



King's Research Portal

DOI: 10.1002/erv.2639

Document Version Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):

Cardi, V., Leppanen, J., Mataix-Cols, D., Campbell, I. C., & Treasure, J. (2019). A case series to investigate food-related fear learning and extinction using in vivo food exposure in anorexia nervosa: A clinical application of the inhibitory learning framework. *European Eating Disorders Review*, *27*(2), 173-181. https://doi.org/10.1002/erv.2639

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

•Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research. •You may not further distribute the material or use it for any profit-making activity or commercial gain •You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

FOOD EXPOSURE IN ANOREXIA NERVOSA

1	TITLE PAGE
2	A CASE SERIES TO INVESTIGATE FOOD-RELATED FEAR LEARNING AND
3	EXTINCTION USING IN-VIVO FOOD EXPOSURE IN ANOREXIA NERVOSA: A
4	CLINICAL APPLICATION OF THE INHIBITORY LEARNING FRAMEWORK.
5	Running Title
6	FOOD EXPOSURE IN ANOREXIA NERVOSA
7	Valentina Cardi ^{a*} PhD, Jenni Leppanen ^a PhD, David Mataix-Cols ^b PhD, Iain C. Campbell ^a
8	PhD, Janet Treasure ^a PhD FRCPsych
9	^a Dept. of Psychological Medicine, Section of Eating Disorders, King's College London's
10	Institute of Psychiatry, Psychology and Neuroscience, UK.
11	^b Centre for Psychiatric Research and Education, Dept. of Clinical Neuroscience, Karolinska
12	Institutet, Stockholm, Sweden.
13	*Corresponding author
14	Address of corresponding author: Department of Psychological Medicine, Institute of
15	Psychiatry, Psychology and Neuroscience, King's College London, The Basement, P059, 103
16	Denmark Hill, London, SE5 8AF. Email: valentina.cardi@kcl.ac.uk
17	
18	Abstract words: 200
19	Manuscript words: 3699
20	Number of tables: 1
21	Number of figures: 2

22 ABSTRACT

23 Objective: Anorexia nervosa is characterized by severe malnutrition. This study tested the 24 hypothesis that fear of food is a learned behavior and evaluated the feasibility and 25 effectiveness of gradual exposure to food to improve eating behavior in people with anorexia 26 nervosa. Methods: Eighteen women were recruited and completed baseline self-reports. They 27 were interviewed regarding early experiences of eating and the development of food-related 28 anxiety. Participants received eight sessions of in vivo food exposure. Results: Findings 29 indicated that fear of food is a learned behavior, associated with catastrophic thoughts around 30 the consequences of eating and safety behaviors. Patients consumed at least half of the food 31 item selected in all, but one session. Body mass index increased and food restriction, eating 32 concern, eating disorder-related preoccupations and overall anxiety reduced (medium/large 33 ES). Conclusion: Findings corroborate an anxiety-based model of anorexia nervosa and 34 support the relevance of targeting food-related fears using exposure-based protocols. 35 36 37 38 39 40 Key words Anorexia Nervosa, Exposure, Food, Fear, Anxiety. 41 Trial name: A fMRI Pilot Study of the Effects of Meal-support in Eating Disorders 42

Highlights

- Fear of food is a core symptom of anorexia nervosa
- Patients report early experiences of learned fear of food.
- Food exposure based on inhibitory learning is acceptable and associated with clinical benefit.

43 ACKNOWLEDGEMENTS

To conduct this work, VC was supported by a Marie Curie Fellowship ("ET4AN New 44 technologies to support eating in Anorexia Nervosa: a neuroimaging study", 299232) and by 45 46 the Biomedical Research Centre (imaging department). JL was supported by a scholarship 47 from the Psychiatry Research Trust. JT receives salary support from the National Institute for 48 Health Research (NIHR), Mental Health Biomedical Research at South London and Maudsley NHS Foundation Trust, and King's College London. The views expressed are those 49 of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. 50 51 The authors do not report any financial or non-financial competing interests in 52 relation to the work described.

53 INTRODUCTION

54 Anorexia nervosa is a serious mental illness (Klump, Bulik, Kave, Treasure, 2009) and has the highest mortality rates amongst psychiatric disorders (Chesney, Goodwin, Fazel, 2014). 55 56 Given the health-threatening consequences of starvation, improving nutrition and restoring weight are of key importance in the first stages of treatment (American Psychiatric Association, 57 58 2006). Fear of food is probably the most challenging obstacle to successful weight restoration 59 (e.g. Steinglass et al., 2010; McFarlane, Olmsted, Trottier, 2008) and predicts the desire to 60 maintain low weight after discharge above and beyond negative affect and general anxiety 61 sensitivity (Levison, Brosof, Fewell, Lenze, 2017). The therapeutic strategies to tackle food-62 related anxiety vary. Empowering parents to provide meal support is successful in adolescent, 63 short onset cases (Couturier, Kimber, Szatmari, 2013), but is more difficult in older patients. 64 Inpatient care with nursing meal support ensures the most rapid weight gain (American 65 Psychiatric Association, 2006; National Institute of Clinical Excellence, 2004), but patients report fear and negative emotions in relation to eating (Steinglass et al., 2010; Soussignan, 66 67 Schaal, Rigaud, Royet, Jiang, 2011) and experience refeeding as a battle (Long, Wallis, Leung, Meyer, 2012). Accordingly, the high rates of relapse and readmission after inpatient treatment 68 69 (Wallier, Vibert, Berthoz, Huas, Hubert, Godart, 2009; Castro, Gila, Puig, Rodriguez, Toro, 70 2004) are suggestive of treatment iatrogenic effects in relation to eating-related anxiety.

