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Set Shifting and Inhibition Deficits as Potential Endophenotypes for Depression

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ABSTRACT

The etiology of Major Depressive Disorder (MDD) is poorly understood, and identifying endophenotypes, or intermediate processes implicated in pathophysiology, for MDD may inform treatment and identification/prevention efforts. Impaired set-shifting and inhibition are commonly observed in MDD; however, few studies have examined they are endophenotypes for MDD. Thus, the present study tested whether set-shifting and/or inhibition satisfy several endophenotype criteria: specifically, whether they were (1) impaired in current MDD, (2) impaired in remitted MDD, and (3) familial (i.e., correlated within sibling pairs). Set-shifting and inhibition were assessed using subtests from the Delis-Kaplan Executive Function System. Psychopathology was assessed using the Structured Clinical Interview for DSM-5. Results indicated set-shifting deficits were familial and present in both current MDD and in remitted MDD individuals who had no current disorders, suggesting they may be state-independent. Inhibition was familial, but was generally not impaired in current nor remitted MDD (although the remitted MDD group with no current disorders exhibited impairments on one of the two inhibition tasks). These findings indicate that impaired set-shifting is a promising endophenotype candidate for MDD. Findings are limited to young adults, and further research is needed to test generalizability to other populations, evaluate longitudinal relationships, and examine other endophenotype criteria.

1. Introduction

Major Depressive Disorder (MDD) is one of the most prevalent and costly illnesses in the world (Kessler et al., 2003; Lopez et al., 2006). Despite its considerable public health impact, existing treatments and preventative interventions are only moderately efficacious (Calear and Christensen, 2010). Identifying MDD endophenotypes, or intermediate components in the pathway between genes and MDD (Gottesman and Gould, 2003), could elucidate processes involved in the etiology of depression and highlight novel targets for treatment and prevention.

In their seminal paper, Gottesman and Gould (2003) specified that an endophenotype must be (1) associated with the illness in the population, (2) heritable, (3) state-independent (i.e., observable before illness onset or in remission), (4) co-segregated with illness within families, and (5) present at higher rates within affected families than in the general population. It is also important to examine whether a putative endophenotype is specific to a certain disorder or is reflective of a transdiagnostic or general liability to psychopathology (Beauchaine and Constantino, 2017; Chan and Gottesman, 2008).

1.1. Set-Shifting and inhibition as candidate endophenotypes for depression

Two candidate endophenotypes for MDD are the executive functioning (EF) domains of set-shifting and inhibition. Deficits in both set-shifting and inhibition have been consistently observed in individuals with MDD (Austin et al., 2001; Snyder, 2013). Set-shifting and inhibition deficits are theorized to be involved in the etiology and maintenance of MDD (Beck, 1987; Kuehner and Weber, 1999; Nolen-Hoeksema, 1991) by contributing to difficulties with attentional disengagement from negative information, which in turn is thought to underlie negative interpretation biases and rumination (Koster et al., 2011). Meta-analytic

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evidence that impairments in both set-shifting and inhibition (but not working memory) are associated with rumination supports this impaired disengagement hypothesis (Yang et al., 2017). Furthermore, Hsu et al. (2015) showed that rumination mediated the relationship between attentional control (which encompasses both set-shifting and inhibition) and depression symptoms.

The importance of set-shifting and inhibition in cognitive theories of depression suggests that they may be endophenotypes for MDD. Studies that have examined whether set-shifting meets certain endophenotype criteria have often yielded mixed findings regarding its state-independence and heritability. Stange et al. (2016) found that set-shifting predicted first onset of MDD, whereas other studies found no relationship between set-shifting and later MDD onset (Papmeyer et al., 2015). Similarly, studies examining set-shifting in remitted MDD have produced inconsistent results. Some studies suggest that set-shifting is impaired in individuals with remitted MDD compared to healthy controls (Hasselbalch et al., 2012, 2011; Lange et al., 2012), while others found no set-shifting deficits in remitted MDD (Ahern and Semkovska, 2017; Jermann et al., 2013; Peters et al., 2017). There have also been mixed findings from twin and family studies examining the heritability of set-shifting. Some twin studies found moderate to substantial heritability (Anokhin et al., 2010, 2003; Friedman et al., 2008) and another study reported that set-shifting was significantly correlated within sibling pairs (Loo et al., 2008), but other studies reported minimal heritability (Kremen et al., 2007; Zhou et al., 2018). In sum, although impaired set-shifting is a theoretically plausible candidate endophenotype for MDD, it remains unclear whether set-shifting deficits are state-independent or heritable.

As previously noted, inhibition deficits have been observed in individuals with current MDD, and may also be present in remitted MDD (Årdal and Hammar, 2011; Bora et al., 2013; Schmid et al., 2011; Schmid and Hammar, 2013) and prior to MDD onset (although this may be specific to females; van Deurzen et al., 2012). However, some studies have found no inhibition deficits in remitted MDD (Merens et al., 2008), and meta-analytic evidence that inhibition improves over the course of antidepressant treatment, suggesting it may not be fully state-independent (Wagner et al., 2012). Preliminary evidence suggests that inhibition may be moderately to highly heritable (Friedman et al., 2008; Kuntsi et al., 2006), but further twin and family studies are needed. There is also some difficulty in measuring inhibition reliably, as some measures capitalize on speed (e.g., interference resolution), whereas others focus on accuracy (e.g., inhibitory control; Bessette et al., 2020). Within inhibitory control, many measures also struggle with ceiling effects that limit generalizability.

