RESEARCH ARTICLE

A Randomised Controlled Comparison of Second-Level Treatment Approaches for Treatment-Resistant Adults with Bulimia Nervosa and Binge Eating Disorder: Assessing the Benefits of Virtual Reality Cue Exposure Therapy

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Abstract

A question that arises from the literature on therapy is whether second-level treatment is effective for patients with recurrent binge eating who fail first-level treatment. It has been shown that subjects who do not stop binge eating after an initial structured cognitive-behavioural treatment (CBT) programme benefit from additional CBT (A-CBT) sessions; however, it has been suggested that these resistant patients would benefit even more from cue exposure therapy (CET) targeting features associated with poor response (e.g. urge to binge in response to a cue and anxiety experienced in the presence of binge-related cues). We assessed the effectiveness of virtual reality-CET as a second-level treatment strategy for 64 patients with bulimia nervosa and binge eating disorder who had been treated with limited results after using a structured CBT programme, in comparison with A-CBT. The significant differences observed between the two groups at post-treatment in dimensional (behavioural and attitudinal features, anxiety, food craving) and categorical (abstinence rates) outcomes highlighted the superiority of virtual reality-CET over A-CBT. Copyright © 2017 John Wiley & Sons, Ltd and Eating Disorders Association.

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INTRODUCTION

The combined lifetime prevalence of bulimia nervosa (BN) and binge eating disorder (BED) in the general population is around 5% in women and 2.5% in men (Hudson, Hiripi, Pope, & Kessler, 2007). Both disorders are characterised by recurrent binge eating (i.e. eating unusually large quantities of food accompanied by subjective feelings of loss of control) which, in the case of BN, is also associated with regular compensatory behaviours (e.g. self-induced vomiting) aimed at counteracting the caloric intake and weight gain from binge eating (Al-Adawi et al., 2013; American

Psychiatric Association, 2013; Dakanalis, Carrà, Clerici, & Riva, 2015). Successful treatment of BN and BED is critical because of their association with psychosocial impairment, medical complications and high mortality rates (Crow & Peterson, 2003; Mehler, 2011; Mitchell, 2016; Suokas et al., 2013).

Although cognitive-behavioural therapy (CBT) is regarded as the treatment of choice for both BN and BED (Wilson, Grilo, & Vitousek, 2007) and was given the highest rating in the National Institute for Clinical Excellence (2004) review of evidence-based treatments, a substantial number of patients with BN and BED fail to respond by the end of the treatment, and the effects tend to wane

in the long term (Amianto, Ottone, Abbate Daga, & Fassino, 2015; Berkman, Lohr, & Bulik, 2007; Dakanalis et al., 2016; Dakanalis & Clerici, in press; Dakanalis, Colmegna, Riva et al., 2017; Lampard & Sharbanee, 2015; Linardon, de la Piedad Garcia, & Brennan, 2017; Wilson, Wilfley, Agras, & Bryson, 2010).

The research question that arises from this evidence is whether second-level treatment would be effective for those who fail the first level, that is, CBT (Nazar et al., 2017; Wilson et al., 2007). The few studies that have attempted to respond to this question (Halmi, 2013) have revealed that patients with BN and BED unsuccessfully treated with CBT did not benefit from additional interpersonal psychotherapy (Agras et al., 1995; Mitchell et al., 2002). Although there is some evidence that subjects who do not stop binge eating after an initial structured programme of CBT benefit from additional CBT sessions focusing on the specific problem areas identified at the end of the initial programme (Eldredge et al., 1997), it has been suggested that patients who are resistant to CBT would benefit even more from (second level) interventions targeting specific features associated with poor response (Agüera et al., 2013; Dakanalis et al., 2016; Dakanalis, Colmegna, Riva et al., 2017; Halmi, 2013) such as emotional dysregulation (Fagundo et al., 2013; Juarascio et al., 2017) and the urge to binge in response to a cue. For example, acceptance and mindfulness-based techniques have been incorporated to CBT to target not only patients' difficulty coping with negative affect and binge eating symptoms (Juarascio et al., 2017; Leahey, Crowther, & Irwin, 2008) but also emotional regulation strategies based on video games (Fernandez-Aranda et al., 2015) and brain therapies (namely repetitive transcranial magnetic stimulation) (Sutoh et al., 2016). As explained in the succeeding texts, the exposure with response prevention of bingeing, also known as cue exposure therapy (CET), is another type of intervention aiming at reducing and/or extinguishing anxiety and food craving responses to binge-related cues (Gutiérrez-Maldonado, Ferrer-Garcia, & Riva, 2013; Koskina, Campbell, & Schmidt, 2013).

CET is based on the classical conditioning model of binge eating. Jansen (1998), for example, conceptualises the intake of food as the unconditioned stimulus and its metabolic effects as unconditioned responses. Cues that reliably signal food intake, such as the sight, smell and taste, or even the context in which one eats, may act as a conditioned stimulus (CS) that triggers cue reactivity. According to this model, the presence of CSs (cues) elicits physiological responses that are experienced as craving (i.e. an almost irresistible urge to eat), which can increase the probability of binge episodes (Boswell & Kober, 2016; García-García et al., 2013; Lyu, Zheng, & Jackson, 2016; Wolz et al., 2017). The main objective of CET is to extinguish craving by breaking the bond between the CSs and the binge response (Brockmeyer, Hahn, Reetz, Schmidt, & Friederich, 2015; Yela-Bernabé, Gómez-Martínez, Cortés-Rodríguez, & Salgado-Ruiz, 2013). With this aim in mind, patients are exposed to the cues associated with binge eating (the sight, smell, touch and handling of food), while bingeing is prevented. Thus, participants learn that food-related cues are not necessarily associated with eating behaviour. It has been argued, however, that the presence of these cues also elicits a state of anticipatory anxiety that precedes eating binges (Martínez-Mallén et al., 2007; Yela-Bernabé et al., 2013). Indeed, research revealed that anxiety and food craving of patients with BN and BED

are experienced simultaneously in the presence of binge-related cues (Pla-Sanjuanelo et al., 2015). Following the extinction explanation, Bulik and colleagues (1998) suggested that exposing an individual to these cues and preventing bingeing would extinguish anxiety and food craving. Accordingly, case studies (Jansen, Van Den Hout, De Loof, Zandbergen, & Griez, 1989; Kennedy, Katz, Neitzert, Ralevsky, & Mendlowitz, 1995; Martínez-Mallén et al., 2007; Schmidt & Marks, 1989; Toro et al., 2003) and non-randomised (Jansen, Broekmate, & Heymans, 1992; Schmidt & Marks, 1989) and randomised (Bulik, Sullivan, Carter, McIntosh, & Joyce, 1998; Cooper & Steere, 1995) controlled studies conducted between 1989 and 2007 revealed that in vivo CET is effective in reducing food craving and anxiety and also yields positive results in terms of reducing episodes of binge eating and associated purging behaviours. Moreover, some of these studies also showed promising results in patients who did not improve with CBT and/or pharmacological treatments (Martínez-Mallén et al., 2007; Toro et al., 2003), suggesting that in vivo CET may be of use as a second level of treatment in these situations (Koskina et al., 2013).