The importance of targeting anxiety in anorexia nervosa is supported by the genetic correlation with the neuroticism trait (Duncan et al., 2017) and by the phenotypical overlap with phobic and obsessive-compulsive disorders (Steinglass, et al., 2011). This overlap includes a hypothesized increased tendency to learn fear associations (Strober, 2004) and the development of compulsive behaviors, avoidance and irrational beliefs around the phobic stimulus (Steinglass et al., 2011). In line with an anxiety-based model of anorexia nervosa, abnormal eating behaviors might develop from direct associations between food and traumatic 78 experiences (classical conditioning), vicarious learning of food-related avoidance and aversion 79 (learning of attitudes and behaviors through observing these in close others) and operant conditioning based on learning that eating is followed by aversive consequences (e.g. negative 80 81 judgment from others, shame and criticism) (Treasure, Cardi, Kan, 2012). These hypotheses 82 are supported by evidence that critical comments and teasing about eating, weight and 83 appearance are risk factors for disordered eating (e.g. Fairweather-Schmidt and Wade, 2017; 84 Menzel, Schaefer, Burke, Mayhew, Brannick, Thompson, 2010), and that pressures from 85 parents, peers and the media on losing weight predict the use of extreme weight loss strategies 86 over time (McCabe & Ricciardelli, 2005). Likewise, parental coercive control over eating has 87 been associated with the development of disordered eating over time (e.g. Ellis, Galloway, 88 Webb, Martz, Farrow, 2016).

89 Based on the proposition that fear of food is a key symptom in anorexia nervosa and 90 that it might be underlined by some of the basic mechanisms of learning, exposure-based 91 treatments might hold promise in the treatment of food-related anxiety and avoidance 92 (Steinglass et al., 2011). Exposure-based treatments are evidence-based, first-line interventions 93 for anxiety disorders and involve gradual exposure to the phobic stimulus. The first well 94 established hypothesis regarding the mechanisms of effect of these interventions was that repeated exposure to the feared stimulus would allow habituation to anxiety and therefore fear 95 96 extinction (e.g. Foa & Kozak, 1986). Recent advances in the science of learning and extinction 97 have led to refinements of this hypothesis introducing the concept of inhibitory learning 98 (Craske et al., 2014). The theory of inhibitory learning proposes that successful exposure 99 therapy operates through new learning about the threatened stimulus (e.g. learning that the 100 stimulus is not associated with aversive consequences as previously thought) rather than habituation to anxiety. Based on the inhibitory learning hypothesis, strategies such as 101 102 maximizing the violation of expectancies regarding the intensity or frequency of the threatened outcomes, exposure to multiple threatened cues at the same time, variability of the contexts in
which exposure takes place and use of retrieval cues to strengthen new learning have been
suggested to improve the efficacy of exposure-based therapies (Craske et al., 2014).

106 The potential of this rationale and strategies to enhance exposure treatment in anorexia 107 nervosa has also been proposed (Murray, Treanor, Liao, Loeb, Griffiths, Le Grange, 2016; 108 Reilly, Anderson, Gorrell, Schaumberg, Anderson, 2017). To date, only a handful of studies 109 have tested the use of food exposure in anorexia nervosa and findings have indicated that it is 110 associated with increased caloric intake and reduced anxiety (Steinglass, Albano, Simpson, 111 Wang, Zou, Attia, Walsh, 2014; Steinglass, Sysko, Schebendach, Broft, Strober, Walsh, 2007) 112 and also with increased body mass index when used in conjunction with D-cycloserine (an N-113 methyl-d-aspartate receptor modulator thought to augment glutamatergic function and increase 114 fear extinction; Levinson et al., 2015). These studies have looked at the use of food exposure 115 during or towards the end of inpatient treatment, have mostly involved weight recovered participants and have reported on the use of a protocol based on anxiety habituation rather than 116 117 inhibition learning.

118 Based on the urgent need to implement and improve strategies for aftercare (Berends, 119 et al., 2016; Cardi et al., 2017) and on the evidence-based framework of inhibition learning, 120 the aim of this study is to test the feasibility, acceptability and preliminary effectiveness of food 121 exposure-based therapy in a case series of women with anorexia nervosa who were not 122 receiving hospital treatment at the time they participated. The main outcomes were: 123 intervention adherence (i.e. number of sessions attended and amount of food consumed during 124 each session), participants' willingness to continue with the intervention beyond the set time 125 and changes in body mass index. A secondary aim was to validate an anxiety-based model of 126 anorexia nervosa encompassing the following hypotheses: i) fear of food is a learned behavior,

- ii) patients have catastrophic expectations regarding the implications of eating and iii) patientsuse a range of safety-behaviors to cope with the anxiety of eating.
- 129

130 METHODS AND MATERIALS

131 Study design and outcome measures

132 This study employed a longitudinal design. Eighteen patients with anorexia nervosa 133 recruited from the community completed self-report assessments before and at the end of 134 eight sessions of *in vivo* exposure to food. Number of sessions attended, whether participants 135 brought to the session and consumed the food item that they had decided to be exposed to 136 during each session and willingness to continue with the intervention beyond the sessions 137 offered were recorded and interpreted as an index of feasibility. Body mass index was 138 measured by the researcher at baseline and end of treatment. At these same two-time points, 139 eating disorders symptoms, mood and confidence to change were assessed using self-report 140 measures. In each session, participants were asked to rate their anxiety on a visual analogue 141 scale during food consumption.

