiological responsivity seen in DDD. It will be crucial for future studies to better control for comorbid diagnoses, and to ensure that DDD is the primary diagnosis at hand, not secondary symptoms in the context of another psychiatric condition. In general, larger samples, control for relevant confounds, and clear hypotheses based on previous theoretical models are important ways forward. There is a particular lack of research in the areas of self-referential processing, interoception (specifically neuroimaging and behavioural/subjective studies), and a paucity of high-quality studies across multiple samples examining responses to facial expressions, suggesting these may be particularly important areas to investigate further. Being able to unpack the mixed evidence seen within certain domains is a necessary step to further critically evaluate theoretical models of DDD.

**Conclusions**

Experimental research currently suggests that some alterations across behavioural, subjective, and physiological functioning may be present in DDD. The strongest evidence emerged for differences in affective reactivity and regulation, and associated neural circuit alterations, pointing towards reduced emotional processing and excessive emotion regulation and corroborating the neurobiological model of DDD (Sierra & Berrios, 1998). However, this relatively small and inconsistent literature means that it is difficult to draw strong conclusions, there is mixed evidence for theoretical models (Ciaunica, Seth, Limanowski, & Friston, 2022; Gatus, Jamieson, & Stevenson, 2022; Gerrans, 2019; Hunter et al., 2003; Saini et al., 2022), and further studies are required to better understand possible interactions across domains, discrepancies between different types of responsivity, and the mechanisms underlying DP/DR symptoms. Further experimental research will help to inform interventions, whether psychological, pharmacological, or body-oriented, that specifically target core symptoms of DDD, another area in critical need of study (Wang et al., 2023).

**References**

Adler J., Beutel M.E., Knebel A., Berti S., Unterrainer J., & Michal M. (2014). Altered orientation of spatial attention in depersonalization disorder. *Psychiatry Research*, *216*(2), 230–235. <https://doi.org/10.1016/j.psychres.2014.02.021>

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). <https://doi.org/10.1176/appi.books.9780890425596>

Baker, D., Hunter, E., Lawrence, E., Medford, N., Patel, M., Senior, C., Sierra, M., Lambert, M. V., Phillips, M. L., & David, A. S. (2003). Depersonalisation disorder: clinical features of 204 cases. *The British journal of psychiatry: the journal of mental science*, *182*, 428–433.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of child psychology and psychiatry, and allied disciplines*, *42*(2), 241–251.

Campbell, M. C., Smakowski, A., Rojas-Aguiluz, M., Goldstein, L. H., Cardeña, E., Nicholson, T. R., Reinders, A. A., & Pick, S. (2023). Dissociation and its biological and clinical associations in functional neurological disorder: systematic review and meta-analysis. *BJPsych Open*, *9*(1), e2.

Ciaunica, A., Seth, A., Limanowski, J., Hesp, C., & Friston, K. J. (2022). I overthink—therefore I am not: An active inference account of altered sense of self and agency in depersonalisation disorder. *Consciousness and Cognition*, *101*, 103320. <https://doi.org/10.1016/j.concog.2022.103320>

Giesbrecht T., Merckelbach H., van Oorsouw K., & Simeon D. (2010). Skin conductance and memory fragmentation after exposure to an emotional film clip in depersonalization disorder. *Psychiatry Research*, *177*(3), 342–349. <https://doi.org/10.1016/j.psychres.2010.03.010>

Guralnik, O., Schmeidler, J., & Simeon, D. (2000). Feeling unreal: Cognitive processes in depersonalization. *The American Journal of Psychiatry*, *157*(1), 103–109. <https://doi.org/10.1176/ajp.157.1.103>

Hedrick, A. N., & Berlin, H. A. (2012). Implicit self-esteem in borderline personality and depersonalization disorder. *Frontiers in Psychology*, *3*(101550902), 91. <https://doi.org/10.3389/fpsyg.2012.00091>

Heydrich, L., Marillier, G., Evans, N., Seeck, M., & Blanke, O. (2019). Depersonalization- and derealization-like phenomena of epileptic origin. *Ann Clin Transl Neurol*, *6*(9), 1739-1747. <https://doi.org/10.1002/acn3.50870>

