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Toward valid and reliable brain imaging results in eating disorders

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Abstract

Human brain imaging can help improve our understanding of mechanisms underlying brain function and how they drive behavior in health and disease. Such knowledge may eventually help us to devise better treatments for psychiatric disorders. However, the brain imaging literature in psychiatry and especially eating disorders has been inconsistent, and studies are often difficult to replicate. The extent or severity of extremes of eating and state of illness, which are often associated with differences in, for instance hormonal status, comorbidity, and medication use, commonly differ between studies and likely add to variation across study results. Those effects are in addition to the well-described problems arising from differences in task designs, data quality control procedures, image data preprocessing and analysis or statistical thresholds applied across studies. Which of those factors are most relevant to improve reproducibility is still a question for debate and further research. Here we propose guidelines for brain imaging research in eating disorders to acquire valid results that are more reliable and clinically useful.

Keywords

brain imaging; eating disorders; guideline; method; reliability; validity

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1 | INTRODUCTION

Eating disorders are psychiatric disorders with complex bio-psychosocial underpinnings (American Psychiatric Association, 2013). Understanding the neurobiology of eating disorders, similar to other psychiatric disorders, has been challenging due to the complexity of the human brain. One way to understand human brain function is brain imaging, which has exponentially increased over the past two decades and produced thousands of published articles. Such studies have helped identify brain circuits that, for example, control motor function or emotion regulation, or that are involved in the processing of rewarding, aversive, or generally salient stimuli (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Moran & Zaki, 2013). In fact, review articles of the available brain imaging literature have repeatedly implicated for example reward processing circuits, as well as pathways involved in cognition or emotion processing in eating disorders (Berner & Marsh, 2014; Frank, 2015a; Garcia-Garcia et al., 2013; Kaye et al., 2013; Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; King, Frank, Thompson, & Ehrlich, 2017; Martin Monzon, Hay, Foroughi, & Touyz, 2016; Steward, Menchon, Jimenez-Murcia, Soriano-Mas, & Fernandez-Aranda, 2017). The hope and expectation now are that with increasing capability of novel research methods to study the human brain, we will eventually understand mechanisms of brain function in health and disease and be able to use this information to develop better treatments.

A host of neuroimaging tools has been developed that can be used in eating disorder research. To study brain gray (GM) and white matter (WM) volumes or cortical thickness and surface area, magnetic resonance imaging (MRI) is commonly used (Jalbrzikowski et al., 2013). Relatively novel methods, also based on MRI technology, are diffusion weighted (DWI) and diffusion tensor (DTI) imaging to assess WM microstructure (Filler, 2009). DWI measures the diffusion of water molecules in brain pathways (Jones et al., 2013). DTI uses those diffusion data and calculates tensors to determine how strongly water diffuses along axons. These data have been associated with neuronal myelination but even more with the axon structure itself, such as axon diameter, as well as packing density of fibers, membrane permeability and crossing of fibers (Jones, Knosche, & Turner, 2013; Song et al., 2002; Takahashi et al., 2002). The now most commonly used functional brain imaging technique is functional magnetic resonance imaging (fMRI), which measures changes in local blood flow and resulting (de)oxyhemoglobin levels during brain activation (Raichle, 1998), the so-called blood oxygen level dependent (BOLD) fMRI. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radioactive ligands that distribute throughout the brain. These methods can provide information about regional cerebral glucose metabolism or distribution of neurotransmitter receptors.

While the number of brain imaging studies has dramatically increased, there has been recent criticism that many or maybe even most brain imaging studies have been too lenient in the control of statistical thresholds (Poldrack et al., 2017). This leads to poor reliability of the data and, in fact, a major problem in human brain imaging research has been the poor reproducibility of study results. Other potential confounds in brain imaging are of methodological nature such as reliability of DWI and DTI, or partial volume effects (Dukart

& Bertolino, 2014; Jones et al., 2013). Aside from such general methodological issues, brain imaging research aimed at understanding etiologic factors underlying eating disorders has additional potential confounds, such as the acute or chronic effects of malnutrition, excessive exercise, and comorbid psychiatric disorders and medications (Barbarich-Marsteller et al., 2013; Shetty, 1999). These factors could contribute to the inconsistencies found in eating disorder brain imaging research (Van den Eynde et al., 2012).