142

143 Participants

Women (19 to 60 years) with a diagnosis of anorexia nervosa according to the 144 145 Diagnostic and Statistical Manual of Mental Disorders (5th edition; American Psychiatric 146 Association, 2013) who were not receiving inpatient or outpatient treatment at the time of 147 recruitment and who were proficient in English and right-handed were eligible to take part in 148 the study. A tailored version of the SCID-I (First et al., 2002) (i.e. overview, screening and 149 eating disorder modules, open questions on past or present history of anxiety and mood 150 disorders) was used to ascertain that participants met the inclusion criteria. Twenty subjects 151 with anorexia nervosa were assessed. Two patients did not start the intervention due to

152 difficulty in attending weekly appointments (N=1) and an unexpected admission to hospital 153 (N=1). All patients were receiving regular physical monitoring by their general practitioners. 154 Participants were recruited from the community through advertisements posted on 155 eating disorder charities websites (i.e. Beating Eating Disorders and SUCCEED), circular emails to students and staff at King's College London (KCL) and emails sent to individuals 156 157 from the volunteer database of the Eating Disorders Research Unit at KCL. After complete 158 description of the study, written informed consent was obtained. The study was approved by 159 a National Research Ethics Service (NRES) committee (i.e. South West London Research 160 Ethics Committee; approval number: 11/LO/0373). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and 161 162 institutional committees on human experimentation and with the Helsinki Declaration of 163 1975, as revised in 2008.

164

165 Intervention

166 Participants received two assessment and psycho-education sessions and eight, 60-167 minute sessions of food exposure-based therapy. The assessment sessions consisted in: i) 168 completion of the baseline questionnaires, ii) description of the study rationale (i.e. learning processes involved in food-related fears, role of food-related fears in the maintenance of 169 170 anorexia nervosa, anxiety and its time course, role of avoidance, irrational fears and safety 171 behaviors, fear learning and inhibition) and iii) case formulation to assess traumatic 172 experiences related to food, eating disordered behaviors in the family, family's eating 173 attitudes, imagined worst consequences associated with eating "scary" foods (i.e. irrational 174 beliefs around eating), safety behaviors currently used to manage food-related anxiety and threatening foods to tackle. The intervention was developed by the study team (VC, JT, 175 176 DMC) with supervision from an expert trainer (DMC) and it was based on the clinical

177	recommendations derived from the inhibitory learning framework (Craske, Hermans,					
178	Vervliet, 2018). The sessions were delivered by a clinical psychologist with experience in					
179	eating disorders (VC) and occurred on average twice/week. Based on the inhibitory learning					
180	framework, particular emphasis was given to: paying attention to the feared stimulus,					
181	maximizing the mismatch between frequency and intensity of expected negative					
182	consequences of exposure to the threatening stimulus and actual consequences, affect					
183	labelling, exposure to different food items during each session, supportive and non-					
184	judgmental attitude from the therapist and encouragement to undertake self-exposure sessions					
185	in own environments to generalize the learning occurred during the sessions. The last therapy					
186	session included a summary of skills learned and included a plan for maintaining the changes					
187	made.					
188						
189	Assessment measures					
190	The following questionnaires were administered at baseline and end of intervention:					
191	• Eating disorder symptoms (Eating Disorders Examination – Questionnaire; EDE-Q;					
192	Fairburn & Beglin, 1994).					
193	• Depression, anxiety and stress (Depression Anxiety and Stress Scale; DASS 21;					
194	Lovibond & Lovibond, 1995). Only anxiety subscale considered in the study.					
195	• Confidence to change: (visual analogue scale ranging from 0 - not at all - to 10 - very					
196	much).					
197	• Preoccupations and rituals around eating (Yale-Brown-Cornell Eating Disorder Scale;					
198	YBC-EDS; Mazure, Halmi, Sunday, Romano, Einhron, 1994).					
199	At baseline and after the end of the intervention, the researcher measured participant's					
200	body mass index. Anxiety during food consumption was measured in each session on a scale					
201	ranging from 0 ("not anxious at all") to 10 ("extremely anxious"). At the end of the final					

session, participants were asked the question: "If given the opportunity, would you choose to
continue with this intervention?". Finally, the therapist recorded the number of sessions
attended and whether participants brought in and ate the food item chosen during each
exposure session.

206

207 Data Analyses

Statistical analyses were conducted using SPSS version 20. Mean and standard deviations of demographic and clinical characteristics were calculated. Paired *t*-tests were used to compare pre- and post-intervention scores for the primary and secondary outcomes in the patient group. A *p* value of 0.05 was considered to be significant. Cohen's *d* effect sizes (*ES*) (Cohen, 1992) were calculated and described as negligible (= 0 and < 0.15), small (\geq 0.15 and < 0.40), medium (\geq 0.40 and < 0.75), large (\geq 0.75 and < 1.10), very large (\geq 1.10 and < 1.45) and huge (> 1.45).

