EDITORIAL

Treatment of Eating Disorders can not Remain 'Brainless': The Case for Brain-Directed Treatments

The eating disorders (ED), [anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED) and related partial or mixed syndromes (eating disorder not otherwise specified)] are highly distinctive disorders at the brain–body interface. Although 'malleable' during the early stages, once established, they are remarkably persistent (Walsh, 2013), and long-term physical and psychosocial disability is common. Within the broader context of much disquiet about the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), there is ongoing debate on classification in ED (Knoll, Bulik and Hebebrand, 2011; Hebebrand & Bulik, 2011). Nonetheless, ED are generally accepted as being on a spectrum of over-eating and under-eating, associated with altered weight and with altered food reward. This may manifest as a dread of food, and phobic avoidance of eating, fullness and fatness, or an excessive desire and over-eating of highly palatable foods, or a mixture of both dread and desire, and over-consumption and under-consumption. Historical and epidemiological perspectives on time trends in ED suggest there is considerable pathoplasticity in these disorders (Schmidt & Treasure, 1993; Russell & Treasure, 2013; Mitchison, Hay, Slewa-Younan, & Mond, 2012; Micali, Hagberg, Petersen, & Treasure, 2013). They also show that over time, there have been marked changes in aetiological models and associated treatment modalities, with biological, psychological and environmental models dominating at different times

An estimated 1.5 million EU citizens suffer from AN or BN, with a cost of illness estimate of 0.8 billion Euros per annum (Gustavsson et al., 2011; Wittchen et al., 2011). This figure severely underestimates the true costs of ED as the most common ED (BED and eating disorder not otherwise specified) were not included in the estimate. Moreover, key resource items (e.g. outpatient resource use), the cost of lost productivity of families and the indirect costs due to reduced length of life and poor health were also not included in the estimate. These wider costs are much higher than the actual healthcare costs of ED (Pro Bono Economics, 2012). For example, a recent report on the cost of ED in Australia estimated the productivity impact of ED as 15.1 billion Australian dollars in 2012, similar to that estimated for anxiety and depression (Butterfly Foundation, 2012) Thus, the personal and societal costs of ED in general are large, but nowhere is this perhaps more evident than in patients with severe and enduring AN.

Available treatments for ED are only moderately effective. Medication has a limited role (Aigner et al., 2011), and psychological therapies are widely considered the treatment of choice. Undoubtedly, progress has been made and is being made in developing, testing and disseminating effective psychological treatments, for example, in the form of family-based treatments for adolescents with AN (Lock et al., 2010; Godart et al., 2012), therapist-aided and self-care versions of cognitive-behavioural therapy (CBT) for adolescents and adults with BN (e.g. Fairburn et al., 2009; Mitchell et al., 2011; Schmidt et al., 2007; 2008; Lavender et al., 2012; Sánchez-Ortiz et al., 2011; Carrard et al., 2010), and treating binge eating in BED (e.g. Carrard et al., 2011, De Zwaan et al., 2012). However, 40–60% of people with BN do not fully recover following a well-conducted course of CBT, and it remains unclear how to intensify, sequence or augment treatments for best effect in these cases. Moreover, the changing 'weightscape' of bulimic ED has been noted (Bulik, Marcus, Zerwas, Levine, & La Via, 2012) with the combination of ED and obesity an increasingly common presentation (Mitchison et al., 2012), and CBT unable to effectively prevent or treat comorbid obesity in these cases (Vocks et al., 2010).

Psychological treatments for adults with AN have limited efficacy, and currently, attempts are in progress to develop (i) more tailored, trait-focused treatments (e.g. Schmidt et al., 2012; Davies et al., 2012), (ii) treatments for those with a very chronic form of the illness (Touyz et al., 2013), (iii) treatments focusing on transdiagnostic overlaps with other ED (Fairburn et al., 2013; Wild et al., 2009) and (iv) treatments focusing on relapse prevention (Fichter et al., 2012). Augmentation of individual treatment with interventions involving carers is also being investigated with some success (Goddard et al., 2011, Grover et al., 2011, Hoyle, Slater, Williams, Schmidt, & Wade, 2013). However, despite all these efforts, AN in adulthood remains remarkably persistent and difficult to treat (Walsh, 2013) with the holy grail of an effective, replicable outpatient treatment remaining highly elusive.

Novel approaches to treatment of ED in general and specifically for AN have been called for by august bodies such as the National Institute for Health and Care Excellence (NICE) in the UK and the National Institutes of Health (NIH) in the USA, and this has led to growing interest in brain-directed treatments such as those being discussed in this special edition.

Improved treatments ultimately depend on improved understanding of aetiology. However, the aetiology of ED is complex and remains poorly understood, with evidence for overlapping and distinct risk factors for different types of ED. These include sociocultural and other environmental factors, temperamental, developmental, genetic and epigenetic factors (e.g. see Campbell, Mill, Uher, & Schmidt, 2011; Koskina, Campbell & Schmidt, 2013 for review).