1.2. Methodological limitations of studies of neurocognitive endophenotypes for depression

There are several methodological limitations that may explain why prior studies of set-shifting and inhibition in MDD have produced mixed findings. First, relationships between MDD and set-shifting or inhibition may be confounded with comorbid psychiatric conditions such as anxiety disorders (Basso et al., 2007; Baune et al., 2009; Kessler et al., 2003; Shankman and Klein, 2003). For example, Lyche et al. (2011) compared healthy controls to individuals with MDD only or comorbid MDD and anxiety, and found that only the comorbid group had impaired inhibition compared to healthy controls. Crane et al. (2016) reported that individuals with comorbid MDD and anxiety exhibited different patterns of brain activation during inhibition those with MDD only. Importantly, many studies of EF in MDD have compared individuals with current or remitted MDD to healthy controls without accounting for psychiatric comorbidity, making them unable to evaluate whether observed EF deficits are specific to MDD, attributable to a comorbid disorder, or reflective of transdiagnostic or general liabilities to psychopathology (Beauchaine and Constantino, 2017).

Second, set-shifting and inhibition impairments observed in MDD may not be specific to these EF processes, and instead may reflect deficits in more basic or more general cognitive abilities. Processing speed is associated with both MDD (Austin et al., 2001; Sarapas et al., 2013) and set-shifting and inhibition, and many set-shifting or inhibition tasks are conducted under time constraint, meaning that processing speed can directly affect the measurement of set-shifting and inhibition (Bessette et al., 2020). Similarly, measures of general intellectual functioning (e.g., full scale IQ [FSIQ]) are correlated with specific EF components such as set-shifting and inhibition (e.g., Biesmans et al., 2019), and are also lower in individuals with MDD relative to healthy controls (Ahern and Semkovska, 2017). Therefore, studies that do not address processing speed or general intellectual functioning as potential confounds cannot disentangle whether deficits in set-shifting or inhibition performance are truly deficits in these processes or instead reflect deficits in processing speed or general cognitive functioning.

In addition, isolating specific EF deficits (e.g., comparing set-shifting to inhibition) can be difficult because EF processes are often measured by separate neuropsychological tests that were normed on different samples. This is problematic because interpretation of neuropsychological test performance can vary greatly based on which normative sample(s) was used by the test (Kalechstein et al., 1998). Thus, studies examining relationships between MDD and multiple EF processes would benefit from utilizing EF tests that were normed on the same sample.

1.3. The present study

Using data from a larger family study of young adults (Shankman et al., 2018), the present study examined whether set-shifting and/or inhibition deficits meet several endophenotype criteria for MDD – specifically, whether they are present in current MDD, state-independent (i.e., impaired in remission), and familial (i.e., correlated between siblings). To test these criteria, we compared four groups: (1) current MDD, (2) remitted MDD and no current DSM-5 disorder, (3) remitted MDD and at least one current DSM-5 disorder, and (4) healthy controls. The inclusion of two remitted MDD groups that differed on current comorbid diagnostic status allowed us to directly test whether EF deficits in remission were specific to MDD or due to psychiatric comorbidities. FSIQ and processing speed were examined as potential covariates to determine whether EF deficits were specific to set-shifting and/or inhibition. It was predicted that set-shifting and inhibition would be familial and poorer in individuals with current or remitted MDD compared to healthy controls. However, it was unclear whether any deficits in remitted MDD would be attributable to the presence of current non-MDD disorders or would also be observed in individuals with remitted MDD and no current diagnoses. It was also possible that both remitted MDD groups would exhibit EF impairments compared to healthy controls, but these impairments would be greater in individuals with current non-MDD diagnoses, which would suggest that the EF deficits are *partially* attributable to psychiatric comorbidity.

2. Methods

2.1. Participants

Participants were recruited from the community and area mental health clinics and enrolled in a larger family study on emotional and cognitive processes (Correa et al., 2019; Funkhouser et al., 2019; Shankman et al., 2018; Weinberg et al., 2015). Participants were required to be between the ages of 18 and 30 (to ensure they were in the peak risk window for internalizing psychopathology; Kessler et al., 2005) and have a biological sibling within the same age range who was also interested in participating. Minimal symptom-based inclusion and exclusion criteria were used to ensure recruitment of a sample with a broad range of internalizing symptomatology. However, to ensure the clinical relevance of the sample, we oversampled individuals with severe internalizing psychopathology by screening potential participants using

the Depression, Anxiety, and Stress Scale (Lovibond and Lovibond, 1995). Exclusion criteria included personal or family history of psychosis or mania, inability to read or write in English, history of head trauma with loss of consciousness, and left-handedness. The larger study enrolled a total of 503 individuals.

A subset of participants from the larger family study was divided into four groups for the purposes of the present study (total $N = 327$). These groups included individuals with (1) current MDD ($n = 23$), (2) remitted MDD and at least one current assessed DSM-5 disorder ($n = 70$), (3) remitted MDD without any current DSM-5 disorders ($n = 77$), and (4) healthy controls without any lifetime (i.e., current or past) disorder or current psychiatric medication use ($n = 157$). The inclusion of two separate remitted MDD groups that differed only in the presence of current disorder(s) allowed us to test whether any EF deficits were attributable to the presence of current non-MDD disorder(s). Additionally, the 'remitted MDD with current disorder(s)' group and current MDD group were matched on lifetime history of depression, lifetime and current non-MDD diagnoses, and demographic characteristics ($ps > 0.05$), increasing the likelihood that any differences between these two groups would be attributable to MDD status (current versus remitted) and not to another disorder or the lifetime experience of a depressive episode. All participants provided informed consent. Procedures were carried out in accordance with the latest version of the Declaration of Helsinki and were approved by the University of Illinois–Chicago Institutional Review Board. Demographic and clinical characteristics of each group are presented in Table 1.

2.2. Psychopathology assessment

Current and lifetime diagnoses of MDD and other DSM-5 disorders (see Table 1) were assessed via the Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015). Interviewers were trained to criterion on the SCID-5 by watching the *SCID 101* training videos (Biometrics Research Department, 2002), observing interviews by other interviewers previously trained to criterion, and completing 2–3 supervised interviews in which all diagnoses were in agreement with those made by trained interviewers.

