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Depression research and treatment: Are we skating to where the puck is going to be?

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Abstract

This paper critically reviews empirical findings regarding current key assumptions underlying the nature and treatment of depression which heavily rely on the DSM approach. This review shows that empirical evidence provides little support for these assumptions. In response to these findings, an etiologically based, biopsychosocial, dynamic interactionism model of depression is proposed. This model could foster further integration in research on depression and assist in the development of guidelines for the treatment of depression that are better informed by research findings and more congruent with complex clinical realities.

Keywords: Depression; Classification; Treatment; Diathesis stress model

Current research efforts and treatment guidelines concerning depression heavily rely on the DSM approach of depression and major depression in particular (Blatt & Zuroff, 2005; Parker, 2005; Zuroff, Mongrain, & Santor, 2004). Research funds and major scientific journals typically demand that studies use a diagnosis of depression according to DSM nomenclature, while treatment guidelines (e.g., American Psychiatric Association, 2000; Chambless & Ollendick, 2001; RANZCP Clinical Practice Guidelines for the treatment of depression, 2004) almost invariably refer to DSM categories to specify empirically supported treatments, although, in principle, any reliable and valid approach to defining a sample can be used. Yet, at the same time, the a-etiological, descriptive DSM approach of depression and treatment guidelines that rely on the DSM approach, are increasingly under attack. In particular, critics have pointed out that, despite the progress DSM has made possible, the current a-etiological classification of mood disorders may be hampering fundamental research (Heim, Plotsky, & Nemeroff, 2005; Nemeroff et al., 2003; Parker, 2005) as well as the identification of more effective treatments (Blatt & Zuroff, 2005; Nemeroff et al., 2003). These concerns are part of a more general dissatisfaction with DSM (e.g., Beutler & Malik, 2002; McHugh, 2005; Shedler & Westen, 2004) and have led to a variety of reactions, ranging from calls for further refinement of DSM (e.g., see Kupfer, First, & Regier,

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2002; Phillips, First, & Pincus, 2003 for an overview), to calls for a fundamental change in the way we classify depression and psychopathology in general (e.g., Genova, 2003).

Concerning depression, these concerns about the validity of the DSM approach mainly have been fuelled by a fundamental change in our view of this disorder that has emerged over the last decades. Once considered to be the 'common cold' of psychopathology, (i.e., a relatively benign disorder with a good prognosis, even when left untreated), depression now is increasingly considered to be a highly prevalent, recurrent and, in a substantial number of patients, even a chronic disorder (Judd, 1997; Kupfer & Frank, 2001; Segal, Pearson, & Thase, 2003), which has high comorbidity with other Axis I and Axis II disorders (Klein & Hayden, 2000; Mulder, 2002), and which is much more difficult to treat than once assumed (Westen & Morrison, 2001).

The time seems ripe to address the consequences of these findings for the validity of the assumptions underlying the DSM approach of depression and treatment guidelines. Are we heading in the right direction? Or, as Frank et al. (2002) formulated it, referring to the great hockey player Wayne Gretsky, are we skating to where the puck is going to be? With this question in mind, we first review empirical findings pertaining to the assumptions underlying the DSM approach to depression. Second, we discuss implications of these findings for the assumptions underlying contemporary guidelines for the treatment of depression. This is followed by a discussion of the efficacy and effectiveness of so-called Empirically Supported Treatments (ESTs) of depression. Strengths and weaknesses of current approaches towards depression and its treatment, as well as implications for further research and the future development of guidelines for the treatment of depression, are discussed. Finally, we propose an etiologically based dynamic interactionism model of depression with the purpose of fostering further integration in depression research, and consider the clinical implications of this model.

1. Empirical review of key assumptions underlying the DSM approach of depression

Introduction of DSM, and particularly DSM-III (American Psychiatric Association, 1980), has led to considerable advances in our understanding of the nature of depression. DSM has not only provided both researchers and clinicians with a common language, but also has facilitated a wide range of research, ranging from large scale epidemiological studies on the prevalence of depression to detailed neurobiological and genetic studies that have addressed the pathophysiology of this disorder. In addition, the adoption of a common classification system has greatly facilitated the identification of effective treatments. Yet, as noted, growing concerns question the validity and clinical utility of the DSM approach to depression (e.g., Blatt & Levy, 1998; Blatt & Zuroff, 2005; Kendler & Gardner, 1998). In what follows, we review empirical evidence concerning the key assumptions of the DSM approach to depression, and their implications for the further development of a classification system for this disorder. Briefly, the (implicit) key assumptions underlying the DSM approach of depression can be summarized as follows (Blatt & Zuroff, 2005; Luyten, Blatt, & Corveleyn, 2005; Parker, 2005; Van Praag, de Kloet, & van Os, 2004):

(1) Depression is categorically distinct from subclinical depression and from normality.
(2) Depression can and should be diagnosed based on symptoms, not on etiological and/or pathogenetic considerations.
(3) Depression is a relatively discrete disorder, relatively distinct from other Axis I disorders.
(4) Depression is unrelated to personality disorders and personality.

Assumption 1. Depression is categorically distinct from subclinical depression and from normality.

Although this assumption is the cornerstone of the DSM approach to depression, the bulk of empirical evidence suggests that a dimensional view, which conceptualizes depression on a continuum ranging from mild dysphoria to full-blown clinical depression (Blatt, 1974), is more valid than the categorical view promoted by DSM (Blatt & Levy, 1998; Fergusson, Horwood, Ridder, & Beautrais, 2005; Haslam, 2003; Kendler & Gardner, 1998; Ruscio & Ruscio, 2002, 2000; Solomon, Haaga, & Arnow, 2001). The categorical approach has undoubtedly impeded research on depression. For example, influenced by DSM, researchers have mainly concentrated on studying etiological and pathogenetic factors associated with clinical depression and particularly major depression (Parker, 2005). However, congruent with a dimensional view, there is continuity among the various biopsychosocial factors implied in both 'subclinical' and 'clinical' mood disturbances (Kendler & Gardner, 1998; Ormel, Oldehinkel, & Brilman, 2001). In addition, the creation of 'pseudo-entities' (Parker, 1999, p. 102) has contributed to an underestimation of the

importance of so-called 'subclinical' depressive symptoms and syndromes (e.g., minor depression) (Hankin, Fraley, Lahey, & Waldman, 2005; Kessler et al., 2003). For example, studies have shown that subclinical mood disturbances predict severe psychosocial impairment as well as later psychopathology (Fergusson et al., 2005; Judd, Akiskal, & Paulus, 1997; Kessler et al., 2003). Most treatment research, however, has again focused on clinical depression and major depression in particular, resulting in limited data on the efficacy and effectiveness of treatments for 'subclinical' syndromes and other types of depression such as dysthymic disorder (Parker, 2005; Rush & Thase, 2002; Westen, Novotny, & Thompson-Brenner, 2004).

On the other hand, these findings do not necessarily imply that some discrete depression categories do not exist. For example, there is evidence for a melancholic (Haslam, 2003; Parker, 2000) and for an anxious and hostile/irritable non-melancholic subtype of depression (Fava & Rosenbaum, 1999; Parker et al., 1998, 1999a,b). However, the universal adoption of a categorical approach should clearly be reconsidered (Demyttenaere, Van Oudenhove, & De Fruyt, 2005; Haslam, 2003). Though clinicians, as well as insurance companies and governmental agencies, continue to find it easier to work with a categorical approach, future research should try to identify clinically meaningful cut-off criteria to combine dimensional and categorical approaches. Such mixed classification systems, which combine dimensional and categorical approaches, have, for example, already been proposed for personality disorders (e.g., Shedler & Westen, 2004).

Assumption 2. Depression is best diagnosed based on symptoms, not on etiological and/or pathogenetic considerations.

Research also points to serious problems with this assumption, as a growing consensus indicates that it is extremely unlikely that a classification system of depression based on an assessment of manifest symptoms alone is feasible (Blatt, 2004; Parker, 2000; Westen et al., 2004). Increasing evidence indicates that factors such as personality (Blatt & Zuroff, 2005; Clark & Beck, 1999; Kendler, Kuhn, & Prescott, 2004; Parker, 2005), and early (Claes, 2003; Gilmer & McKinney, 2003; Gold & Chrousos, 2002; Gutman & Nemeroff, 2003; Heimet al., 2005) as well as current (Hammen, 2005; Kendler et al., 2004; Kessler, 2003) life stress are associated with a different etiology, pathogenesis, clinical presentation, course, and/or treatment response of depression. Thus, attempts to diagnose depression based on manifest symptoms alone have led to categories that are often heterogeneous and therefore impede research efforts and limit the clinical utility of DSM (Blatt and Zuroff, 2005). In addition, research suggests that many psychopathological disorders share etiological and pathogenetic factors (Kessler et al., 2003; Ormel et al., 2001; Weissman, Wolk, Goldstein et al., 1999, Weissman, Wolk, Wickramaratne et al. ,1999), leading to an artificial separation between research on the etiology of depression and other disorders. Future research should thus aim at developing a classification system that extends beyond manifest symptoms and takes into account factors of etiology and pathogenesis (Blatt & Zuroff, 2005).