Hunter, E. C., Phillips, M. L., Chalder, T., Sierra, M., & David, A. S. (2003). Depersonalisation disorder: a cognitive-behavioural conceptualisation. *Behaviour research and therapy*, *41*(12), 1451–1467. [https://doi.org/10.1016/s0005-7967(03)00066-4](https://doi.org/10.1016/s0005-7967%2803%2900066-4)

Hunter E.C.M., Salkovskis P.M., & David A.S. (2014). Attributions, appraisals and attention for symptoms in depersonalisation disorder. *Behaviour Research and Therapy*, *53*(1), 20–29. <https://doi.org/10.1016/j.brat.2013.11.005>

Hunter, E. C. M., Sierra, M., & David, A. S. (2004). The epidemiology of depersonalisation and derealisation: A systematic review. *Social Psychiatry and Psychiatric Epidemiology: The International Journal for Research in Social and Genetic Epidemiology and Mental Health Services, 39*(1), 9–18. [https://doi.org/10.1007/s00127-004-0701-4](https://psycnet.apa.org/doi/10.1007/s00127-004-0701-4)

Howard, R., & Ford, R. (1992). From the jumping Frenchmen of Maine to posttraumatic stress disorder: The startle response in neuropsychiatry. *Psychological Medicine*, 22(3), 695-707. doi:10.1017/S0033291700038137

Jay E.-L., Sierra M., Van Den Eynde F., Rothwell J.C., & David A.S. (2014). Testing a neurobiological model of depersonalization disorder using repetitive transcranial magnetic stimulation. *Brain Stimulation*, *7*(2), 252–259. <https://doi.org/10.1016/j.brs.2013.12.002>

Ketay S., Hamilton H.K., Haas B.W., & Simeon D. (2014). Face processing in depersonalization: An fMRI study of the unfamiliar self. *Psychiatry Research - Neuroimaging*, *222*(1), 107–110. <https://doi.org/10.1016/j.pscychresns.2014.02.003>

Lawrence E.J., Dumigan R., Schoenberg P., Mauricio S., Murphy D.G., & David A.S. (2012). Conditional reasoning in asperger’s syndrome and depersonalization disorder. *Journal of Nervous and Mental Disease*, *200*(9), 796–800. <https://doi.org/10.1097/NMD.0b013e318266ba2b>

Lawrence E.J., Shaw P., Baker D., Patel M., Sierra-Siegert M., Medford N., & David A.S. (2007). Empathy and enduring depersonalization: The role of self-related processes. *Social Neuroscience*, *2*(3), 292–306. <https://doi.org/10.1080/17470910701391794>

Lemche, E., Anilkumar, A., Giampietro, V. P., Brammer, M. J., et al. World Health Organization, World Medical Association. (2008). Cerebral and autonomic responses to emotional facial expressions in depersonalisation disorder. *The British Journal of Psychiatry*, *193*(3), 222–228. <https://doi.org/10.1192/bjp.bp.107.044263>

Lemche E., Brammer M.J., David A.S., Surguladze S.A., Phillips M.L., Sierra M., Williams S.C.R., & Giampietro V.P. (2013). Interoceptive-reflective regions differentiate alexithymia traits in depersonalization disorder. *Psychiatry Research - Neuroimaging*, *214*(1), 66–72. <https://doi.org/10.1016/j.pscychresns.2013.05.006>

Lemche E., Sierra-Siegert M., David A.S., Phillips M.L., Gasston D., Williams S.C.R., & Giampietro V.P. (2016). Cognitive load and autonomic response patterns under negative priming demand in depersonalization-derealization disorder. *European Journal of Neuroscience*, *43*(7), 971–978. <https://doi.org/10.1111/ejn.13183>

Lemche, E., Surguladze, S. A., Brammer, M. J., Phillips, M. L., Sierra, M., David, A. S., Williams, S. C. R., & Giampietro, V. P. (2016). Dissociable brain correlates for depression, anxiety, dissociation, and somatization in depersonalization-derealization disorder. *CNS Spectrums*, *21*(1), 35–42. <https://doi.org/10.1017/S1092852913000588>

Lemche, E., Surguladze, S. A., Giampietro, V. P., Anilkumar, et al. (2007). Limbic and prefrontal responses to facial emotion expressions in depersonalization. *NeuroReport: For Rapid Communication of Neuroscience Research*, *18*(5), 473–477. <https://doi.org/10.1097/WNR.0b013e328057deb3>