2.3. Executive functioning assessments

Executive functions were measured using the Verbal Fluency, Design Fluency, Trail Making, and Color-Word Interference subtests from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001a). Each subtest contains several conditions that measure either more basic cognition (e.g., psychomotor speed) or higher-order EF processes (e.g., set-shifting, inhibition) that require these basic cognitive abilities. The Verbal Fluency subtest includes two conditions that measure phonemic or semantic word generation and a third condition (Category Switching) that assesses verbal set-shifting by asking participants to generate as many words as possible in two different categories, switching back and forth each time between the two categories. The Design Fluency subtest also contains three conditions. In condition one (Filled Dots), participants are asked to generate as many different designs connecting filled dots as possible in 60 s, which assesses basic visuospatial ability in generating designs. The second condition (Empty Dots Only) asks participants to draw designs connecting only empty dots while ignoring filled dots. This condition assesses selective attention and inhibition of task-irrelevant information. In the third condition (Switching), participants are asked to draw designs by following the more complex rule of alternating between connecting two types of dots, thereby indexing visual set-shifting. The Trail Making Test contains five conditions during which participants mark targets or connect letters or numbers, four of which assess psychomotor speed, visuospatial attention, and processing speed. The fifth condition, Number-Letter Sequencing, assessing shifting abilities and asks respondents to switch between connecting numbers and letters (i.e., 1-A-2-B…). Lastly, the Color-Word Interference Test contains the following four conditions: (1) Color Naming, (2) Word Reading, (3) Inhibition (analagous to the classic Stroop test; Stroop, 1935), and (4) Inhibition/Switching. In the first two conditions, participants are asked to name colors or read words as quickly as possible.

Table 1
Demographic and Clinical Characteristics.

	Current MDD ($n = 23$)	Remitted MDD with current disorder(s) ($n = 70$)	Remitted MDD without current disorders ($n = 77$)	Healthy Controls ($n = 157$)	Total Sample ($N = 327$)
Age (SD)	22.65 (3.89)^{ab}	22.86 (3.42)^{a}	22.88 (3.36)^{a}	21.66 (2.91)^{b}	22.27 (3.25)
Sex (% Female)	18 (78.3)^{a}	51 (72.9)^{a}	52 (67.5)^{a}	99 (63.1)^{a}	220 (67.30)
Race (%)					
Caucasian	9 (39.1)	30 (42.9)	42 (54.5)	56 (35.7)	137 (41.9)
Black	8 (34.8)	15 (21.4)	11 (14.3)	18 (11.5)	52 (15.9)
Hispanic	1 (4.3)	12 (17.1)	17 (22.1)	34 (21.7)	64 (19.6)
Asian	0 (0.0)	6 (8.6)	3 (3.9)	36 (22.9)	45 (13.8)
Other/ Multiple Races	5 (21.7)	7 (10.0)	4 (5.2)	13 (8.3)	29 (8.9)
Predicted FSIQ (SD)	109.50 (8.42)^{ab}	105.31 (9.50)^{ab}	107.77 (8.44)^{a}	104.28 (9.10)^{b}	105.67 (9.12)
GAF (SD)	52.52 (8.28)^{a}	61.91 (10.52)^{b}	70.36 (10.68)^{c}	83.68 (8.14)^{d}	73.69 (14.09)
SOFAS (SD)	56.00 (8.54)^{a}	64.81 (11.57)^{b}	72.09 (9.99)^{c}	84.38 (8.55)^{d}	75.30 (13.55)
Psychiatric Medication (%)	6 (26.1)^{a}	12 (17.1)^{a}	15 (19.5)^{a}	–	33 (10.1)
Lifetime Diagnoses (%)					
PTSD	7 (30.4)^{a}	14 (20.0)^{a}	6 (7.8)^{b}	–	27 (8.3)
Panic Disorder	7 (30.4)^{a}	14 (20.0)^{ab}	7 (9.1)^{b}	–	28 (8.6)
Agoraphobia	1 (4.3)^{a}	4 (5.7)^{a}	0 (0.0)^{a}	–	5 (1.5)
Social Anxiety Disorder	11 (47.8)^{a}	40 (57.1)^{a}	12 (15.6)^{b}	–	63 (19.3)
Specific Phobia	9 (39.1)^{a}	31 (44.3)^{a}	8 (10.4)^{b}	–	48 (14.7)
OCD	3 (13.0)^{a}	13 (18.6)^{a}	3 (3.9)^{b}	–	19 (5.8)
GAD	8 (34.8)^{a}	14 (20.0)^{ab}	10 (13.0)^{b}	–	32 (9.8)
AUD or SUD	8 (34.8)^{a}	39 (55.7)^{a}	43 (55.8)^{a}	–	90 (27.5)
Current Diagnoses (%)					
PTSD	3 (13.0)^{a}	3 (4.3)^{a}	–	–	6 (1.8)
Panic Disorder	3 (13.0)^{a}	3 (4.3)^{a}	–	–	6 (1.8)
Agoraphobia	1 (4.3)^{a}	3 (4.3)^{a}	–	–	4 (1.2)
Social Anxiety Disorder	7 (30.4)^{a}	32 (45.7)^{a}	–	–	39 (11.9)
Specific Phobia	8 (34.8)^{a}	26 (37.1)^{a}	–	–	34 (10.4)
OCD	3 (13.0)^{a}	11 (15.7)^{a}	–	–	14 (4.3)
GAD	5 (21.7)^{a}	7 (10.0)^{a}	–	–	12 (3.7)
AUD or SUD	4 (17.4)^{a}	19 (27.1)^{a}	–	–	23 (7.0)

Note. Different superscripts in the same row reflect significant group differences ($p < .05$) using χ^2 or Tukey tests; FSIQ = Full Scale Intelligence Quotient; GAF = Global Assessment of Functioning (Aas, 2010); SOFAS = Social and Occupational Functioning Assessment Scale (Goldman et al., 1992); MDD = Major Depressive Disorder; PTSD = Posttraumatic Stress Disorder; OCD = Obsessive Compulsive Disorder; GAD = Generalized Anxiety Disorder; SUD = Substance Use Disorder; AUD = Alcohol Use Disorder.

