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Sex differences in the mediators of functional disability in Major Depressive Disorder

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ABSTRACT

The aim of this study was to investigate sex differences in discrete domains of psychopathology as mediators of functional disability among individuals with Major Depressive Disorder (MDD). Adults (ages 18–65) with moderate-to-severe MDD (n = 100) and age-, sex-, and education-matched healthy controls (HC; n = 100) participated in a clinical trial validating the THINC-integrated tool, a newly developed cognitive assessment tool for patients with MDD. Variables assessed as possible mediators included depression symptom severity, anxiety symptoms, sleep disturbance, perceived cognitive deficits, and objective cognitive performance. Functional disability was assessed using the total score on the Sheehan Disability Scale. Separate mediation analyses were conducted for men and women. No significant differences were detected between men and women on the assessed domains of psychopathology or functional disability (ps > 0.05). However, the mediation analyses demonstrated different patterns with respect to determinants of functional disability in MDD between men and women. Functional disability was mediated by anxiety (95% CI: −3.17, −0.28) and sleep disturbance (95% CI: −0.69, −0.05) among men and by depressive symptom severity (95% CI: −7.82, −0.32) among women. These preliminary results instantiate the need to dimensionalize psychopathology in MDD. Our results at least in part support the hypothesis that, consistent with the sex differences in the prevalence and illness presentation of MDD, determinants of functional outcomes also differ between men and women, underscoring the need to consider sex differences in order to improve functional outcomes in the treatment of MDD.

1. Introduction

Major depressive disorder (MDD) is a common mental illness, with an estimated lifetime prevalence of 16.2% (Kessler et al., 2005). Moreover, the detrimental effects of MDD on patient quality of life and functioning are observed from patient and societal perspectives, underscored by the significant economic burden of MDD due to both direct and indirect healthcare and work-related costs (Birnbaum et al., 2010; Greenberg et al., 2003; Kessler et al., 2006). Additionally, MDD is associated with significant morbidity and mortality, rendering it a major public health concern (Cuijpers and Smit, 2002; Moussavi et al., 2007). In fact, MDD is the leading cause of disability worldwide and in 2010, MDD was found to be the second leading cause of years lived with a disability (Ferrari et al., 2013; World Health Organization, 2017). Specifically, the disability experienced by individuals with MDD is pervasive across several domains of living, including workplace productivity, social life, and family and home responsibilities (Fried and Nesse, 2014).

Estimates indicate that rates of disability for individuals experiencing a Major Depressive Episode (MDE) exceed 90% (IsHak et al., 2016, 2014). Moreover, the reciprocal relationship between depressive symptoms and functional disability has been well established, with functional disability increasing with greater depression severity and decreasing with improvements in depression severity (IsHak et al.,

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2014; Judd et al., 2000; Soczynska et al., 2014). Consequently, the majority of antidepressants target the improvement of depressive symptomatology, where subsequent improvements in functional impairment are also seen (IsHak et al., 2014; Soczynska et al., 2014). Notwithstanding, evidence indicates that up to 23% of individuals with MDD who achieve symptomatic recovery with antidepressant treatment continue to experience disability (IsHak et al., 2016; Sheehan et al., 2011).

The discordance between resolution of core depressive symptoms (i.e., low mood and anhedonia) and rates of functional recovery in MDD provides the impetus for exploring the relative impact of other non-core depressive symptoms on disability. Sleep disturbance, change in appetite, anxiety, and cognitive dysfunction are examples of such symptoms that are commonly experienced in MDD. It has been found that impairments in these domains can persist into periods of euthymia and result in lasting disability, in addition to increasing the risk of relapse and morbidity (Conradi et al., 2011; Trivedi, 2006).

To date, research has identified depressed mood, cognitive impairment, and embarrassment as significant mediators of overall disability in MDD (Buist-Bouwman et al., 2008; Fried and Nesse, 2014). However, the nature of the experience of disability in MDD differs between men and women. For example, one study found that women report increased functional impairment particularly in marital and family relationships, while social and work impairment are more commonly reported among men (Deshpande et al., 2014; Kornstein et al., 1995; Scott, 2011; Wang and Gorenstein, 2015). Put differently, men and women may endorse equal amounts of functional disability, but the particular domains affected by a diagnosis of MDD may differ between sexes. Additionally, the indirect costs to employers associated with disability among depressed women exceeds that of depressed men by $763 USD per year, indicative of increased work impairment and absenteeism (Birnbaum et al., 2003).

Notwithstanding these differences, the authors are not aware of any studies to date that have investigated differences in mediators of disability between men and women with MDD. In addition to the increased prevalence (Kessler et al., 1993; Marcus et al., 2008, 2005) and severity (Marcus et al., 2008) of MDD among women, MDD is also heterogeneous in the manifestation of symptoms between the sexes (Lai, 2011; Romans et al., 2007). For example, compared to men, women tend to experience a greater number of depressive symptoms, particularly those associated with mood, such as sadness (Lai, 2011). Additionally, women with MDD experience increased anxiety and more severe somatic symptoms, including fatigue, sleep disturbance, pain, and appetite disturbance (Lai, 2011; Picco et al., 2016; Silverstein, 2002).