215 **RESULTS**

216 Sample description

217 Patients' mean age was 32.83 (SD=12.67). The mean body mass index was "severely 218 low" (Mean=15.98, SD=1.28) (American Psychiatric Association, 2013) and they reported clinically significant levels of eating disorder symptoms, anxiety, depression and stress. Six 219 220 patients had a comorbid diagnosis of anxiety disorders (i.e. social anxiety disorder, or panic 221 disorder, or generalized anxiety disorder or obsessive-compulsive disorder) and nine of major 222 depression. Ten people were using antidepressants at the time of their participation. The 223 mean duration of illness was 15.88 years (SD=11.07; min = 1; max = 36; N = 15 patients > 3 years). Patients did not change the dose of medication or receive any other psychological or 224 225 nutritional treatment for the duration of their participation in the project. The baseline clinical 226 data are reported in Table 1. 227

228 -----Table 1-----

229

230 *Experiences of fear learning, expectations and safety behaviors*

231 The following areas were investigated during the assessment sessions: 1) traumatic experiences related to food, eating disordered behaviors in the family, family's eating 232 attitudes; 2) imagined worst consequences associated with eating "scary" foods (i.e. expected 233 234 outcomes of eating); 3) safety behaviors currently used to manage food-related anxiety. 235 None of the patients reported traumatic experiences involving food and eating prior to illness 236 onset. However, 14 reported witnessing fear and anxiety around eating in at least one of their 237 primary carers and 13 reported having experienced the use of rigid rules about food intake in their family prior to illness onset. The most frequent responses to the question "what is the 238 worst consequence of eating?" were: 'fear of losing control', 'fear of changing shape 239

FOOD EXPOSURE IN ANOREXIA NERVOSA

240	immediately after eating', 'fear of feeling distressed', 'fear of feeling disgusted' and 'fear of
241	being disgusting' (figure 1a). These expectations were discussed and disconfirmed during the
242	sessions. Finally, when participants were asked about the types of safety behaviors used, a
243	broad range of behaviors was identified (figure 1b).
244	Figures 1a, 1b here
245	
246	Exposure sessions: attendance, food consumption, anxiety ratings and acceptability
247	All participants completed eight sessions of therapist-guided exposure to food stimuli
248	and one exposure session/week at home. None dropped-out from the intervention and all
249	expressed an interest in continuing beyond the agreed timeline. Over the sessions,
250	participants were encouraged to eat always a different food item listed on their threatening
251	foods' hierarchy. All patients consumed at least half of the food item selected during the
252	sessions, except for one participant who did not consume any food in session two. Patients
253	did not habituate to eating-related anxiety over time, as demonstrated by the average anxiety
254	scores reported during food consumption (figure 2).
255	In response to the question "If given the opportunity, would you choose to continue
256	with this intervention?", all participants, but one reported that they would. The one person
257	who said they wouldn't, mentioned that travelling to the sessions was physically exhausting.
258	Figure 2
259	
260	Clinical change associated with the treatment
261	Baseline-to-end of treatment changes associated with the intervention are reported in
262	table 1. Overall, a significant increase in body mass index was found. A significant reduction
263	in food restriction and eating concern, eating disorder-related preoccupations and anxiety
264	(medium ES) were found. Increased confidence to change was also observed (large ES).

265 **DISCUSSION**

266 Summary of findings

The aim of the current study was to provide evidence for the feasibility, acceptability 267 268 and preliminary effectiveness of an *in vivo* food exposure intervention in patients with anorexia nervosa. Overall, the findings supported the acceptability of the intervention, in that 269 270 none of the patients dropped-out and that in all but one session, patients consumed at least 271 half of the food item selected. The quantitative data demonstrated that body mass index 272 increased and that food restriction, eating concern, eating disorder-related preoccupations and 273 overall anxiety reduced (medium to large ES). Confidence to change also improved from the beginning to the end of the sessions (large ES). The latter finding is particularly relevant to 274 275 explain the mechanisms of effect of exposure therapy, suggesting the potential involvement 276 of complex cognitive processes, such as self-efficacy (i.e. belief about own' ability to cope 277 with the feared stimulus) (e.g. Craske, Kircanski, Zelikowsky, Mystkowski, Chowdhury, 278 Baker, 2008). The data collected during the assessment phase further validates the use of 279 food exposure therapy in anorexia nervosa. Premorbid experiences of abnormal (vicarious) 280 learning associated with eating were recalled by the majority of the patients and might 281 contribute to the development of food-related anxiety and avoidance. Patients also reported catastrophic consequences about the consequences of eating and a large number of safety 282 283 behaviors to manage the anxiety related to food.

These findings overall align to the literature regarding the phenotypic overlap between anorexia nervosa and anxiety disorders (Steinglass et al., 2011) and suggest the possibility to treat food-related fears and anxiety using *in vivo* exposure based on inhibitory learning (Craske et al. 2014). Participants in this study reported that they felt empowered and in control of the therapy, as probably reflected in the significant increase in confidence to change obtained at the end of it. Throughout the intervention, they were encouraged to take

290 responsibility of the sessions, by selecting which food to buy, buying it and deciding how 291 much to eat. On the other hand, the role of the therapist was to encourage them to keep the focus on the food, label the difficult emotions experienced and to highlight the mismatch 292 293 between feared and actual outcomes of the exposure. In anorexia nervosa, this could 294 represent a potential conundrum, considering that weight gain is often the most threatening 295 consequence of eating, as well as one of the most important treatment goals. A successful 296 approach to this was to highlight the mismatch between the *specific* characteristics of the 297 expected weight gain (e.g. how much, how quickly and what implications it would have), 298 rather than weight gain as such, and the actual outcomes of eating during the sessions. Fear of 299 losing control over food was also very often reported by participants and disconfirmed when 300 reflecting on the actual amount of food consumed during each session.