In the third condition (Inhibition), color words are printed in a different colored ink and participants are asked to inhibit reading the words and instead name the ink colors the words are printed in as quickly as possible. In the fourth condition (Inhibition/Switching), participants are asked to switch back and forth between word reading and color naming. Although conditions 3 and 4 both measure inhibition, Condition 4 also implicates set-shifting processes with the additional rule-switching component.

All conditions yield raw scores that reflect either the time required to complete a task (for Trail Making and Color-Word Interference) or the number of correct responses within a given time limit (for Verbal Fluency and Design Fluency). These four subtests have demonstrated moderate to high internal consistency (Spearman-Brown corrected *r*s = 0.43–0.85) and test-retest reliability in individuals aged 18–30 (*r*s = 0.49–90; Delis et al., 2001b). Raw scores reflecting completion time were reverse scored so that higher scores reflected better performance for all variables. Condition scores greater than 3 standard deviations from the sample mean were considered outliers and excluded. Mean condition scores and error scores by group are presented in Tables 2 and 3, respectively. There were no group differences in error frequency for any of the examined D-KEFS conditions (false discovery rate [FDR]-adjusted *p*s > 0.193).

Given the present study's focus on set-shifting and inhibition, we focused on the conditions that measure one of these two processes. Specifically, the following three subtests were examined as measures of set-shifting: the Number-Letter Sequencing (Trail Making), Category Switching (Verbal Fluency), and Switching (Design Fluency).[1] Given the associations between these set-shifting conditions (*r*s = 0.27–0.39, *p*s < 0.001), a set-shifting composite score was calculated by averaging the z-scores of these three conditions. The two conditions that primarily assess inhibition (Empty Dots Only from Design Fluency and Inhibition from the Color-Word Interference Test) were examined as separate dependent variables because they were only weakly correlated, $r = 0.10$, $p = .077$, which is consistent with prior studies (Rey-Mermet et al., 2018). Consistent with prior literature (Miyake et al., 2000), each of the two inhibition scores was moderately correlated with the set-shifting composite (*r*s = 0.39 and 0.45, *p*s < 0.001). Additionally, to examine processing speed as a covariate, a processing speed composite score was calculated by averaging the inverse z-scores of Motor Speed from the Trail Making Test and Word Reading and Color Naming from the Color-Word Interference Test.[2] These three conditions were moderately intercorrelated (*r*s = 0.27–0.72, *p*s < 0.001). Correlations between predictor and outcome variables are presented in Table 4. Preliminary analyses indicated that performance did not differ between D-KEFS conditions that required psychomotor speed (e.g., Design Fluency and Trail Making Test conditions) and those that did not, $F(1, 2368.83) < 0.01$, $p = .990$.

2.4. Wechsler test of adult reading

As general intelligence is associated with set-shifting and inhibition (e.g., Biesmans et al., 2019), the Wechsler Test of Adult Reading (Holdnack, 2001) was used to estimate each participant's full-scale IQ (FSIQ). The WTAR asks participants to pronounce 50 irregularly spelled words, with each participant's raw score reflecting the number of words correctly pronounced. Raw scores were first converted to standard scores by age group using the US standardization sample and reference group norms from the WTAR manual. Next, standard scores were converted to predicted FSIQs (co-normed with WAIS-III). WTAR scores are highly correlated with FSIQ ($r = 0.73$; Strauss et al., 2006), and predicted FSIQ scores obtained from the WTAR were considered as a potential statistical covariate in the present study.

2.5. Data analysis

We considered FSIQ, demographics (i.e., age, sex, race/ethnicity), and psychiatric medication use as possible covariates. Diagnoses were not considered as possible covariates because certain groups were intentionally matched on rates of lifetime and/or current diagnoses (see Participants section). We first tested whether possible covariates were significantly related to set-shifting or inhibition. If so, we then used analyses of variance (ANOVAs) or chi-square tests to examine whether they differed across groups. Variables that (a) were significantly related to set-shifting or inhibition, and (b) differed across groups were retained as covariates. Processing speed was included as a covariate because all of the examined D-KEFS conditions were timed and due to processing speed's theoretical and empirical importance in analyses of executive functioning (e.g., Anderson, 2002).

To examine whether set-shifting and/or inhibition were impaired in individuals with current MDD or remitted MDD compared to healthy controls, mixed effects models with random family-level intercepts were used to separately examine group differences in set-shifting, Design Fluency inhibition, and Color-Word Interference inhibition. Mixed effects models were used instead of standard linear regression models to account for the non-independent cases (i.e., sibling pairs) nested within families (see Correa et al., 2019 for a similar approach). The statistical significance of fixed effects (e.g., group) was examined using *F*-tests, and post-hoc *t*-tests were used to test pairwise group differences. As the exact null distributions for test statistics are typically unknown in mixed effects models with unbalanced designs, we used Satterthwaite's method to adjust the denominator degrees of freedom for *F*-tests and degrees of freedom for post-hoc *t*-tests to approximate the corresponding distribution (Satterthwaite, 1946). This method involves the calculation of a pooled variance across groups via a linear combination weighted by group size, thereby increasing power without assuming homogeneity of variances or equal group sizes. As a result, the estimated degrees of freedom of a post-hoc pairwise *t*-test relative to the omnibus F-test reflects the sizes of the two groups being compared relative to the other groups. This approach has performed well in simulation studies of type I error rates (Luke, 2017). The *p*-values of pairwise t-tests were adjusted for multiple comparisons using FDR correction.