It is worth noting, however, that in vivo CET also presents considerable logistical difficulties, a fact that may explain the decline in research in this type of intervention after the initial surge of studies (mentioned in the preceding texts) of its use for BN and BED (Ferrer-Garcia, Gutierrez-Maldonado, Treasure, & Vilalta-Abella, 2015; Gutiérrez-Maldonado, Wiederhold, & Riva, 2016; Gutiérrez-Maldonado et al., 2013; Koskina et al., 2013). For instance, the in vivo CET requires patients to bring sufficient quantities of binge foods to the therapy sessions. Another limitation is related to the ecological validity of the in vivo CET; as it is performed in the therapist's office, the setting does not include the contextual cues (refer in the succeeding texts) that may be relevant to the reduction and/or extinction of craving/anxiety responses to everyday situations (Gutiérrez-Maldonado, Wiederhold et al., 2016). Shiban, Pauli, and Mühlberger (2013) found that exposure therapy for specific phobias was more efficient if delivered in different virtual reality environments and recommend the application of multiple contexts during exposure treatments in order to reduce the likelihood of renewal. As virtual reality (VR) places the exposure in the context of virtual environments that simulate natural situations, it may represent a valid way of overcoming these drawbacks and a good medium for the implementation of CET in treatment of eating disorders (EDs) characterised by binge eating (Gutiérrez-Maldonado, Wiederhold et al., 2016; Koskina et al., 2013; Pla-Sanjuanelo et al., 2015). Moreover, VR exposure provides high internal validity as it allows the therapist to control the parameters of the exposure, thereby facilitating the adaptation of the intervention process to a specific patient's needs at each stage of treatment (Gutiérrez-Maldonado, Wiederhold et al., 2016; Serino et al., 2016).

Previous research provides evidence of the ability of food-related VR-based environments to elicit anxiety and craving responses similar to those expected in real-life situations in both healthy and clinical (i.e. patient with BN and BED) groups. The food craving and anxiety experienced in VR environments are associated with trait and state food craving and anxiety assessed outside VR environments (Agliaro-López, Ferrer-Garcia, Pla-Sanjuanelo, & Gutiérrez-Maldonado, 2014; Ferrer-Garcia, Gutiérrez-Maldonado, Caqueo-Urízar, & Moreno, 2009; Ferrer-Garcia, Gutiérrez-Maldonado, & Pla-Sanjuanelo,

2013; Ferrer-Garcia et al., 2014; Ferrer-Garcia et al., 2015; Gorini, Griez, Petrova, & Riva, 2010; Perpiñá et al., 2013). There is even evidence that exposure to VR environments incorporating both specific stimuli (e.g. high calorie food) and contextual cues (e.g. kitchen) significantly reduces food craving and anxiety (Gutiérrez-Maldonado, Pla-Sanjuanelo, & Ferrer-Garcia, 2016; Pla-Sanjuanelo et al., 2016; Perpiñá et al., 2013). Furthermore, six sessions of CET based on VR technology (VR-CET) were sufficient to extinguish episodes of binge eating (but also associated purging behaviours) in a patient with BN who initially failed to successfully respond to the first level of treatment, that is, CBT (Pla-Sanjuanelo et al., 2016). Given that binge eating is a core behavioural feature of both BN and BED, treatments that have beneficial effects on BN should also benefit patients with BED (Dakanalis, Carrà, Calogero et al., 2015; Dakanalis, Carrà, Timko et al., 2015; Dakanalis, Favagrossa et al., 2015; Fairburn et al., 2009; Perpiñá et al., 2013); however, larger studies, including controlled studies, evaluating the efficacy of VR-CET as a second-level treatment strategy are now required (Gutiérrez-Maldonado, Pla-Sanjuanelo et al., 2016).

Given also the recent increase interest in the treatment of ED psychopathology whatever the DSM-5 diagnosis (the transdiagnostic approach; refer to Fairburn et al., 2015; Fairburn et al., 2009), we undertook a randomised controlled trial to examine the effectiveness of six VR-CET sessions as a second-level treatment strategy for patients with ED characterised by recurrent binge eating (i.e. with BN or BED) who were initially treated unsuccessfully with a structured CBT programme, compared with six additional CBT sessions (A-CBT). The A-CBT treatment modality was selected in view of reports that subjects who did not stop binge eating after an initial structured programme of CBT benefited from A-CBT sessions (Eldredge et al., 1997), making it a potentially more rigorous condition for comparison (Gutiérrez-Maldonado, Pla-Sanjuanelo et al., 2016). Outcome measurement was based on behavioural and attitudinal features of EDs, in addition to state and trait anxiety and food craving (refer to the "Measures" section).

METHODS

Design

A randomised, parallel-group study was conducted at five well-established ED centres (clinical sites) in three European cities (Barcelona and Tarragona, Spain and Milan, Italy) in which patients with BED and BN who showed active behavioural symptoms at the end of the first level of treatment with the structured programme of CBT were randomised to one of the two second-level treatment conditions, that is, VR-CET or A-CBT sessions (refer to the "Participants and procedure" section). The clinical sites involved in the protocol were Hospital de Bellvitge, Adult Mental Health Centre of the Consorcio Sanitario de la Anoia, Centro ABB, Hospital Universitari Joan XXIII and Istituto Auxologico Italiano. All subjects were assessed in the pre-randomisation phase (i.e. at the end of treatment with the structured programme of CBT) and at the end of the second-level treatment conditions. Recruitment and the entire course of treatment (first and second level) were carried out between February

2015 and March 2016. Written informed consent was obtained from all participants after the procedures had been fully explained. The study protocol was approved by the ethics review board of each local institution (clinical site) and of the trial data centre, and the trial was registered at clinicaltrials.gov (identifier: NCT02237300, https://clinicaltrials.gov).