Liu S., Jia Y., Zheng S., Feng S., Zhu H., Wang R., & Jia H. (2022). An Experimental Study of Subliminal Self-Face Processing in Depersonalization-Derealization Disorder. *Brain Sciences*, *12*(12), 1598. <https://doi.org/10.3390/brainsci12121598>

Medford N., Brierley B., Brammer M., Bullmore E.T., David A.S., & Phillips M.L. (2006). Emotional memory in depersonalization disorder: A functional MRI study. *Psychiatry Research - Neuroimaging*, *148*(2), 93–102. <https://doi.org/10.1016/j.pscychresns.2006.05.007>

Medford, N., Sierra, M., Stringaris, A., Giampietro, V., Brammer, M. J., & David, A. S. (2016). Emotional Experience and Awareness of Self: Functional MRI Studies of Depersonalization Disorder. *Frontiers in Psychology*, *7*(101550902), 432. <https://doi.org/10.3389/fpsyg.2016.00432>

Medford N: Emotion and the unreal self: depersonalization disorder and De-affectualization. Emotion Review. 2012, 4 (2): 139-144. 10.1177/1754073911430135.

Medford, N. (2014). Dissociative symptoms and epilepsy. *Epilepsy Behav*, *30*, 10-13. <https://doi.org/10.1016/j.yebeh.2013.09.038>

Michal M., Koechel A., Canterino M., Adler J., Reiner I., Vossel G., Beutel M.E., & Gamer M. (2013). Depersonalization Disorder: Disconnection of Cognitive Evaluation from Autonomic Responses to Emotional Stimuli. *PLoS ONE*, *8*(9), e74331. <https://doi.org/10.1371/journal.pone.0074331>

Michal M., Reuchlein B., Adler J., Reiner I., Beutel M.E., Vogele C., Schachinger H., & Schulz A. (2014). Striking discrepancy of anomalous body experiences with normal interoceptive accuracy in depersonalization-derealization disorder. *PLoS ONE*, *9*(2), e89823. <https://doi.org/10.1371/journal.pone.0089823>

Millman, L. S., Hunter, E. C., Orgs, G., David, A. S., & Terhune, D. B. (2021). Symptom variability in depersonalization–derealization disorder: A latent profile analysis. *Journal of Clinical Psychology*, *78*(4), 637–655. <https://doi.org/10.1002/jclp.23241>

Millman, L. S. M., Hunter, E. C. M., Terhune, D. B., & Orgs, G. (2023). Online structured dance/movement therapy reduces bodily detachment in depersonalization-derealization disorder. *Complementary Therapies in Clinical Practice*, *51*, 101749. <https://doi.org/10.1016/j.ctcp.2023.101749>

Monde K.-M., Ketay S., Giesbrecht T., Braun A., & Simeon D. (2013). Preliminary physiological evidence for impaired emotion regulation in depersonalization disorder. *Psychiatry Research*, *209*(2), 235–238. <https://doi.org/10.1016/j.psychres.2013.02.020>

Montagne B., Sierra M., Medford N., Hunter E., Baker D., Kessels R.P.C., De Haan E.H.F., & David A.S. (2007). Emotional memory and perception of emotional faces in patients suffering from depersonalization disorder. *British Journal of Psychology*, *98*(3), 517–527. <https://doi.org/10.1348/000712606X160669>

Murphy R. J. (2023). Depersonalization/Derealization Disorder and Neural Correlates of Trauma-related Pathology: A Critical Review. *Innovations in clinical neuroscience*, *20*(1-3), 53–59.

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic reviews*, *5*(1), 210. <https://doi.org/10.1186/s13643-016-0384-4>

Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive

regulation of emotion. J Cogn Neurosci 2002; 14:1215–1229.

Owens A.P., David A.S., Low D.A., Mathias C.J., & Sierra-Siegert M. (2015). Abnormal cardiovascular sympathetic and parasympathetic responses to physical and emotional stimuli in depersonalization disorder. *Frontiers in Neuroscience*, *9*, 089. <https://doi.org/10.3389/fnins.2015.00089>

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME.

Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol Psychiatry 2005; 57:210–219.