The results obtained in this study are particularly relevant because they indicate that new learning can develop despite the aversive consequences of starvation and malnutrition and that patients are willing to take controlled risks when confronting eating-related fears and breaking habits. The use of an experimental approach to clarify who might benefit the most from the use of food exposure protocols, based on idiosyncratic differences in fear learning and extinction might further contribute to strengthen the rationale and clinical effectiveness of this approach to psychopathology.

308

309 *Clinical implications*

Several studies highlight the importance of weight gain in the early phase of treatment
for long term recovery in anorexia nervosa (Madden, Miskovic-Wheatley, Wallis, Kohn,
Hay, Touyz, 2015; Nazar, Gregor, Albano, Marchica, Lo Coco, Cardi, Treasure, 2017). The
subjective implications that this has for patients have been less described. It is likely that
rapid weight gain in the early phase of treatment will need to be balanced with the

315 consequences of patient's perceived (or actual) coercion, such as feelings of depression and 316 suicidality (Norrington, Stanley, Tremlett, Birrell, 2012) and also with the sustainability of 317 change after discharge (Garber et al., 2016), a time when discontinuous care jeopardizes 318 treatments gains. The tension between early, effective weight gain and acceptable, sustainable 319 refeeding practices posits a challenge for those involved in the treatment of anorexia nervosa. 320 Teaching patients, carers and hospital staff members the principles of inhibition learning and 321 techniques of food exposure to better manage mealtimes could maximize clinical change both 322 in the early phase of treatment and aftercare, to ensure that changes are maintained over time.

323 The use of novel technologies, such as virtual reality, holds great promise in 324 delivering exposure therapy. In eating disorders, virtual cue exposure to target urge to binge 325 and anxiety associated with binge cues has been successfully used in the treatment of patients 326 with binge eating (bulimia nervosa or binge eating disorders) who did not respond to standard 327 CBT (Ferrer-Garcia, et al., 2017). Furthermore, the use of virtual reality to "update" negative body representations stored in memory has been shown to improve the efficacy of CBT at 328 329 one year in obese patients with binge eating disorder (Cesa et al., 2013; Manzoni et al., 2016). 330

331 The use of virtual reality in anorexia nervosa hasn't been researched as much. Two early case studies indicated that the use of virtual reality to enhance outcomes from standard 332 333 treatment for anorexia nervosa, was associated with weight gain, decreased eating disorder 334 symptoms and psychological distress (Cardi, Krug, Perpiñá, Mataix-Cols, Roncero, Treasure, 335 2012) and with increased body awareness and reduced body dissatisfaction (Riva, Bacchetta, 336 Baruffi, Rinaldi, Molinari, 1999). Two recent studies indicated that one session of immersive 337 virtual reality jogging led to a reduction of the urge to exercise (Paslakis, Fauck, Röder, 338 Rauh, Rauh, Erim, 2017) and that one session of full body illusion reduced body size 339 estimation up to 2-3 hours after exposure (Keizer, van Elburg, Helms, Dijkerman, 2016).

Based on the inhibitory learning framework (Craske et al., 2014), virtual exposure to food
would be particularly advantageous considering the potential of using multiple different cues
and environments over time to favor new learning, whilst ensuring high controllability of the
variables in an experimental setting.

344

345 Strengths and limitations

346 The main strength of this study is the investigation of a non-standard and yet illnessspecific treatment approach in a sample of patients with anorexia nervosa who were not 347 348 receiving any other treatments at the time of recruitment. A limitation of this study is the lack 349 of a comparison group of patients who did not receive the intervention. In the preparation 350 phase for this study, we tested the possibility of randomizing patients to either receiving the 351 intervention or being on a waiting list. The first three patients randomized to the waiting list 352 condition declined to participate further and we decided to proceed with a case series, 353 feasibility study. Patients with eating disorders seem to have strong treatment preferences 354 (Halmi et al., 2005). Indeed, different forms of interventions such as cognitive-behavioral 355 therapy, specialist supportive clinical management (SSCM), the Maudsley Anorexia Nervosa 356 Treatment for Adults (MANTRA) and psychodynamic therapies have been used as comparators in treatment trials of anorexia nervosa, rather than waiting lists (Hay, Claudino, 357 358 Touyz, Abd Elbaky, 2015). A possibility to test food exposure in anorexia nervosa using a 359 randomized controlled trial design, would be to identify patients characterized by abnormal 360 food-related fear learning and inhibition and randomize them to either treatment as usual 361 enhanced by food exposure or treatment as usual alone.

362

363 *Conclusion*

Fear and anxiety around of food are the core psychopathological feature of anorexia nervosa and the greatest obstacle to successful refeeding. Gradual exposure to food is feasible, acceptable and associated with preliminary clinical change in patients with anorexia nervosa who are living in the community. The use of translational research to increase the understanding of individual differences in fear learning and extinction, and the employment of novel technologies such as virtual reality to deliver exposure therapy are promising approaches to improve current treatments for eating disorders.