In general, in mental health research, the optimist's view is that 'new tools in biomedical research have created an era of unprecedented discovery' (Insel, 2009) and that these advances are beginning to lead to a greater understanding of the neurobiological

dysfunctions underpinning psychiatric disorders (Insel et al., 2013). This position is further reflected in the view that a biomarker approach combining genetic, neuroimaging, cognitive and other biological measures will facilitate development of early, effective 'precision' treatments (Insel et al., 2013; Cuthbert & Insel, 2013) tailored to the 'profile' of a given individual. While this will remain the "Holy Grail" of psychiatry/neuroscience, it has to be accepted that because of the complexity of the brain, meaningful progress is likely to take time.

Recent years have seen a marked increase in neuroscience data related to ED and to the emergence of testable neurobiological models. For example, neuroimaging (e.g. Uher et al., 2004; Brooks et al., 2011) and other studies, for example, those using animal models (Kas & Adan, 2011), suggest that people with ED show fear-related brain responses to food and body cues, altered reward processing, and dysregulation of central serotoninergic and dopaminergic systems (e.g. Kaye, Wagner, Fudge, & Paulus, 2011, Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013a; Kaye et al., 2013b; Smith & Robbins, 2013; Zhu et al., 2012). These and other findings have demonstrated clinical and neurobiological overlaps between ED, anxiety disorders and addictions and have led to the emergence of broadly based so-called 'top down versus bottom up' aetiological models of ED. In essence, these propose that a core issue in ED results from altered interactions at the cognition ('top down') emotion ('bottom up') interface, with AN being seen as a condition that involves excessive top-down control.

Given poor treatment outcomes for many ED patients and especially those with AN, treatment innovations are urgently needed but are unlikely to come from refinement of talking therapies alone. One key aspect of talking psychotherapies is that they target 'top down' cognitive processes, that is, they work by teaching patients to employ effortful and conscious strategies to divert attention from anxiety-provoking thoughts. It is arguable therefore that novel approaches that directly and implicitly influence early and sub-cortical processes, such as those involved in anxiety/threat responsivity and addictive-type or pathologically rewarding behaviours, are needed as treatments or as adjuncts to talking therapies to improve outcomes.

The focus of this edition on brain-directed treatments is on established and emerging neurotechnologies, and their potential for the treatment of ED. Thus, we have included articles on both invasive and non-invasive brain stimulation methods (see articles by Treasure & Keyoumars, *this volume*; De Zwaan & Schläpfer; *this volume*; Lipsman and al; *this volume*; Mcclelland et al., *this volume*), on attention modifying procedures using dot-probe and eye tracking technologies (Renwick et al., *this volume*; Giel et al., *this volume*), on different neurofeedback methods (Bartholdy et al., *this volume*; Fernandez-Aranda et al., *this volume*),and finally, based on evidence suggesting trait-based socio-emotional processing difficulties in AN (Tapajos Pereira de Sampaio et al., this volume) on the use of intranasal oxytocin as an exemplar of a novel pharmacological treatment strategy (Maguire et al., *this volume*).

It has been noted previously that 'the ED field lags behind other psychiatric disorders in terms of progress in understanding responsible brain circuits and pathophysiology' (Kaye et al., 2011) and that in relation to developing new treatments, it is possible that we have not been 'paddling as hard as we can' to catch up (Bulik, 2013). This special edition on brain-directed treatment provides tantalising early glimpses into the possibilities of different neurotechnologies that might in the not too distant future become stand-alone treatments or adjuncts to psychological therapies of different ED and hopefully goes some way in addressing these concerns.

In order to achieve a vision of a 'cure based on understanding of causes' and to make personalised treatment tailored to individual characteristics and illness stage a reality (Insel et al., 2013; Cuthbert & Insel, 2013), there is a need to advance understanding of brain function in relation to ED and associated comorbidities. In the context of brain-based treatment interventions, it will be important to improve knowledge related to neural networks as this will allow the development of system-based models which integrate activity from different brain areas such as the so-called 'rich club' (van den Heuvel & Sporns, 2011; Van den Heuvel et al., 2013) and/or will improve our conceptualisation of existing 'top down versus bottom up' models. This information will, in turn, improve the targeting and the theoretical rationale for neural-based treatments. There is also a need for studies examining Genes × Treatment (G × T) interactions in ED in relation to both psychological and brain-directed (e.g. neuromodulatory) treatments, as is happening in other fields (e.g. Lester & Eley, 2013; Plewnia et al., 2013). In addition, there is a need for studies of neural correlates of brain-directed and other treatments in ED (e.g. Vocks et al., 2011). Finally, initiatives such as the US National Institute of Mental Health's research domain criteria (RDoC) approach to classification for mental disorders (which is based upon dimensions of neurobiology and observable behaviour) will promote research into the mechanisms underpinning ED and their comorbidities (Cuthbert & Insel, 2013).

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