Participants and procedure

Participants were drawn from a sample of 65 adults of both sexes meeting DSM-5 (American Psychiatric Association, 2013) diagnosis of BN ($M_{\text{age-of-BN-onset}} = 18.06$, $SD = 0.77$) or BED ($M_{\text{age-of-BED-onset}} = 24.55$, $SD = 1.82$) and no current comorbid severe mental disorders (substance use disorders, bipolar disorder, psychosis) who had been proposed for participation in the study by their referral therapist after an initially unsuccessful first-level treatment (CBT structured intervention) at the clinical sites involved; as in prior research (Dakanalis et al., 2016; Dakanalis, Colmegna, Riva et al., 2017; Fairburn et al., 2009), a constant dose of antidepressant medication (for a minimum of 6 weeks) was not exclusionary. The presence of ED diagnosis (according to the diagnostic items of the ED Examination Interview 12.0D) (Fairburn & Cooper, 1993), rated for DSM-5 stipulations (Dakanalis et al., 2016; Dakanalis, Carrà, Calogero et al., 2015; Dakanalis, Colmegna, Riva et al., 2017), and the absence of comorbid severe mental disorders (according to the Structured Clinical Interview for DSM-5; First, Spitzer, Gibbon, & Williams, 1996) were judged by experienced assessors available at all sites ($\kappa s = 1.0$) and not involved in treatment delivery. CBT, the only psychological intervention that patients received at the clinical site to which they were originally referred, was administered in weekly individual 60-min sessions by clinical psychologists (with experience in treating EDs) available at all sites following a published manualised protocol (Fairburn, Marcus, & Wilson, 1993). At the end of the first-level treatment with the structured programme of CBT for BED and BN (pre-randomisation), which matched the one described in earlier studies (refer to Grilo, Masheb, & Wilson, 2005; Treasure et al., 1994 for details), all patients were assessed relative to their status (refer to the "Measures" section).[1] Those with active episodes of binge eating (and purging, in the case of BN) during the last 2 weeks of the structured programme of CBT and who agreed to participate in the study were eligible for randomisation to one of the two second-level treatment conditions (i.e. A-CBT or VR-CET sessions). Sixty-four participants met these criteria (Figure 1). Randomisation was performed using biased coin randomisation developed by Efron (1971) to ensure approximately equal representation of participants in both treatment conditions at each site (Mitchell et al., 2002, 2011). The treatment assignment was determined after completing the pre-randomisation assessment and after enrolment on the study; until then, neither the clinical psychologists nor participants knew the treatment assignment. The time lag

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[1]The results of this initial treatment period with the structured programme of CBT are not detailed in the current manuscript, which focuses on the comparison of the effects of the second-level treatment modalities (VR-CET vs. A-CBT sessions).
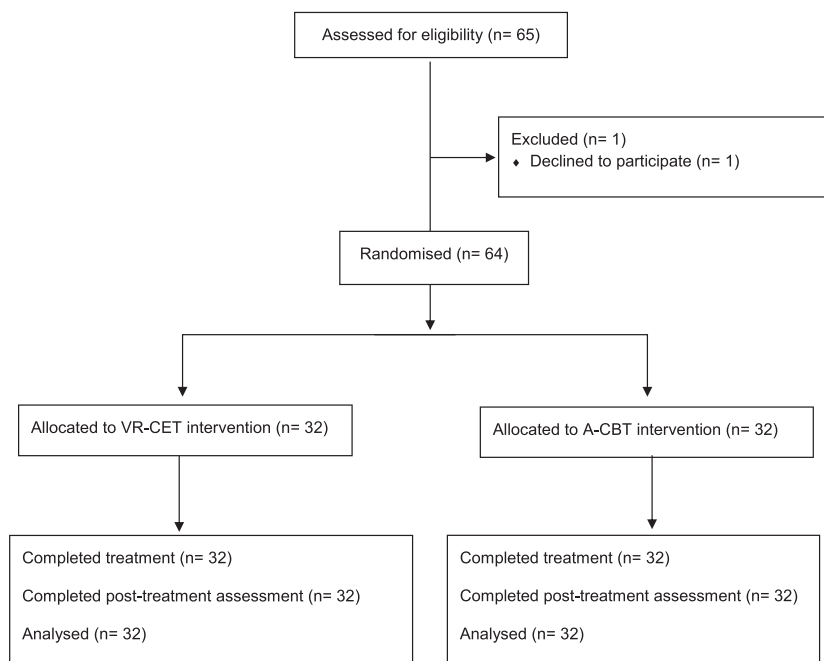
Figure 1. Consort flow diagram

between randomisation and the beginning of the second-level treatment conditions ranged between 2 and 3 weeks.

The A-CBT group consisted of 8 men and 24 women (19 with BN and 13 with BED, 20 of whom were taking antidepressant medication), and the VR-CET group of 11 men and 21 women (16 with BN and 16 with BED, 17 of whom were taking antidepressant medication). Neither sex nor antidepressant medication use rates nor diagnostic rates differed (all $ps > 0.05$) across groups, in agreement with prior trials based on the transdiagnostic approach (Fairburn et al., 2009; Fairburn et al., 2015). Moreover, as shown in Table 1, participants assigned to either A-CBT ($N = 32$) or VR-CET ($N = 32$) sessions did not differ significantly in terms of age, measured body mass index (kg/m^2), clinician-rated frequency of episodes of binge eating and purging, self-reported tendency to engage in episodes of uncontrollable overeating (binge eating) and on mean scores of self-reported measures of attitudinal features of EDs (i.e. drive for thinness, body dissatisfaction) and state and trait anxiety and food craving assessed in the pre-randomisation phase. All participants assigned to A-CBT and to VR-CET conditions received and completed the assigned intervention (Figure 1) and re-completed the clinician-rated and self-reported study measures (described in the succeeding texts) at the end of the second-level treatment.