Although an a priori power analysis was not performed, sensitivity analyses were conducted using Monte Carlo simulations. We substituted the effect of group (for *F*-tests) or each individual pairwise group difference (for *t*-tests) with effect sizes ranging from 0.10 to 0.80 in increments of 0.05. For each effect size, we simulated each model 1000 times and then extracted the proportion of iterations for which the main effect of group (for *F*-tests) or a specific pairwise group difference (for *t*-tests) was statistically significant (i.e., power) at alpha = 0.05. The resulting power curves are plotted in Figures S1 and S2 in the supplementary materials.

As there is some evidence that age of MDD onset, number of depressive episodes, and time since remission may influence relationships between MDD and executive functioning components such as set-shifting and inhibition (Bora et al., 2013; Hasselbalch et al., 2011), exploratory analyses examined whether these factors moderated differences between the two groups with remitted MDD.

To estimate the familial concordances of set-shifting and inhibition, participants that were part of a complete sibling pair ($n = 97$ sibling pairs) were randomized to be either sibling 1 or 2 within their sibling pair. We then computed one-way random single-measure intraclass correlation coefficients (ICCs [1,1]) between siblings for the set-shifting and inhibition scores. This also allowed for the calculation of the upper

[1] The Inhibition/Switching subtest of the Color-Word Interference Test measures both set-shifting and inhibition processes, and therefore was not included in the set-shifting composite score. However, the pattern of results remained identical if this subtest was included in the set-shifting composite.

[2] Although conditions 1-3 of the Trail Making Test also measure processing speed, these conditions were excluded from the processing speed composite because they involved some inhibition processes.

Table 2
Means and standard deviations of D-KEFS scores by group.

D-KEFS Condition	Current MDD (n = 23)	Remitted MDD with current disorder(s) (n = 70)	Remitted MDD without current disorders (n = 77)	Healthy Controls (n = 157)	Total Sample (N = 327)
Verbal Fluency (total correct)					
Letter Fluency	47.10 (10.59)	42.58 (10.36)	43.42 (10.17)	41.90 (10.51)	42.74 (10.44)
Category Fluency	43.95 (5.52)	41.47 (7.65)	43.90 (8.58)	41.92 (8.06)	42.42 (7.98)
Category Switching	13.81 (1.94)	15.09 (4.73)	15.03 (2.64)	14.91 (6.45)	14.90 (5.19)
Category Switching: Switching Responses	13.14 (2.83)	13.61 (2.50)	14.37 (2.64)	13.99 (3.05)	13.94 (2.84)
Design Fluency (total correct)					
Filled Dots	9.90 (3.25)	9.99 (3.25)	10.28 (3.46)	11.09 (3.48)	10.59 (3.43)
Empty Dots Only	10.87 (2.78)	11.16 (3.59)	11.55 (3.16)	12.06 (3.56)	11.67 (3.44)
Switching	8.96 (2.01)	9.69 (2.58)	9.31 (3.12)	9.96 (2.71)	9.68 (2.75)
Trail Making (completion time)					
Visual Scanning	21.05 (6.01)	18.37 (4.96)	18.48 (5.49)	17.74 (4.46)	18.27 (4.98)
Number Sequencing	32.41 (11.94)	26.91 (7.03)	27.79 (13.26)	25.71 (8.72)	26.93 (10.01)
Letter Sequencing	29.49 (8.07)	26.24 (6.69)	26.65 (9.28)	26.39 (8.40)	26.64 (8.26)
Number-Letter Switching	67.19 (17.11)	66.61 (22.28)	65.71 (25.62)	63.83 (20.13)	65.10 (21.72)
Motor Speed	23.61 (5.80)	24.55 (7.93)	21.57 (7.27)	22.28 (7.57)	22.68 (7.52)
Color-Word Interference (completion time)					
Color Naming	26.21 (3.41)	26.59 (3.75)	26.21 (4.36)	26.88 (5.12)	26.61 (4.56)
Word Reading	20.28 (3.46)	19.97 (2.44)	19.09 (3.18)	19.88 (3.59)	19.74 (3.28)
Inhibition	47.01 (9.36)	46.58 (10.00)	46.56 (10.18)	45.09 (11.64)	45.89 (10.80)
Inhibition/Switching	53.92 (12.17)	54.94 (11.49)	52.72 (12.63)	53.08 (11.17)	53.45 (11.64)

Table 3
Means and standard deviations of D-KEFS errors by group.