Assumption 3. Depression is a relatively discrete disorder, relatively distinct from other Axis I disorders.

Research, however, has consistently shown that depression tends to be a highly recurrent disorder, which becomes chronic in a substantial number of patients (Frank et al., 2002; Judd, 1997; Segal et al., 2003; Solomon et al., 2000), and that high levels of comorbidity with other Axis I disorders, particularly with anxiety disorders, are the rule rather than the exception (Mulder, 2002; Nemeroff, 2002; Westen et al., 2004), suggesting the usefulness of mixed categories (e.g., see Phillips, Price, Greenberg, & Rasmussen, 2003).

Assumption 4. Depression is unrelated to personality disorders and personality.

Comorbidity between depression and Axis II disorders is very high (Mulder, 2002; Westen et al., 2004), which renders the assumption of orthogonality between depression and personality disorders (and personality in general) improbable. This view is further reinforced by studies showing that personality disorders (Krueger & Tackett, 2003; Shea et al., 2004) and both broad and specific personality dimensions, such as Neuroticism (Kendler et al., 2004; Ormel et al., 2001) and Dependency/Sociotropy and Self-Critical Perfectionism/Autonomy (Blatt & Zuroff, 2005; Cox, McWilliams, Enns, & Clara, 2004; Zuroff et al., 2004) respectively, are implicated in the etiology and pathogenesis of depression. The assumption that depression and personality are independent thus has hampered our understanding of the etiology and pathogenesis of depression (Blatt & Zuroff, 2005; Luyten et al., 2005; Westen et al., 2004). For example, recent studies suggest that Depressive Personality Disorder (DPD), which is now included in the Appendix of DSM as a category that needs further research, may be the most prevalent personality disorder in outpatient samples (Morrison, Bradley, & Westen, 2003). Moreover, studies show that many depressed patients suffer from subclinical

personality problems, including enduring problems concerning autonomy, intimacy and relatedness, which negatively influence treatment response, especially in brief treatments (Blatt & Zuroff, 2005; Blatt, Zuroff, Bondi, Sanislow, & Pilkonis, 1998; Morrison et al., 2003). Furthermore, by assuming that depression is independent from personality, DSM has promoted the view that individuals with depression are passive 'hosts' for a certain 'pathogen' (Westen & Shedler, 2000). Research on gene and person–environment correlations and interactions (Kendler et al., 2004; Moffitt, Caspi, & Rutter, 2005), however, strongly suggests that depressed patients, often unwittingly, in part generate their own stressors (Blatt & Zuroff, 1992; Luyten et al., 2005; Mongrain, Lubbers, & Struthers, 2004; Shahar, Joiner, Zuroff, & Blatt, 2004). Likewise, depression itself is associated with stress generation, particularly in close interpersonal relationships (Hammen, 2005). Taken together, these findings clearly indicate that it is time to re-evaluate the key assumptions of the DSM approach to depression.

2. Empirically supported treatments of depression: assumptions and findings

2.1. Problems with assumptions of randomized clinical trials

Most current guidelines for the treatment of depression are primarily based on evidence from Randomized Clinical Trials (RCTs) (e.g., American Psychiatric Association, 2000; Chambless & Ollendick, 2001; RANZCP Clinical Practice Guidelines for the treatment of depression, 2004). The assumption behind this is that the RCT design is the best design or 'gold standard' to test the efficacy of treatments because it allows the strictest control of confounding variables in treatment research (Philips et al., 2001). Yet, empirical evaluation of this assumption points to serious problems with this view because RCTs are based on several assumptions of experimental design which, for many disorders, including depression, are not valid (Blatt & Levy, 1998; Blatt & Zuroff, 2005; Westen et al., 2004; Zimmerman, Mattia, & Posternak, 2002). For example, as Westen et al. (2004) have argued, RCT studies are based on the implicit assumption that depression is a highly malleable condition; or else it would make little sense to investigate the effect of brief treatments for this disorder. However, this assumption is clearly at odds with data showing the highly recurrent nature of depression (Judd, 1997; Mueller et al., 1999) and with evidence, reviewed in more detail below, indicating that brief psychopharmacological and psychosocial treatments have limited effectiveness for most depressed patients (Blatt & Zuroff, 2005; Westen & Morrison, 2001). Furthermore, RCTs are based on the assumption that specific therapeutic techniques or neurobiological agents explain most of the effect of treatments. Studies, however, have shown that specific techniques account for only about 15% of outcome in psychosocial treatments for most disorders including depression, while common factors (such as the therapeutic relationship, empathy, etc.) explain about 30% in outcome (Beutler, Clarkin, & Bongar, 2000; Blatt & Zuroff, 2005; Division 29 Task Force on Empirically Supported Therapy Relationships, 2002; Gaudiano & Herbert, 2005; Lambert & Barley, 2002). Although results might be different for the antidepressant treatment of depression, data reviewed below suggest modest differences between drug and placebo treatments (e.g., Williams et al., 2000). Consistent with this assumption, in the NIMH Treatment of Depression Collaborative Research Program (Elkin, Parloff, Hadley, & Autry, 1985), little or no differences were found in the outcome of all active treatments (CBT, IPT, and Imipramine). Patient, alliance, and therapist factors, in contrast, consistently predicted outcome (Blatt & Zuroff, 2005; Zuroff & Blatt, in press). Moreover, many antidepressants are as effective in the treatment of anxiety disorders as in the treatment of depression, raising questions concerning the specificity of the neurobiological mechanisms targeted by antidepressants (Van Praag et al., 2004).

Furthermore, because of their heterogeneous etiological background, depressed patients are not uniformly responsive to different pharmacological and psychosocial treatments (Gaudiano & Herbert, 2005; Lambert & Ogles, 2004; Parker, 2005). One compelling example illustrating this is provided by a re-analysis by Nemeroff et al. (2003) of data from a controlled trial comparing the efficacy of 12-week Cognitive Behavioral Analysis System of Psychotherapy (CBASP), antidepressant treatment with nefazodone, and a combination of both in a sample of 681 chronically depressed patients. Prior analyses indicated that a combination of CBASP and medication was associated with better outcome as compared to either monotherapy (Keller et al., 2000). However, in a re-analysis of these data, Nemeroff et al. (2003) found that response to CBASP was superior to antidepressant medication in patients with a history of early childhood trauma, both in terms of mean post-treatment depression severity scores and remission rates. Moreover, in patients with a history of early trauma (but not in patients without such history), the combination of CBASP with nefazodone was not superior to treatment with CBASP alone. Findings such as these indicate that patients are likely to show a differential response to different treatments as a function of etiological and/or pathogenetic factors, and not primarily as a function of currently

adopted DSM diagnoses. These findings also suggest that the famous dodo bird verdict, (i.e., the finding that all bona fide therapies have similar efficacy), partly may be the consequence of comparing etiologically heterogeneous groups of patients, thus limiting the specific effects of treatments (Parker, 2000). Yet, because current guidelines for the treatment of depression continue to promote the view that treatments should prove their efficacy in RCTs in comparison to already established treatments, with notable exceptions (Beutler et al., 2000; Blatt & Zuroff, 2005; Gaudiano & Herbert, 2005; Nemeroff, et al., 2003), treatment research is often more concerned with establishing the efficacy of treatments of depression rather than with understanding the processes of therapeutic change.

2.2. How empirically supported are 'Empirically Supported Treatments' for depression?

In addition to serious problems with the assumptions underlying current guidelines for the treatment of depression, recent overview studies have argued that the effects of psychosocial ESTs for depression are limited in several ways (Parker, Roy, & Eyers, 2003; Rush & Thase, 2002; Westen & Morrison, 2001). Meta-analyses have shown that only about 50% of depressed patients respond (defined as a 50% reduction in symptoms) to these treatments (Westen & Morrison, 2001). Furthermore, many patients who respond to brief treatments continue to show subclinical symptomatology, with an average post-treatment BDI score of 10.98 (Westen & Morrison, 2001; see also Fava, 1999a; Kupfer & Frank, 2001). Thus, symptom reduction as a primary outcome measure in treatment research may not only have resulted in an overestimation of treatment effects, but may also have led to insufficient attention to the importance of residual symptoms in the prediction of recurrence/relapse (Fava, 1999a), and of 'subclinical' mood disturbances such as minor depression (Kupfer & Frank, 2001; Westen & Morrison, 2001). Moreover, there is relatively little research evidence indicating that the observed response to psychosocial ESTs for depression is primarily due to particular theoretical factors or specific therapeutic techniques. For example, in many studies of CBT, most therapeutic gain is observed in the first few sessions, before specific techniques such as targeting dysfunctional attitudes, are used (Parker et al., 2003). These findings are congruent with the bulk of evidence showing that common factors such as empathy and the quality of the therapeutic relationship are important factors in the treatment of depression (Blatt & Zuroff, 2005; Shaw et al., 1999). Thus, little current evidence indicates that psychosocial ESTs produce theory-consistent changes (Elkin et al., 1989; Parker et al., 2003), and future research should therefore concentrate on the identification of processes of therapeutic change rather than simply comparing the efficacy of different types of treatments (Blatt & Zuroff, 2005).