Both second-level treatment regimes, consisting of six twice-weekly individual 60-min sessions over 3 weeks, were delivered by experienced clinical psychologists (two per site) with close ongoing supervision of the treatment conditions by the senior ED specialists at each site, as recommended (Eldredge et al., 1997; Mitchell et al., 2002). The A-CBT sessions, which were based on the approach described by Eldredge et al. (1997), aimed at strengthening behavioural changes by the rehearsal and reinforcement of the strategies developed during the initial structured

programme of CBT, with particular attention to specific problem areas identified by subjects and clinical psychologists at the end of their initial course of CBT (e.g. self-monitoring records, meal planning, eating regular meals, ability to eat forbidden foods and specific strategies for identifying, correcting dysfunctional cognitions and coping with triggers for binge eating). The VR-CET sessions were based on the approach described by Pla-Sanjuanelo et al. (2016). During the time lag mentioned in the preceding texts between randomisation and the beginning of the VR-CET sessions, participants were assessed through a validated VR-based cue exposure software (Gutiérrez-Maldonado, Pla-Sanjuanelo et al., 2016; Pla-Sanjuanelo et al., Submitted) in order to construct the exposure hierarchy of 3D interactive (environment and food) situations for use in the VR-CET sessions. This software comprises a library of 30 virtual foods frequently consumed by patients with BED and BN during binge eating episodes and four everyday real-life VR environments (kitchen, dining room, bedroom and cafeteria) where they usually binge (Pla-Sanjuanelo et al., 2015). Participants were exposed to 2D images of these foods and environments and indicated the level of food craving elicited per item on a visual analogue scale (from 0 to 100). Using this information, the software created a first individualised exposure hierarchy by combining the four virtual environments and the ten foods that produced the highest levels of food craving (Figure 2) for a total of 40 3D interactive (environment and food) situations (Gutiérrez-Maldonado, Pla-Sanjuanelo et al., 2016; Pla-Sanjuanelo et al., 2016). Then, participants were exposed to these 40 environments and indicated the level of anxiety experienced in each one of them after 20 s of exposure (on a virtual analogue scale from 0 to 100). A previous study conducted to assess the ability of this software to elicit craving and anxiety responses in patients with BN and BED showed

Table 1 Comparison between additional cognitive-behavioural treatment and virtual reality cue exposure therapy groups in pre-test and post-test measures

	Pre-test measures		Post-test measures		A-CBT and VR_CET pre-test comparisons				A-CBT and VR_CET post-test comparisons			
	A-CBT M (SD)	VR-CET M (SD)	A-CBT M (SD)	VR-CET M (SD)	$t_{(62)}$	$p^\star$	$\eta^\dagger$	95% CI	$t_{(62)}$	$p^\ddagger$	$\eta^\dagger$	95% CI
Age	34.56 (9.08)	34.75 (10.04)	—	—	−0.078	0.938	0.0001	−40.97–4.59	—	—	—	—
BMI	29.47 (6.86)	27.78 (5.60)	—	—	1.074	0.287	0.018	−1.44–4.81	—	—	—	—
Binges[§]	12.37 (6.82)	11.21 (6.28)	5.59 (5.66)	0.87 (1.16)	0.705	0.483	0.008	−2.12–4.43	4.624	**<0.001**	0.253	2.68–6.76
Purges[†]	10.05 (7.87)	9.69 (7.93)	4.37 (5.76)	0.44 (0.81)	0.136	0.892	0.0003	−5.09–5.82	2.942	0.008	0.202	1.13–6.73
EDI-DT	18.44 (7.08)	17.75 (7.35)	13.94 (6.79)	15.03 (5.95)	0.381	0.705	0.002	−2.92–4.29	−0.686	0.496	0.007	−4.28–2.09
EDI_B	19.34 (7.21)	20.31 (7.54)	16.00 (8.27)	7.03 (6.40)	−0.525	0.601	0.004	−4.65–2.72	4.851	**<0.001**	0.275	5.27–12.66
EDI-BD	20.31 (9.20)	24.62 (8.19)	20.50 (9.66)	19.56 (5.85)	0.775	0.441	0.009	−2.66–6.04	0.469	0.641	0.003	−3.07–4.95
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Z	p	r		Z	p	r	
STAI-T	38.00 (16.75)	37.50 (19.75)	33.00 (12.75)	25.00 (7.25)	−0.040	0.968	0.005	—	−2.992	**0.003**	0.379	—
STAI-S	31.00 (18.50)	29.50 (29.75)	26.00 (12.50)	24.00 (7.50)	−0.087	0.930	0.011	—	−3.362	**0.001**	0.427	—
FCQ-T	156.5 (29.25)	150.5 (49.75)	135.5 (62.25)	57.50 (87)	−0.410	0.682	0.052	—	−3.747	**<0.001**	0.475	—
FCQ-S	46.00 (22.25)	47.00 (18.25)	33.50 (32.50)	19.00 (12)	−0.565	0.572	0.072	—	−2.899	**0.004**	0.368	—

Note: Given that STAI and FCQ scores were not normally distributed in this sample, non-parametric analyses comparing A-CBT and VR-CET groups before after booster sessions are included. Statistically significant differences are highlighted in bold.
BMI, body mass index; EDI, Eating Disorder Inventory; DT, drive for thinness; B, bulimia; BD, body dissatisfaction; STAI, State–Trait Anxiety Inventory; FCQ, Food Craving Questionnaire; T, trait; S, state.
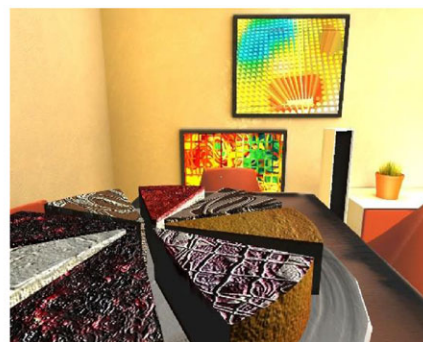*Bonferroni adjustment (11 comparisons): $p < 0.004$.
[†]Number of purge episodes during the last 2 weeks (only patients with BN, $N = 19$ in A-CBT group and $N = 169$ in VR-CET group; $df = 18.85$).
[‡]Bonferroni adjustment (nine comparisons): $p < 0.005$.
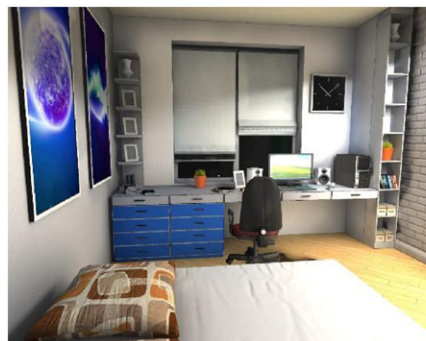[§]Number of binge episodes during the last 2 weeks.