371 **REFERENCES**

- 372 American Psychiatric Association Steering Committee on Practice Guidelines. Practice
- 373 *Guideline for the Treatment of Patients with Eating Disorders (Third Edition).*
- 374 <u>http://psychiatryonline.org/guidelines</u>, 2006.
- 375 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders.
- 376 5th ed. (2013). Arlington, VA: American Psychiatric Association.
- 377 Berends, T., van Meijel, B., Nugteren, W., Deen, M., Danner, U.N., Hoek, H.W., van Elburg,
- A.A. (2016). Rate, timing and predictors of relapse in patients with anorexia nervosa
- following a relapse prevention program: a cohort study. *BMC Psychiatry*, *16*(1):316. doi:
- 380 10.1186/s12888-016-1019-y.
- 381 Cardi, V., Ambwani, S., Robinson, E., Albano, G., MacDonald, P., Aya, V., Rowlands, K.,
- 382 Todd, G., Schmidt, U., Landau, S., Arcelus, J., Beecham, J., Treasure, J. (2017). Transition
- 383 Care in Anorexia Nervosa Through Guidance Online from Peer and Carer Expertise
- 384 (TRIANGLE): Study Protocol for a Randomised Controlled Trial. *European Eating*
- 385 *Disorders Review*, 25(6):512-523.
- 386 Cardi, V., Krug, I., Perpiñá, C., Mataix-Cols, D., Roncero, M., Treasure, J. (2012). The use of
- 387 a nonimmersive virtual reality programme in anorexia nervosa: a single case-report.
- 388 *European Eating Disorders Review, 20*(3):240-5.
- 389 Castro, J., Gila, A., Puig, J., Rodriguez, S., Toro, J. (2004). Predictors of rehospitalization
- 390 after total weight recovery in adolescents with anorexia nervosa. International Journal of
- 391 *Eating Disorders*, *36*(1):22-30.
- 392 Cesa GL, Manzoni GM, Bacchetta M, Castelnuovo G, Conti S, Gaggioli A, Mantovani F,
- 393 Molinari E, Cardenas-Lopez G, Riva G. (2013). Virtual reality for enhancing the cognitive
- 394 behavioral treatment of obesity with binge eating disorder: randomized controlled study with
- 395 one-year follow-up. *Journal of Medical Internet Research*, 15, e113.

- 396 Chesney E, Goodwin GM, Fazel S. (2014). Risks of all-cause and suicide mortality in mental
- disorders: a meta-review. World Psychiatry 13, 153-60.
- 398 Cohen J. A power primer. (1992). *Psychologial Bulletin*, 112, 155-9.
- 399 Couturier, J., Kimber, M., Szatmari, P. (2013). Efficacy of family-based treatment for
- 400 adolescents with eating disorders: A systematic review and meta-analysis. *International*
- 401 Journal of Eating Disorders, 46(1), 3-11.
- 402 Craske MG, Hermans D, Vervliet B. (2018). State-of-the-art and future directions for
- 403 extinction as a translational model for fear and anxiety. *Philosophical Transactions of the*
- 404 Royal Society of Londond. Series B, Biological Sciences, 373(1742).
- 405 Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. (2008).
- 406 Optimizing inhibitory learning during exposure therapy. Behaviour Research and Therapy,
- 407 46(1):5-27.
- 408 Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. (2014). Maximizing exposure
- 409 therapy: an inhibitory learning approach. *Behaviour Research and Therapy*, 58:10-23.
- 410 Duncan L, Yilmaz Z, Gaspar H, Walters R, Goldstein J, Anttila V, Bulik-Sullivan B, Ripke
- 411 S; Eating Disorders Working Group of the Psychiatric Genomics Consortium, Thornton L,
- 412 Hinney A, Daly M, Sullivan PF, Zeggini E, Breen G, Bulik CM. (2017). Significant Locus
- 413 and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of
- 414 Anorexia Nervosa. *The American Journal of Psychiatry*, 174(9): 850-858.
- 415 Ellis JM, Galloway AT, Webb RM, Martz DM, Farrow CV. (2016). Recollections of pressure
- 416 to eat during childhood, but not picky eating, predict young adult eating behavior. *Appetite*,
- 417 *97*:58-63.
- 418 Fairburn C, Beglin FJ. (1994). Assessment of eating disorders: Interview or self-report
- 419 questionnaire? International Journal of Eating Disorders, 16: 363-70.

- 420 Fairweather-Schmidt AK, Wade TD. (2017). Weight-related peer-teasing moderates genetic
- 421 and environmental risk and disordered eating: twin study. *British Journal of Psychiatry*,
- 422 *210*(5):350-355.
- 423 Ferrer-García M, Gutiérrez-Maldonado J, Pla-Sanjuanelo J, Vilalta-Abella F, Riva G, Clerici
- 424 M, Ribas-Sabaté J, et al. (2017). A Randomised Controlled Comparison of Second-Level
- 425 Treatment Approaches for Treatment-Resistant Adults with Bulimia Nervosa and Binge
- 426 Eating Disorder: Assessing the Benefits of Virtual Reality Cue Exposure Therapy. *European*
- 427 *Eating Disorders Review*, 25(6):479-490.
- 428 First MB, Spitzer RL, Gibbon M, Williams JBW, editors. (2002). Structured Clinical
- 429 Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-
- 430 I/NP). New York: Biometrics Research: New York State Psychiatric Institute.
- Foa EB, Kozak MJ. (1986). Emotional processing of fear: exposure to corrective information. *Psychologial Bulletin*, *99*: 20-35.
- 433 Garber AK, Sawyer SM, Golden NH, Guarda AS, Katzman DK, Kohn MR, et al. (2016). A
- 434 systematic review of approaches to refeeding in patients with anorexia nervosa. *International*
- 435 *Journal of Eating Disorders*, 49(3): 293-310.
- 436 Halmi KA, Agras WS, Crow S, Mitchell J, Wilson GT, Bryson SW, Kraemer HC. (2005).
- 437 Predictors of treatment acceptance and completion in anorexia nervosa: implications for
- 438 future study designs. *Archives of General Psychiatry*, 62: 776-81.
- 439 Hay PJ, Claudino AM, Touyz S, Abd Elbaky G. (2015). Individual psychological therapy in
- 440 the outpatient treatment of adults with anorexia nervosa. *Cochrane Database of Systematic*
- 441 *Reviews*, 27(7):CD003909.
- 442 Keizer A, van Elburg A, Helms R, Dijkerman HC. (2016). A virtual reality full body illusion
- 443 improves body image disturbance in anorexia nervosa. *PLoS ONE*, *11*, e0163921.