In this article, we propose recommendations for study design, data analysis, and presentation of brain imaging research involving patients with eating disorders. We believe that such guidelines are critical to developing a comprehensive understanding of brain structure and function across research groups and methodologies. A caveat is that recruiting study participants can be difficult, and study populations will always have confounds that need to be addressed in data analysis and interpretation. Nevertheless, the eating disorders field is small when compared with other areas of psychiatric research, making it even more important that we use similar standards and methods to advance the field.

Ideally, we would be able to provide definitive recommendations specific to brain imaging methodology and identify more and less important parameters to assess and report. However, there is no single best, but rather multiple ways to analyze a neuroimaging dataset (Gorgolewski & Poldrack, 2016), and no consensus in the eating disorder or broader neuroimaging field for what is needed to increase reproducibility. The meaning of the term reproducibility has in fact been challenged and there is no common definition (Nichols et al., 2017). In addition, out of a sample of 100 brain imaging studies in the field of psychology, findings from only 39 could be replicated (Open Science Collaboration, 2015). Eklund, Nichols, and Knutsson (2016) studying significance thresholds addressing the multiple comparison problem across imaging studies have suggested elevated false positive rates. Therefore, the current best approach is to be as transparent as possible with reporting of the general study methods, data acquired, code used and manuscripts derived from the study (Gorgolewski et al., 2016; Gorgolewski & Poldrack, 2016; Nichols et al., 2017; Poldrack et al., 2017). In this manuscript, we similarly argue for the importance of being as transparent and detailed in data gathering and description in order to support an “open science” approach.

The current state of human brain imaging has just started to use this type of research to identify potential biomarkers for psychiatric illnesses. For instance, one could use brain imaging to test symptom or performance validity (Bigler, 2015). Accurate modeling of relationships between brain function and behavior is key in this effort but needs much more work (Rigoux & Daunizeau, 2015). Yet, reliable methods are needed before we can truly move toward brain imaging that will bring the results that are valid for clinical work.

2 | DEVELOPMENT, DEMOGRAPHIC DATA, AND ILLNESS STATE

Eating disorders most commonly develop during adolescence, a time of very active brain development before brain volume, cortical thickness, neurotransmitter receptors, and so on reach their adult levels (Gogtay et al., 2004). This has important implications, as brain development could be directly related to the etiology of eating disorders. We do not know

how neurodevelopmental trajectories are disrupted by the onset and severity of an eating disorder, which is an important direction of research to pursue. The majority of individuals with eating disorders are female. However, there are also a substantial number of males with eating disorders, and gender issues are completely unexplored from a neurobiological perspective. Sex is associated with differences in brain activation, and brain alterations found in females with eating disorders might not apply to males (Gur & Gur, 2017). There is also some indication that individuals with anorexia nervosa are, on average, more lefthanded than unaffected controls (Tenconi et al., 2010). Cognitive neuroscience has indicated that handedness accounts for significant variation in the brain signal and therefore needs to be taken into account (Pool, Rehme, Eickhoff, Fink, & Grefkes, 2015). Also unexplored are differences in brain structure and function across different racial and ethnic groups. The majority of individuals who seek or receive treatment in North America and Europe continue to be non-Hispanic whites, but the demographics of individuals afflicted with an eating disorder are changing, and we will need to test whether different racial and ethnic backgrounds are associated with variations in brain function (Monge et al., 2015). Age, sex, and ethnicity are variables that are relatively easy to define and describe. However, variables such as height and weight differ vastly, and using body mass index (BMI, weight in kg divided by height in meters squared, kg/m^2) provides a commonly used measure in adults that combines height and weight. In order to account changing BMI targets during development, age adjusted BMI percentile or BMI standard deviation scores should be assessed in youth. Duration of illness is frequently measured in weeks, months or years, with no standard. More concerning is the lack of a uniform definition of “recovery”. For instance, a person’s recovery status may be determined by achieving a certain weight, or not meeting diagnostic criteria for a certain period of time.

We suggest the following recommendations:

1. Study groups should be age matched, and age may need to beincluded as a covariate in between-group analyses.
2. Race and ethnicity should be considered, either by matching groups or factoring these characteristics into analyses.
3. Duration of illness should be reported and its effects on study results tested.
4. Handedness should be assessed, and either only right-handed individuals should be included or handedness should be accounted for in the data analysis.
5. The effects of height-adjusted weight (body mass index) on brain measures should be tested. In youth, an age adjusted BMI percentile or BMI standard deviation scores should be reported.
6. While recovery is not uniformly defined, every effort should be made to describe level of recovery (duration, BMI history, eating disorder psychopathology) in a study sample and its relationship with brain findings. Future studies should investigate brain changes over the course of short and long-term recovery.

