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EDITORIAL

Time to make a change: A call for more experimental research on key mechanisms in anorexia nervosa

Anorexia nervosa (AN) is a life-threatening eating disorder, characterised by persistent pathological weight loss behaviours and an intense fear of weight gain and food consumption. Although there is an abundance of scientific theories on the neurobiological, psychological and sociocultural factors thought to be involved in the maintenance of AN (e.g., Fairburn, Shafran, & Cooper, 1999; Steinglass & Walsh, 2016; Treasure et al., 2020), there is little experimental research testing these ideas. The need for theory firmly grounded in empirical evidence becomes strikingly clear when we consider that current treatments for patients with AN are limited in their effectiveness, and relapse after treatment is common (e.g., Berends, Boonstra, & van Elburg, 2018; Murray, Quintana, Loeb, Griffiths, & Le Grange, 2018). More knowledge about which causal mechanisms are involved in maintaining AN and which factors are crucial targets in the journey towards clinical improvement can help to develop more effective treatments for AN (cf. Holmes, Craske, & Graybiel, 2014). Although observational findings from cross-sectional and longitudinal studies are important to explore associations, these research designs often do not allow for the clear determination of causality. In contrast, experimental designs involving the systematic manipulation of potential key factors can shed light on causality, making experimental hypothesis testing a crucial step in the translational process from theory to therapy (cf. Nielsen et al., 2018). We believe that it is time to conduct more experimental research on key processes that contribute to the persistence of AN. Although experimental research is important for the whole spectrum of eating disorders (Jansen, 2016), the aim of this article is to address both the challenges and opportunities of experimental research in AN.

Sometimes quasi-experiments with a control group (but not necessarily an experimental manipulation) or studies relying on performance-based measures (without using an experimental design) are called 'experimental'. However, in this article, we use the word *experimental* for studies in which an independent variable (i.e., Factor 'A') is systematically manipulated (increased or reduced) in the experimental condition and compared with at least one control condition in which factor A is not manipulated (see Figure 1). Subsequently, the effect on a dependent variable (i.e., Factor 'B') is investigated to determine whether changes in Factor A cause changes in Factor B in the experimental condition but not in the control condition. To ensure that effects are solely attributable to this manipulation, randomisation of participants to conditions is key, which should ensure the equal distribution of potentially confounding variables across conditions. Although randomised controlled treatment trials (RCTs) technically are experimental designs, they do not necessarily give detailed insight into the causality of maintaining mechanisms (Jansen, 2016; Nielsen et al., 2018). In interventional RCTs, several factors (e.g., both normalising eating pattern and addressing body satisfaction) are usually targeted simultaneously by comprehensive treatment programmes, which makes it difficult to distinguish which components of the intervention precisely caused the treatment effect. In addition, RCTs of good quality are challenging to conduct (labour intensive and expensive) and therefore might not be a wise expense of energy and money when it is unclear whether the intervention addresses causal factors (e.g., Fairburn, 2005). This lack of clarity may have contributed to a lack of any observed differences between different outpatient therapies for adult AN evaluated over the last 30 years (Zeeck et al., 2018). In addition to testing comprehensive treatment approaches containing different interventions, series of experimental manipulations of the putative mechanisms of efficacy should be performed (e.g., see also the guidelines for developing and evaluating complex interventions of the Medical Research Council; Craig et al., 2019). In contrast to RCTs, experiments are designed to isolate one key process and investigate its unique (causal) influence on an outcome measure within a mechanistic framework. That is why experimental designs are a relatively cost- and time-effective way to manipulate presumed key processes in AN and hence determine the factors that are causally involved in AN (Jansen, 2016).

Experimental manipulations already successfully advanced treatments for other psychiatric disorders. For example, with respect to panic disorder, many experimental studies were conducted that not only helped in