- 444 Klump KL, Bulik CM, Kaye WH, Treasure J, Tyson E. (2009). Academy for eating disorders
- position paper: eating disorders are serious mental illnesses. *International Journal of Eating Disorders 42*, 97-103.
- 447 Levinson CA, Rodebaugh TL, Fewell L, Kass AE, Riley EN, Stark L, McCallum K, Lenze
- 448 EJ. (2015). D-Cycloserine facilitation of exposure therapy improves weight regain in patients
- 449 with anorexia nervosa: a pilot randomized controlled trial. Journal of Clinical Psychiatry,
- 450 *76*(6):e787-93.
- 451 Levinson, C. A., Brosof, L.C., Ma, J., Fewell, L., Lenze, E.J. (2017). Fear of food
- 452 prospectively predicts drive for thinness in an eating disorder sample recently discharged
- 453 from intensive treatment. *Eating Behaviors*, 27, 45-51.
- 454 Long S, Wallis D, Leung N, Meyer C. (2012). "All eyes are on you": anorexia nervosa
- 455 patient perspectives of in-patient mealtimes. *Journal of Health Psychology*, 17(3):419-28.
- 456 Lovibond SH, Lovibond PF. (1995). *Manual for the depression anxiety stress scales*. Sydney:
 457 Psychology Foundation.
- 458 Madden S, Miskovic-Wheatley J, Wallis A, Kohn M, Hay P, Touyz S. (2015). Early weight
- 459 gain in family-based treatment predicts greater weight gain and remission at the end of
- 460 treatment and remission at 12-month follow-up in adolescent anorexia nervosa. *International*
- 461 *Journal of Eating Disorders*, 48(7): 919-22.
- 462 Manzoni GM, Cesa GL, Bacchetta M, Castelnuovo G, Conti S, Gaggioli A, Mantovani F,
- 463 Molinari E, Cardenas-Lopez G, Riva G. (2016). Virtual reality-enhanced cognitive-
- 464 behavioral therapy for morbid obesity: a randomized controlled study with 1 year follow-up.
- 465 *Cyberpsychology, Behavior & Social Networking, 19, 134–140.*
- 466 Mazure CM, Halmi KA, Sunday SR, Romano SJ, Einhorn AM. (1994). The Yale-Brown-
- 467 Cornell Eating Disorder Scale: development, use, reliability and validity. *Journal of*
- 468 Psychiatric Research, 28: 425-45.

- 469 McCabe MP, Ricciardelli LA. (2005). A prospective study of pressures from parents, peers,
- 470 and the media on extreme weight change behaviors among adolescent boys and girls.
- 471 *Behaviour Research and Therapy*, *43*(5):653-68.
- 472 McFarlane, T., Olmsted, M. P., & Trottier, K. (2008). Timing and prediction of relapse in a
- 473 transdiagnostic eating disorder sample. *International Journal of Eating Disorders*, 41(7),
- 474 587–593. http://dx.doi.org/10.1002/eat.20550.
- 475 Menzel JE, Schaefer LM, Burke NL, Mayhew LL, Brannick MT, Thompson JK.
- 476 Appearance-related teasing, body dissatisfaction, and disordered eating: A meta-analysis.
- 477 (2010). *Body Image*, 7(4):261-70.
- 478 Murray SB, Treanor M, Liao B, Loeb KL, Griffiths S, Le Grange D. (2016). Extinction
- 479 theory & anorexia nervosa: Deepening therapeutic mechanisms. Behaviour Research and

480 *Therapy*, 87:1-10.

- 481 Nazar BP, Gregor LK, Albano G, Marchica A, Coco GL, Cardi V, Treasure J. (2017). Early
- 482 Response to treatment in Eating Disorders: A Systematic Review and a Diagnostic Test
- 483 Accuracy Meta-Analysis. *European Eating Disorders Review*, 25(2):67-79.
- 484 NICE (2004). Eating disorders: Core interventions in the treatment and management of
- 485 anorexia nervosa, bulimia nervosa and related eating disorders; a national clinical practice
- 486 guideline. London: National Institute of Clinical Excellence.
- 487 Norrington A, Stanley R, Tremlett M, Birrell G. (2012). Medical management of acute severe
- 488 anorexia nervosa. Archives of Disease in Childhood. Education and Practice Edition, 97(2):
- 489 48-54.
- 490 Paslakis G, Fauck V, Röder K, Rauh E, Rauh M, Erim Y. (2017). Virtual reality jogging as a
- 491 novel exposure paradigm for the acute urge to be physically active in patients with eating
- 492 disorders: Implications for treatment. International Journal of Eating Disorders,
- *493 50*(11):1243-1246.