Taken together, extant literature supports the notion that sex differences in discrete domains of psychopathology may be an important determinant of functional disability in MDD. In the present study, we aim to assess differences in the pattern of clinical, psychosocial, and cognitive mediators of functional disability between men and women with MDD. Elucidating potential sex differences in the determinants of functional disability within MDD would be useful in helping healthcare providers develop more specific and individualized treatments to increase the rates of functional recovery in MDD. We hypothesized that the mediators of disability in persons with MDD would differ between men and women; however, due to the exploratory nature of our analyses, we did not generate any hypotheses as to which individual symptoms would better predict functional disability as a function of sex.

2. Materials and methods

2.1. Participants

The present study is a post hoc analysis of data from the clinical trial validating the THINC-integrated tool (THINC-it), a newly developed cognitive assessment tool for patients with MDD. Participants were recruited by the Brain and Cognition Discovery Foundation, associated with the Mood Disorders Psychopharmacology Unit, in Toronto, Ontario, Canada. Participation was voluntary and eligible participants provided informed written consent. This study was approved by a community Research Ethics Board in Toronto (https://www.chesapeakeirb.com/about-us/accreditation-and-compliance/).

A convenience sample of 100 participants with a diagnosis of MDD currently experiencing a moderate-to-severe MDE (i.e., a Montgomery-Åsberg Depression Rating Scale [MADRS] score ≥ 22) of at least 3 months in duration (Müller et al., 2000), were age-, sex-, and education-matched to healthy controls (HC; n = 107). As a result of the rolling basis for enrollment, 7 participants were recruited that did not match MDD participants on age, sex, and/or education, and were therefore excluded from endpoint analyses. Additional inclusion and exclusion criteria have been described in detail elsewhere (McIntyre et al., 2017).

2.2. Measures

Our primary outcome measure was the Sheehan Disability Scale (SDS; Sheehan et al., 1996). The SDS is a self-rated measure of functional disability in three domains—work, social, and family life—using a discretized analog format. Each domain is rated from 0 (not at all impaired) to 10 (extremely impaired), and scores from each domain are summed to yield a global disability score ranging from 0 to 30 (Sheehan et al., 1996; Sheehan and Sheehan, 2008).

Depressive symptom severity was assessed using the MADRS (Montgomery and Asberg, 1979; Müller et al., 2000), a 10-item scale assessing severity of symptoms commonly experienced among individuals with MDD with established validity, reliability, and sensitivity (Müller et al., 2000). Similarly, the Clinical Global Impression–Severity (CGI-S) scale was included as a clinician-rated measure of severity of mental illness (Guy, 1976).

The THINC-it, developed by the THINC Task Force (http://thinc.progress.im/en), is a user-friendly computerized cognitive assessment tool developed specifically for the measurement of cognitive impairments among depressed individuals. The THINC-it consists of a number of pre-validated and commonly used cognitive paradigms that assess cognitive domains found to be impaired in MDD (Ragguett et al., 2016), including the Choice Reaction Time paradigm (*Spotter*), One Back Memory Task (*Symbol Check*), Digit Symbol Substitution Test (*Codebreaker*), Trail Making Test—Part B (*Trails*), and the self-reported Perceived Deficits Questionnaire—5 item for Depression (*PDQ-5-D*) (Bruder et al., 2014; Joy et al., 2004; Marquand et al., 2008; Reitan, 1958). The *PDQ-5-D* consists of items covering attention/concentration, retrospective memory, prospective memory, and planning/organization from the full-length, 20-item version of the PDQ for Depression (Fehnel et al., 2016; Lam et al., 2013), and has demonstrated good internal consistency (Chronbach's α = 0.84) (Cha and McIntyre, 2016).

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) is a self-rated questionnaire that assesses sleep disturbances over the previous 1-month period. The PSQI consists of 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Component scores are summed to yield a global score. Higher global and component scores denote greater sleep disturbances. The PSQI has demonstrated strong reliability and validity in both clinical and non-clinical samples (Mollayeva et al., 2016).

Anxiety symptoms were assessed using the Generalized Anxiety Disorder—7-Item (GAD-7; Spitzer et al., 2006). The GAD-7 is a brief self-report scale designed to identify probable cases of GAD and is also used as an anxiety severity measure. The scale has demonstrated strong reliability, validity, specificity, and ability to differentiate between GAD and depression (Spitzer et al., 2006).

Finally, The National Adult Reading Test–Revised (NART-R; Blair and Spreen, 1989) was included as a measure of premorbid intellectual