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A Review of Selected Candidate Endophenotypes for Depression

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Abstract

Endophenotypes are proposed to occupy an intermediate position in the pathway between genotype and phenotype in genetically complex disorders such as depression. To be considered an endophenotype, a construct must meet a set of criteria proposed by Gottesman and Gould (2003). In this qualitative review, we summarize evidence for each criterion for several putative endophenotypes for depression: neuroticism, morning cortisol, frontal asymmetry of cortical electrical activity, reward learning, and biases of attention and memory. Our review indicates that while there is strong support for some depression endophenotypes, other putative endophenotypes lack data or have inconsistent findings for core criteria.

Keywords

depression; endophenotype; neuroticism; cortisol; frontal asymmetry; cognitive biases

In light of the complicated genetics underlying psychological disorders, endophenotypes, constructs that dot the pathway between genes and clinical phenotypes, have been proposed as a strategy to study pathology and discover susceptibility genes (Cannon & Keller, 2006; Gottesman & Gould, 2003; Miller & Rockstroh, 2013). Gottesman and Gould (2003) hypothesized that endophenotypes can be used to parse the genetics of a given disorder into smaller, more tractable, components. Presumably, these components would have simpler genetic architectures than the disorder itself. Moreover, utilizing multiple endophenotypes for the same disorder could accelerate finding genes and pathways that have remained elusive (Kendler & Neale, 2010).

Hasler and colleagues (2004, 2011) provided two reviews of putative endophenotypes for depression; the first, for a variety of endophenotypes, and the latter, focusing primarily on neuroimaging. Hasler et al. emphasized the dearth of heritability, family, and prospective studies of most putative endophenotypes at the time of their reviews. To determine which

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endophenotypes are most promising currently, we evaluated the empirical support for a select group of putative depression endophenotypes: neuroticism, morning cortisol, asymmetry in frontal cortical activity on EEG, reward learning, and several laboratory-based cognitive measures. This is not an exhaustive list – we selected the candidates with the most relevant evidence and excluded putative neuroimaging endophenotypes due to the recency of Hasler et al.'s (2011) review.

Gottesman and Gould's criteria: A guide for empirical scrutiny

Several requirements must be met for a construct to be considered an endophenotype. Gottesman and Gould (2003; Chan & Gottesman, 2008; Gould & Gottesman, 2006) originally proposed five, and later added a sixth, criteria. An endophenotype must: (1) be associated with the target illness; (2) be heritable; (3) be detectable independent of the disorder's current manifestation (however, challenges can be used to unmask the endophenotype if necessary); (4) cosegregate within families of probands with the disorder; (5) be more common in the healthy family members of individuals with the disorder than in the general population; and (6) be reliably measured. Gottesman and Gould's (2003) criteria distinguish endophenotypes from related concepts such as biomarkers, which are not necessarily heritable or trait-like (see Lenzenweger, 2013 for a discussion of the distinction between these concepts).

We will review evidence for each of these criteria and use this to evaluate each candidate endophenotype's status. Some of the study designs that can be used to address each criterion are illustrated in Table 1. The first criterion, association between the endophenotype and depression, can be assessed by comparing levels of the endophenotype among depressed and never depressed individuals. The second criteria, heritability of the endophenotype, can be evaluated using twin and adoption studies. The third criteria, detecting the state-independence of an endophenotype, can be assessed in longitudinal or cross sectional studies using within-person and between-person analyses, respectively. In longitudinal studies, the premorbid level of the endophenotype can be compared to the depressed state level or the depressed state level can be compared to the remitted level of the endophenotype. In cross-sectional studies, the level of the endophenotype is compared between currently depressed individuals and individuals who have recovered from a depressive episode.

The next two criteria are closely related and can often be addressed in the same study. The fourth criterion, familial cosegregation, is shown when, in relatives of depressed probands, the endophenotype occurs more often (or at higher levels) in depressed or previously depressed family members compared to never depressed relatives. Alternatively, one could compare one twin from a pair that is concordant for depression with the never depressed twin from a pair that is discordant for depression. However, some never depressed relatives may have a high liability and eventually develop the disorder. This leads to the fifth criterion: the endophenotype should occur more often in the never depressed relatives of depressed probands compared to never depressed individuals from the general population. A single study using depressed probands, their affected and non-affected relatives, and never depressed controls could address both criteria four and five.

The final criteria concerns the reliability of the endophenotype. Studies of test re-test stability, and if applicable, internal consistency and inter-rater reliability address this criterion.

Unfortunately, there are insufficient data on most criteria for most putative endophenotypes to conduct a quantitative review. Hence, we evaluated the evidence for the six criteria for each endophenotype qualitatively and summarized it in Table 2 using a method similar to Hasler et al. (2004). Due to space limitations, we cannot provide references to all studies reporting data relevant to the endophenotype criteria. Relevant studies that are not cited here are listed in a supplemental appendix.

Interestingly, studies that examine shared genetic influences between endophenotypes and psychiatric disorders are not included in Gottesman and Gould's criteria. However, multivariate twin studies that estimate the shared genetic variance between an endophenotype and a clinical phenotype would indicate whether they have common genetic influences. Thus, we contend that studies of shared genetic influences between a clinical phenotype and an endophenotype should be included as a seventh criterion on the Gottesman and Gould list. We will review these studies when available, but due to their rarity, do not include them in Table 2.