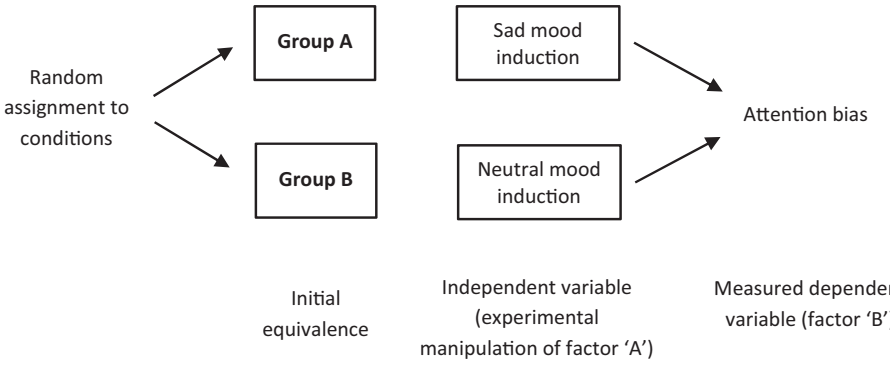

FIGURE 1 Schematic overview of an experimental design

the theoretical understanding of panic disorder but also advanced empirically based treatments for panic disorder contributing to high remission rates (see e.g., Van den Hout, 2010). The clear advantages of an experimental design raise the question as to why experimental studies on key processes in AN are so scarce (e.g., Glashouwer, van der Veer, Adipatria, de Jong, & Vocks, 2019). For example, when examining the scientific literature over the last 5 years, only eight studies were published in which an experimental design was used in an AN sample (between-subjects designs, as in Figure 1: Hartmann, Thomas, Greenberg, Rosenfield, & Wilhelm, 2015; Loeber et al., 2016; Naumann, Tuschen-Caffier, Voderholzer, Schäfer, & Svaldi, 2016; Turton, Cardi, Treasure, & Hirsch, 2018; Preis et al., 2020; within-subjects designs: Cardi, Esposito, Clarke, Schifano, & Treasure, 2015; Svaldi et al., 2016; Leppanen et al., 2017].[1] At least three important obstacles exist for performing experimental studies in AN. First, compared with many other mental disorders, AN has a low prevalence affecting around 1–4% of women during their lifetime (e.g., Keski-Rahkonen & Mustelin, 2016). Hence, data collection of patients with AN can be quite effortful and time consuming. Second, in contrast to many other mental disorders, the severity and potential mortality of AN often demand immediate interventions. This can make it difficult to include individuals in experimental research. Relatedly, the severity of the disorder might – to some degree – limit the options for testing certain experimental manipulations in an isolated fashion (e.g., to focus on experimentally manipulating body dissatisfaction without addressing food deprivation). Third, for ethical reasons, it is difficult to investigate the starvation component of AN in analogue samples.

Despite these substantial challenges, we see many opportunities for applying experimental designs in AN samples. Several features of experimental designs directly contribute to their feasibility. Following a mechanistic view, the focus within experiments lies on single mechanisms. Limiting a study design to a single mechanism and a specific outcome measure might appear like a restriction, but can actually be considered a strength, as it makes research more feasible and cost effective. Research questions are rarely solved in one experiment, and typically, a series of experiments is needed to unravel the mechanism in question. Such a series of experimental studies creates the opportunity to redirect along the way, because the outcomes of one experiment can directly be taken into account when designing a subsequent experiment. Then, once the initial causal mechanism is established, the impact of the mechanism on related AN symptoms can be investigated. Finally, this empirically based understanding of the mechanism in action can inspire novel ideas on how to tackle the mechanism in order to reduce symptoms. This transfer from basic experimental research towards clinical application could then, in turn, be investigated in a series of experiments before moving towards larger and more complex RCTs. Another advantage of such a step-by-step approach is that one can start with a simple step and only add complexity when necessary. For example, as a first step, often a control condition can be used in which participants receive no manipulation at all in order to establish the effect of the manipulation. Then, when findings are as expected, the mechanism can be disentangled further by adding more complex control conditions. Adding further to the feasibility, experiments typically take place within a short time-frame, making them relatively time efficient research endeavours. Even when effects of a manipulation are of short duration, there is still the opportunity to study the impact on specific proxies for AN (i.e., surrogate measures such as state body satisfaction, food intake in a specific situation). An option to amplify (the power and duration of) effects may be to intensify the dose of the manipulation in order to manipulate more ingrained mechanisms, for example, by administering several sessions within a short time period. Add-on designs can be employed in which the effects of 'mini-interventions' are investigated next to treatment as usual to overcome problems with randomisation to control

conditions (e.g., Glashouwer et al., 2018; Turton et al., 2018). Finally, where appropriate, online experiments may be considered as alternatives to laboratory studies. Despite all advantages, experimental designs also have their limitations. It can be quite challenging to design manipulations that solely address one specific component of interest. In addition, short-term effects of an experimental manipulation might not necessarily be applicable to the longer term