Results concerning the long-term effects of psychosocial ESTs for depression call for even more modest views on the efficacy of these treatments. To begin with, there is a lack of controlled studies on the long-term outcome of ESTs of depression. Westen and Morrison (2001), for instance, could locate only 5 RCT studies published in the 1990s that investigated the long-term effects (from 12 to 18 months) of psychosocial treatments for depression. In these studies, only 37% of the patients did not relapse in that time period. Only two studies were available with follow-up data of 2 years or more, and in these two studies only 27% of patients (8% of all patients initially screened) did not relapse.

Meta-analyses concerning the effects of brief pharmacotherapy for depression reveal similar response rates of 50–60% compared to 30–35% response rates of placebo (Lieberman et al., 2005; Williams et al., 2000). Reviews that have included non-published negative studies have claimed that drug-placebo differences are smaller or even non-existent (Khan & Khan, 2003; Kirsch, Moore, Scoboria, & Nicholls, 2002; Kirsch & Sapirstein, 1998). Furthermore, a recent meta-analysis suggests that progress in the pharmacological treatment of depression has mainly been limited to progress in limiting side effects, but not in developing more effective treatments. Hence, 'new' antidepressants are not more effective than 'older' ones (Barbui & Hotopf, 2001). In addition, current evidence suggests that long-term antidepressant treatment is becoming the rule rather than the exception in treating depressed patients (Kupfer & Frank, 2001). Yet, no relationships have been found between the duration of antidepressant treatment and the probability of relapse/recurrence after discontinuation (Fava, 2002; Viguera, Baldessarini, & Friedberg, 1998). Taken together, these findings clearly warn against therapeutic optimism concerning the effects of so-called ESTs for depression (Antonucci, Danton, DeNelsky, Greenberg, & Gordon, 1999; Kupfer & Frank, 2001; Westen & Morrison, 2001).

3. Implications for future guidelines and treatment research

First, future guidelines for the treatment of depression should use the term 'empirically supported' in more qualified ways (Blatt & Zuroff, 2005; Westen & Morrison, 2001). They should report typical exclusion criteria and rates and

multidimensional outcome measures, including percent improved and percent recovered, post-treatment symptomatology and percent improved and recovered at follow-up. Second, most current treatment guidelines have been erroneously based on the assumption that one can develop and manualize treatments for depression, analogous to the development of a drug specifically designed for a particular 'disease'. This simple disease–drug metaphor (Stiles & Shapiro, 1989), implicit in the DSM approach to depression, is clearly hampering the development of more effective treatment strategies for depression (Heim et al., 2005; Luyten et al., 2005; Parker, 2005).

The response to these findings has been threefold. First, recent studies and treatment guidelines emphasize the benefits of continuation and maintenance treatment (Hollon et al., 2002), which have been shown to significantly reduce relapse rates (e.g., Fava et al., 2004; Jarrett et al., 2001; Winkler, Tauscher, & Kasper, 2002). However, something may be wrong with the universal application of the continuation/maintenance of treatments. Some thirty years ago researchers were convinced that many treatments practiced at that time (e.g., psychodynamic therapy or humanistic therapies) were needlessly long and costly. Thus, their attempt to develop more brief, effective, and less costly treatments seemed completely justified. However, three decades of treatment research findings indicate that these brief treatments, despite important short-term effects, do not produce lasting effects in most patients. The only justified conclusion from this body of research would be that depression in many patients is not amenable to brief treatment (at least not to currently tested brief treatments), and therefore we should consider either developing better brief treatments and/or other extended treatments (Westen & Morrison, 2001). However, with few exceptions, this conclusion is seldom considered. To the contrary, guidelines now recommend using what is the long-term version (continuation or maintenance treatment) of short-term treatments such as CBT and IPT (Westen & Morrison, 2001).

A second strategy has been to develop new treatments, including Mindfulness Based Cognitive Therapy (MBCT) (Teasdale et al., 2000), Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (McCullough, 2003), and Well-Being Therapy (Fava, 1999b). These treatments, which focus more on relapse prevention, have developed out of a growing dissatisfaction with "traditional" brief treatments. In addition, evidence is accruing for the efficacy and effectiveness of traditional long-term treatments for depression (Elliott, Greenberg, & Lietaer, 2004) and personality disorders (Bateman & Fonagy, 2004; Blatt & Shahar, 2004; Leichsenring & Leibling, 2003; Linehan, 1993). These latter findings are relevant in this context because, as noted above, many depressed patients suffer from clinical and subclinical personality problems (Blatt, 2004; Kendler et al., 2004; Westen et al., 2004). Hence, after an era in which brief treatments were believed to be effective for most patients, the pendulum seems to be swinging in the other direction as the case for long-term treatment of a considerable subgroup of depressed patients is growing.

A third, and complementary, approach consists in trying to identify patient characteristics that predict outcome in different treatments (Beutler et al., 2000; Blatt & Zuroff, 2005; Parker, 2005). As noted, because of its a-etiological approach, the DSM has hampered identification of such characteristics in psychosocial (Blatt & Zuroff, 2005) as well as antidepressant (Parker, 2005; Nemeroff et al., 2003; Schatzberg et al., 2005; Zimmerman et al., 2002) treatments. Despite this limitation, increasing evidence indicates that several characteristics, such as genetic liability (Zhang, Beaulieu, Sotnikova, Gainetdinov, & Caron, 2004), early adversity (Heim et al., 2005; Craighead & Nemeroff, 2005), and clinical (Mulder, 2002) and subclinical (Blatt & Zuroff, 2005; Ilardi, Craighead, & Evans, 1997) personality pathology, predict poor outcome in brief treatments. Evidence also indicates that clinicians need to take such findings into account. For example, in a naturalistic study of randomly selected psychiatrists and clinical psychologists, Morrison et al. (2003) found that, regardless of theoretical orientation, average treatment length doubled when patients had Axis I or Axis II comorbidity. Subclinical personality pathology also predicted longer treatment. However, when Morrison et al. (2003) considered only those patients that had neither noteworthy comorbidity nor subclinical or clinical personality pathology, average treatment length, as reported by clinicians, ranged between 12–16 sessions, as is recommended in treatment guidelines.

Hence, future research should be aimed at disentangling the interplay between specific psychosocial techniques and neurobiological processes as well as patient, therapist, and alliance factors in predicting outcome. Recent research on the neurobiological effects of placebo (Khan & Khan, 2003) and of positive social relationships (Adler, 2002; Hofer, 2005) should assist in further integrating psychosocial and biological approaches. Moreover, given the high relapse rates of depression, these studies should include a broad range of outcome measures in addition to symptom remission, including interpersonal functioning and personality (Blatt & Zuroff, 2005; Luyten et al., 2005), well-being and quality of life (Fava, 1999b), and the capacity to cope with new life stress (Zuroff, Blatt, Krupnick, & Sotsky, 2003) using multi-method assessments of change (e.g., self-report, interview assessment, etc.) (Gaudiano & Herbert, 2005). Finally, these studies should focus on clinically meaningful follow-up intervals (e.g., 2–5 years) (Westen et al., 2004). Rather

than trying to establish dichotomous distinctions between empirically supported and unsupported treatments, and adopting a simple disease model (Moncrieff & Cohen, 2005), these studies could lead to establishing empirically informed treatments based on etiological considerations (Blatt & Zuroff, 2005; Westen et al., 2004).

4. Towards an etiologically based alternative for the DSM approach of depression

4.1. A dynamic interactionism model of depression

The research findings discussed in this paper point to limitations in the DSM approach of depression and its treatment, mainly related to its a-etiological foundation. In this context, findings from a wide variety of fields, including psychiatric genetics, neurobiology, developmental psychopathology, cognitive, psychodynamic, social and personality psychology converge to suggest that depression can be best understood in the context of an etiologically based, dynamic interactionism model (see Fig. 1) (e.g., Blatt & Zuroff, 1992; Heim et al., 2005; Kendler, Gardner, & Prescott, 2002; Luyten et al., 2005; Nemeroff et al., 2003; Zuroff et al., 2004). The primary aim of this biopsychosocial model is to integrate findings from these various strands of research into a comprehensive model of depression in order to facilitate further research efforts on depression and the identification of more effective treatments. Hence, we do not propose that this model should replace current classification systems of depression, nor do we assume that this model encompasses all relevant research findings concerning depression. Rather, we assume that this broader model could assist in guiding future research concerning the etiology, pathogenesis, and treatment of depression.

Briefly, this dynamic interactionism model assumes that genetic and early environmental factors reciprocally interact, leading to relatively stable personality dimensions or cognitive-affective schemas that, in interaction with life stress, pave the way to depression and other related disorders.