Endophenotypes and the Research Domain Criteria

The endophenotype concept fits comfortably with the Research Domain Criteria (RDoC; see Miller & Rockstroh, 2013). The RDoC has recently been proposed as a framework to integrate genetic and neuroscience findings to develop a pathophysiology-based classification system that is hoped to improve prevention, early intervention, and treatment outcomes (Insel et al., 2010). To this end, RDoC largely abandons the current diagnostic system and favors dimensionally measured constructs, and neural circuits that are related to upstream genetics and downstream behavior. Importantly, endophenotypes are frequently at the level of the intermediate units of analysis in the RDoC system (molecules, cells, circuits, physiology). Although endophenotypes have traditionally been associated with diagnostic categories, there is no reason why they cannot also be related to dimensional clinical phenotypes. Thus, many of the endophenotypes reviewed below are highly relevant to key RDoC domains, particularly the negative and positive valence, and cognitive systems.

Neuroticism

Neuroticism is characterized by a disposition to report and experience negative emotions (Eysenck, 1967). Among personality traits, neuroticism has consistently distinguished depressed and non-depressed individuals (Klein, Kotov, & Bufferd, 2011). Furthermore, depressed individuals with higher levels of neuroticism have a more chronic course, poorer treatment outcome, increased likelihood of recurrent episodes, and more frequent hospitalizations compared to depressed individuals with lower neuroticism scores (Mulder, 2002).

Neuroticism is typically assessed through self-report, although informant reports and some observational measures are also used. Self-report measures of neuroticism generally possess

strong psychometric properties. For example, the neuroticism scale on the NEO Personality Inventory has high internal consistency (Cronbach's $\alpha = 0.93$) and excellent long term test-retest stability ($r = 0.83$; Costa & McCrae, 1992). The psychometric properties are largely retained in depressed populations (Cronbach's $\alpha = 0.91$ and short term test-retest reliability $r = 0.70$; Costa, Bagby, Herbst, & McCrae, 2005). While self-report measures do have strong psychometric properties, neuroticism and depression measures often have overlapping content and are based on reports by the same individual; both features inflate associations. One solution, which has been used only infrequently, is to use observational methods or informant reports of neuroticism (Klein et al. 2011). Concerns about the content overlap could be addressed by removing depression items from neuroticism scales and correlating the remaining items (Nicholls, Licht, & Pearl, 1982).

Although neuroticism is relatively stable, it also possesses state-like characteristics. Many studies have reported differences in neuroticism between the depressed state and before or after depressive episodes (e.g. De Fruyt, Van Leeuwen, Bagby, Rolland, & Rouillon, 2006). Thus, studies have shown elevated neuroticism scores during depressive episodes relative to premorbid (e.g. Kendler, Neale, Kessler, Heath, & Eaves, 1993) or remitted levels (Costa, Bagby, Herbst, & McCrae, 2005). However, neuroticism also has a large trait component. For example, remitted individuals display higher levels of neuroticism than never depressed controls (De Fruyt et al., 2006). Moreover, even though absolute levels of neuroticism diminish after remission, it still exhibits high rank order stability (i.e., those who had the highest levels of neuroticism when depressed continue to do so after remission) (De Fruyt et al., 2006; Klein et al., 2011). Additionally, changes in depressive symptoms are not necessarily accompanied by changes in personality (Quilty et al. 2008, Tang et al. 2009). Finally, there is substantial evidence that neuroticism predicts the subsequent first onset of depression (e.g. Kendler, Gatz, Gardner, & Pedersen, 2006; Kendler, Neale, Kessler, Heath, & Eaves, 1993). Overall, neuroticism satisfies the state-independence criterion, but should be considered to possess both state- and trait- like features since it is characterized by rank order stability and absolute change (Klein et al., 2011).

The heritability of neuroticism has received strong support from twin studies (e.g. Lake, Eaves, Maes, Heath, & Martin, 2000). Studies, with very large samples, typically estimate heritability between .35 and .55, (e.g. Jang, Livesley, & Vernon, 1996; Tellegen et al., 1988).

There is also evidence that neuroticism cosegregates with depression in families. Several studies of families with a currently depressed proband found higher levels of neuroticism in relatives with a history of depression than in relatives who were never depressed (e.g. Farmer et al., 2002; Ouimette, Klein, & Pepper, 1996).

Several family studies have also found that the healthy relatives of depressed individuals have higher levels of neuroticism than healthy controls (e.g. Modell, Huber, Holsboer, & Lauer, 2003). However, a number of studies have not found differences between healthy relatives of depressed individuals and healthy controls (e.g. Farmer et al., 2002; Ouimette et al., 1996). Interestingly, the studies that did not find differences tended to use older samples, raising the possibility that many of the high risk family members may have already

developed depression, narrowing the relatives in the unaffected group to those at the lowest risk (Klein et al., 2011). However, a study that sampled at-risk adolescent offspring failed to show increased levels of neuroticism compared to controls (Ouimette, Klein, Clark, & Margolis, 1992).

Twin studies have been conducted to estimate the shared genetic correlation between neuroticism and depression. In a seminal longitudinal twin study, Kendler and colleagues (1993) found that 55% of the genetic variance in depression is shared with neuroticism. Subsequent twin studies have reported similar results (e.g., Fanous, Gardner, Prescott, Cancro, & Kendler, 2002; Kendler, et al., 2006). Thus, neuroticism and depression appear to share a genetic basis.

Overall, the evidence indicates that neuroticism is a promising candidate endophenotype for depression (see Table 2). Most criteria are supported by a large literature. Although neuroticism is influenced by mood state, it also possesses a trait component. Findings for the fifth criterion (differences between unaffected relatives and healthy controls) are least consistent; studies using younger unaffected relatives are necessary to ensure that participants with the highest levels of vulnerability have not been selected out by having already developed the disorder. Importantly, neuroticism has been found to share genes with depression. While neuroticism is not specific to depression and may also be involved in the development of other disorders (Kotov et al., 2010), compared to the other endophenotypes discussed below, neuroticism has the strongest and most comprehensive support.