Phillips M.L., Medford N., Senior C., Bullmore E.T., Suckling J., Brammer M.J., Andrew C., Sierra M., Williams S.C.R., & David A.S. (2001). Depersonalization disorder: Thinking without feeling. *Psychiatry Research - Neuroimaging*, *108*(3), 145–160. <https://doi.org/10.1016/S0925-4927%2801%2900119-6>

Salami, A., Andreu-Perez, J., Gillmeister, H. (2020). Symptoms of depersonalisation/derealisation disorder as measured by brain electrical activity: A systematic review. *Neuroscience & Biobehavioral Reviews*, 118, 524-537. <https://doi.org/10.1016/j.neubiorev.2020.08.011>.

Schandry, R. (1981). Heart Beat Perception and Emotional Experience. *Psychophysiology*, *18*(4), 483-488. [https://doi.org/https://doi.org/10.1111/j.1469-8986.1981.tb02486.x](https://doi.org/https%3A/doi.org/10.1111/j.1469-8986.1981.tb02486.x)

Schoenberg P.L.A., Sierra M., & David A.S. (2012). Psychophysiological Investigations in Depersonalization Disorder and Effects of Electrodermal Biofeedback. *Journal of Trauma and Dissociation*, *13*(3), 311–329. <https://doi.org/10.1080/15299732.2011.606742>

Schulz, A., & Vögele, C. (2015). Interoception and stress. *Frontiers in psychology*, *6*, 993. <https://doi.org/10.3389/fpsyg.2015.00993>

Schulz A., Koster S., Beutel M.E., Schachinger H., Vogele C., Rost S., Rauh M., & Michal M. (2015). Altered patterns of heartbeat-evoked potentials in depersonalization/derealization disorder: Neurophysiological evidence for impaired cortical representation of bodily signals. *Psychosomatic Medicine*, *77*(5), 506–516. <https://doi.org/10.1097/PSY.0000000000000195>

Schulz A., Matthey J.H., Vogele C., Schaan V., Schachinger H., Adler J., Beutel M.E., & Michal M. (2016). Cardiac modulation of startle is altered in depersonalization-/derealization disorder: Evidence for impaired brainstem representation of baro-afferent neural traffic. *Psychiatry Research*, *240*, 4–10. <https://doi.org/10.1016/j.psychres.2016.03.051>

Sedeño, L., Couto, B., Melloni, M., Canales-Johnson, A., Yoris, A., Baez, S., Esteves, S., Velásquez, M., Barttfeld, P., Sigman, M., Kichic, R., Chialvo, D., Manes, F., Bekinschtein, T. A., & Ibanez, A. (2014). How do you feel when you can't feel your body? Interoception, functional connectivity and emotional processing in depersonalization-derealization disorder. *PloS one*, *9*(6), e98769. <https://doi.org/10.1371/journal.pone.0098769>

Seth, A. K. (2013). Interoceptive inference, emotion, and the embodied self. *Trends in Cognitive Sciences*, *17*(11), 565–573. <https://doi.org/10.1016/j.tics.2013.09.007>

Sierra, M., & Berrios, G. E. (1998). Depersonalization: neurobiological perspectives. *Biological psychiatry*, *44*(9), 898–908. [https://doi.org/10.1016/s0006-3223(98)00015-8](https://doi.org/10.1016/s0006-3223%2898%2900015-8)

Sierra, M., & David, A. S. (2011a). Depersonalization: A selective impairment of self-awareness. *Consciousness and Cognition*, *20*(1), 99–108. <https://doi.org/10.1016/j.concog.2010.10.018>

Sierra M., Senior C., Dalton J., McDonough M., Bond A., Phillips M.L., O’Dwyer A.M., & David A.S. (2002). Autonomic response in depersonalization disorder. *Archives of General Psychiatry*, *59*(9), 833–838. <https://doi.org/10.1001/archpsyc.59.9.833>

Sierra M., Senior C., Phillips M.L., & David A.S. (2006). Autonomic response in the perception of disgust and happiness in depersonalization disorder. *Psychiatry Research*, *145*(2), 225–231. <https://doi.org/10.1016/j.psychres.2005.05.022>

Simeon D., Guralnik O., Knutelska M., Hollander E., & Schmeidler J. (2001). Hypothalamic-pituitary-adrenal axis dysregulation in depersonalization disorder. *Neuropsychopharmacology*, *25*(5), 793–795. <https://doi.org/10.1016/S0893-133X%2801%2900288-3>

Simeon D. & Knutelska M. (2023). Depersonalization Disorder: Directed Forgetting as a Function of Emotionality. *Journal of Trauma and Dissociation*, *24*(2), 241–251. <https://doi.org/10.1080/15299732.2022.2136328>