D-KEFS Condition	Current MDD (n = 23)	Remitted MDD with current disorder (s) (n = 70)	Remitted MDD without current disorders (n = 77)	Healthy Controls (n = 157)	Total Sample (N = 327)
Verbal Fluency					
Letter Fluency	1.24 (1.14)	0.74 (0.92)	1.07 (1.30)	1.20 (1.29)	1.08 (1.22)
Category Fluency	0.50 (1.00)	0.42 (0.66)	0.60 (0.91)	0.61 (1.01)	0.56 (0.92)
Category Switching	1.20 (1.44)	0.68 (0.96)	0.61 (0.86)	0.93 (1.29)	0.82 (1.16)
Design Fluency					
Filled Dots	1.52 (1.12)	2.00 (2.69)	1.94 (3.33)	2.25 (2.61)	2.08 (2.74)
Empty Dots Only	0.81 (1.17)	1.57 (2.15)	1.35 (2.46)	1.57 (2.03)	1.47 (2.12)
Switching	1.76 (1.70)	1.73 (1.79)	1.94 (1.99)	1.84 (1.78)	1.84 (1.82)
Trail Making					
Visual Scanning	0.05 (0.22)	0.11 (0.36)	0.17 (0.51)	0.12 (0.40)	0.13 (0.41)
Number Sequencing	0.00 (0.00)	0.08 (0.32)	0.01 (0.12)	0.01 (0.16)	0.03 (0.20)
Letter Sequencing	0.00 (0.00)	0.05 (0.27)	0.04 (0.27)	0.44 (5.17)	0.24 (3.64)
Number-Letter Switching	0.38 (0.59)	0.43 (0.71)	0.46 (0.80)	0.67 (0.80)	0.56 (0.77)
Motor Speed	0.05 (0.22)	0.09 (0.29)	0.24 (0.49)	0.14 (0.41)	0.14 (0.40)
Color-Word Interference (self-corrected errors)					
Color Naming	0.05 (0.22)	0.17 (0.45)	0.24 (0.55)	0.42 (0.78)	0.30 (0.65)
Word Reading	0.10 (0.31)	0.18 (0.39)	0.17 (0.41)	0.24 (0.47)	0.20 (0.43)
Inhibition	0.75 (1.07)	0.89 (1.15)	0.90 (1.06)	0.90 (1.10)	0.89 (1.09)
Inhibition/Switching	0.50 (1.00)	1.11 (1.60)	0.80 (1.10)	0.97 (1.19)	0.93 (1.26)
Color-Word Interference (uncorrected errors)					
Color Naming	0.00 (0.00)	0.03 (0.17)	0.13 (0.51)	0.11 (0.37)	0.09 (0.36)
Word Reading	0.05 (0.22)	0.05 (0.21)	0.08 (0.37)	0.09 (0.40)	0.08 (0.35)
Inhibition	0.35 (1.57)	0.38 (0.78)	0.42 (0.89)	0.51 (1.04)	0.45 (1.00)
Inhibition/Switching	0.30 (0.73)	0.95 (1.45)	0.65 (1.27)	0.93 (1.74)	0.83 (1.53)

limit of narrow-sense heritability for each EF component using the formula $h^2 = 2^*r_{xy}$, in which r_{xy} is the observed ICC between siblings (Visscher et al., 2008). Analyses were conducted in R using the lme4 (Bates et al., 2015), lmerTest (Kuznetsova et al., 2017), simr (Green and Macleod, 2016), and psych packages (Revelle, 2017).

3. Results

3.1. Examination of potential covariates

Age, sex, and psychiatric medication use were not significantly related to the set-shifting composite or either of the two inhibition scores ($ps > 0.05$). FSIQ was associated with set-shifting and both inhibition scores ($rs = 0.18$–0.37, $ps < 0.002$) and significantly differed across groups, $F(3, 314) = 3.95$, $p = .009$, and therefore was included as a covariate in all models testing group differences. Race (white/non-white) was also included as a covariate because it was significantly associated with set-shifting and both inhibition scores ($ps < 0.026$) and differed across groups, $\chi^2(3) = 10.68$, $p = .014$.

3.2. Group differences in set shifting and inhibition

There was a significant effect of group on set-shifting, $F(3, 297.32) = 3.54$, $p = .015$ (see Fig. 1). Post-hoc pairwise comparisons indicated that individuals with current MDD, $\beta = -0.48$, $t(296.83) = -2.64$, $p = .041$, and the remitted MDD group without current disorders, $\beta = -0.29$, $t(303.78) = -2.48$, $p = .041$, exhibited poorer set-shifting abilities than healthy controls. Set-shifting was not significantly impaired in the remitted MDD group with current disorder(s) group relative to healthy controls, $\beta = -0.21$, $t(315.99) = -1.29$, $p = .298$, however, and did not

Table 4
Correlations [95% CIs] between study variables.

Variable	1	2	3	4
1. Set-shifting composite	–			
2. Design Fluency inhibition	.45** [.36, 0.53]	–		
3. Color-Word Interference inhibition	.39** [.29, 0.48]	.10 [−0.01, 0.21]	–	
4. Predicted FSIQ	.37** [.28, 0.47]	.18** [.07, 0.28]	.20** [.09, 0.30]	–
5. Processing speed composite	.48** [.39, 0.56]	.28** [.18, 0.38]	.57** [.49, 0.64]	.20** [.09, 0.31]

Note. Design Fluency inhibition = Empty Dots Only condition. Color-Word Interference inhibition is reverse-coded so that higher scores indicate better performance for all variables.
** $p < .001$.

significantly differ between the two remitted MDD groups, $\beta = 0.02$, $t(295.45) = 0.99$, $p = .321$. The two remitted MDD groups also did not significantly differ from the current MDD group on set-shifting ($ps = 0.183$ and 0.321), suggesting that set-shifting is not *more* impaired in the acute stage of depression than in remission.

There was a similar pattern of differences in group means for both inhibition measures (see Fig. 2). The main effect of group was significant for Color-Word Interference inhibition, $F(3, 297.91) = 2.95$, $p = .033$, but not Design Fluency inhibition, $F(3, 310.81) = 1.99$, $p = .116$. Post-hoc group comparisons indicated that the remitted MDD without current disorders group had poorer Color-Word Interference inhibition performance compared to healthy controls, $\beta = -0.34$, $t(302.63) = -2.81$, $p = .032$. No other pairwise group differences were statistically significant ($ps > 0.230$).

Neither set-shifting nor inhibition differences between the two remitted MDD groups were moderated by age of MDD onset, number of depressive episodes, or time since MDD remission ($ps > 0.05$).

3.3. Familial concordance of set shifting and inhibition

The ICC between siblings' set-shifting scores was significant, ICC = 0.31, $F(96, 96) = 1.90$, $p < .001$, and corresponded to an upper limit of narrow-sense heritability of $h^2 = 0.62$. Inhibition scores from Design Fluency, ICC = 0.23, $F(96, 96) = 1.59$, $p = .012$, and Color-Word Interference, ICC = 0.23, $F(96, 96) = 1.61$, $p = .010$, were also significantly familial. The upper limits of narrow-sense heritability were $h^2 = 0.46$ for both Design Fluency and Color-Word Interference inhibition.