3 | EFFECTS OF EXERCISE, HYDRATION STATUS, BINGE EATING AND PURGING, AND MALNUTRITION

The hallmark signs of eating disorders are extremes of self-starvation, binge eating, self-induced vomiting or use of laxatives and diuretics, as well as excessive exercise. Research in noneating disorder populations has shown that some of these behaviors can significantly affect brain structure and function (Boraxbekk et al., 2015; Freund et al., 2012; Hadjikhani et al., 2015; Stice, Burger, & Yokum, 2013). Although exercise has the potential to increase brain volumes in old age, the opposite may be the case in young adults, and the amount of exercise also plays an important role (Williams et al., 2017; Wobrock, Hasan, & Falkai, 2012). For example, extreme exercise in ultramarathon runners was associated with reductions in temporal, occipito-parietal and anterior cingulate gray matter volumes, as well as reduced brain volume in the caudate nucleus (Freund et al., 2014); these alterations normalized on follow-up after 8 months.

Findings from studies investigating short-term dehydration in the context of 1–2 h of thermal exercise suggested increased or decreased ventricular volume, but no change in total GM or WM volumes (Kempton et al., 2009; Watson, Head, Pitiot, Morris, & Maughan, 2010). In another study, 12 h of hyperhydration followed by an overnight fast (dehydration condition) did not reveal differences in total brain volume or water content (Meyers et al., 2016). However, 16 h of dehydration in another study led to significantly lower brain volume (Duning et al., 2005). Individuals with eating disorders often have longer periods of severe malnutrition with dehydration or hyperhydration, food restriction or excessive food intake (American Psychiatric Association, 2013; Hart, Abraham, Franklin, & Russell, 2011; Lowinger, Griffiths, Beumont, Scicluna, & Touyz, 1999), and studies over a longer period of time may be more reflective of the effects that those behaviors have on brain structure or function in this population. One study investigated the effects of hydration status in a group of healthy individuals over up to 2 days of altered hydration status (Streitburger et al., 2012). That study reported that 10 h of hyperhydration was associated with larger volumes in caudate and temporo-parietal regions, while 2 days of dehydration led to reduced gray and white matter volume in temporo-parietal and orbito-frontal regions, as well as enlarged ventricular space. Brain function may also be affected by dehydration. In one study in adolescents, short-term dehydration after exercise over 90 min did not show altered brain volume, but greater brain response when compared with a control group in fronto-parietal cortex while performing an executive function task; task performance was similar between groups (Kempton et al., 2011). To date, three studies tried to address the question of whether brain abnormalities in underweight anorexia nervosa may be due to dehydration by measuring urine specific gravity immediately prior to neuroimaging, but found no evidence of dehydration related to brain morphology (Bernardoni et al., 2016; King et al., 2015; Vogel et al., 2016). However, this does not exclude the existence and effects of dehydration in eating disorders. For one, a single measure of urine specific gravity may not be sufficient to diagnose hydration status (Armstrong, Kavouras, Walsh, & Roberts, 2016). Another possible confound is that osmoregulation may be disturbed in anorexia nervosa and urine specific gravity may not accurately reflect hydration status (Evrard, da Cunha, Lambert, & Devuyst, 2004). There is also an indication that osmoregulation is altered or inefficient in bulimia

nervosa (Chiodera et al., 1993). All in all, the effects of hydration status on brain structure or function in eating disorders continue to be an area of debate and need further exploration.

Anatomical MRI studies in individuals with bulimia nervosa indicate that binge-eating and purging behaviors may be directly related to reduced brain cortical thickness (Marsh et al., 2015), and fMRI data suggest that binge-eating/purging episodes are inversely associated with regional brain activations. The mechanisms explaining how binge-eating/purging behaviors affect those measures are not known, but purging causes profound dehydration and electrolyte depletion, as well as altering neurotransmitter levels (Bahia, Mascolo, Gaudiani, & Mehler, 2012; Kaye et al., 1990).