Kitchen

Dining room

Bedroom

Bakery-Cafe

Figure 2. Pictures of the virtual reality scenarios. [Colour figure can be viewed at wileyonlinelibrary.com]

that the anxiety experienced during the exposure to the food-related environments discriminated between clinical and non-clinical samples better than the measure of craving (Pla-Sanjuanelo et al., Submitted). Indeed, anxiety in the presence of food is considered a specific anticipatory response commonly associated with binge episodes in patients with ED (Toro et al., 2003), but not usual in non-clinical samples, while craving in the presence of food is also common in healthy participants, although lower than in patients with ED (Perpiñá et al., 2013). Consequently, anxiety experienced during exposure to the 40 food-related virtual environments assessed as elicitors of the highest craving levels was taken as a criterion to construct the individualised 13-step exposure hierarchy to be used throughout the six therapist-assisted VR-CET sessions.

During the first minutes of each exposure session, the therapist reminded the patients of the purpose of the exposure, that was, to place them in contact with food despite the levels of anxiety they may experience. Doubts and questions raised by the participants were also attended at that time. Then, participants were exposed to the corresponding virtual environments and foods based on the previously established hierarchy. During exposure, participants were asked to move around the VR situation so as to find and sit at the table (where they found the corresponding food according to the predetermined, individualised hierarchy, Figure 2) and to handle the food displayed using the laptop's mouse; the food could be lifted, rotated and zoomed but not eaten. During the VR-CET sessions, conducted in a quiet darkened room to increase the sense of immersion in the VR interactive situations, craving and anxiety levels were assessed periodically, and when the anxiety level decreased by 40% in relation to the level registered at the initiation of the exposure session (Pla-Sanjuanelo et al., 2016), the participant moved to another 3D interactive (environment and food) situation according to the individualised hierarchy created by the VR-CET software (Gutiérrez-Maldonado, Pla-Sanjuanelo et al., 2016). In the event the session terminated before the anxiety level had been sufficiently reduced in the virtual situations, the patients were exposed to the same situation in the following session. During exposure, the therapist remained behind the patient and only intervened if some instruction was needed (e.g. asking the patient to handle the food) or if the patient needed assistance. Once the exposure session was finished, the therapist also responded to potential (but unusual) patients' concerns or discomfort. VR (environment and food) situations were displayed on a 15.6-in stereoscopic monitor. Earphones and polarised glasses were also used.

MEASURES

Outcome assessment for core behavioural features (conducted by experienced assessors available at all sites and not involved in treatment delivery) included frequency (i.e. number) of binge eating episodes and purging (i.e. self-induced vomiting and laxative and diuretic use, in the case of patients with BN) over the previous 2 weeks, as measured by the questions extracted from the ED Examination Interview 12.0D (Fairburn & Cooper, 1993) adapted to cover the specified time frame, that is, past 2 weeks (Bulik et al., 1998; Mitchell et al., 2002). In addition, to determine entry to the randomised phase of the study, these questions

extracted from the ED Examination Interview were the method for determining abstinence from behavioural features (i.e. no episodes of binge eating and purging in the case of BN) over the past 2 weeks. The self-reported tendency to engage in episodes of uncontrollable overeating (binge eating) was also assessed through the eight-item bulimia subscale of the ED Inventory-3 (EDI-3) (Garner, 2004). Additional outcome measures for attitudinal features of EDs included the 7-item drive for thinness and the 10-item Body Dissatisfaction scales of the EDI-3 (Garner, 2004); all EDI-3 scales (αs ≥ 0.87) are rated on a 5-point scale (ranging from 0 to 4). Several measures were also included to assess specific variables targeted by VR-CET (Pla-Sanjuanelo et al., 2016) including the State–Trait Anxiety Inventory-Form Y (STAI-Y; Spielberger, Gorsuch, & Lushene, 1983) and the Food Craving Questionnaire Trait (FCQ-T; Cepeda-Benito et al., 2000) and State (FCQ-S; Cepeda-Benito et al., 2000). The STAI-Y consists of two 20-item scales (rated on a 4-point scale from 1 to 4) for measuring the level of anxiety as a state (STAI-S; i.e. at the moment of evaluation) and trait (STAI-T) (αs ≥ 0.89). The FCQ-S (consisting of 15 items rated on a 5-point scale, ranging from 1 to 5) and the FCQ-T (consisting of 39 items rated on a 6-point scale, ranging from 1 to 6) were designed to assess state (i.e. at the moment of evaluation) and trait food craving (αs ≥ 0.92). Data collected through the aforementioned instruments in the pre-randomisation phase (*pre-test measures* hereafter) and at the end of the second-level treatment conditions (*post-test measures* hereafter) were used for the study.

STATISTICAL ANALYSES

Sample size was calculated on the basis of findings from first-generation studies that tested CBT and CET. Recovery rates (understood as the elimination of binge behaviour) use to be low in treatment-resistant patients with BN and BED. Mitchell and colleagues, for example, reported binge abstinence percentages from 11 to 15% at the end of the treatment and from 18 to 26% at 1-year follow-up in non-responder patients with BN that were treated with CBT, in one condition, and with a CBT-based stepped-care intervention, in another condition (Mitchell et al., 2011). CET has been reported to be an effective alternative intervention for reducing bulimic behaviour in BN treatment-resistant patients (Martínez-Mallén et al., 2007; Toro et al., 2003). McIntosh, Carter, Bulik, Framptom, and Joyce (2011) found that adding CET sessions to previous CBT sessions produced a bingeing abstinence rate (assessed for the last year) of 54% at 5-year follow-up. Given previously mentioned information and having into account that our sample is composed of treatment-resistant patients, percentage of recovery in A-CBT group was expected to be around 20% whereas in VR-CET was expected to be around 50%. Establishing a risk level of 0.05 and a statistical power of 0.8, 30 participants in each group were considered to be necessary to detect significant differences between the interventions. Assuming an expected loss rate of 5%, 32 patients per group were finally recruited ($N = 64$).