Cortisol

Cortisol, a stress hormone that is frequently used as a marker of HPA-axis functioning, has received substantial attention in the depression literature for decades. Cortisol is relevant to depression since it is linked to lab-induced acute and chronic stress (e.g. Burke, Davis, Otte, & Mohr, 2005; Stetler & Miller 2011) and may be a pathway for depression transmission (Halligan, Herbert, Goodyer, & Murray, 2007). Cortisol activity is appealing because it can be assessed in naturalistic contexts (e.g. levels at specific time points or daily patterns) or in response to laboratory manipulations (e.g. stress inducing tasks or the dexamethasone suppression test). It can be measured in blood, saliva, urine, cerebral spinal fluid, and hair (note, these measures index cortisol activity in different ways, e.g. hair cannot be used to measure diurnal variation). However, different cortisol measures are not always correlated, associated with the same clinical features, or equally heritable (Harris et al., 2000; Kupper et al., 2005; Stetler & Miller, 2011); thus, evidence from different methods should not be combined when assessing endophenotype status. For this reason, we are not able to review stress inducing tasks since there are a variety of paradigms that may tap different processes (see Burke et al., 2005, as an example of the number of different tasks). Lab-induced stress paradigms that have been more widely studied may be better characterized as endophenotypes for other disorders such as social phobia. Instead, we separately evaluated the evidence for morning cortisol and the cortisol awakening response (CAR).

Before reviewing the evidence for each putative endophenotype we will briefly define and describe how they are assessed. Fixed clock/or single time point morning cortisol is

typically assessed based on the individuals waking time or at a fixed time in the morning. The CAR refers to the increase in cortisol soon after awakening and is typically measured as the difference between, or the area under the curve of, cortisol levels upon waking and 20–45 minutes later. Morning cortisol and CAR are related, but not identical.

When compared to healthy controls, depressed individuals have elevated morning cortisol (e.g. Michael, Jenaway, Paykel, & Herbert, 2000) and CAR (e.g., Bhagwagar, Hafizi, & Cowen, 2005; Vreeburg et al., 2009). However, a few studies have found a blunted CAR in those with depression (e.g. Huber, Issa, Schik, & Wolf, 2006; Stetler & Miller, 2005). Similar to neuroticism, aberrant cortisol activity may not be specific to depression (e.g., Chida & Steptoe, 2009).

Intra-individual fluctuations are common for cortisol measures, but reliability is improved substantially by taking samples on multiple days (Hellhammer et al., 2007). Morning cortisol and CAR possess moderate test-retest reliability with correlations ranging from .39 –.67 in a variety of populations (e.g. Pruessner et al., 1997).

There is somewhat greater evidence for state-independence for CAR than morning cortisol, which appears to be somewhat state-dependent. Thus, the CAR remains elevated in remission and is comparable to depressed individuals (e.g. Vreeburg et al., 2009), whereas one study found that morning cortisol in remitted individuals was similar to non-depressed controls (Michael et al., 2000). A number of studies have found that both elevated morning cortisol (e.g. Harris et al., 2000; Goodyer, Herbert, & Tamplin, 2003) and a greater CAR (e.g. Adam et al 2010; Halligan et al., 2007) predict the onset of depressive episodes or depressive symptoms. However, some conflicting findings regarding the prediction of depression have been reported for both morning cortisol (Bockting et al., 2012) and CAR (Carnegie et al., 2014).

Recent studies have found substantial, but variable genetic influence on morning cortisol and CAR. Several studies have estimated that the heritability of CAR ranged from .40 – .64 (e.g. Riese, Rijdsdijk, Rosmalen, Snieder, & Ormel, 2009; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000; but see Kupper et al., 2005 for negative findings). Some have found that morning cortisol has no genetic influences (Wüst et al., 2000), but others have estimated heritability at .21 –.59 (e.g. Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma, 2003). These studies also indicate that morning cortisol based on a fixed clock time is less heritable than morning sampling based on individuals' wake times.

Data on cosegregation of cortisol within families are extremely limited. In the only relevant study we could identify, depressed twins with a depressed co-twin had elevated morning cortisol compared to healthy twins with a depressed co-twin, but the difference was not statistically significant (Young, Aggen, Prescott, & Kendler, 2000).

Studies have documented increased morning cortisol (e.g. Dougherty, Klein, Olino, Dyson, & Rose, 2009) and CAR (e.g. Vreeburg et al., 2010) in healthy offspring of depressed parents in comparison to offspring of healthy parents. Another study found differences between healthy relatives and controls only when morning cortisol was sampled on non-work days, but not work days (Le Masurier, Cowen, & Harmer, 2007). A study comparing

morning cortisol in healthy twins of depressed co-twins did not find significant differences when compared to healthy twins with healthy co-twins (Young, Aggen, Prescott, & Kendler, 2000).

In conclusion, morning cortisol and the CAR have moderate support for each Gottesman and Gould endophenotype criterion with the exception of cosegregation, for which the only relevant study did not find a significant association. Overall, the evidence suggests that morning cortisol and CAR are promising candidate endophenotypes.

Frontal Asymmetry

Another putative endophenotype is asymmetry in electrical activity in frontal regions of the scalp as measured by electroencephalography (EEG). In most studies, frontal asymmetry (FA) is assessed while participants are at rest; however some studies have examined FA in response to specific tasks. FA profiles are relevant to depression since activity in the right frontal region is thought to reflect withdrawal behavior and negative affect whereas activity in the left frontal region is hypothesized to reflect approach behavior and positive affect (Davidson, 1998; Tomarken, Davidson, Wheeler, & Doss, 1992). Depression, often associated with loss of interest and anhedonia, is thought to be characterized by decreased relative left FA.