Several recent studies show that many alterations in brain structure are rather short lived and probably due to malnutrition (Bernardoni et al., 2016; King et al., 2015). Therefore, acute eating disorder behaviors and similarly nutritional rehabilitation probably affect brain structure and function in human brain imaging studies and may contribute to the inconsistent findings in the literature (Van den Eynde et al., 2012). An important question in this context is to ask to what extent those alterations are contributing to eating disorder pathology, or whether they are effects of the nutritional status with questionable impact on driving illness behavior (Frank, 2015b). However, the optimal methods to measure the effects of dehydration, malnutrition, or binge-eating and purging behaviors are not established. Recent data suggest that brain structure (volume) may affect brain function (Dukart & Bertolino, 2014). If true, this could have several important implications for eating disorder research. First, studies of brain function should adjust for alterations in brain volume. Second, brain volume could then be a proxy for brain function and used as a biomarker that is less difficult to acquire than functional imaging data. Third, behavior could be affected by a combination of brain structure and function and we would have to combine methodologies to bridge the brain imaging research–behavior gap.

The status of food intake is best described in calories per day or meal to reduce ambiguity across studies, and fluid intake should be described by volume. If such data are not available, changes in weight in the weeks prior to brain imaging should be documented. Frequency of distinct binge-eating or purging episodes can be counted and described by week. Exercise can be difficult to measure because of the various forms and their differing impact on weight (e.g., cardioexercise vs. yoga), however, exercise, acute, and habitual, can have important effects on the brain (Huang, Larsen, Ried-Larsen, Moller, & Andersen, 2014). The amount of exercise in the 24 h prior to the study and habitual exercise in hours per week together with some qualitative description is probably the best approach.

We, therefore, propose the following guidelines

1. The methods and procedures should indicate under what nutritional conditions a study was conducted, whether study participants controlled their own food intake or whether they were in a structured program where they had to follow a dietician’s directed meal plan adjusted for nutritional needs.
2. Binge-eating and purging frequency should be reported and tested against study outcome measures.

3. The methods should indicate whether patients have lost or gained weight or BMI in the weeks prior to brain imaging.
4. Food intake prior to brain imaging should be standardized within studies (e.g., an 8 h fast or a standardized meal) and reported.
5. Exercise should be quantified and the effects tested on brain imaging data. This is especially important for studies that recruit individuals who are not in a treatment program. The amount of exercise over the past 24 h prior to the study should be reported. Habitual exercise may also be of interest as it affects brain structure and function and should be reported and tested for effects on brain function or structure if available.
6. Whether an individual has a history of an additional eating disorder other than the type described in a particular study should also be recorded and its effects on brain measures tested.
7. We should specifically test to what extent regional brain structure measures, such as gray or white matter volume, may contribute to regional functional imaging findings.

4 | STAGE OF TREATMENT

Eating disorder treatment can take a long time and involve various levels of care (Halmi, 2005). Furthermore, there is no unified treatment approach, so that the types of treatments that patients receive vary greatly. There are different reasons why a person “does not eat” (Dignon, Beardsmore, Spain, & Kuan, 2006) and it is unclear how treatment type and duration—aside from nutritional rehabilitation—affects brain-imaging results. However, treatments that do not solely rely on weight gain but also include individual or group therapy, emotion regulation or family therapy, etc., may have a significant impact on brain imaging, for example, during cognitive–emotional tasks. Some research suggests that learning or effort can modulate brain function, however, we know not much about whether high amounts of evidence-based psychotherapy, for instance affects brain response to anxietyprovoking or salient stimuli.

We, therefore, recommend that:

1. Publications should describe whether study participants were in a specific treatment setting or not.
2. Studies should indicate whether study participants that were in treatment were all in the same setting or treated with the same treatment modality, or not.
3. The length of time in treatment and BMI change between starting treatment and scanning should be reported.