4.1.1. Early environment

Various research traditions suggest that early life stress (e.g., abuse, emotional neglect) plays an important role in the etiology of depression and may be associated with neurobiologically different subtypes of depression (Gladstone et al., 2004; Heim et al., 2005). In addition, dysfunctional parental styles (Blatt & Homann, 1992; Goodman & Gotlib, 1999; Gunnar, 2002; Ingram & Ritter, 2000; Parker et al., 1997), such as low parental care and overprotection as well as the

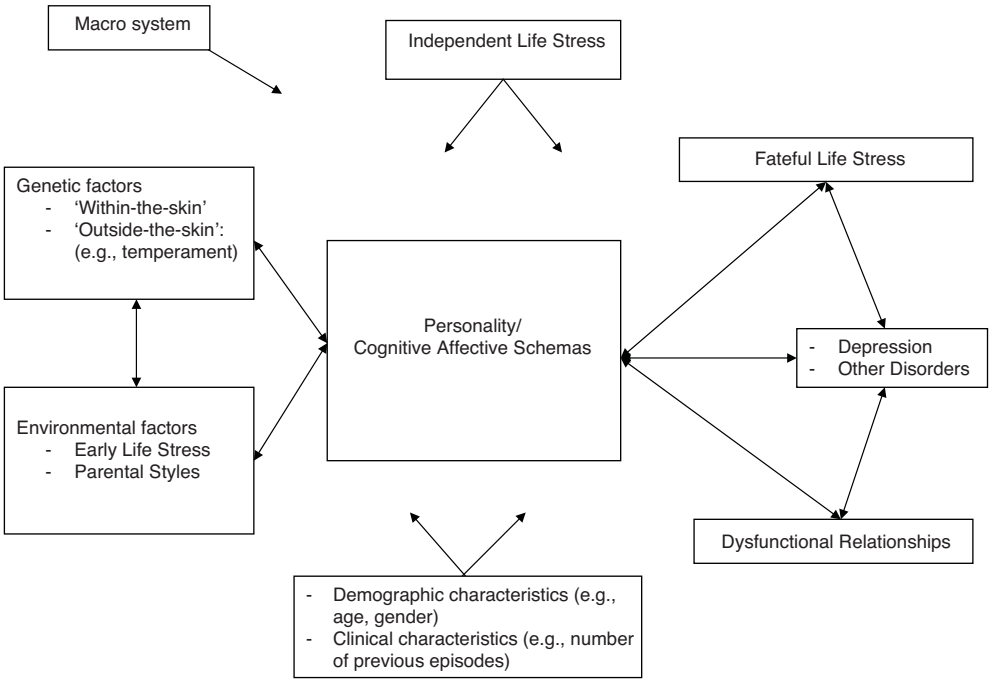

Fig. 1. A dynamic interactionism model of depression.

imposition of harsh, punitive, judgmental standards (Besser & Priel, 2005; Blatt, 1995; Frost, Lahart, & Rosenblate, 1991; Soenens et al., 2005), have been linked to depression (Blatt & Maroudas, 1992). Genetic factors implied in the etiology of depression include both 'within-the-skin' and 'outside-the-skin' effects (Kendler, 2001), the former referring to direct physiological effects of genes on neuroregulatory mechanisms implied in mood regulation and/or stress responsivity (Claes & Nemeroff, 2005), the latter to the influence of genes on the environment (and vice versa). One implication of these interactions is that earlier models of depression, which often assumed a relatively rigid distinction between heredity and environmental factors, are too simplistic (Rose, 2001). For example, because environmental factors influence the expression of genes, and genes influence the environment individuals live in, there is probably no 'true' heritability of depression; that is, genetic liability for depression most probably varies under different environmental factors (Kendler, 2001). Gene–environment correlations and interactions are most likely mediated by temperamental (Ando et al., 2004; Öngür, Farabaugh, Iosifescu, Perlis, & Fava, 2005; Stelmack, 2004; Van Gestel et al., 2002) and personality dimensions (Kendler, 2001).

4.1.2. Personality or cognitive-affective schemas

Personality dimensions that have been linked to depression include broad dimensions such as Neuroticism/Extraversion and Positive/Negative Affect (N/NA, E/PA) (Kendler et al., 2004; Klein, Durbin, Shankman, & Santiago, 2002), as well as specific personality dimensions such as Dependency/Sociotropy (D/S) and Self-Critical Perfectionism/Autonomy (SCP/A) (Blatt, 2004; Blatt & Zuroff, 1992; Clark & Beck, 1999), the character dimensions of Self-Directedness (SD), Cooperativeness (CO), and Self-Transcendence (ST) (Cloninger, Svrakic, & Przybybeck, 1993), and cognitive-affective schemas related to insecure attachment (Bifulco, Moran, Ball, & Bernazzani, 2002).

4.1.3. Current life stress

The relationship between both dependent (fateful) and independent current life stress and depression is well documented (Hammen, 2005; Tennant, 2002). Although personality is itself partly genetically determined (for an overview, see Savitz & Ramesar, 2004), studies have shown how broad personality dimensions such as N/NA may explain genetic influences on the occurrence of dependent (fateful) life events, thus increasing the risk for depression (Kendler, Neale, Kessler, Heath, & Eaves, 1993; Kendler et al., 2004; Ormel, Stewart, & Sanderman, 1989; Ormel et al., 2001; Saudino, Pedersen, Lichtenstein, McClearn, & Plomin, 1997; Van Os & Jones, 1999; Van Os, Park, & Jones, 2001). In addition, evidence is accruing that a functional polymorphism of the serotonin transporter gene may lead to increased sensitivity to life stress associated with depression (Caspi et al., 2003; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; however see Gillespie, Whitfield, Williams, Heath, & Martin, 2005). Thus, the relationship between current life stress and depression should not be merely conceptualized in terms of passive reactions of individuals to life stress. Rather, individuals, in part and often unwittingly, create their own stressful environment. In particular, studies are increasingly indicating how individuals that are prone to depression create problems and conflicts in close relationships (Blatt, 2004; Blatt & Zuroff, 1992; Hammen, 2003; Mongrain et al., 2004; Shahar et al., 2004; Zuroff et al., 2004).

4.1.4. Dysfunctional interpersonal relationships

The relationship between depression and interpersonal relationships is complex (Hammen, 2003; Segrin, 2000). There is increasing evidence that personality factors such as N/NA (Cooper & Sheldon, 2002) and Self-Critical Perfectionism/Autonomy (Zuroff et al., 2004) lead to deterioration in interpersonal relationships, which further increases the risk for depression. Hence, relationship factors and personality probably mutually influence each other, leading to vicious cycles that increase the risk for depression. In addition, evidence is accumulating that temperament and personality are important mediating factors in the association between genes and the social environment in general. Studies have shown, for example, that social support is for a substantial part genetically determined through the effects of temperament and personality (Kendler, 1997; Kendler, Myers, & Prescott, 2005).

4.1.5. Demographic and clinical characteristics

Demographic characteristics such as age and gender (Kendler, Kuhn, et al., 2005; Kendler, Myers, et al., 2005) and clinical variables such as number of previous depressive episodes (Hammen, 2005; Post, 1992) play a role in the epidemiology and/or etiology of depression. Hence, future research should be aimed at untangling the interplay between demographic, clinical, psychosocial and neurobiological factors in the etiopathogenesis of depression.

4.1.6. Macro context

Finally, research has shown that the experience and expression of depression is influenced by developmental (Blatt & Homann, 1992; Goodman & Gotlib, 1999) and cultural (Littlewood, 2003) factors, pointing to the need to consider such factors in the prevention, diagnosis, and treatment of depression. Thus, depression should not be considered as a static disease entity, but as a culturally and developmentally influenced disorder.

4.2. Reciprocal interactions among biological and psychosocial factors in depression

Research evidence suggests that most relationships between biological, psychological and social factors implicated in the etiology of depression are reciprocal.[1] For instance, as noted, studies suggest that the expression of certain genes is influenced by environmental factors (Kaufman et al., 2004; Kandel, 1998; Kendler, 2001). Kaufman et al. (2004), for example, reported that maltreated children who had the 5-HTT gene polymorphism had elevated levels of depression compared to normal controls, but only when they also had low levels of social support. Depression levels in maltreated children with the 5-HTT gene polymorphism who had high levels of social support did not differ from normal controls. And while personality is associated with increased risk for depression, both directly and indirectly by its effect on the generation of (fateful) life stress, it is likely that both depression and life stress also influence the expression of personality factors ('scar' effects, see Sanathara, Gardner, Prescott, & Kendler, 2003; Zuroff et al., 2004). Dysfunctional interpersonal relationships, in turn, are not only an antecedent, but also a concomitant and consequence of depression (Segrin, 2000; Tse & Bond, 2004), leading to vicious circles that deteriorate the interpersonal environment of depressed individuals, giving rise to temporary as well as lasting changes in both personality functioning and interpersonal relationships, thereby increasing the risk for relapse (Blatt, 2004; Luyten et al., 2005; Wachtel, 1997). Hence, from this perspective, depression is as much an interpersonal as an intrapersonal disorder (Hammen, 2003).