Decreased relative left FA has been shown to differentiate depressed and non-depressed individuals (e.g. Henriques & Davidson, 1991; Shankman et al., 2007, 2013; Stewart, Bismark, Towers, Coan, & Allen, 2010). Although there have been negative reports (e.g. Reid, Duke, & Allen, 1998), a meta-analysis reported a moderate relationship between decreased relative left FA and depression (Thibodeau, Jorgensen, & Kim, 2006).

FA appears to possess both trait- and state- like components (see Coan & Allen, 2004). However, FA still possess moderate temporal stability. Studies of FA have found that 2 to 6 week test-retest reliability coefficients range between .50 and .60 (e.g., Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005).

There is evidence that FA does not change as a function of mood state, symptoms, or clinical status (Allen, Urry, Hitt, & Coan, 2004; Papousek & Schulter, 2002; Vuga et al., 2006). In addition, several studies have shown that individuals in remission from depression have greater FA than never depressed controls (e.g. Gotlib, Raganathand, & Rosenfeld, 1998; Henriques & Davidson, 1990; Stewart, Bismark, Towers, Coan, & Allen, 2010). Furthermore, currently depressed and remitted individuals do not significantly differ on FA (Gotlib, et al., 1998). Finally, decreased relative left FA has been found to predict the first onset of depression in young adults (e.g. Nusslock et al., 2011). Taken together, these studies suggest that EEG FA is at least partially independent of depressive symptoms.

Twin studies reveal only modest heritability for FA. A study of twins ages 9–10 found that genetic factors accounted for 11%–28% of observed variance (Gao, Tuvblad, Raine, Lozano, & Baker, 2009). A large twin study of adults estimated FA heritability in young men and women to be .33 and .37, respectively (Smit, Posthuma, Boomsma, & De Geus, 2007). However, evidence for heritability vanished in middle adulthood for both men and

women. Finally, a third study found that heritability depended on electrode recording site, with low-moderate heritability found for some (F3 and F4), but not other (F7 and F8) sites typically used to assess FA (Anokhin, Heath, & Myers, 2006).

We are not aware of any studies examining the cosegregation of FA within depressed families. However, relative left FA distinguished infant (e.g. Diego et al., 2004) and adolescent (Tomarken, Dichter, Garber, & Simien, 2004) offspring of depressed individuals compared to offspring of healthy controls. Indeed, a meta-analysis showed that the effect size of decreased relative left FA in infants of depressed, compared to infants of non-depressed, mothers was similar to adults with a depression diagnosis compared to controls (Thibodeau et al., 2006).

Smit and colleagues (2007) found some evidence that FA shares genes with depression and anxiety symptoms. However, this was apparent only in young females, and not in males or older females.

In summary, the strongest support for FA as an endophenotype stems from evidence indicating an association with depression even after recovery, abnormalities in healthy offspring of depressed parents, and prediction of onset (see Table 2). However, no studies have been conducted to address cosegregation with depression in families. Perhaps most importantly, FA is only modestly heritable. Even if heritability is modest, it is still possible that FA shares genes with depression. However, the one study examining this issue combined depressive and anxiety symptoms and reported mixed findings (Smit et al., 2007).

Reward Learning

There is growing interest in deficits in reward processing as a putative endophenotype for depression (Bogdan, Nikolova, & Pizzagalli, 2013). Several behavioral tasks have been developed that tap into various aspects of reward (e.g. reward valuation, effort valuation/willingness to work, preference-based decision making, reward learning) and are commonly used in conjunction with imaging techniques. However, these tasks reflect very different processes, and therefore cannot be lumped together. The task with the most relevant data concerning endophenotype status is a probabilistic reward learning task (PRT) developed by Pizzagalli and colleagues (Pizzagalli, Jahn, & O'Shea, 2005). Hence, we will focus on this task here. Further research into other tasks such as Knutson's monetary incentive delay paradigm (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008) and Treadway's effortful decision making task (Treadway, Buckholz, Schwartzman, Lambert, & Zald, 2009) is needed to determine if they meet criteria for an endophenotype (also see Bogdan, Nikolova, & Pizzagalli, 2013 for a review of reward processing and stress reactivity as potential endophenotypes).

Pizzagalli and colleagues developed a reward learning task based on signal-detection procedures. On each trial participants are shown one of two stimuli and instructed to press a key corresponding to the particular stimuli presented on that trial. The stimuli are differentially reinforced such that one is more valued than the other, which leads individuals to develop a response bias for that stimuli. When compared to controls, depressed individuals fail to develop a bias to select the more valued stimuli (e.g. Pizzagalli, Iosifescu,

Hallett, Ratner, & Fava, 2009). As is the case with many putative endophenotypes for depression, reward learning may not be specific to depression. A recent study found that within a group of schizophrenics those with greater nicotine dependence failed to develop a bias to select the more valued stimuli (AhnAllen et al., 2012).

This reward learning task has been found to possess adequate psychometric properties. One month test-retest reliability was $r = .57$ in a sample of 25 undergraduates (Pizzagalli, et al., 2005).

Evidence suggests that the response bias on the PRT is stable over time. Individuals who had remitted from depression, and on average experienced their last episode more than three years prior to taking the PRT, failed to develop a response bias for the more valued stimulus compared to controls. The differences between remitted individuals and controls remained significant even when accounting for current depression symptoms (Pechtel, Dutra, Goetz, & Pizzagalli, 2013).