5 | HORMONAL EFFECTS

Weight fluctuations, stress, and behaviors (e.g., excessive exercise) associated with eating disorders result in characteristic endocrine adaptations that may impact brain structure and

function (Yau & Potenza, 2013). For example, in restrictive eating disorders such as anorexia nervosa, chronic starvation may lead to hypothalamic amenorrhea with hypoestrogenemia, low testosterone levels, hypercortisolemia, growth hormone resistance (high growth hormone, but low downstream IGF-1 levels), and altered secretion of appetite-regulating hormones (e.g., low anorexigenic hormones leptin and oxytocin; high orexigenic ghrelin [Culbert, Racine, & Klump, 2016; Misra & Klibanski, 2014] and AGRP [Merle et al., 2011]). While many hormonal alterations in response to low-weight are adaptive (i.e., to stimulate food consumption and/or conserve limited resources) and resolve with weight restoration, evidence of seemingly paradoxical hormone levels in some cases (e.g., high levels of anorexigenic PYY) and persistent abnormalities after weight gain (e.g., in PYY [Misra et al., 2006; Nakahara et al., 2007; Pfluger et al., 2007]), ghrelin (Holsen, Lawson, Christensen, Klibanski, & Goldstein, 2014; Nakahara et al., 2007), oxytocin (Afinogenova et al., 2016), hypothalamic–pituitary–adrenal axis (e.g., cortisol) (Grinspoon et al., 2001; Lawson et al., 2013; Mayer et al., 2005) argue for a potential etiologic role versus scar or delayed recovery from chronic starvation, or effects of residual psychopathology (Misra & Klibanski, 2014). Endocrine changes, including reproductive dysfunction, activation of the hypothalamic–pituitary–adrenal axis, and differences in secretion of appetite-regulating hormones, have also been demonstrated in other eating disorders, such as bulimia nervosa and binge-eating disorder (Culbert et al., 2016; Poyastro Pinheiro et al., 2007). Recognizing these differences is important as these are neurotrophic hormones that may affect brain volume (Brown et al., 2015; Giedd, Raznahan, Mills, & Lenroot, 2012) or function (Dedovic, D'Aguiar, & Pruessner, 2009; Kim, 2016). In imaging studies in females, for example, sex hormone status (e.g., menstrual cycle phase and oral contraceptives) has been shown to impact brain structure (e.g., GM volume of limbic regions) (Catenaccio, Mu, & Lipton, 2016) and function (e.g., fMRI activation in brain regions involved in reward or emotional processing and cognitive functioning) (Dreher et al., 2007; Toffoletto, Lanzenberger, Gingnell, Sundstrom-Poromaa, & Comasco, 2014). Also, hormones often have a diurnal rhythm, and their secretion may be stimulated or suppressed by food intake, exercise or stress. It is critical to take these factors into account in neuroimaging studies of eating disorder patients. Most hormones have to be measured directly, requiring special laboratory facilities. However, investigators could also use a calendar method to assess menstrual cycle, a method that has good congruence with serum sex hormone levels (Wideman, Montgomery, Levine, Beynnon, & Shultz, 2013) and can be used to schedule MRI scans within a certain cycle phase without need for a blood draw and lab costs. In summary, future studies investigating the link between endogenous hormone levels and brain structure and function in eating disorders are warranted.

We, therefore, recommend that:

1. Given the effects of sex hormones on the brain, sex must be considered and, when possible, males and females studied separately.
2. Menstrual status (e.g., pre- vs. postmenarcheal, presence, and duration of amenorrhea) should be documented and used in the analyses.
3. In menstruating females, imaging should ideally be done during the same menstrual cycle phase for all study participants (e.g., the early follicular phase

when estradiol and progesterone levels are low). If conducting brain imaging during the same cycle phase is too impractical and difficult to undertake, the cycle phase (or sex hormone levels) should be recorded and taken into consideration when analyzing the brain imaging data.

4. If possible, females should be studied at least eight weeks off of oral contraceptive pills (OCPs). Alternatively, if taking OCPs, females can be when compared with a control population also taking OCPs or, if a longitudinal study, participants taking OCPs at baseline should be taking OCPs (during the same phase—either active or placebo, but not switching back and forth) at each of the time points. If these approaches are not possible, then OCP use can be used as a covariate in analyses.

5. If hormone levels are measured, similar to the recommendation to standardize nutritional status, the conditions under which hormones are assessed (e.g., early morning and fasting) should be standardized and reported.

6. Other factors that influence the hormonal milieu, such as exercise, sleep patterns, the level of stress, drugs, or supplements, and medical and psychiatric comorbidities, should be considered.