Moreover, recursive models are also consistent with research on the neurobiology of depression, which increasingly suggests that depression is associated with dysregulation of the Hypothalamic Pituitary Adrenal (HPA) axis (Gold & Chrousos, 2002; Heim et al., 2005). The HPA axis plays a central role in autonomic, endocrine, immunological and behavioral responses to stress. Early life stress in particular, has been shown to be associated with HPA axis dysregulation (Heim et al., 2005; Gunnar, 2002), leading to increased sensitivity for later life stress, which in turn leads to increased hyperreactivity which, when a certain threshold is reached, probably also leads to hypoactivity of the HPA axis system (Claes & Nemeroff, 2005; Fries, Hesse, Hellhammer, & Hellhammer, 2005; Luyten, in press; Van Houdenhove & Egle, 2004). Future research should thus investigate the interplay between HPA axis dysregulation, early and current life stress, temperament, and broad and specific personality dimensions. These studies might also clarify the relationship between personality, depression and other disorders that are associated with HPA axis dysregulation, such as Posttraumatic Stress Disorder (PTSD), borderline personality disorder, Chronic Fatigue Syndrome, and Fibromyalgia, as well as immunological and cardiovascular diseases (Blatt, Cornell, & Eshkol, 1993; Gold & Chrousos, 2002; Luyten, Van Houdenhove, Cosyns, & Van den Broeck, in press; Van Houdenhove, Egle, & Luyten, 2005).

5. Clinical implications

A major limitation of DSM, as noted above, is its limited clinical utility (Parker, 2005). The proposed dynamic interactionism model of depression, in contrast, provides both general and specific hypotheses for assessment, prevention and treatment of depression. According to this model, assessment should be aimed at documenting various etiological and pathogenetic mechanisms implied in depression, on various levels (social, psychological, and biological). In addition, because depression tends to be a recurrent disorder and developmental factors play a crucial role in the etiology of depression, assessment should also include a developmental life time perspective. Prevention and treatment, in turn, should also be aimed at etiological and pathogenetic factors, not solely at symptomatic improvement (Blatt & Zuroff, 2005; Gaudiano & Herbert, 2005; Moncrieff & Cohen, 2005; Zuroff, Blatt, Sanislow, Bondi, & Pilkonis, 1999). In addition, future research should be aimed at enabling clinicians to distinguish between various types of depressive patients based on etiological and pathogenetic considerations (Zuroff & Blatt, in press). Finally, the

[1] Consistent with this view, reciprocal relationships are indicated in Fig. 1 with bi-directional arrows.

proposed dynamic interactionism model might guide further research concerning the mechanisms of change in the treatment of depression at the biopsychosocial level. For instance, increased resilience in dealing with new stressors should be reflected at the neurobiological level in changes in HPA axis responsiveness to new stressors. Hence, adopting an etiologically based, dynamic interactionism model of depression may lead to more theoretically driven and empirically based measures of therapeutic response instead of current, broad, consensus-based measures of outcome (Aitchison, Basu, McGuffin, & Craig, 2005).

6. Conclusions

This paper shows that our knowledge concerning depression has increased considerably in the last decades, which has contributed to the development of a broad range of both pharmacological and psychosocial treatments. Thus, it cannot be denied that we are skating to where the puck is going to be. Research data reviewed in this paper, however, also warn against optimism. Key assumptions underlying the current dominant classification system of depression have little validity. Although the time has not yet come to replace the current descriptive approach to depression with an etiologically based classification system, research programs aimed at developing such a classification system are desperately needed as accurate diagnoses are vital in advancing our understanding of depression (Kendler, 2002). In addition, congruent with other recent reviews (Parker, 2005; Westen & Morrison, 2001), current treatment guidelines for depression are inadequately informed by recent research findings on depression. Treatment research, based on etiological theories of depression, is urgently needed.

In conclusion, although the debate on the nature and treatment of depression is likely to continue, the issues discussed in this paper need to be resolved before important decisions can be made that will influence the future of research and practice such as the further development of more effective classification systems and treatment guidelines for depression.

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References

Adler, H. M. (2000). The sociophysiology of caring in the doctor–patient relationship. *Journal of General Internal Medicine*, *17*, 883−890.

Aitchison, K. J., Basu, A., McGuffin, P., & Craig, I. (2005). Psychiatry and the 'new genetics': Hunting for genes for behaviour and drug response. *British Journal of Psychiatry*, *186*, 91−92.

American Psychiatric Association (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: American Psychiatric Association.

American Psychiatric Association (2000). *Practice guidelines for the treatment of patients with major depression.* Retrieved September 3, 2004 from http://www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm

Ando, J., Suzuki, A., Yamagata, S., Kijima, N., Maekawa, H., Ono, Y., et al. (2004). Genetic and environmental structure of Cloninger's temperament and character dimensions. *Journal of Personality Disorders*, *18*, 379−393.

Antonucci, D. O., Danton, W. G., DeNelsky, G. Y., Greenberg, R. P., & Gordon, J. S. (1999). Raising questions about antidepressants. *Psychotherapy and Psychosomatics*, *68*, 3−14.

Barbui, C., & Hotopf, M. (2001). Amitriptyline v. the rest: Still the leading antidepressant after 40 years of randomised controlled trials. *British Journal of Psychiatry*, *178*, 129−144.

Bateman, A., & Fonagy, P. (2004). *Psychotherapy for borderline personality disorder. Mentalization-based treatment.* Oxford: Oxford University Press.

Besser, A., & Priel, B. A. (2005). The apple does not fall far from the tree: Attachment styles and personality vulnerabilities to depression in three generations of women. *Personality and Social Psychology Bulletin*, *31*, 1052−1073.

Beutler, L. E., Clarkin, J. F., & Bongar, B. (2000). *Guidelines for the systematic treatment of the depressed patient.* New York/Oxford: Oxford University Press.

Beutler, L. E., & Malik, M. L. (Eds.). (2002). *Rethinking the DSM. A psychological perspective.* Washington, DC: American Psychological Association.

Bifulco, A., Moran, P. M., Ball, C., & Bernazzani, O. (2002). Adult attachment style I. Its relationship to clinical depression. *Social Psychiatry and Psychiatric Epidemiology*, *37*, 50−59.

Blatt, S. J. (1974). Levels of object representation in anaclitic and introjective depression. *Psychoanalytic Study of the Child*, *29*, 107−157.