Although we are not aware of any studies that address cosegregation or increased rates within affected families, the heritability of the PRT has been estimated in a small twin sample. Heritability of response bias on the PRT was estimated to be 0.46. Furthermore, this study also found that some of the genes for depressive symptoms and response bias are the same, estimating the genetic correlation to be 0.29 (Bogdan & Pizzagalli, 2009).

In contrast to other putative endophenotypes, the PRT has largely been studied by the group that developed the task. However, it has received support for four endophenotype criteria. Moreover, unlike many putative endophenotypes, there is preliminary evidence that response bias on the PRT shares genes with depression.

Cognitive Endophenotypes

There are studies addressing most of the Gottesman and Gould criteria for the depression endophenotypes reviewed thus far. The next section will focus on endophenotypes with fewer studies for many criteria. Of the many putative endophenotypes with a more limited evidence base, we chose to include attention and memory biases because of their prominent role in cognitive models of the etiology of depression (e.g. Gotlib & Joormann, 2010). Furthermore, these putative cognitive endophenotypes have important links to depression-related neural dysfunction (for a review see Disner, Beevers, Haigh, & Beck., 2011). For simplicity, we will present evidence for multiple measures of these putative endophenotypes under the same heading, but this should not be interpreted as implying that the differences between tasks are unimportant. Rather, there may be many distinct endophenotypes within each of these cognitive domains. We have attempted to select the tasks that have the most available evidence at this time.

Attention Biases

Attentional biases can be studied using numerous paradigms that typically involve measuring reaction time to, or time spent looking at, an emotional stimulus. Specific methodological features, such as the length of exposure to the stimuli or the use of a

negative mood induction prior to the task may be important influences on the results (Kujawa et al., 2011; Gibb, Benas, Grassia, & McGeary, 2009). Some might consider mood inductions as violating the state independence criteria. However, they can also be viewed as a type of challenge, which is consistent with Gould and Gottesman's (2006) revised criteria. Although many paradigms have been used to assess attentional biases, we will focus on eye-tracking, the Stroop, and dot-probe tasks (for descriptions of other attention and cognitive tasks see Bistricky, Ingram, & Atchley, 2011).

Negative attentional biases have been reported on the Stroop and dot-probe tasks in a variety of depressed populations (e.g. Epp, Dobson, Dozois, & Frewen, 2012; Gotlib, Krasnoperova, Yue, & Joormann, 2004). While the classic Stroop task assesses executive function, the emotional Stroop task, which consists of emotionally valenced words or faces, is commonly used to assess biased attention for sad stimuli. A recent meta-analysis of emotional and classic Stroop studies revealed robust group differences between clinically depressed individuals and controls for negative stimuli (Epp, Dobson, Dozois, & Frewen, 2012). However, the classic Stroop also differentiated the groups, which implies that attentional deficits in depression extend beyond emotional biases. Another recent meta-analysis of dot-probe and emotional Stroop studies showed that negative attentional biases in depression are stronger on the dot-probe than the Stroop (Peckham, McHugh, & Otto, 2010).

Eye-tracking studies show that individuals diagnosed with depression spend more time attending to negative stimuli than healthy controls (Kellough, Beevers, Ellis, & Wells, 2008). However, another study found that dysphoric individuals spent less time attending to positive images, but not negative images when compared to controls (Sears, Thomas, LeHuquet, & Johnson, 2010). Importantly, meta-analysis of eye-tracking studies reported more sustained attention for dysphoric stimuli and less attention to positive stimuli in depressed samples (Armstrong & Olatunji, 2012). Although it is not entirely clear which attentional bias paradigm best distinguishes depressed and non-depressed individuals, these studies suggest that negative attentional biases warrant consideration as a putative endophenotype.

The emotional Stroop has been shown to possess high test-retest reliability when using mean reaction times (e.g. happy stimuli $r = 0.88$ – 0.89 ; sad stimuli $r = 0.82$ – 0.89); however, when difference scores are used, for example between sad and neutral stimuli, test-retest reliability is poor. The threat based dot-probe (procedures that use neutral, happy, and angry faces) has also been reported to have poor test-retest reliability (e.g. no significant reliability coefficients; Staugaard, 2009). We are not aware of any studies of the test-retest reliability of the sad dot-probe or emotional eye-tracking paradigms.

There is conflicting evidence on whether attentional tasks are independent of mood state. Several studies failed to find differences between depressed individuals in remission and healthy controls on threat/sadness-based dot-probe tasks (Merens, Booi, & Van Der Does, 2008), and the emotional Stroop (e.g. Fritzsche et al., 2010). However, Joormann & Gotlib (2007) reported that individuals who had remitted from a depressive episode exhibited a significantly greater bias for sad faces on the dot probe than never depressed controls, and

did not differ from currently depressed subjects. Additionally, a dot-probe study showed that biases for various negative stimuli predicted future increases in dysphoria (Beevers & Carver, 2003).

Similarly, on an eye-tracking task, individuals who had remitted from depression were more likely to initially focus on depression-relevant images than never depressed individuals, and did not differ from currently depressed participants (Sears, Newman, Ference, & Thomas, 2011). Finally, a longitudinal study of soldiers found that attentional biases in an eye-tracking paradigm predicted later depression symptoms (Beevers, Lee, Wells, Ellis, & Telch, 2011). Thus, the evidence regarding state-independence of attentional biases is mixed, but appears to be stronger for the dot-probe and eye-tracking tasks than the Stroop.