Analyses were conducted using SPSS Statistics for Windows version 23; no patients dropped out during second-level treatment conditions, and there were no missing data. Skewness and

kurtosis values were checked. Given that anxiety (STAI-S and STAI-T) and food craving (FCQ-S and FCQ-T) scores were not normally distributed in our sample, non-parametric analyses were used with these variables. Specifically, Wilcoxon tests were conducted to assess within-group differences between pre-randomisation/pre-test and end of treatment/post-test values on state and trait anxiety and food craving for each treatment group separately, and Mann–Whitney tests were used for between-group comparisons (A-CBT vs. VR-CET). Student's 't'-tests were also conducted to assess between-group differences in clinician-rated frequency of episodes of binge eating and purging and EDI-3 scale scores at pre-randomisation/pre-test and end of treatment/post-test. Mixed between-within subject analyses of variance were used to compare the treatment groups with regard to the change in clinician-rated frequency of binge eating and purge episodes, self-reported tendency to engage in episodes of uncontrollable overeating (i.e. the EDI-3 bulimia scale) and attitudinal ED features (i.e. the EDI-3 drive for thinness and body dissatisfaction) over time, with one between-subject factor (treatment groups: VR-CET vs. A-CBT) and one within-subject factor (time: pre-randomisation/pre-test, end of treatment/post-test). Treatment groups were compared on abstinence from the pathological behaviour (i.e. no episodes of binge eating and purging) at the end of the second-level treatment conditions using the χ^2 test. Purge episodes and abstinence from purging were only assessed in patients with BN ($N = 35$) given that by definition, patients with BED do not engage in these behaviours (Fairburn et al., 2009).

RESULTS

VR-CET was significantly superior to A-CBT at the end of second-level treatment/post-test in terms of the proportion of participants who achieved abstinence from binge eating episodes. Seventeen (53%) of those treated with VR-CET ($N = 32$) achieved abstinence from binge eating episodes, compared with eight (25%) of those treated with A-CBT ($N = 32$) ($\chi^2 = 5.32$, $p = 0.02$).[2] Amongst patients with BN, VR-CET was also superior to A-CBT at the end of second-level treatment in terms of the percentage of participants that achieved abstinence from purging episodes [12 of the 16 participants (75%) in the VR-CET group and 6 of the 19 participants (31.5%) in the A-CBT group ($\chi^2 = 6.56$,

$p = 0.02$].[3] Consistent with these results, the VR-CET group showed a lower clinician-rated frequency of binge and purge episodes and a lower self-reported tendency to engage in episodes of uncontrollable overeating (assessed by the bulimia scale of the EDI-3) than the A-CBT group at the end of second-level treatment, although there were no significant differences between groups at the pre-randomisation/pre-test phase (as also anticipated in the section "Participants and procedure" and displayed in Table 1—pre-test measures).

Results of mixed between-within subject analyses of variance are summarised in Table 2 and Figure 3. Regarding the number of binge episodes, a significant simple effect of time and group and a significant time × group interaction were found. In both A-CBT and VR-CET groups, the number of binge episodes decreased significantly at the end of second-level treatment, but this reduction was significantly higher in the VR-CET group (refer to means in Table 1). However, when analysing the number of purge episodes (in patients with BN, refer to the "Statistical analyses" section), only the simple effect of time was significant. Both VR-CET and A-CBT groups reported a significant lower number of purge episodes at the end of second-level treatment than before starting the trial/pre-randomisation (Table 2), although the decrease was higher in the VR-CET group (refer to means in Table 1). Likewise, only time had a significant effect over scores obtained in the drive for thinness and Body Dissatisfaction scales of the EDI-3. Scores on both these scales were significantly lower in both groups at the end of second-level treatment (refer to means in Table 1); neither the simple effect of the group nor the time × group interaction was significant (Table 2). Conversely, results showed a significant simple effect of time and group and a significant time × group interaction on the EDI-3 bulimia scale (Table 2). The effect size of time × group interaction was remarkably large in the bulimia scale ($\eta^2 = 0.326$) and highlights the superiority of VR-CET over A-CBT in this measure (Figure 3). Although scores on this scale fell significantly at the end of second-level treatment in both groups, in the VR-CET, the reduction was significantly higher (refer to means in Table 1).

Anxiety (STAI-S and STAI-T) and food craving (FCQ-S and FCQ-T) scores were not normally distributed in this sample, so non-parametric analyses were conducted (refer to the "Statistical analyses" section). Both A-CBT and VR-CET groups reduced food craving trait and state at the end of second-level treatment/post-test (Table 3), but scores on FCQ-T and FCQ-S were significantly lower in the VR-CET group than in the A-CBT group at post-test (Table 1). Further, while the VR-CET group experienced a significant reduction of both trait and state

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[2]The patients with BN ($n = 35$) and BED ($n = 29$) entered the randomisation phase of the study with very similar binge eating symptomatology (at pre-randomisation, the average number of clinician-rated binge eating episodes was 11.66 ($SD = 7.39$) for patients with BN and 11.96 ($SD = 5.44$) patients with BED), and no significant ($p > 0.05$) differences between patients with BED and BN were evidenced. This similarity was also present at end of (second level) treatment (the average number of binge eating episodes was 3.31 ($SD = 4.76$) for patients with BN and 3.14 ($SD = 4.70$) for patients with BED), and on repeated-measures analysis of variance, there was no significant main effect of diagnosis at this point ($p > 0.05$); in addition, there were no significant differences ($p > 0.05$) between the two diagnostic groups at end of (second-level) treatment on the abstinence (from binge eating) rates (data not shown).

[3]At pre-randomisation, antidepressant medication (not an exclusionary factor; refer to "Participants and procedure" section) was used by 20 of 32 participants allocated to A-CBT and by 17 of 32 participants allocated to VR-CET. While it would be difficult to tease apart any potential benefit due to the anti-binge/bulimic effects of the selective serotonin reuptake inhibitors, we did not find any differences (all ps > 0.05) in abstinence from binge eating and from purging between participants allocated to A-CBT and to VR-CET who received medication and those who did not. Although a similar pattern has been observed in past outcome research (Dakanalis et al., 2016; Dakanalis, Colmegna, Riva et al., 2017; le Grange et al., 2007), a separate study examining moderators and mediators of treatment response needs to address these issues in more detail.