Wang, S., Zheng, S., Zhang, X., Ma, R., Feng, S., Song, M., Zhu, H., & Jia, H. (2023). The treatment of depersonalization-derealization disorder: A systematic review. *Journal of Trauma &amp; Dissociation*, 1–24. <https://doi.org/10.1080/15299732.2023.2231920>

Wells, G. A., Shea, B., O’Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. <https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp>

World Health Organization (2019). International Statistical Classification of Diseases and Related Health Problems (11th ed.). <https://icd.who.int/>

Yang, J., Millman, L.S.M., David, A.S., & Hunter, E.C.M. (2022) The Prevalence of Depersonalization-Derealization Disorder: A Systematic Review. *Journal of Trauma & Dissociation*, <https://doi.org/10.1080/15299732.2022.2079796>



Notes. DDD = depersonalisation-derealisation disorder; fMRI = functional magnetic resonance imaging.

**Figure 2.** Study characteristics: outcome measures, year, sample size.

| **Table 1.** Overview of included studies and key results by domain.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Article** | **Experimental Task** | **Control** | **Outcome measure**  | **Significance** |
| **BEHAVIOURAL/SUBJECTIVE OUTCOMES (N=18)** |
| ***COGNITIVE PROCESSING*** |
| Adler et al., 2014Germany | Spatial Cueing Paradigm | HC | Total attention directing effect | ß |
| Guralnik et al., 2000USA | Emotional Stroop Task | HC | Interference effect | X |
| Hunter et al., 2014UK | Dot Staring, Paired Associates, Mental Arithmetic, Dichotic Listening | HC, AD | Dot staring (DDD symptoms pre-post) | X |
|  |  |  | Paired associates, Mental Arithmetic, Dichotic Listening (DDD symptoms pre-post) | à |
| Lemche, Sierra-Siegert et al., 2016UK | Stroop/Negative Priming Task | HC  | Interference effect  | X |
|  |  |  | Reaction time (negative) | à |
|  |  |  | Correct responses (negative) | ß |
| Lawrence et al., 2012UK | Conditional Reasoning Task | HC, AS | Simple: neutral–valid suppression with additional statement added | ß |
|  |  |  | Alternative: neutral–fallacies  | ß\* |
|  |  |  | All conditions: emotional–fallacies  | X |
| ***EMOTIONAL MEMORY***  |
| Giesbrecht et al., 2010USA | Emotionally provocative movie clip | HC | Objective and subjective memory fragmentation | à |
|  |  |  | Free recall | X |
| Guralnik et al., 2000USA | Emotional Stroop Task with Incidental Learning | HC | Recall of depersonalisation-related/emotional words | à |
|  |  |  | Recall of neutral, negative, positive words | X |
| Medford et al., 2006UK | Emotional verbal memory task  | HC | All words (emotional vs neutral)  | X\* |
|  |  |  | Target words (emotional vs neutral)+  | à\* |
|  |  |  | Embedded words (emotional vs neutral)  | X\* |
| Montagne et al., 2007 | Emotional Memory Task | HC | Emotional memory task  | X |
| Simeon & Knutelska, 2023UK | Directed Forgetting Task | HC  | Directed forgetting effect (neutral, positive) | X |
|  |  |  | Directed forgetting effect (negative) | ß |
| ***RESPONSES TO FACIAL EXPRESSIONS*** |
| Lawrence et al., 2007UK | Reading the Mind in the Eyes task | HC | Reading the Mind in the Eyes | X |
| Montagne et al., 2007UK | Emotion Recognition Task | HC | Emotion Recognition Task (sensitivity) | ß |
| Sierra et al., 2006UK | Facial expressions (happiness and disgust) | HC, GAD | Intensity of expression ratings (disgust) | ß |
|  |  |  | Intensity of expression ratings (happiness)  | X |
|  |  |  | Emotion recognition (happiness, disgust) | X |
| ***RESPONSES TO AFFECTIVE STIMULI*** |
| Michal et al., 2013Germany  | Emotional auditory stimuli from International Affective Digitized Sounds (IADS) | PC | Negative sounds (valence) | à |
|  |  |  | Positive sounds (valence) | X |
| Phillips et al., 2001UK | Emotionally salient stimuli (aversive, neutral) from the IAPS | HC, OCD | Intensity of emotional response (disgust, fear, anxiety ratings) | X\* |