Heritability has yet to be addressed for the emotional Stroop, sad dot-probe, and eye-tracking tasks. There has been one study that investigated the heritability of a threat based dot-probe, which found moderate heritability when stimuli were presented to the left visual field, but no significant genetic influences on stimuli presented to the right (Rijsdijk et al., 2009). It is unclear why heritability varies by visual location. Additionally, there is evidence of specific genes influencing attentional biases, including studies showing that a polymorphism on the serotonin transporter gene is related to attentional avoidance of sad faces and dysphoric words on the dot-probe task (e.g. Beevers, Gibb, McGeary, & Miller, 2007; Gibb et al., 2009) and biased visual attention using eye-tracking (Beevers et al., 2011). These studies suggest that attentional biases have a genetic component, although the broad heritability of the depression relevant tasks has not been explored.

Evidence of familial cosegregation with depression has been non-supportive for the emotional Stroop task. In a sample of family members of depressed probands, relatives who had remitted from depression and never depressed relatives did not differ on negative biases (van Oostroom et al., 2013). We are not aware of any studies that examine cosegregation of the dot probe or eye-tracking within depressed families.

Other studies have shown that attentional biases are more common in healthy relatives of depressed individuals compared to healthy controls. Two studies of the emotional faces dot-probe found greater attentional biases for sad stimuli in the offspring of depressed parents compared to offspring of healthy parents when a negative mood induction was used (Joormann, Talbot, & Gotlib, 2007; Kujawa et al., 2011); however attentional avoidance was found in an offspring study that did not use a negative mood induction (Gibb et al., 2009). One study of the emotional Stroop, found that healthy individuals with a family history of depression were more likely to attend to negative words when compared to controls (van Oostrom et al., 2013).

Despite promising support for some criteria for attentional biases as an endophenotype, the evidence for state-independence is mixed, heritability is unknown for the most depression-relevant tasks, and cosegregation was not supported in the only study relevant to this criterion (Table 2).

Memory Biases

Biased recall for negative material is consistently found in individuals with depression (Gotlib & Joormann, 2010). We will focus on biases in self-referential recall and overgeneral autobiographical memory, which appear to have the most relevant evidence regarding endophenotype status.

Self-referential recall is typically assessed with the self-referent encoding task (SRET), in which participants are read a list of negative and positive adjectives and asked to indicate whether or not each word characterizes them. After making these self-relevance judgments, participants are unexpectedly asked to recall as many adjectives as possible. Biases are determined by the proportion of positive and negative words recalled out of those initially endorsed (e.g. Kircanski, Mazur, & Gotlib, 2013). Overgeneral autobiographical memory (OGM) is typically assessed using the autobiographical memory test (AMT), in which participants are shown a series of positive and negative cue words and are asked to report an autobiographical memory for each cue. They are instructed to provide memories of specific events at discrete times (i.e., particular events lasting less than one day (Williams et al 2007)).

The association of memory biases with depression has been supported in a number of studies. For instance, self-referential biases differentiate highly dysphoric or depressed individuals from healthy controls (e.g. Derry & Kuiper, 1981; Moulds, Kandris, & Williams, 2007). In addition, currently depressed individuals report more OGM than controls (e.g. van Vreeswijk & de Wilde, 2004; Williams et al., 2007).

Recent studies have examined the test-retest reliability of the SRET. In a study that assessed the 6 month stability of the SRET for negative stimuli in a community sample of adolescents, the correlation was not significant ($r = 0.16$; Black & Pössel, 2012). However, a second study with a larger sample of children, assessed the stability of the SRET for negative stimuli across 12 and 24 months, and the correlation was modest, but significant at each time point (12 and 24 months, $r = 0.24$ and $r = 0.25$, respectively; Hayden et al., 2013). The AMT has acceptable psychometric properties. Inter-rater agreement on this task is consistently high (e.g. Kappa < 0.90 in Rawal & Rice, 2012). One study of depressed subjects reported moderate-high test-retest reliabilities over 3 to 4 weeks for specific memories ($r = 0.88$) and overgeneral memories ($r = 0.53 - 0.66$; Hermans et al., 2008). A recent study found modest, but significant stability across a 3–6 year interval for specific ($r = 0.31$) and categoric memories ($r = 0.32$), and that stability did not differ as a function of depression history (Sumner et al., 2014).

The state dependence of biased self-referential recall has received mixed support. In a cross-sectional study, remitted individuals did not differ from controls in memory for negative self-referential stimuli (Dobson & Shaw, 1987). In a longitudinal study, individuals exhibited a trend for less negative self-referential recall after remission compared to when they were depressed (Dozois & Dobson, 2001). However, neither of these studies used mood inductions before the SRET. In contrast, when challenges, such as mood inductions or priming self-focus, are used, individuals who are remitted from depression consistently

exhibit negatively biased self-referent recall (e.g. Fritzsche et al., 2010; Kircanski et al., 2013; Ramel et al., 2007).

There is relatively consistent support for the state independence criterion for OGM. A number of studies show that remitted individuals report more OGM than never depressed individuals (e.g. Park, Goodyer, & Teasdale, 2002), and that OGM predicts increases in depressive symptoms and recurrence (e.g. Rawal & Rice, 2012; Stange, Hamlat, Hamilton, Abramson, & Alloy, 2013; Sumner, Griffith, & Mineka, 2010). However, one study found that remitted individuals were more likely than controls to report general memories when presented with self relevant cues, but overall the groups did not differ in the number of specific memories (Crane, Barnhofer, Mark, & Williams, 2007). Another study found that OGM in remitted depressed individuals did not significantly differ from currently or never depressed controls (Rawal & Rice, 2012). Overall, however, the majority of studies suggest that overgeneral memory is likely state-independent.