6 | COMORBIDITY AND MEDICATION

A plethora of brain imaging studies has shown alterations in structure and function across most psychiatric disorders (Shenton & Turetsky, 2011). Eating disorders are associated with high comorbidity, and it seems therefore highly important that effects of those comorbid conditions on brain imaging results are taken into consideration (Hudson, Hiripi, Pope, & Kessler, 2007). Studies often covary with measures for anxiety or depression severity, such as the Beck Depression Inventory for instance (Miller & Chapman, 2001). It is unclear whether this is adequate. An argument for the use of such measures is that the severity of a condition might directly correlate with the brain response; however, this could be problematic as correlations between behavior and biology have been notoriously weak. Furthermore, comorbid depressive symptoms in AN may be a direct consequence of acute undernutrition and may improve with weight gain, although the available data are inconsistent (Godart et al., 2003; Mattar, Huas, Duclos, Apfel, & Godart, 2011; Meehan, Loeb, Roberto, & Attia, 2006). Nonetheless, accounting for comorbid diagnoses in imaging analyses would have the benefit that if diagnosed for instance according to DSM-5, the impairment criterion would support a certain severity of the syndrome or illness, which might reduce false positives and could be better reflected in generally altered brain response (Spitzer & Wakefield, 1999). This needs further study. Suitable instruments for assessing diagnoses are for instance the Structured Clinical Interview for DSM Disorders (SCID), now compatible with DSM-5 (First, Williams, Karg, & Spitzer, 2015); another possibility would be for instance the MINI International Neuropsychiatric Interview, which has a paper and electronic version as well as a version for youth (Sheehan et al., 1998, 2010); a common instrument for children and adolescents is the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997). It may be self-evident, but we do want to

stress that also the eating disorder diagnoses should be assessed using validated instruments such as the SCID or the Eating Disorder Examination (Fairburn, 2005).

Psychoactive medications, in particular antipsychotics, as well as frequent use of psychoactive substances such as drugs, alcohol, tobacco or caffeine, have also been found to influence brain imaging data and also need to be accounted for in the analysis (Ewing, Sakhardande, & Blakemore, 2014; Moncrieff & Leo, 2010; Schneider et al., 2014). The time frame for reporting of substances, including illicit drugs, cannabis, alcohol, nicotine and caffeine may vary dependent on the study design. Study designs also differ with respect to whether use of substances has to be excluded or not from the study. The problem with abstaining from for instance nicotine on the day prior to the study is that it would not reflect "normal conditions" for a habitual smoker. To reach steady state conditions, medication has to be taken for 4–5 half-lives and this should be taken into consideration when studying individuals on medication (Ito, 2011).

We recommend the following procedure:

1. Study participants should be assessed using diagnostic instruments that go beyond the eating disorder diagnosis and those conditions should be reported.
2. If a study sample includes individuals with comorbid conditions, the effects of these conditions on the brain imaging results should be assessed.
3. Any substances and alcohol for the past 24 h prior to the study should be recorded and reported and the effects on brain data assessed. Habitual use of substances over the past 3 months prior to the study are also of interest and should be reported if available.
4. Ideally, medication use should be stable for four to five half-lives before brain imaging to accomplish at least steady state conditions.

7 | TECHNICAL AND STATISTICAL CONSIDERATIONS, AND STUDY DESIGN

Research over the past few years has repeatedly raised concerns about the validity of brain imaging data, for instance because of insufficient statistical thresholds (Bennett, Wolford, & Miller, 2009; Eklund et al., 2016; Woo, Krishnan, & Wager, 2014). On the other hand, whole-brain multiple comparison corrections may be overly conservative (Lindquist & Mejia, 2015). Poldrack et al. (2017) have laid out detailed guidelines to address this problem in the analysis of brain imaging data. Outliers and non-normally distributed data are an important issue in brain imaging research in general and appropriate tests (parametric, nonparametric) should be selected depending on the data at hand. A problem here is that brain imaging software commonly uses parametric tests although the imaging data often violate those assumptions (Hanson & Bly, 2001). Larger sample sizes always improve data reliability and reduce type I (false positive) and type II (false negative) errors. Individuals with eating disorders and especially youth with anorexia nervosa are often difficult to recruit (McDermott et al., 2004) and a careful power analysis (determination of the sample size required to detect an effect of a given size with a given degree of confidence) to justify