Blatt, S. J. (1995). The destructiveness of perfectionism: Implications for treatment of depression. *American Psychologist*, *50*, 1003−1020.
Blatt, S. J. (2004). *Experiences of depression: Theoretical, clinical and research perspectives.* Washington, DC: American Psychological Association.
Blatt, S. J., Cornell, C. E., & Eshkol, E. (1993). Personality style, differential vulnerability and clinical course in immunological and cardiovascular disease. *Clinical Psychology Review*, *13*, 421−450.
Blatt, S. J., & Homann, E. (1992). Parent–child interaction in the etiology of dependent and self-critical depression. *Clinical Psychology Review*, *12*, 47−91.
Blatt, S. J., & Levy, K. N. (1998). A psychodynamic approach to the diagnosis of psychopathology. In J. W. Baron (Ed.), *Making diagnosis meaningful. Enhancing evaluation and treatment of psychological disorders* (pp. 73−109). Washington, DC: American Psychological Association.
Blatt, S. J., & Maroudas, C. (1992). Convergence of psychoanalytic and cognitive behavioural theories of depression. *Psychoanalytic Psychology*, *9*, 157−190.
Blatt, S. J., & Shahar, G. (2004). Psychoanalysis: With whom, for what, and how? Comparisons with psychotherapy. *Journal of the American Psychoanalytic Association*, *52*, 393−447.
Blatt, S. J., & Zuroff, D. C. (1992). Interpersonal relatedness and self-definition: Two prototypes for depression. *Clinical Psychology Review*, *12*, 527−562.
Blatt, S. J., & Zuroff, D. C. (2005). Empirical evaluation of the assumptions in identifying evidence-based treatments in mental health. *Clinical Psychology Review*, *25*, 459−486.
Blatt, S. J., Zuroff, D. C., Bondi, C. M., Sanislow, C. A., & Pilkonis, P. A. (1998). When and how perfectionism impedes the brief treatment of depression: Further analyses of The National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Journal of Consulting and Clinical Psychology*, *66*, 423−428.
Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*, 386−389.
Chambless, D. L., & Ollendick, T. H. (2001). Empirically supported psychological interventions: Controversies and evidence. *Annual Review of Psychology*, *52*, 685−716.
Claes, S. (2003). Corticotropin-releasing hormone (CRH) in psychiatry: From stress to psychopathology. *Annals of Medicine*, *35*, 1−12.
Claes, S. J., & Nemeroff, C. B. (2005). Corticotropin-Releasing Factor (CRF) and major depression: Towards an integration of psychology and neurobiology in depression research. In J. Corveleyn, P. Luyten, & S. J. Blatt (Eds.), *The theory and treatment of depression: Towards a dynamic interactionism model* (pp. 227−252). Leuven/Mahwah NJ: Leuven University Press/Lawrence Erlbaum Associates.
Clark, D. A., & Beck, A. T. (1999). *Scientific foundations of cognitive theory and therapy of depression.* New York: John Wiley & Sons.
Cloninger, C. R., Svrakic, D. K., & Przybybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry*, *50*, 975−990.
Cooper, M. L., & Sheldon, M. S. (2002). Seventy years of research on personality and close relationships: Substantive and methodological trends over time. *Journal of Personality*, *70*, 783−812.
Cox, B. J., McWilliams, L. A., Enns, M. W., & Clara, I. P. (2004). Broad and specific personality dimensions associated with major depression in a nationally representative sample. *Comprehensive Psychiatry*, *45*, 246−253.
Craighead, W. E., & Nemeroff, C. B. (2005). The impact of early trauma on response to psychotherapy. *Clinical Neuroscience Research*, *4*, 405−411.
Demyttenaere, K., Van Oudenhove, L., & De Fruyt, J. (2005). The lifecycle of depression. In J. Corveleyn, P. Luyten, & S. J. Blatt (Eds.), *The theory and treatment of depression: Towards a dynamic interactionism model* (pp. 17−41). Leuven/Mahwah, NJ: Leuven University Press/Lawrence Erlbaum Associates.
Division 29 Task Force on Empirically Supported Therapy Relationships (2002). Conclusions and recommendations of the Division 29 Task Force. In J. C. Norcross (Ed.), *Psychotherapy relationships that work* (pp. 441−443). Oxford: Oxford University Press.
Elkin, I., Parloff, M. B., Hadley, S. W., & Autry, J. H. (1985). NIMH treatment of depression collaborative research program. *Archives of General Psychiatry*, *42*, 305−316.
Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F., et al. (1989). NIMH treatment of depression collaborative research program: General effectiveness of treatments. *Archives of General Psychiatry*, *46*, 971−983.
Elliott, R., Greenberg, L. S., & Lietaer, G. (2004). Research on experiential psychotherapies. In M. J. Lambert (Ed.), *Bergin and Garfield's handbook of psychotherapy change* (5th ed.) (pp. 493−539). New York: John Wiley & Sons.
Fava, G. A. (1999a). Subclinical symptoms in mood disorders: Pathophysiological and therapeutic implications. *Psychological Medicine*, *29*, 47−61.
Fava, G. A. (1999b). Well-being therapy: Conceptual and technical issues. *Psychotherapy and Psychosomatics*, *68*, 171−179.
Fava, G. A. (2002). Long-term treatment with antidepressant drugs: The spectacular achievements of propaganda. *Psychotherapy and Psychosomatics*, *71*, 127−132.
Fava, M., & Rosenbaum, J. F. (1999). Anger attacks in patients with depression. *Journal of Clinical Psychiatry*, *60*, 21−24.
Fava, G. A., Ruini, C., Rafanelli, C., Finos, L., Conti, S., & Grandi, S. (2004). Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *American Journal of Psychiatry*, *161*, 1872−1876.
Fergusson, D. M., Horwood, L. J., Ridder, E. M., & Beautrais, A. L. (2005). Subthreshold depression in adolescence and mental health outcomes in adulthood. *Archives of General Psychiatry*, *62*, 66−72.
Frank, E., Rush, A. J., Blehar, M., Essock, S., Hargreaves, W., Hogan, M., et al. (2002). Skating to where the puck is going to be: A plan for clinical trials and translation research in mood disorders. *Biological Psychiatry*, *52*, 631−654.
Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology*, *30*, 1010−1016.
Frost, R., Lahart, C. M., & Rosenblate, R. (1991). The development of perfectionism: A study of daughters and their mothers. *Cognitive Therapy and Research*, *15*, 469−489.
Gaudiano, B. A., & Herbert, J. D. (2005). Methodological issues in clinical trials of antidepressant medications: Perspectives from psychotherapy outcome research. *Psychotherapy and Psychosomatics*, *74*, 17−28.

Genova, P. (2003). *Dump the DSM. Psychiatric times, 20.* Retrieved on November 10, 2004, from http://www.psychiatrictimes.com/p030472.html.
Gillespie, N. A., Whitfield, J. B., Williams, B., Heath, A. C., & Martin, N. G. (2005). The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. *Psychological Medicine*, *35*, 101−111.
Gilmer, W. S., & McKinney, W. T. (2003). Early experience and depressive disorders: Human and non-human primate studies. *Journal of Affective Disorders*, *75*, 97−113.
Gladstone, G. L., Parker, G. B., Mitchell, P. B., Malhi, G. S., Wilhelm, K., & Austin, M. P. (2004). Implications of childhood trauma for depressed women: An analysis of pathways from childhood sexual abuse to deliberate self-harm and revictimization. *American Journal of Psychiatry*, *161*, 1417−1425.
Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Molecular Psychiatry*, *7*, 254−275.
Goodman, S., & Gotlib, I. (1999). Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review*, *106*, 458−490.
Gunnar, M. R. (2002). Integrating neuroscience and psychological approaches in the study of early experiences. *Annals of the New York Academy of Sciences*, *1008*, 238−247.
Gutman, D. A., & Nemeroff, C. B. (2003). Persistent central nervous system effects of an adverse early environment: Clinical and preclinical studies. *Physiology and Behavior*, *79*, 471−478.
Hammen, C. (2003). Interpersonal stress and depression in women. *Journal of Affective Disorders*, *74*, 49−57.
Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, *1*, 293−319.
Hankin, B., Fraley, R. C., Lahey, B. B., & Waldman, I. D. (2005). Is depression best viewed as a continuum or discrete category? A taxometric analyses of childhood and adolescent depression in a population-based sample. *Journal of Abnormal Psychology*, *114*, 96−110.
Haslam, N. (2003). Categorical versus dimensional models of mental disorder: The taxometric evidence. *Australian and New Zealand Journal of Psychiatry*, *37*, 696−704.
Heim, C., Plotsky, P. M., & Nemeroff, C. B. (2005). Importance of studying the contributions of early adverse experiences to neurobiological findings in depression. *Neuropsychopharmacology*, *29*, 641−648.
Hofer, M. A. (2005). The psychobiology of early attachment. *Clinical Neuroscience Research*, *4*, 291−300.
Hollon, S. D., Munoz, R. F., Barlow, D. H., Beardslee, W. R., Bell, C. C., Bernal, G., et al. (2002). Psychosocial intervention development for the prevention and treatment of depression: Promoting innovation and increasing access. *Biological Psychiatry*, *52*, 610−630.
Ilardi, S. S., Craighead, W. E., & Evans, D. D. (1997). Modeling relapse in unipolar depression: The effects of dysfunctional cognitions and personality disorders. *Journal of Consulting and Clinical Psychology*, *65*, 381−391.
Ingram, R. E., & Ritter, J. (2000). Vulnerability to depression: Cognitive reactivity and parental bonding in high-risk individuals. *Journal of Abnormal Psychology*, *109*, 588−596.
Jarrett, R. B., Kraft, D., Doyle, J., Foster, B. M., Eaves, G. G., & Silver, P. C. (2001). Preventing recurrent depression using cognitive therapy with and without a continuation phase. *Archives of General Psychiatry*, *58*, 381−388.
Judd, L. L. (1997). The clinical course of unipolar major depressive disorders. *Archives of General Psychiatry*, *54*, 989−991.
Judd, L. L., Akiskal, H. S., & Paulus, M. P. (1997). The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *Journal of Affective Disorders*, *45*, 5−17.
Kandel, E. R. (1998). A new intellectual framework for psychiatry. *American Journal of Psychiatry*, *155*, 457−469.
Kaufman, J., Yang, B. -Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., et al. (2004). Social support and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the USA*, *101*, 17316−17321.
Keller, M. B., McCullough, J. P., Klein, D. N., Arnow, B., Dunner, D. L., Gelenberg, A. J., et al. (2000). A comparison of nefazodone, the cognitive behavioral analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New England Journal of Medicine*, *342*, 1462−1472.
Kendler, K. S. (1997). Social support: A genetic–epidemiologic analysis. *American Journal of Psychiatry*, *154*, 1398−1404.
Kendler, K. S. (2001). Twin studies of psychiatric illness. An update. *Archives of General Psychiatry*, *58*, 1005−1014.
Kendler, K. S. (2002). Editorial. Hierarchy and heritability: The role of diagnosis and modeling in psychiatric genetics. *American Journal of Psychiatry*, *159*, 515−518.
Kendler, K. S., & Gardner, C. O. (1998). Boundaries of major depression: An evaluation of DSM-IV criteria. *American Journal of Psychiatry*, *155*, 172−177.
Kendler, K. S., Gardner, C. O., & Prescott, C. A. (2002). Toward a comprehensive developmental model for major depression in women. *American Journal of Psychiatry*, *159*, 1133−1145.
Kendler, K. S., Kuhn, J., & Prescott, C. A. (2004). The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry*, *161*, 631−636.
Kendler, K. S., Kuhn, J. W., Vittum, J., Prescott, C. A., & Riley, B. (2005). The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression. *Archives of General Psychiatry*, *62*, 529−535.
Kendler, K. S., Myers, J., & Prescott, C. A. (2005). Sex differences in the relationship between social support and risk for major depression: A longitudinal study of opposite-sex twin pairs. *American Journal of Psychiatry*, *162*, 250−256.
Kendler, K. S., Neale, M., Kessler, R., Heath, A., & Eaves, L. (1993). A longitudinal twin study of personality and major depression in women. *Archives of General Psychiatry*, *50*, 853−862.
Kessler, R. C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders*, *74*, 5−13.
Kessler, R. C., Merikangas, K. R., Berglund, P., Eaton, W. W., Koretz, D. S., & Walters, E. E. (2003). Mild disorders should not be eliminated from the DSM-V. *Archives of General Psychiatry*, *60*, 1117−1122.
Khan, A., & Khan, S. (2003). Placebo in mood disorders: The tail that wags the dog. *Current Opinion in Psychiatry*, *16*, 35−39.