No studies have directly addressed the heritability of self-referential recall biases or OGM. Similarly, there is no evidence bearing on the cosegregation of self-referential memory biases with depression in families. However, cosegregation of OGM was supported by a recent study that found affected offspring of depressed parents reported overgeneral memories more frequently than never depressed offspring of depressed parents (Rawal & Rice, 2012).

There is some evidence of negative self-referential memory biases in relatives at risk for depression. Thus, a negative self-referent recall bias was observed in the healthy offspring of depressed mothers compared to healthy offspring of healthy mothers when using a mood induction procedure. Interestingly, these differences were not evident without a mood induction (Taylor & Ingram, 1999). A recent study, found associations between negative self-referent recall in healthy offspring fathers, but not mothers (Hayden et al., 2013). A recent study also reported that the healthy relatives of individuals with depression exhibited increased OGM compared to healthy controls; furthermore, healthy relatives and currently depressed individuals did not differ on OGM (Young, Bellgowan, Bodurka, & Drevets, 2013).

Thus, self-referential recall biases and OGM have reasonably strong associations with depression and are moderately state-independent (see Table 2). Similar to many candidate endophenotypes reviewed above, they both lack studies addressing the heritability criterion. In contrast to some of the candidate endophenotypes discussed earlier, there are also few studies examining cosegregation and comparing healthy relatives of depressed and non-depressed individuals.

Genetic Associations between Endophenotypes

We have suggested that the degree of genetic overlap between a putative endophenotype and depression is a crucial consideration. However, it is also informative to explore the genetic relatedness among different endophenotypes. We would expect endophenotypes that share a large proportion of genes to implicate the same set of risk genes for depression, and endophenotypes that do not overlap would implicate different sets of risk genes. If several

putative endophenotypes share significant genetic factors, it would provide converging evidence for their status as endophenotypes. However, endophenotypes that do not share the same genes may be helpful in discovering more genes and pathways for depression.

The degree of shared genes has been examined for a few of the putative endophenotypes reviewed here. Riese and colleagues (2009) investigated the shared genetic influences of neuroticism and morning cortisol. Despite finding substantial heritability of both putative endophenotypes, they did not find any evidence of shared genetic influences.

The same group of researchers conducted a study exploring shared genetic relationships between neuroticism, a threat based dot-probe, and recall of pleasant/unpleasant words (Rijsdijk et al., 2009). They again found that all three measures were at least partially heritable, but again there was no evidence of shared genes. However, it should be noted that the threat-based dot probe and recall of valenced words are not the same as dot-probe tasks using sad stimuli and the recall of self-referent words that are used in the depression literature. Clearly, this is an area in which further research is needed.

Conclusion

We evaluated whether putative depression endophenotypes meet the required benchmarks for endophenotype status. We used Gottesman and Gould's (2003, 2006) definition of an endophenotype, which is distinct from related concepts such as biomarkers (Lenzenweger, 2013), and expanded it to include shared heritability between the endophenotype and the clinical phenotype. Hasler's (2004) review of putative depression endophenotypes highlighted the lack of evidence bearing on many of Gottesman and Gould's criteria. Despite increased attention to endophenotypes in recent years, many of the same criteria remain understudied. While we reported moderate to strong evidence on all criteria for neuroticism, there is little evidence bearing on heritability and familial cosegregation with depression for most of the other putative endophenotypes, typically due to the lack of family and twin studies. Additionally, for most putative endophenotypes there was no more than a single study that addressed psychometric concerns and these studies were often conducted with small samples. We also noted that even putative endophenotypes that received strong or moderate support for most criteria, such as neuroticism, morning cortisol, and CAR, were found to have associations with other disorders.

A second challenge concerns how to assess and weight conflicting studies for a given criterion. Meta-analysis would be useful in aggregating data across studies. Unfortunately, most candidate endophenotypes lack a large enough literature to support meta-analyses for any criteria other than the first criterion of an association between the endophenotype and depression. However, as this literature continues to grow, meta-analyses may become feasible.

Third, depression itself is a heterogeneous category. Unfortunately, very few putative endophenotypes have been studied in relation to subtypes of depression. However, studying the associations of endophenotypes to subtypes of depression may not prove to be fruitful if current subtypes are not biologically valid. Furthermore, most putative endophenotypes that

have the strongest support are also associated with other disorders, and therefore may have transdiagnostic value that go beyond specific subtypes of a single disorder. Thus, endophenotypes may be more useful for developing clinical phenotypes from the bottom up, cutting across traditional diagnostic categories.

Another concern is whether, as is typically assumed, endophenotypes possess simpler genetic architectures than the clinical phenotypes they are related to. A selective review of the schizophrenia literature concluded that the putative endophenotypes considered were as genetically complex as schizophrenia itself (Flint & Munafo, 2007). To address this question for depression endophenotypes, gene finding studies are necessary to compare the effect size of genes' contributions to the endophenotype and the clinical phenotype.

Studies of specific genetic influences on endophenotypes have typically used candidate genes previously linked to depression. Unfortunately, this does not aid in discovering new genes nor should it be the sole basis for evaluating the genetic complexity/simplicity of endophenotypes. Although these studies may explain mechanisms through which candidate genes influence depression, genome wide association studies (GWAS) and gene sequencing studies of endophenotypes may be better for discovering new genes and evaluating genetic simplicity. Interest in endophenotypes partially stems from the disappointing results of linkage and association studies of clinical phenotypes, and it is conceivable that GWAS may be more successful for endophenotypes than for traditional psychiatric disorders.