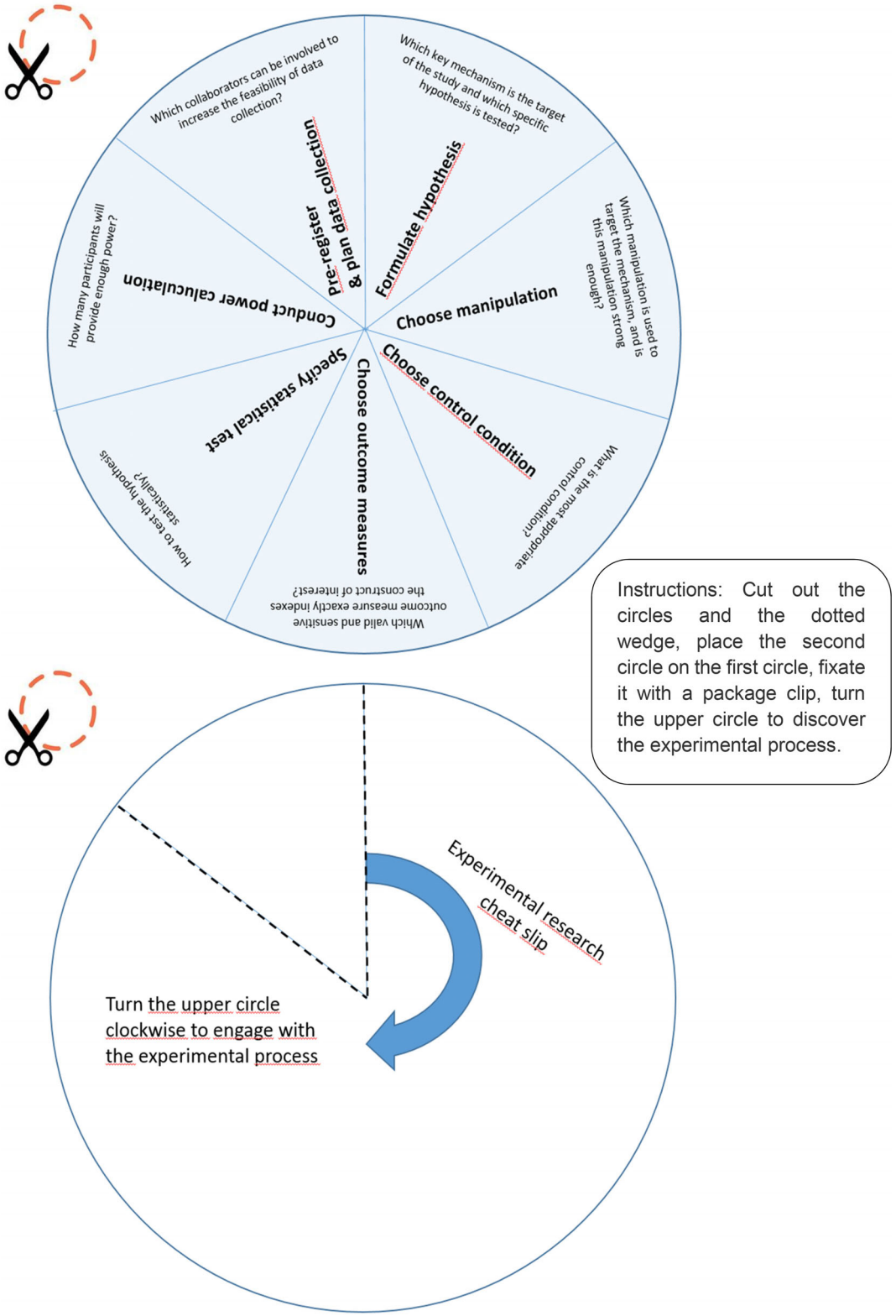

FIGURE 2 Cheat slip for designing experimental research (in anorexia nervosa) [Colour figure can be viewed at wileyonlinelibrary.com]

outcomes. Because experimental designs clearly limit the number of factors and outcome measures that can be investigated, it forces one to think hard and select carefully beforehand. However, we argue that 'less can become more'. Experimental studies designed to test theory-driven hypotheses with carefully selected outcome measures might really have the potential to enhance our understanding of the persistence of AN (cf. Platt, 1964).