Table 2 Mixed between-within subject analyses of variance comparing treatment groups on behavioural (number of binge eating and purge episodes) and attitudinal eating disorder features (bulimia, drive for thinness and body dissatisfaction) before and after booster sessions

	Time (pre–post test)					Group (A-CBT vs. VR-CET)					Time × group		
				95% CI					95% CI				
	$F_{(1, 62)}$	p	η^*	Pre-test	Post-test	$F_{(1, 62)}$	p	η^*	A-CBT	VR-CET	$F_{(1, 62)}$	p	η^*
Binges[†]	117.65	<**0.001**	0.655	10.16–13.43	2.21–4.25	6.954	**0.011**	0.101	7.41–10.56	4.47–7.62	5.092	**0.028**	0.076
Purges[†]	39.728	<**0.001**	0.546	7.14–12.60	0.92–3.88	1.422	0.242	0.041	4.73–9.69	2.36–7.76	2.265	0.142	0.064
EDI-DT	48.111	<**0.001**	0.437	16.29–19.90	12.89–16.08	0.016	0.901	<0.001	13.89–18.48	14.10–18.68	2.929	0.092	0.045
EDI-B	84.112	<**0.001**	0.576	17.98–21.67	9.67–13.36	6.184	**0.016**	0.091	15.40–19.94	11.40–15.94	30.053	<**0.001**	0.326
EDI-BD	48.464	<**0.001**	0.439	23.29–27.64	18.03–22.03	0.459	0.501	0.007	20.67–26.15	19.36–24.83	0.231	0.633	0.004

Note: Simple effect of variable time (before and after booster sessions) and group (A-CBT and VR-CET) and interaction between the two variables are shown.
EDI, Eating Disorder Inventory; DT, drive for thinness; B, bulimia; BD, body dissatisfaction. Statistically significant differences are highlighted in bold.
*Number of purge episodes during the last 2 weeks (only patients with BN, $N = 19$ in A-CBT group and $N = 16$ in VR-CET-group; $df = 33$).
[†]Number of binge episodes during the last 2 weeks.
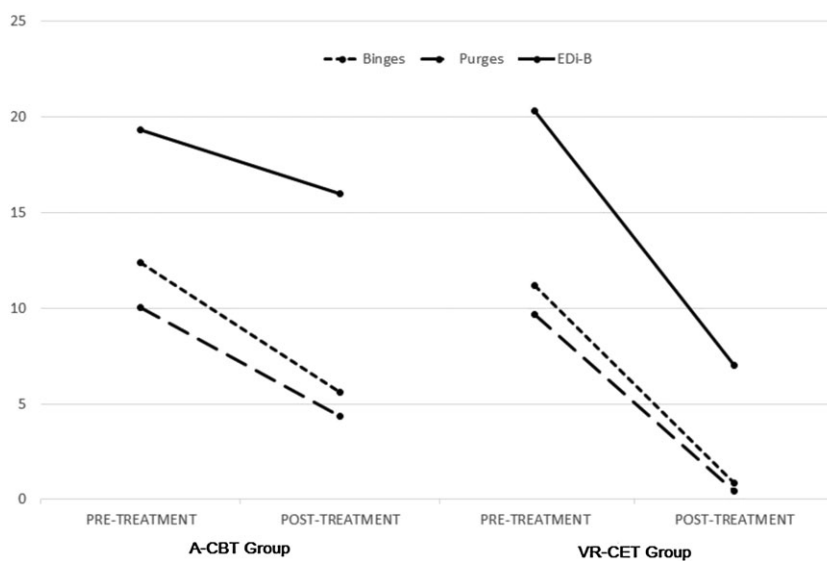
Figure 3. Frequency of binge and purge episodes (during the last 2 weeks) and bulimia scale score of the Eating Disorder Inventory-3 at pre-treatment and post-treatment in additional cognitive-behavioural treatment and virtual reality cue exposure therapy groups

anxiety at the end of second-level treatment/post-test, the A-CBT group experienced a significant reduction only in trait anxiety (Table 3); STAI-T and STAI-S scores were significantly lower in the VR-CET group than in the A-CBT group at post-test (Table 1).

DISCUSSION

The current study evaluated the effectiveness of VR-CET as a second-level treatment strategy for patients with ED characterised by recurrent binge eating (i.e. with BN or BED) who were initially treated unsuccessfully with a structured CBT programme and compared it with A-CBT. While previous research (Eldredge et al., 1997) showed that subjects who did not stop binge eating after an initial structured CBT programme benefited from A-CBT (i.e. additional CBT sessions focusing on specific problem

areas identified at the end of the initial structured CBT programme), it has been suggested that these resistant patients would benefit even more from CET interventions targeting specific features associated with poor response (Dakanalis et al., 2016; Dakanalis, Colmegna, Riva et al., 2017; Halmi, 2013) such as urge to binge in response to a cue (Bulik et al., 1998) and anxiety experienced simultaneously in the presence of binge-related cues (Bulik et al., 1998; Gutiérrez-Maldonado, Pla-Sanjuanelo et al., 2016; Martínez-Mallén et al., 2007; Toro et al., 2003; Pla-Sanjuanelo et al., 2016). Consistent with these statements, both treatment groups improved at the end of (second-level) treatment on all dimensional measures of outcome (i.e. clinician-rated frequency of episodes of binge eating and purging, self-reported tendency to engage in episodes of uncontrollable overeating, drive for thinness, body dissatisfaction, anxiety and food craving), but a better overall outcome was evidenced in the VR-CET group.

Table 3 Comparisons between pre-test and post-test measures in additional cognitive-behavioural treatment and virtual reality cue exposure therapy groups

	A-CBT pre-post comparisons			VR-CET pre-post comparisons		
	Z	p	r	Z	p	r
STAI-T	−2.631	**0.009**	0.465	−4.259	**<0.001**	0.753
STAI-S	−1.521	0.128	0.269	−3.096	**0.002**	0.547
FCQ-T	−3.362	**0.001**	0.594	−4.566	**<0.001**	0.807
FCQ-S	−4.313	**<0.001**	0.762	−4.374	**<0.001**	0.773

Note: Given that STAI and FCQ scores were not normally distributed in this sample, non-parametric analyses comparing pre–post treatment measures in A-CBT and VR-CET groups separately are included. Statistically significant differences are highlighted in bold.
EDI, Eating Disorder Inventory; DT, drive for thinness; B, bulimia; BD, body dissatisfaction; STAI, State–Trait Anxiety Inventory; FCQ, Food Craving Questionnaire; T, trait; S, state.

Moreover, there were significant differences between the two second-level treatment conditions in rates of abstinence (i.e. no episodes of binge eating or purging for 2 weeks), highlighting the superiority of VR-CET over A-CBT.