Kirsch, I., Moore, T. J., Scoboria, A., & Nicholls, S. S. (2002). The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention and Treatment*, *5* (Article 23. Retrieved September 3, 2004, from http://journals.apa.org/prevention/volume5/pre0050023a.html).

Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention and Treatment*, *1* (Article 0002a. Retrieved September 3, 2004, from http://journals.apa.org/prevention/volume1/pre0010002a.html).

Klein, D. N., Durbin, E., Shankman, S. A., & Santiago, N. J. (2002). Depression and personality. In I. H. Gotlib & C.L. Hammen (Eds.), *Handbook of depression* (pp. 115−140). New York/London: The Guilford Press.

Klein, D. N., & Hayden, E. P. (2000). Dysthymic disorder: Current status and future directions. *Current Opinion in Psychiatry*, *13*, 171−177.

Krueger, R. F., & Tackett, J. L. (2003). Personality and psychopathology: Working toward the bigger picture. *Journal of Personality Disorders*, *17*, 109−128.

Kupfer, D. J., First, M. B., & Regier, D. A. (2002). *A research agenda for DSM-V.* Washington, DC: American Psychiatric Association.

Kupfer, D. J., & Frank, E. (2001). The interaction of drug- and psychotherapy in the long-term treatment of depression. *Journal of Affective Disorders*, *62*, 131−137.

Lambert, M. J., & Barley, D. E. (2002). Research summary on the therapeutic relationship and psychotherapy outcome. In J. C. Norcross (Ed.), *Psychotherapy relationships that work* (pp. 17−32). Oxford: Oxford University Press.

Lambert, M. J., & Ogles, B. M. (2004). The efficacy and effectiveness of psychotherapy. In M. J. Lambert (Ed.), *Bergin and Garfield's handbook of psychotherapy and behavior change* (5th ed.) (pp. 139−193). New York: John Wiley & Sons.

Leichsenring, D., & Leibling, E. (2003). The effectiveness of psychodynamic therapy and cognitive behavior therapy in the treatment of personality disorders: A meta-analysis. *American Journal of Psychiatry*, *160*, 1223−1232.

Lieberman, J. A., Greenhouse, J., Hamer, R. M., Krishnan, K. R., Nemeroff, C. B., Sheehan, D. V., et al. (2005). Comparing the effects of antidepressants: Consensus guidelines for evaluating quantitative reviews of antidepressant efficacy. *Neuropsychopharmacology*, *30*, 445−460.

Linehan, M. M. (1993). *Cognitive-behavioral treatment of borderline personality disorder.* New York: The Guilford Press.

Littlewood, R. (2003). *Pathologies of the West. An anthropology of mental illness in Northern America and Europe.* London: Continuum.

Luyten, P. (in press). Psychopathology: A simple twist of fate or a meaningful distortion of normal development? Towards an etiologically based alternative for the DSM approach. *Psychoanalytic Inquiry.*

Luyten, P., Blatt, S. J., & Corveleyn, J. (2005). Towards integration in the theory and treatment of depression? The time is now. In J. Corveleyn, P. Luyten, & S. J. Blatt (Eds.), *The theory and treatment of depression: Towards a dynamic interactionism model* (pp. 265−296). Leuven/Mahwah, NJ: Leuven University Press/Lawrence Erlbaum Associates.

Luyten, P., Van Houdenhove, B., Cosyns, N., & Van den Broeck, A. (in press). Are patients with Chronic Fatigue Syndrome perfectionistic — Or were they? A case–control study. *Personality and Individual Differences*.

McCullough, J. P. (2003). *Treatment for chronic depression: Cognitive Behavioral Analysis System of Psychotherapy (CBASP).* London: The Guilford Press.

McHugh, P. R. (2005). Striving for coherence: Psychiatry's efforts over classification. *Journal of the American Medical Association*, *293*, 2526−2528.

Moffitt, T. E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry*, *62*, 473−481.

Moncrieff, J., & Cohen, D. (2005). Rethinking models of psychotropic drug action. *Psychotherapy and Psychosomatics*, *74*, 145−153.

Mongrain, M., Lubbers, R., & Struthers, W. (2004). The power of love: Mediation of rejection in roommate relationships of dependents and self-critics. *Personality and Social Psychology Bulletin*, *30*, 94−105.

Morrison, K. H., Bradley, R., & Westen, D. (2003). The external validity of controlled clinical trials of psychotherapy for depression and anxiety: A naturalistic study. *Psychology and Psychotherapy: Theory, Research and Practice*, *76*, 109−132.

Mueller, T. I., Leon, A. C., Keller, M. B., Solomon, D. A., Endicott, J., Coryell, W., et al. (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *American Journal of Psychiatry*, *156*, 1000−1006.

Mulder, R. T. (2002). Personality pathology and treatment outcome in major depression: A review. *American Journal of Psychiatry*, *159*, 359−371.

Nemeroff, C. B. (2002). Editorial. Comorbidity of mood and anxiety disorders: The rule not the exception? *American Journal of Psychiatry*, *159*, 3−4.

Nemeroff, C. B., Heim, C. M., Thase, M. E., Klein, D. N., Rush, J. A., Schatzberg, A. F., et al. (2003). Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 14239−14296.

Öngür, D., Farabaugh, A., Iosifescu, D. V., Perlis, R., & Fava, M. (2005). Tridimensional Personality Questionnaire factors in major depressive disorder: Relationship to anxiety disorder comorbidity and age of onset. *Psychotherapy and Psychosomatics*, *74*, 173−178.

Ormel, J., Oldehinkel, A. J., & Brilman, E. I. (2001). The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *American Journal of Psychiatry*, *158*, 885−891.

Ormel, J., Stewart, R., & Sanderman, R. (1989). Personality as modifier of the life change–distress relationship: A longitudinal modelling approach. *Social Psychiatry and Psychiatric Epidemiology*, *24*, 187−195.

Parker, G. (1999). Clinical trials of antidepressant medications are producing meaningless results. *British Journal of Psychiatry*, *183*, 102−103.

Parker, G. (2000). Classifying depression: Should paradigms lost be regained? *American Journal of Psychiatry*, *157*, 1195−1203.

Parker, G. (2005). Beyond major depression. *Psychological Medicine*, *35*, 467−474.

Parker, G., Gladstone, G., Wilhelm, K., Mitchell, P., Hadzi-Pavlovic, D., & Austin, M. -P. (1997). Dysfunctional parenting: Over-representation in non-melancholic depression and capacity of such specificity to refine sub-typing depression measures. *Psychiatry Research*, *73*, 57−71.

Parker, G., Hadzi-Pavlovic, D., Roussos, J., Wilhelm, K., Mitchell, P., Austin, M. -P., et al. (1998). Non-melancholic depression: The contribution of personality, anxiety and life events to subclassification. *Psychological Medicine*, *28*, 1209−1219.

Parker, G., Roy, K., & Eyers, K. (2003). Cognitive behavior therapy for depression? Choose horses for courses. *American Journal of Psychiatry*, *160*, 825−834.

Parker, G., Roy, K., Wilhelm, K., Mitchell, P., Austin, M. -P., & Hadzi-Pavlovic, D. (1999a). Subgrouping non-melancholic major depression using both clinical and aetiological features. *Australian and New Zealand Journal of Psychiatry*, *33*, 217−225.

Parker, G., Roy, K., Wilhelm, K., Mitchell, P., Austin, M. -P., Hadzi-Pavlovic, D., et al. (1999b). Sub-grouping non-melancholic depression from manifest clinical features. *Journal of Affective Disorders*, *53*, 1−13.

Philips, B., Ball, C., Sackett, D. L., Badenoch, D., Straus, S., Haynes, B., et al. (2001). *Levels of evidence and grades of recommendation.* (Centre for Evidence Based Medicine web site), Retrieved February 11, 2005 from http://www.cebm.net/levels_of_evidence.asp#notes

Phillips, K. A., First, M. B., & Pincus, H. A. (Eds.). (2003). *Advancing DSM. Dilemmas in psychiatric diagnosis.* Washington, DC: American Psychiatric Assocation.

Phillips, K. A., Price, L. H., Greenberg, B. D., & Rasmussen, S. A. (2003). Should the DSM diagnostic groupings be changed? In K. A. Phillips, M. B. First, & H. A. Pincus (Eds.), *Advancing DSM. Dilemmas in psychiatric diagnosis* (pp. 57−84). Washington, DC: American Psychiatric Association.

Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry*, *149*, 999−1010.

RANZCP Clinical Practice Guidelines Team for Depression. (2004). Australian and New Zealand clinical practice guidelines for the treatment of depression. *Australian and New Zealand Journal of Psychiatry*, *38*, 1283−1289.