4. Discussion

The present study tested whether deficits in set-shifting and/or inhibition meet several criteria of an endophenotype for MDD in a sample of young adults. Results demonstrated that set-shifting deficits were familial and were present in the acute stage of depression and in remission, although not in a group with remitted MDD who also had other current disorder(s). The two inhibition tasks, which were examined separately because they were only weakly correlated, generally did not differ between groups. Post-hoc sensitivity analyses indicated that insufficient statistical power may have contributed to these nonsignificant group differences in inhibition. Taken together, these findings suggest that set-shifting impairment is a promising endophenotype candidate for MDD, and further research is needed to clarify whether inhibition satisfies endophenotype criteria.

The finding that set-shifting was impaired in individuals with current MDD compared to healthy controls was consistent with our hypothesis and with prior findings (Snyder, 2013). We also found that set-shifting deficits were present in those with remitted MDD and no current disorders. Previous studies examining whether set-shifting is impaired in remitted MDD have yielded mixed results (Hasselbalch et al., 2012; Jermann et al., 2013; Lange et al., 2012; Peters et al., 2017), potentially due to inconsistent consideration of psychiatric comorbidities. Although the present study found that set-shifting was poorer in those with remitted MDD and current disorder(s) relative to healthy controls, this difference (and differences between the remitted MDD and current disorder[s] group and the other groups) were not statistically significant. This pattern may suggest that the presence of 'other' current comorbid conditions confounded the results. However, the comorbid diagnoses present in the remitted MDD with current disorder(s) group were quite heterogeneous, preventing an exploration of which comorbid current disorders affected these results. Additionally, as analyses were sufficiently powered to detect medium to large group differences in set-shifting, small group differences may have emerged in a larger sample. In short, it is unclear why those with remitted MDD with current comorbid disorders did not differ from the other groups, although it is noteworthy that the "clean" remitted MDD group exhibited deficits in set-shifting relative to controls and did not differ from those with current

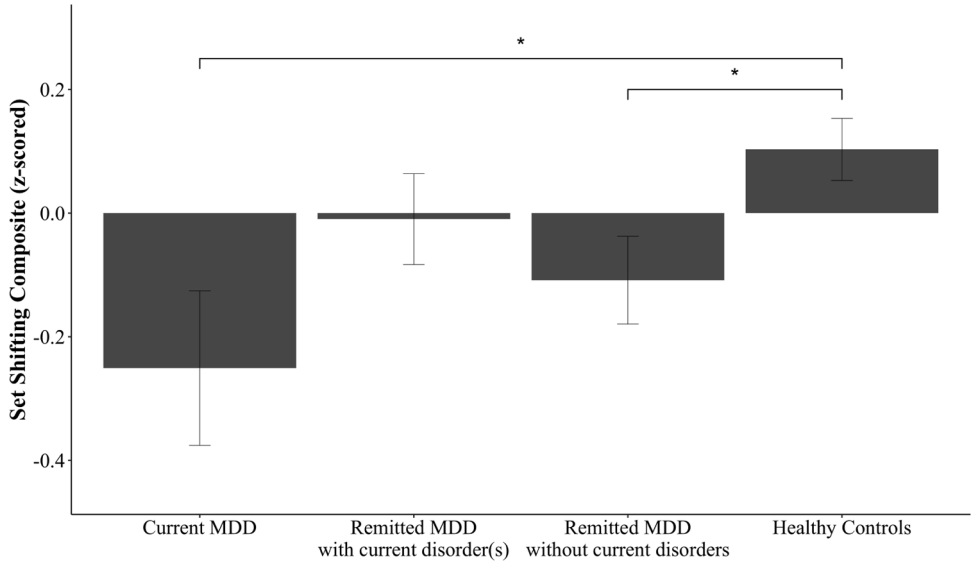

Fig. 1. Group differences in set-shifting (covarying for estimated full-scale IQ, processing speed, and race). Error bars represent standard errors. * $p < .05$.

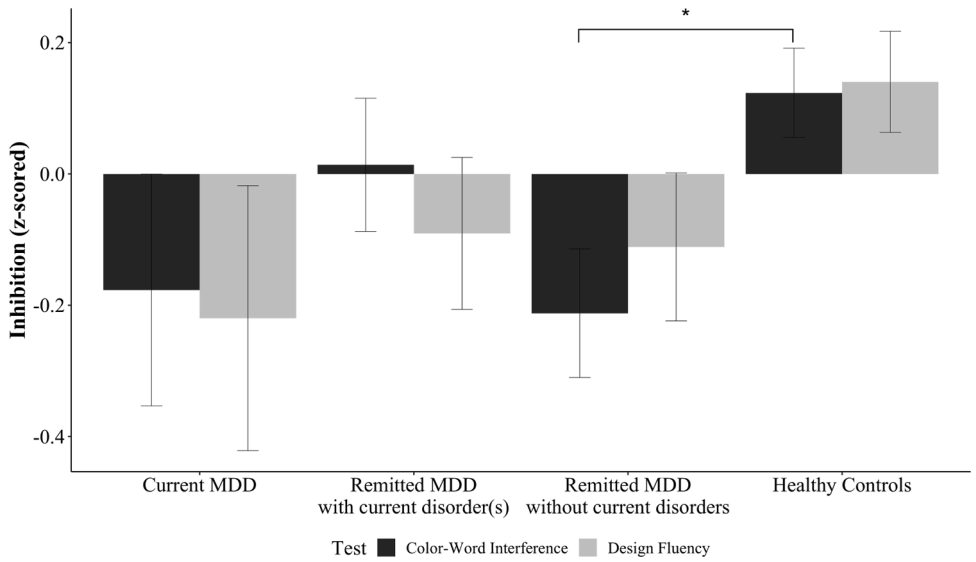

Fig. 2. Group differences in inhibition (covarying for estimated full-scale IQ, processing speed, and race) as measured by condition 2 (Empty dots only) of the Design Fluency test and condition 3 (Inhibition) of the Color-Word Interference test. Error bars represent standard errors. * $p < .05$.

depression.