- 494 Reilly EE, Anderson LM1, Gorrell S, Schaumberg K, Anderson DA. (2017). Expanding
- 495 exposure-based interventions for eating disorders. *International Journal of Eating Disorders*,
- 496 50(10):1137-1141. doi: 10.1002/eat.22761. Epub 2017 Aug 16.
- 497 Riva G, Bacchetta M, Baruffi M, Rinaldi S, Molinari E. (1999). Virtual reality based
- 498 experiential cognitive treatment of anorexia nervosa. Journal of Behavior Therapy and
- 499 *Experimental Psychiatry*, *30*(3):221-30.
- 500 Soussignan, R., Schaal, B., Rigaud, D., Royet, J.-P., Jiang, T., 2011. Hedonic reactivity to
- 501 visual and olfactory cues: rapid facial electromyographic reactions are altered in anorexia
- 502 nervosa. *Biological Psychology*, 86, 265–272.
- 503 Steinglass J, Sysko R, Schebendach J, Broft A, Strober M, Walsh BT. (2007). The
- 504 application of exposure therapy and D-cycloserine to the treatment of anorexia nervosa: a
- 505 preliminary trial. Journal of Psychiatric Practice, 13: 238-45.
- 506 Steinglass JE, Sysko R, Mayer L, Berner LA, Schebendach J, Wang Y, Chen H, Albano AM,
- 507 Simpson HB, Walsh BT. (2010). Pre-meal anxiety and food intake in anorexia nervosa.
- 508 *Appetite* 55(2), 214-8.
- 509 Steinglass JE, Sysko R, Glasofer D, Albano AM, Simpson HB, Walsh BT. (2011). Rationale
- 510 for the application of exposure and response prevention to the treatment of anorexia nervosa
- 511 International Journal of Eating Disorders, 44, 134-41.
- 512 Steinglass JE, Albano AM, Simpson HB, Wang Y, Zou J, Attia E, Walsh BT. (2014).
- 513 Confronting fear using exposure and response prevention for anorexia nervosa: A
- 514 randomized controlled pilot study. *International Journal of Eating Disorders*, 47(2): 174-80.
- 515 Strober, M. (2004). Pathologic fear conditioning and anorexia nervosa: on the search for
- 516 novel paradigms. *International Journal of Eating Disorders*, 35(4): 505-8.
- 517 Treasure J, Cardi V, Kan C. (2012). Eating in eating disorders. *European Eating Disorders*
- 518 *Review*, **20**: e42-9.

- 519 Wallier J, Vibert S, Berthoz S, Huas C, Hubert T, Godart N. (2009). Dropout from inpatient
- 520 treatment for anorexia nervosa: critical review of the literature. *International Journal of*
- 521 *Eating Disorders*, 42(7):636-47.

522 AUTHOR CONTRIBUTIONS

- 523 VC designed the study under the supervision of JT and IC. DMM and JT provided clinical
- 524 guidance in the development and delivery of the intervention. JL, MS, AS and OOD provided
- 525 guidance in the development of the methods and conducted the statistical analyses of
- 526 neuroimaging data. JT, IC, OOD revised the manuscript and provided expert guidance during
- 527 manuscript preparation. VC conducted the assessments and clinical sessions with the patients.
- 528
- 529

530 ADDITIONAL INFORMATION

531 The authors report no competing financial interests.

532 TABLES

533 Table 1 Pre and post-intervention clinical scores

534 Pre- (t1) and post- (t2) intervention scores on body mass index, subscales and total score of

- 535 the Eating Disorder Examination Questionnaire (EDE-Q), anxiety subscale of the Depression,
- 536 Anxiety and Stress Scales (DASS), eating disorders (ED)-related preoccupations and rituals
- 537 and confidence to change ruler. Data expressed as means and standard deviations (SD).
- 538 Statistics for paired samples *t*-tests and effect sizes are reported. Bonferroni correction
- applied (p = <.01 for the EDE-Q subscales; p = <.025 and ED-related preoccupations and
- 540 rituals). Significances surviving Bonferroni correction marked with *.

	Mean t1	SD t1	Mean t2	SD t2	Statistics	<i>p</i> values	Effect size
Body Mass Index	15.98	1.28	16.47	1.54	<i>t</i> (17) = -2.8	.001*	0.70
EDE-Q Eating Concern	3.90	1.01	3.30	1.25	t (17) = 2.80	.001*	0.67
EDE-Q Restraint	4.27	1.60	3.53	1.61	<i>t</i> (17) = 2.76	.001*	0.63
EDE-Q Shape Concern	4.53	1.26	4.15	1.46	<i>t</i> (17) = 1.25	.22	0.29
EDE-Q Weight Concern	3.97	1.58	3.52	1.58	<i>t</i> (17) = 1.14	.26	0.26
EDE-Q Total score	4.17	1.19	3.62	1.31	<i>t</i> (17) = 2.39	.002*	0.56
ED-related preoccupations	11.76	2.79	10.11	3.73	t (17) = 2.61	.02*	0.67
ED-related rituals	10.17	3.66	9.64	3.46	<i>t</i> (17) = .90	.37	0.22
DASS Anxiety	17.88	7.74	13.66	7.67	t (17) = 3.49	.003	0.80
Confidence to change	5.31	1.85	6.68	2.27	<i>t</i> (17) = - 3.22	.006	0.81

541 FIGURES LEGEND

- 542 Figure 1 Feared consequences of eating and use of safety behaviours
- 543 (a) Number of participants reporting specific feared consequences of eating ("fear of
- 544 appearing disgusting", "fear of experiencing disgust", "fear of experiencing intense distress",
- ⁵⁴⁵ "fear of changing shape very quickly" and "fear of losing control") and (b) number of
- 546 participants reporting the use of safety-behaviours to manage food-related anxiety.

547

- 548 Figure 2 Anxiety associated with eating during the sessions
- 549 Participants' anxiety ratings during food consumption in each session.