Studies that estimate shared heritability between endophenotypes are also needed to help determine whether endophenotypes with shared genetic influences should be aggregated, and to point to endophenotypes with narrower genetic influences that may lead to discovering unique genetic pathways to depression or more homogenous subtypes. Of the putative endophenotypes we reviewed above, few studies have been conducted to address if they share genes with one another and of the studies that were conducted, shared genetic influences were not found.

An anonymous reviewer of an earlier draft noted that method artifacts may obscure associations among endophenotypes and that a latent variable approach may be more productive. Creating latent putative endophenotypes, for example using Patrick et al.'s (2013) recent psychoneurometric approach, is an appealing strategy. However, it must be applied cautiously unless there is evidence that the manifest variables share some genetic variance. Otherwise, variables that are correlated at the phenotypic level but not at the genetic level may be lumped together, obscuring, rather than revealing, associations with genes.

Multivariate, multilevel approaches to conceptualizing endophenotypes are gaining traction (see Miller & Rockstroh, 2013). This is highly compatible with the RDoC framework. Several of the putative depression endophenotypes that we considered are closely related to the RDoC domains (Insel & Cuthbert, 2009), such as the negative (e.g., neuroticism) and positive (e.g., FA and reward learning) valence systems, and cognitive systems (e.g., attention and memory biases), and cut across multiple units of analysis. Future research that systematically examines correlates of endophenotypes as well as the relationships between

endophenotypes, may facilitate understanding of the levels within, and boundaries between, these domains.

Another issue is that endophenotypes differ in their relative distance from the genetic and phenotypic levels. Endophenotypes that are close in the causal chain to the phenotype may be complicated, heterogeneous constructs in themselves which need to be parsed into component parts. One method that has been proposed to link the pathways between genes, endophenotypes, and clinical phenotypic domains is the Endophenotype Ranking Value (ERV). Proposed by Glahn and colleagues (2012) as a method for identifying the most promising endophenotypes, ERV is calculated using estimates of the heritability of the endophenotype, the disorder, and, their shared genetic correlation. However, as Miller and Rockstroh (2013) note, because the ERV is partially based on the correlation between the endophenotype and the disorder, as well as the heritability of the endophenotype, it is likely to favor endophenotypes that are causally closer to the clinical phenotype or possibly those that have the simplest genetic structure. For example, Glahn et al. (2012) found that the BDI had the highest ERV in a large set of putative behavioral, neurocognitive, and molecular endophenotypes. However, the BDI is a measure of the very units (symptoms) that define the clinical phenotype. ERV scores may be most useful in selecting molecular endophenotypes as starting points for tracing pathways up from the genetic level (where the ERV may be high due to high endophenotype heritability), and assigning priority to endophenotypes within the same levels.

We are still in the early stages of exploring the potential of endophenotypes to discover depression genes, understand pathophysiological mechanisms, and enhance the classification of psychopathology. Studies that examine multiple endophenotypes simultaneously in genetically informative samples will be important for understanding which converge on similar pathways and which indicate distinct pathways to the disorder. There is reason to be hopeful that continued research on endophenotypes will produce a more nuanced understanding of depression and its etiopathophysiological mechanisms, and contribute to the formulation of emerging clinical phenotypes based on RDoC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Gottesman and Gould's (2003) criteria were used to review depression endophenotypes
- Neuroticism, morning cortisol, CAR, and EEG frontal asymmetry had the most support.
- Cognitive tasks lacked substantial support or necessary studies for many criteria.
- In particular, heritability and cosegregation studies are lacking.
- Studies of shared genetics among endophenotypes and with depression are needed

Table 1

Criteria with Study Examples

Gottesman and Gould Criteria	Example study types
Associated with Depression	Compare individuals with a depressive disorder to individuals who have never had a depressive disorder
Heritability	Estimated from twin and adoption studies
State-independence	Compare within individuals or between groups, before, during, and after a depressive episode
Cosegregation	In families of probands with a depressive disorder, compare those relatives who also have a history of depression to those who have never had a depressive episode previously or currently depressed relatives with never depressed relatives (both must have a first degree relative with a history of depression)
Increased rates within affected families	Compare the unaffected relatives of a depressed proband to the general population
Psychometric properties	In healthy and depressed samples evaluate the test-retest reliability and if applicable, internal consistency and inter-rater reliability

Table 2

Candidate Endophenotypes for Major Depression

	Associated with Depression	State-independence	Heritability	Co-segregation	Increased rates within affected families	Psychometric Properties
Neuroticism	++/-	++/-	+++	+++	+/-	+++
Morning Cortisol	++/-	--/+	++/-	-	++/-	++/-
CAR	++/-	++/-	++/-	0	++/-	++/-
EEG Frontal Asymmetry	++*/-	++/-	--/+	0	+++*	++/-
Probabilistic Reward Learning	++/-	+	+	0	0	+
Cognitive Endophenotypes						
Attention						
Eye-tracking	++*/-	++/-	0	0	0	0
Stroop	+++*	--	±	-	+	+
Dot-probe	+++*	±	±	0	++/-	--
Memory						
Biased self-referent encoding	+++	+++	0	0	+	±
OGM	++	++*/-	0	+	++	+

+++ indicates 3 or more studies in support, ++ indicates 2 studies in support, + indicates 1 study in support, +/- indicates the majority of studies support the criteria, ± indicates approximately equal numbers in both direction, --/+ indicates the majority do not support the criteria, - indicates at least 1 study does not support, -- - indicates 3 or more studies do not support, 0 indicates that no relevant evidence exists, and * indicates at least one meta-analysis. EEG indicates electroencephalography, CAR indicates the cortisol awakening response, and OGM indicates overgeneral autobiographical memories.