sample size is commonly not presented (Poldrack et al., 2017). Using different MRI scanners, pulse sequences, or other equipment in the same study may also bias results, although these effects may be relatively small when compared with participant effects, and specific methods have been developed to ensure consistency of data for multisite studies (Keator et al., 2016; Yendiki et al., 2010). In task-based fMRI, it is important to ensure that contrasts (e.g., food vs. nonfood items) are based on a sufficient number of trials separated by appropriate intertrial or interblock intervals and that the stimulus material has similar visual properties (Jezzard, Matthews, & Smith, 2001). Some and especially chronic and older individuals with eating disorders have severely reduced brain mass, and increased CSF space; therefore, care must be taken to ensure that results from such a person are not outliers due to misalignment that distorts the overall study results. Resting-state fMRI is very sensitive to head motion and the choice (and size) of seed regions in connectivity analyses (Lord et al., 2016; Power, Schlaggar, & Petersen, 2015). The Organization for Human Brain Mapping has recently issued a set of recommendations on how to deal with these and similar issues, and motion correction methods have been reviewed elsewhere (Nichols et al., 2017; Zaitsev, Maclaren, & Herbst, 2015). Although often several approaches can be valid, it is crucial to report all details of a study and MRI processing transparently and completely, so that other researchers understand study limitations and replication attempts are feasible (Nichols et al., 2017). A recent example in the eating disorder field is a set of studies that applied sweet taste stimuli. One study found that individuals with anorexia nervosa had lower but individuals with bulimia nervosa had higher response when compared with controls (Oberndorfer et al., 2013). Other studies however, found the opposite response pattern (Frank et al., 2012; Frank, Reynolds, Shott, & O'Reilly, 2011). We believe that both studies are correct and the crucial issue here is repeated versus random application of the same taste stimuli, which probably activated the reward circuitry differently (Oberndorfer et al., 2013). Therefore, description and discussion of task methodology are essential to correctly interpret the results.

We recommend the following procedures:

1. Sample size and statistical analysis methods should be well justified. Some have suggested minimum numbers of study participants per group to capture the most prominent findings (Thirion et al., 2007). However, there is no standard approach and methods should describe what measures were taken to avoid Type I or Type II errors, including correction for multiple comparisons (Carter, 2016).
2. Task stimuli in fMRI should be well matched with their respective control condition.
3. Studies should ensure that outliers, for instance due to extremely altered brain structure, do not drive group results.
4. Whether data are normally distributed should be assessed and the appropriate test selected for statistical analysis.
5. Studies should follow the latest recommendations for brain imaging analysis (see cited publications above) and describe in detail how motion correction was conducted.

8 | CONCLUSION

Human brain imaging will continue to be an important tool in psychiatry and psychology to better understand brain function and pathologies of brain structure and activation. To improve data quality and reliability, we believe that adherence to certain guidelines is key to accomplishing this goal. This may be especially important in eating disorders because of effects of malnutrition. However, nutritional status may also have important implications for brain imaging in other psychiatric disorders (De Rosa et al., 2017). Table 1 summarizes the above guidelines. The ratings are based on a consensus of the authors of this manuscript.

To move the field forward, it may be necessary to start pooling data from many sites. One example of such an approach is the ENIGMA Consortium (enhancing neuroimaging genetics through meta-analysis, http://enigma.ini.usc.edu), and efforts are under way to begin to analyze structural brain imaging data in eating disorders on larger scale samples than a single research group can access. Such approaches will also be aided by demands for data sharing. Typically, investigators do not frequently share their data. However, the United States National Institute of Mental Health now makes sharing of data in designated repositories a requirement in new grant applications. These types of data repositories will allow for the analysis of large data sets in the future (Mennes, Biswal, Castellanos, & Milham, 2013). Aside from recommendations for individual studies (Table 1), the eating disorders brain imaging field as a whole will need to evolve and make stronger efforts to study males with eating disorders, test brain structure–function interactions, and develop and test complex models that cover biological, psychological, and social factors that affect brain structure and function. At this point, we cannot say which factors and confounds are more or less important to address in brain imaging studies in eating disorders, but more specific recommendations for structural imaging in AN have been laid out in a recent review article (King et al., 2017). For now, we recommend being as detailed and specific as possible in the description of study samples and methods and we expect that over the next decade, new discoveries will better answer the question what potential confounds are more or less impacting brain imaging results. An important area of research will be to assess brain changes during treatment, recovery and relapse over longer time periods and identify associated behaviors. The feasibility of such studies may vary depending on insurance coverage and health systems across societies. Although we have moved from “brain region” to “brain circuitry” models, we have to start developing or applying novel methods for study design and data analysis. For instance, brain imaging in eating disorders must go beyond group comparisons and correlation analyses and start adapting techniques to model disease and related brain function to develop and test mechanistic models of behavior (Frank, 2011; Hazy, Frank, & O’Reilly, 2007; Kriegeskorte, 2011; Stephan, Iglesias, Heinzle, & Diaconescu, 2015). After identification of abnormal circuit function, such pathways could then be modulated with for instance noninvasive or invasive neuromodulation such as transcranial magnetic or deep brain stimulation.