These findings suggest that set-shifting deficits may satisfy the endophenotype criterion of state-independence. Set-shifting was also familial, suggesting it may satisfy the heritability endophenotype criterion. This finding is consistent with twin studies that found that performance on set-shifting tasks was significantly heritable (Anokhin et al., 2003; Friedman et al., 2008). However, further work is needed to replicate and extend these findings. In particular, it is unclear whether set-shifting is impaired prior to MDD onset, as prior findings have been mixed (Papmeyer et al., 2015; Stange et al., 2016). If set-shifting is only impaired in current and remitted MDD, it may be a consequence, or 'scar,' of MDD rather than an intermediate process involved in its pathophysiology (Zeiss and Lewinsohn, 1988). For example, it is possible that symptoms of depression may cause lasting damage to neural structures such as the prefrontal cortex, which subsequently contribute to deficits in executive functioning domains such as set-shifting. Impairments in set-shifting have been observed in unaffected twins of co-twins with a history of MDD (Christensen et al., 2006) and in unaffected individuals at familial risk for mood disorders (Papmeyer et al., 2015). These findings suggest set-shifting deficits may precede MDD onset, and may also satisfy the endophenotype criterion of being present at higher rates within affected families than in the general population.

Consistent with prior studies (Rey-Mermet et al., 2018), the two inhibition tasks were only weakly correlated and thus were examined separately rather than as a composite score. Performance on both inhibition tasks was familial, but was not impaired in individuals with current MDD compared to healthy controls. These nonsignificant group differences were unexpected and inconsistent with prior findings (e.g., Snyder, 2013). The pattern of group means was in the hypothesized direction, however. As the association between two measures is a function of each measure's reliability (Spearman, 1904) and individual tasks are generally less reliable than composite scores, the weaker reliabilities of the individual inhibition tasks relative to the set-shifting composite score may have led to greater attenuation of group differences in inhibition, larger standard errors, and type II error. The relatively smaller size of the current MDD group also may have weakened statistical power to detect differences between the current MDD group and other groups. For example, the remitted MDD without comorbid disorders group had poorer Color-Word Interference inhibition performance than healthy controls, but comparable scores with the current MDD group. This suggests that the difference between individuals with current MDD and healthy controls may have reached statistical significance in higher-powered analyses. Additionally, it is possible that previously observed associations between MDD and inhibition are specific to certain kinds of tasks or stimuli. For example, the inhibition tasks used in the present study were not affective in nature, and the association between MDD and inhibition may be specific to (or stronger for) the inhibition of mood-congruent material (Hsu and Davison, 2017; Joormann et al., 2007).

Strengths of this study include the examination of multiple Gottesman and Gould (2003) endophenotype criteria in the same sample, the inclusion of family data (which are required to fully evaluate candidate endophenotypes; Glahn and Blangero, 2011), and the consideration of a variety of potential demographic and clinical confounds through methodological or statistical controls. Third, set-shifting and inhibition were assessed using conditions from the same measure (D-KEFS) that were normed on the same sample, which increased the validity of comparisons of effects between set-shifting and inhibition.

There were also several noteworthy limitations. First, a categorical diagnostic approach was taken because it is difficult to dimensionally quantify remission and current comorbidity. For example, differentiating between remitted and non-remitted individuals on a dimensional depression measure requires an arbitrary cutoff. Although the DSM requirement of five symptoms for a MDD diagnosis may also have limited validity (Kendler and Gardner, 1998), the categorical diagnostic approach facilitates comparisons to previous relevant studies and increases clinical implications given the ubiquity of diagnoses in clinical settings. However, this approach fails to capture subthreshold conditions (Shankman et al., 2009), and future research may benefit from a dimensional approach given taxometric (Haslam et al., 2020) and psychometric (Shankman et al., 2018) evidence favoring dimensional measures of depression over categorical measures. Second, the current MDD group was relatively small in size ($n = 23$) and simulation-based sensitivity analyses indicated that statistical power was lower for differences between the current MDD group and other groups compared to other pairwise group differences. While power was sufficient to rule out large differences between the current MDD group and other groups, there may be small or medium differences that our analyses were underpowered to detect. Third, the study was cross-sectional in nature, and longitudinal studies would be better suited for assessing state-independence. Fourth, the present sample consisted of community members aged 18–30. Although this approach aimed to capture individuals in the peak risk period for internalizing disorders, results may

not generalize to other age groups (e.g., middle-aged or older adults) or settings (e.g., inpatients). Fifth, although the present study included measures of multiple EF processes, other relevant processes (e.g., working memory updating) were not assessed due to concerns about participant fatigue. Measures of processes not tied to executive functioning (e.g., verbal memory) would allow for additional tests of specificity, but were not included for the same reason.

4.1. Conclusions

Set-shifting was familial and was impaired in individuals with current MDD relative to healthy controls. Set-shifting was also impaired in individuals with remitted MDD and no current disorders (but not those with remitted MDD and current disorder[s]), suggesting that it may satisfy the heritability and state-independence criteria of an endophenotype for depression. These impairments were not attributable to lifetime psychiatric comorbidities, demographic characteristics, or general intellectual functioning. Inhibition was unrelated to current MDD, although this may have been due to insufficient statistical power. Although further prospective and family studies are needed to replicate and extend these results, these findings suggest that set-shifting is a promising endophenotype candidate for depression.

Author statement

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Declaration of Competing Interest

none

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.113931.

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