Rose, S. (2001). Moving on from old dichotomies: Beyond nature–nurture towards lifeline perspective. *British Journal of Psychiatry*, *178*(Suppl 40), s3−s7.

Rush, A. J., & Thase, M. E. (2002). Psychotherapies for depressive disorders: A review. In M. Maj & N. Sartorius (Eds.), *Depressive disorders* (2nd ed.) (pp. 161−206) Chichester: Wiley.

Ruscio, A. M., & Ruscio, J. (2002). The latent structure of analogue depression: Should the Beck Depression Inventory be used to classify groups? *Psychological Assessment*, *14*, 135−145.

Ruscio, J., & Ruscio, A. M. (2000). Informing the continuity controversy: A taxometric analysis of depression. *Journal of Abnormal Psychology*, *109*, 473−487.

Sanathara, V. A., Gardner, C. O., Prescott, C. A., & Kendler, K. S. (2003). Interpersonal dependence and major depression: Aetiological inter-relationships and gender differences. *Psychological Medicine*, *33*, 927−931.

Saudino, K. J., Pedersen, N. L., Lichtenstein, P., McClearn, G. E., & Plomin, R. (1997). Can personality explain genetic influences on life events? *Journal of Personality and Social Psychology*, *72*, 196−206.

Savitz, J. B., & Ramesar, R. S. (2004). Genetic variants implicated in personality: A review of the more promising candidates. *American Journal of Medical Genetics*, *131B*, 20−32.

Schatzberg, A. F., Rush, J., Arnow, B. A., Banks, P. L. C., Blalock, J. A., Borian, F. E., et al. (2005). Chronic depression: Medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Archives of General Psychiatry*, *62*, 513−520.

Segal, Z. V., Pearson, J. L., & Thase, M. E. (2003). Challenges in preventing relapse in major depression. Report of a National Institute of Mental Health Workshop on state of the science of relapse prevention in major depression. *Journal of Affective Disorders*, *77*, 97−108.

Segrin, C. (2000). Social skills deficits associated with depression. *Clinical Psychology Review*, *20*, 379−403.

Shahar, G., Joiner, T. E., Zuroff, D. C., & Blatt, S. J. (2004). Personality, interpersonal behavior, and depression: Co-existence of stress-specific moderating and mediating effects. *Personality and Individual Differences*, *36*, 1583−1596.

Shaw, B. F., Elkin, I., Yamaguchi, J., Olmsted, M., Vallis, T. M., Dobson, K. S., et al. (1999). Therapist competence ratings in relation to clinical outcome in cognitive therapy of depression. *Journal of Consulting and Clinical Psychology*, *60*, 441−449.

Shea, M. T., Stout, R. L., Yen, S., Pagano, M. E., Skodol, A. E., Morey, L. C., et al. (2004). Associations in the course of personality disorders and Axis I disorders over time. *Journal of Abnormal Psychology*, *113*, 499−508.

Shedler, J., & Westen, D. (2004). Refining personality disorder diagnosis: Integrating science and practice. *American Journal of Psychiatry*, *161*, 1350−1365.

Soenens, B., Elliot, A. J., Goossens, L., Vansteenkiste, M., Luyten, P., & Duriez, B. (2005). The intergenerational transmission of perfectionism: Parents' psychological control as an intervening variable. *Journal of Family Psychology*, *19*, 358−366.

Solomon, A., Haaga, D. A. F., & Arnow, B. A. (2001). Is clinical depression distinct from subthreshold depressive symptoms? A review of the continuity issue in depression research. *Journal of Nervous and Mental Disease*, *189*, 498−506.

Solomon, D. A., Keller, M. B., Leon, A. C., Mueller, T. I., Lavori, P. W., Shea, M. T., et al. (2000). Multiple recurrences of major depressive disorder. *American Journal of Psychiatry*, *157*, 229−233.

Stelmack, R. N. (Ed.). (2004). *On the psychobiology of personality. Essays in honor of Marvin Zuckerman*. Pergamon.

Stiles, W. B., & Shapiro, D. A. (1989). Abuse of the drug metaphor in psychotherapy process-outcome research. *Clinical Psychology Review*, *9*, 521−543.

Teasdale, J. D., Segal, Z. V., Williams, J. M. G., Ridgeway, V. A., Soulsby, J. M., & Lau, M. A. (2000). Prevention of relapse/recurrence in major depression by mindfulness based cognitive therapy. *Journal of Consulting and Clinical Psychology*, *68*, 615−623.

Tennant, C. (2002). Life events, stress and depression: A review of recent findings. *Australian and New Zealand Journal of Psychiatry*, *36*, 173−182.

Tse, W. S., & Bond, A. J. (2004). The impact of depression on social skills. A review. *Journal of Nervous and Mental Disease*, *192*, 206−268.

Van Gestel, S., Forsgren, T., Claes, S., Del-Favero, J., van Duijn, C. M., Sluijs, S., et al. (2002). Epistatic effects of genes from the dopamine and serotonin systems on the temperament traits of Novelty Seeking and Harm Avoidance. *Molecular Psychiatry*, *7*, 448−450.

Van Houdenhove, B., & Egle, U. T. (2004). Fibromyalgia: A stress disorder? Piecing the biopsychosocial puzzle together. *Psychotherapy and Psychosomatics*, *73*, 267−275.

Van Houdenhove, B., Egle, U., & Luyten, P. (2005). The role of life stress in Fibromyalgia. *Current Rheumatology Reports*, *7*, 365−370.

Van Os, J., & Jones, B. P. (1999). Early risk-factors and adult person–environment relationships in affective disorders. *Psychological Medicine*, *29*, 1055−1067.

Van Os, J., Park, S. B., & Jones, P. B. (2001). Neuroticism, life events and mental health: Evidence for person–environment correlation. *British Journal of Psychiatry*, *178*(Suppl 40), s72−s77.

Van Praag, H. M., de Kloet, R., & van Os, J. (2004). *Stress, the brain and depression.* Cambridge: Cambridge University Press.

Viguera, A. C., Baldessarini, R. J., & Friedberg, J. (1998). Discontinuing antidepressant treatment in major depression. *Harvard Review of Psychiatry*, *5*, 293−306.

Wachtel, P. L. (1997). *Psychoanalysis, behavior therapy, and the relational world.* Washington, DC: American Psychological Association.

Weissman, M., Wolk, S., Goldstein, R. B., Moreau, D., Adams, P., Greenwald, S., et al. (1999a). Depressed adolescents grown up. *Journal of the American Medical Association*, *281*, 1707−1713.

Weissman, M., Wolk, S., Wickramaratne, P., Goldstein, R. B., Adams, P., Greenwald, S., et al. (1999b). Children with prepubertal-onset major depressive disorder and anxiety grown up. *Archives of General Psychiatry*, *56*, 794−801.

Westen, D., & Morrison, K. (2001). A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: An empirical examination of the status of empirically supported therapies. *Journal of Consulting and Clinical Psychology*, *69*, 875−899.

Westen, D., Novotny, C. M., & Thompson-Brenner, H. (2004). The empirical status of empirically supported psychotherapies: Assumptions, findings, and reporting in controlled clinical trials. *Psychological Bulletin*, *130*, 631−663.

Westen, D., & Shedler, J. (2000). A prototype matching approach to diagnosing personality disorders: Toward DSM-V. *Journal of Personality Disorders*, *14*, 109−126.

Williams Jr., J. W., Mulrow, C. D., Chiquette, E., Hitchcock Noël, P., Aguilar, C., & Cornell, J. (2000). A systematic review of newer pharmacotherapies for depression in adults: Evidence report summary. *Annals of Internal Medicine*, *132*, 749−756.

Winkler, D., Tauscher, J., & Kasper, S. (2002). Maintenance treatment in depression: The role of pharmacological and psychological treatment. *Current Opinion in Psychiatry*, *15*, 63−68.

Zhang, X., Beaulieu, J. M., Sotnikova, T. D., Gainetdinov, R. R., & Caron, M. G. (2004). Tryptophan hydroxylase-2 controls brain serotonin synthesis. *Science*, *305*, 217.

Zimmerman, M., Mattia, J. I., & Posternak, M. A. (2002). Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *American Journal of Psychiatry*, *159*, 469−473.

Zuroff, D. C., & Blatt, S. J. (in press). The therapeutic relationship in the brief treatment of depression: Contributions to clinical improvement and enhanced adaptive capacities. *Journal of Consulting and Clinical Psychology.*

Zuroff, D. C., Blatt, S. J., Krupnick, J. L., & Sotsky, S. M. (2003). Enhanced adaptive capacities after brief treatment for depression. *Psychotherapy Research*, *13*, 99−115.

Zuroff, D. C., Blatt, S. J., Sanislow III, C. A., Bondi, C. M., & Pilkonis, P. A. (1999). Vulnerability to depression: Reexamining state dependence and relative stability. *Journal of Abnormal Psychology*, *108*, 76−89.

Zuroff, D. C., Mongrain, M., & Santor, D. (2004). Conceptualizing and measuring personality vulnerability to depression: Comment on Coyne and Whiffen (1995). *Psychological Bulletin*, *130*, 489−511.