Designing an experimental study starts with a clear theory-based idea (i.e., hypothesis) of which key mechanism is thought to causally affect a specific AN symptom and should be the target of the study (see Figure 2 for an interactive simplified illustration of the experimental process). For example, when being interested in the influence of negative affect on eating disorder symptoms, one should start with formulating a specific hypothesis of how negative mood exactly impacts on a specific core symptom (e.g., negative mood leads to more attention towards negatively valenced body parts which might contribute to negative body image; Svaldi et al., 2016). Then, it is important to develop robust, reliable and preferably powerful methods to manipulate the mechanism in question. Excellent experimental manipulations have been developed in many scientific fields. In case of the example, a mood induction could be used to induce feelings of sadness, for example, via sadness-inducing video clips (e.g., Svaldi et al., 2016) or a combination of music that is experienced as sad and autobiographical recall (e.g., Werthmann et al., 2014).

It is also important to consider what would be the best control condition. In case of the example, a happiness or a neutral induction might be used as two control conditions; and then in subsequent experiments, one could investigate whether the effect on body dissatisfaction is specific to sadness, or a response to negative emotions in general (including anger and fear, for instance). A manipulation check should be included to see whether the mechanism of interest was indeed successfully targeted (e.g., measuring state emotions after a mood induction; or measuring whether individuals indeed performed a certain manipulation as supposed) (Nielsen et al., 2018). Then, the next step is to choose the outcome measure(s) on which the manipulation is expected to have an impact and make sure that this measure is sensitive to change, for example, use state measures or behavioural indices in a laboratory setting. Ideally, one primary outcome measure is selected that exactly engages the construct of interest. In case of the example, a behavioural measure could be included of gaze frequency and gaze duration towards self-identified most ugly body parts. However, depending on the research question, it can be useful to think about adding multi-modal assessment methods to fully understand how a potential mechanism affects different intra- or inter-individual processing levels (e.g., physiological and cognitive processes; see also NIMH Research Domain Criteria Initiative; Kozak & Cuthbert, 2016). For instance, in the example, self-reported state body dissatisfaction might be added as additional more distal outcome measure, next to attentional bias for body related cues. Finally, it is important to specify statistical analyses and conduct power calculations to determine the required sample size. Pre-registering the research plan seems a helpful tool in this process which, at the same time, facilitates transparency about the work to others (e.g., Munafò et al., 2017). Insights into causal mechanisms generated by series of experiments could be translated step by step into clinical applications. For example, if negative emotions are indeed causally linked to negative body image via attentional bias towards negatively valenced body parts, clinical interventions could focus on how negative emotions can effectively be reduced by patients and if this impacts subsequent attentional bias and body dissatisfaction. Another option would be to target attentional bias. Such clinical applications could again be tested first experimentally, for example, as adjuvant mini-intervention to determine their clinical potential, before testing its effectiveness as (part of) a clinical intervention.

We believe that it is now time to join recent developments in mental healthcare research (e.g., as initiated by the NIMH) and increase efforts of experimentally investigating the psychological, (neuro)biological and sociocultural mechanisms that are assumed to be involved in AN. This yields not only for promising new mechanisms but also for key factors derived from existing theoretical models (e.g., Pennesi & Wade, 2016). Although it is not an easy job to conduct experimental studies in patients with AN and although there are barriers, we are optimistic and see many opportunities, and a definitive need for applying experimental research in AN. Considering the low prevalence of AN, collaborations between research groups and between research and practice centres are essential (e.g., the Anorexia Nervosa Genetics Initiative). Just as with large-scale RCTs, we should join forces, for example, by conducting multi-centre data collection, by sharing knowledge and practical tips in an open science framework about how experiments can be conducted in this patient population and by formulating a shared research agenda about which maintaining factors show the highest promise regarding the current state of the art of research. In addition, also within the grant schemes and funding landscape it is essential to create awareness both for the unique obstacles as well as the high value of this type of research (see also e.g., Murray, Pila, Griffiths, & Le Grange, 2017). We want to encourage researchers to join the challenge of using experiments to enrich AN research and to develop more effective treatments for AN.

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K.A.G. wrote the first draft of this manuscript. J.W., T.B., V.C., and A.J. critically reviewed and contributed to this first draft. All authors critically reviewed and approved the final manuscript and endorse its message.

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ENDNOTE

[1]Although not included in our selection, some RCTs in which an intervention is targeting one specific mechanism could also be seen as experiments (e.g., Glashouwer, Neimeijer, de Koning, Vestjens, & Martijn, 2018; Hibbs et al., 2015; Levinson et al., 2015; Sproch, Anderson, Sherman, Crawford, & Brandt, 2019; Steinglass et al., 2018).

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