The aim of CET is to reduce and/or extinguish anxiety and food craving responses to binge-related cues, given that these responses are considered triggers of binge behaviour (Martínez-Mallén et al., 2007; Yela-Bernabé et al., 2013). Consequently, CET is specifically addressed to binge behaviour reduction or elimination (Bulik et al., 1998; Jansen et al., 1992). This fact may explain the good results in the VR-CET group. Binge eating is associated with purging behaviours (in BN) aimed at counteracting the caloric intake and weight gain from binge eating (Al-Adawi et al., 2013; American Psychiatric Association, 2013). So, once binges diminish, purges can also be reduced. Previous research has also found *in vivo* CET to be particularly suitable for reducing binge eating (Bulik et al., 1998; Jansen et al., 1992) even in patients who did not improve with CBT and/or pharmacological treatments (Martínez-Mallén et al., 2007; Toro et al., 2003). Although VR-CET overcomes the logistical and generalisation problems of *in vivo* CET (refer to "Introduction" section for details and relevant references), future research comparing the effectiveness of VR-CET (as a second-level treatment for binge eating and associated purging behaviours) with an *in vivo* CET intervention is required.

All patients showed significant reductions in the EDI-3 scales of drive for thinness (assessing desire to be thinner, concern with dieting, preoccupation with weight and an intense fear of weight gain) and body dissatisfaction (assessing discontentment with the overall shape and size of regions of the body) regardless of group assignment (i.e. A-CBT and VR-CET) at the end of second-level treatment. However, patients in both groups still fitted the clinical range (Elosua, López-Jáuregui, & Sánchez-Sánchez, 2010) of drive for thinness (i.e. scores between 9 and 22) and body dissatisfaction (i.e. scores between 13 and 28). Although a higher reduction of drive for thinness and body dissatisfaction would have been desirable, VR-CET does not directly address these issues. Consequently, expecting clinical reductions in these symptoms at the end of second-level treatment may not be realistic. Nevertheless, it would be expected that, once eating

patterns are normalised, attitudinal features of EDs such as drive for thinness and body dissatisfaction would improve (Grilo, Crosby, Wilson, & Masheb, 2012; Roncero & Perpiñá, 2015; Sepúlveda, Carrobles, & Gandarillas, 2010; Serino et al., 2015). Unfortunately, follow-up data were not available at the moment of writing this article, so this assumption will be addressed in another publication. In contrast to VR-CRT, CBT addresses drive for thinness and body dissatisfaction, but as patients entering the randomisation phase of the present study showed resistance to this intervention, a clinically significant reduction in these attitudinal features was not expected. It should also be mentioned that although end of treatment scores in EDI-3 bulimia scale (assessing the tendency to engage in episodes of uncontrollable overeating) improved significantly in both A-CBT and VR-CET groups, the VR-CET group experienced an important reduction, approaching the low clinical range of scores (direct score ≤4 and percentile in adult patients with ED characterised by binge eating ≤16, according to Elosua et al. (2010)), whereas the reduction in the A-CBT group was slight and without clinical significance.

Given that food craving and anxiety are strongly associated with binge behaviour (Pla-Sanjuanelo et al., 2015; Yela-Bernabé et al., 2013) and are considered triggers of binges in the classical conditioning model of binge eating (Jansen, 1998), changes in these variables were also assessed. Self-reported food craving trait and state diminished in both treatment groups. However, craving reported at post-treatment was significantly higher in the A-CBT group than in the VR-CET group despite the fact that there were no differences between groups at pre-treatment. Again, the aim of CET (to extinguish/reduce food craving and anxiety responses) may explain these results (Bulik et al., 1998; Jansen et al., 1992; Martínez-Mallén et al., 2007). Regarding anxiety, patients in the VR-CET group showed a significant decrease in trait and state anxiety levels at the end of treatment, while the A-CBT group only showed a significant decrease in trait anxiety. Furthermore, trait anxiety was significantly lower in the VR-CET group than in the A-CBT group at the end of (second-level) treatment.

The present study has some limitations that should be taken into account. First, only six VR-CET sessions were conducted. Previous studies of the efficacy of *in vivo* CET for treatment of EDs characterised by binge eating usually administered more exposure sessions (i.e. 12 to 36; Martínez-Mallén et al., 2007; Toro et al., 2003). Higher dropout rates appeared associated with lengthy second-level treatments (Mitchell et al., 2002), potentially explaining the absence of participant dropout in this study. Second, given that the control group received an additional intervention (A-CBT), whereas the experimental group received a new/different intervention (VR-CET), it should be considered the possibility that improvements in the VR-CET group were due to a placebo effect from switching treatment. Future research should address this issue by comparing different active treatment groups and, eventually, detect predictors for individual treatment success. Third, the STAI-T/S is a general measure of anxiety as a trait and as a state. An instrument focused on food-related anxiety may provide more accurate results and detect differences between the interventions compared. This issue should be also addressed in future research. Fourth, despite the fact that all sites participating in the study based their first-level interventions in CBT structured programmes, the first-level treatment (which was not the

focus of the current investigation) was not supervised, so equivalence is not guaranteed. Fifth, despite recent evidence from clinical and therapeutic efficacy studies highlighting that neither age-of-BN onset nor age-of-BED onset are reliable and valid indicators of illness severity (e.g. Dakanalis et al., 2016; Dakanalis, Colmegna, Riva et al., 2017; Dakanalis, Colmegna, Zanetti et al., 2017; Dakanalis, Riva et al., 2017; Smink, van Hoeken, Oldehinkel, & Hoek, 2014), the potential impact of age-of-illness onset on therapeutic efficacy has not be considered. Finally, follow-up data were not yet available during the writing of this article. Consequently, the maintenance of the differences found between treatment groups in treatment outcome measures cannot be guaranteed, and the lack of follow-up data does not allow us to check here whether some features (i.e. purge episodes, body dissatisfaction) require more time to reach clinically significant reductions.

Despite these drawbacks, this study has strengths that are worth emphasising. First, it is a randomised trial with no participant dropout. Second, the use of VR environments allows exposure to both specific and contextual cues, which would be expected to increase the ecological validity and generalisation of the outcomes (Shiban et al., 2013), and VR-CET overcomes the logistical problems of *in vivo* CET (Gutiérrez-Maldonado, Pla-Sanjuanelo et al., 2016; Koskina et al., 2013; Perpiñá et al., 2013; Pla-Sanjuanelo et al., 2015). However, as mentioned, research comparing the effectiveness of VR-CET (as a second-level treatment for binge eating and associated purging behaviours) and an *in vivo* CET intervention is needed. Overall, results suggest that VR-CET has potential for improving symptomatic behaviours for patients with BN and BED who were initially treated unsuccessfully with a structured CBT programme. Categorical outcomes and end of treatment effects on dimensional measures of outcome demonstrated the superiority of VR-CET over A-CRT. However, as noted, further research with larger samples and follow-up data is needed, as well as a more rigorous examination of the underlying conceptual model and possible mechanisms of action of VR-CET.

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