| Sierra et al., 2002UK | Visual stimuli from the IAPS | HC, AD | Valence (unpleasant, pleasant, neutral) | X |
|  |  |  | Arousal (pleasant, neutral) | X |
|  |  |  | Arousal (unpleasant)  | ß |
| ***SELF-REFERENTIAL PROCESSING***  |
| Hedrick & Berlin, 2012USA | Implicit Association Task  | HC, BPD | Implicit self-esteem | à |
| Ketay et al., 2014USA | Viewing self and unfamiliar faces | HC | Reaction time, response accuracy  | X |
| Liu et al., 2022China | Facial stimuli and dynamic noise images using Continuous Flash Suppression paradigm | HC | Experimental condition: reaction time (self, famous, stranger’s faces) | X\* |
|  |  |  | Control condition: reaction time (self, famous) | à\* |
| ***INTEROCEPTION*** |
| Michal et al., 2014Germany | Schandry heartbeat counting task, Whitehead heartbeat discrimination task | HC | Interoceptive accuracy | X |
| **PHYSIOLOGICAL OUTCOMES (N=15)** |
| ***RESPONSES TO AFFECTIVE STIMULI***  |
| Giesbrecht et al., 2010 | Emotionally provocative movie clip | HC | SC mean rise time to peak | à  |
|  |  |  | SC mean maximum response amplitude | X |
| Lawrence et al., 2007 | Counting task under emotive diary extracts | HC | Speech rate during sad vignette | à  |
| Medford et al., 2016 | Responses to emotive visual stimuli  | HC | SCR: aversive/unpleasant and neutral images | ß  |
|  |  |  | First 30s neutral vs emotional block fluctuations | X |
|  |  |  | First 30s amplitude, SC level: emotional and neutral block | ß |
|  |  |  | Whole epoch amplitude | ß  |
| Michal et al., 2013  | Emotional auditory stimuli from IADS | PC | SCR amplitudes: negative sounds, highly arousing sounds, neutral sounds | à  |
| Sierra et al., 2002UK | Visual stimuli from the IAPS | HC, AD | SCR amplitude and probability of SCR: unpleasant images | ß |
|  |  |  | SCR amplitude and probability of SCR: pleasant, neutral, physical | X |
|  |  |  | Latency of SCR: nonspecific physical stimuli  | ß |
|  |  |  | Latency of SCR: unpleasant images | à |
| ***RESPONSES TO FACIAL EXPRESSIONS*** |
| Sierra et al., 2006 | Facial expressions of happiness and disgust  | HC, GAD | SCR amplitude: happiness, disgust | X^ |
| Lemche et al., 2008  | Facial stimuli varying in emotional intensity | HC | SC variability: neutral (happy, sad), 50% intensity (happy, sad), 100% intensity (happy) | à  |
| ***EMOTION REGULATION***  |
| Jay et al., 2014 | Right-sided repetitive rTMS  | HC | rTMS to ventrolateral prefrontal cortex: maximum capacity for SCR | à |
|  |  |  | Spontaneous fluctuations in SC: post-TMS | X\* |
| Monde et al., 2013  | Emotion Regulation Task with images from the IAPS | HC | HR: ability to enhance emotion (all valences) | ß  |
|  |  |  | HR: ability to suppress emotion (all valences) | à  |
| ***COGNITIVE PROCESSING*** |
| Lemche, Sierra-Siegert et al., 2016  | Stroop/Negative Priming Task | HC | SCR amplitude: negative condition | à  |
|  |  |  | SCR amplitude: neutral condition | X |
| ***INTEROCEPTION/PROCESSING OF BODILY SIGNALS***  |
| Owens et al., 2015  | Head up Tilt with Anticipated Unpleasant Images, Head up Tilt with Mixed Valence Images | HC | High frequency heart rate variability: simultaneous Head Up Tilt and anticipated unpleasant images | ß |
|  |  |  | Diastolic blood pressure: orienting responses to unpleasant images | à |
| Schoenberg et al., 2012  | Electrodermal biofeedback | HC | Real-time: SC levels  | ß\* |
|  |  |  | Real-time: high and low frequency HRV | à\* |
|  |  |  | Sham: SC levels, high and low frequency HRV | X\* |
|  |  |  | Real-time: SC lability (peaks per minute) | à |
| Schulz et al., 2015  | Schandry heartbeat counting task | HC | Heartbeat evoked potentials: amplitude (task completion vs rest) | X\* |
|  |  |  | Heart rate, low frequency HRV, low/high frequency HRV ratio (task completion, rest) | X |