In summary, brain imaging in eating disorders has made progress, but we as a field must adopt more rigorous methods to make inroads towards understanding disease from a neurobiological perspective and developing treatments based on those findings. Such

rigorous application of methods will also improve grant funding as well as publication record in the competition over journal space with other fields.

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TABLE 1

Summary of recommendations

Recommendations	Author consensus rating 1 = Desirable 2 = Strongly desirable 3 = Essential
Demographic data, illness state, and development	
• Match study groups for age	3
• Consider race and ethnicity in the analyses	1
• Report duration of illness and test for effect on study results	Report = 3, Test = 1
• Assess handedness and account for nonright-handed individuals in the analyses	Report = 3, Test = 2
• Report on the effects of body mass index (BMI, in adults) or age adjusted BMI percentile (youth) on brain measures within groups	3
• Specify in recovered study groups level of recovery and test for its relationship with brain structure and function	3
Effects of starvation, hydration status, exercise, binge eating, and purging	
• Indicate the methods and procedures under what nutritional conditions a study was conducted	3
• Report binge-eating and purging frequency and test against study outcome measures	3
• Report on the weight that a participant lost or gained within the last weeks before brain imaging procedures	2
• Report the last food intake before brain imaging procedures, and standardize pre-scan meals	Report = 3, Test = 2
• Quantify exercise quantity and quality and test their effects on brain imaging data	1
• Report the history of other eating disorders than the type described in study and test whether this affects brain measures	Report 3, Test = 1
• Test to what extent regional brain structure measures, such as gray matter volume, may contribute to regional functional imaging findings	1
Stage of treatment	
• Describe the specific treatment setting (or lack of treatment) of study participants	3
• Indicate whether study participants that were in treatment were all in the same setting or treatment with the same treatment modality and test against each other for effects on brain imaging results	1
• Report the length of time in treatment and weight change between start of treatment and scan and test for effects on brain structure or function	2
Hormonal effects	
• Consider sex effects and when possible study males and females separately	Report = 3, Test = 1
• Document menstrual status (e.g., pre- vs. post-menarcheal, presence, and duration of amenorrhea) and use in the imaging analyses	3
• Study menstruating females during the same menstrual cycle phase or take cycle phase into consideration when analyzing brain imaging data	2
• Study females at least eight weeks off of oral contraceptive pills (OCPs), or if taking OCPs, compare to a control population also taking OCPs or use OCP use as a covariate in the analyses	1
• Standardize and report conditions under which hormones are assessed	Report = 3, Standardize = 1
• Consider other factors that influence hormones, such as exercise or stress level	1
Comorbidity and medication	
• Use diagnostic instruments that go beyond eating disorder diagnosis to assess study participants	3
• Investigate the effects of comorbid conditions on brain imaging results	2
• Report use of medication, alcohol, tobacco and caffeine and test for effects on brain imaging data	Report = 3, Test = 1
• Medication use should be stable before conducting brain imaging procedures	2
Technical and statistical considerations, and study design	

Recommendations	Author consensus rating 1 = Desirable 2 = Strongly desirable 3 = Essential
• Provide a justification for sample size and statistical analysis methods	Sample size = 1, Statistics = 3
• Describe task stimuli and their application during fMRI in detail and match with their respective control condition	3
• Ensure that outliers do not drive group results	3
• Examine whether data are normally distributed or not and select the appropriate tests for statistical analyses (parametric, nonparametric)	3
• Follow the latest recommendations for brain imaging analysis and describe how motion correction was conducted	3

Note. The consensus rating is based on author ratings for desirable and essential information to be included in eating disorder brain imaging studies; report, report descriptive results in the manuscript; test, test data for effects on brain imaging results.