| Schulz et al., 2016  | Cardiac Modulation of Startle | HC | Average startle response magnitude | X |
|  |  |  | Cardiac cycle phase: differences in HCs, not in DDD – no difference in startle response magnitudes  | X\* |
| Simeon et al., 2001  | Administration of oral dexamethasone | HC | Drop in plasma cortisol post-oral dexamethasone | ß |
| **NEUROIMAGING OUTCOMES (N=9)** |
| ***SELF-REFERENTIAL PROCESSING*** |
| Ketay et al. 2014  | Viewing self and unfamiliar faces | HC | Viewing self-faces: right ACC, bilateral medial prefrontal cortex, left middle frontal gyrus activation | à |
| ***RESPONSES TO FACIAL EXPRESSIONS*** |
| Lemche et al., 2007 | Facial stimuli varying in emotional intensity | HC | Increasingly intense emotional expressions: sub-cortical limbic activity (hypothalamus, amygdala)  | ß |
| Lemche et al., 2008 | Facial stimuli varying in emotional intensity | HC | Increasingly intense emotional expressions: BOLD signal  | ß |
|  |  |  | Earlier peak in haemodynamic response post-stimulus | à |
| Lemche et al., 2013  | Facial stimuli varying in emotional intensity: cerebral correlates of alexithymia  | HC | Regression slopes, happy expressions: left globus pallidus externus, insula, left dorsal anterior cingulate, left paracingulate gyrus | à |
|  |  |  | Regression slopes, sad expressions: left dorsal ACC, insula, left posterior cingulate, right orbital gyrus | à |
|  |  |  | Increasingly intense expressions: functional connectivity within discriminatory regions | ß |
| Lemche, Surguladze et al., 2016  | Facial stimuli varying in emotional intensity: cerebral correlates of somatization, dissociation, depression, anxiety  | HC | Regression slopes, happy expressions: right temporal operculum, right supramarginal gyrus, left pulvinar nucleus of the thalamus, left interior frontal gyrus, right caput of the caudate nucleus  | à |
|  |  |  | Regression slopes, sad expressions: bilateral ventral striatum, left inferior temporal gyrus, amygdala, left parahippocampal gyrus, right superior temporal gyrus | à |
| ***COGNITIVE PROCESSING*** |
| Lemche, Sierra-Siegert et al., 2016  | Stroop/Negative Priming Task | HC | Left dorsomedial prefrontal cortex activation  | à |
|  |  |  | Dorsal posterior cingulate cortex activation | ß |
| ***EMOTIONAL MEMORY***  |
| Medford et al., 2006  | Emotional verbal memory task | HC | Activated brain regions: encoding\*\* | X |
|  |  |  | Activated brain regions, target word recognition: bilateral frontal areas, bilateral precuneus, cerebellum activation | ß |
|  |  |  | Activated brain regions, embedded word recognition: cerebellum, primary visual cortex  | à |
| ***RESPONSES TO AFFECTIVE STIMULI*** |
| Medford et al., 2016  | Responses to emotive visual stimuli  | HC | Right dorsolateral prefrontal cortex and bilateral ACC activation (aversive images) | à |
|  |  |  | Bilateral secondary visual cortex (aversive images) | ß |
| Phillips et al., 2001  | Emotionally salient stimuli (aversive, neutral) from the IAPS | HC, OCD | Right ventral prefrontal cortex activation (aversive images) | à |
|  |  |  | Insula activation (aversive images) | ß |

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*Notes.* ACC = anterior cingulate cortex; HC = healthy controls; AD = anxiety disorders; AS = Asperger’s syndrome; BPD = Borderline Personality Disorder; OCD = Obsessive Compulsive Disorder; PC = patient controls; IAPS = International Affective Picture System; SCR = skin conductance response; SC = skin conductance; rTMS = transcranial magnetic stimulation; BOLD = bloody oxygen level dependent; HRV = heart rate variability; HR = heart rate.

+ better recognition of emotional vs neutral words in DDD

^ no significant difference between DDD and HC, significant difference between DDD and AD

\*\* DDD displayed no activation in emotional processing areas