Differential Pharmacological and Cognitive Responses Among Depressive Subtypes

By

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Abstract

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Depression is a devastating and seriously disabling mental illness that despite notable progress in the field continues to challenge the medical community worldwide. Experts generally concede that 1. Neuropathophysiological studies of depression have resulted in contradictory findings; and 2. A major cause of these confusing findings is due to the weakness of the DSM-IV's diagnostic classification of depression, which produces heterogeneity within groups included in neuroscientific studies. Researchers have suggested that the current DSM-IV criteria for both atypical depression (AD) and melancholia needs to be re-conceptualized. The purpose of the three studies described here was to examine whether new criteria may better define two distinct depressive

subtypes than do current DSM-IV criteria sets, using the measures of pharmacologic dissection and perceptual asymmetry (PA). In study one, the current criteria for AD did not significantly predict response to a MAOI on either measure of remission nor did it predict a response to a TCA although on the HAM-D_{17} measure of remission is strongly in the right direction but not significant due to small sample size. Likewise, the criteria for somatic depression (SD) did not predict on either measure of remission a response to a MAOI, neither did it predict response to a TCA on one measure of remission (HAM-D_{17}) but on a second measure of remission (QIDS-C_{30}), it did predict response to a TCA at a borderline significance level using a chi-square test and at a significant level using the Fisher's Exact probability test. In study two, the current criteria for melancholic depression did significantly predict response to a TCA on the HAM-D_{17} measure of remission but in the opposite direction from that reported in the literature and no significant difference was found on the QIDS-C_{30} measure of remission. Modified criteria for melancholic depression did not significantly predict response to a TCA on the HAM-D_{17}, however, they did predict response on the QIDS-C_{30} in the predicted direction at a borderline significance level. In study three, the current criteria for AD versus melancholic depression did not yield a significant difference in PA. However, melancholic depression versus SD did predict differential PA at a borderline significance level in the opposite direction to that predicted. In conclusion, there is some support for a differential response by SD, suggestive of a distinct non-endogenous subtype of depression. The implications of these findings will be discussed.

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I. Introduction

Depression is a devastating and seriously disabling mental illness that despite notable progress in the past half-century, continues to challenge the medical community worldwide. Approximately 10% of persons experience depression each year and 20% experience a depressive episode at some point in their lives, with an 80% relapse rate (Gotlib & Hamilton, 2008; Malhi, Parker, Crawford, & Mitchell, 2005), and women's occurrence of depression exceeds men's by about 2:1 (Gotlib & Hammen, 2002). In the United States (U.S.), the National Comorbidity Survey Replication (NCS-R) figures for major depression suggest a lifetime prevalence of 16.2% and 6.6% for one year (Kessler et al., 2003). These figures translate into some 32.6 to 35.1 million adults aged 18 and older experiencing major depression over the course of their lives and 13.1 to 14.2 million affected each year at substantial human cost.[1]

In addition to the grave consequences in all realms of one's functioning, syndromes under the general umbrella of depression represent a significant economic burden. In the U.S. alone, as of the year 2000, it was estimated that depression costs had doubled since 1990 to $83.1 billion annually, when taking into account several factors. For instance, absenteeism from work alone was estimated to be $12 billion dollars with an overall cost of $51.5 billion in the workplace (e.g., lost work productivity, reduced performance of co-workers, employee turnover, and industrial accidents). Further,

[1] To counter claims that prevalence data derived from community surveys might be inflated by clinically insignificant cases, the researchers noted that virtually all one-year cases were clinically significant and about 90% were categorized as moderate, severe, or very severe.

suicide-related mortality costs were estimated at $5.4 billion annually (Greenberg et al., 2003).

Although 57.3% of respondents reporting depression in 2003 received treatment, (which reflects a significant upward trend from similar research conducted in the early 1980s and 1990s (Kessler et al., 2003), and a 37% increase in treatment for depression over time was reflected, only 41.9% received satisfactory treatment. The overarching conclusion of Kessler et al. is that there is an urgent need for improvement in treating Major Depressive Disorder (MDD).[2] In fact, the World Health Organization (WHO) Global Burden of Disease Study ranks depression as the single most burdensome disease in the world in terms of disability-adjusted life years.[3] WHO further emphasizes this point in a recent study, which predicts depression will be second only to heart disease as the most disabling health condition in the world by the year 2020, given current statistics (Gotlib et al., 2002; Fava, et al, 2003; Murray, & Lopez, 1996). Although this in itself is grim commentary, significant advances in the major fields of depression research -- neurobiological, neuroimaging, pharmacologic, and cognitive -- provide cause for careful hope.

Over the past decade, researchers have utilized neuroimaging techniques to examine the neural substrates of depression. Based on this work, abnormalities in key regions of the brain have been implicated in MDD. In a review, Davidson et al. (2002) highlight significant involvement of the limbic system, a complex of structures including the amygdala, hippocampus, and parts of the anterior cingulate cortex (ACC).

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[2] Concordant with data from the National Medical Expenditures Survey charting trends from 1987-1997.

[3] Years of life lost to premature death and years lived with a disability of specified severity and duration.

Investigators have also examined cortical structures of which the dorsolateral prefrontal cortex (DLPFC) has gained much interest in its regulation of emotion in depression and cognitive control. A vast majority of single photon emission computed tomography (SPECT) and/or positron emission tomography (PET) studies on depression report a global brain hypometabolism or hypoperfusion. However, there are continued controversies among various studies in the specific locations and directions of abnormalities in depressed patient samples (Drevets, 2001; Fountoulakis et al. 2004).

For instance, the amygdala has been shown to play an important role in emotionally mediated attention, in assigning emotional significance to stimuli, and in remembering significant events (Phelps, 2008). Studies examining amygdala volume in depression have yielded contradictory findings. In a number of structural neuroimaging studies, researchers have examined differences in amygdala volume between depressed and non-depressed individuals. Some studies have reported depressed individuals to be characterized by smaller amygdala volume than non-depressed individuals (e.g., Caetano et al., 2004; Sheline, Gado, & Price, 1998; Sheline, Sanghavi, Mintun, & Gado, 1999). Alternatively, studies have reported greater amygdala volume in depressed individuals (e.g., Lange & Irle., 2004), while others have reported no differences in amygdala volume between depressed and non-depressed individuals (e.g., Munn et al., 2007). Furthermore, in a recent meta-analysis of such studies, Gotlib and Hamiltion (2008) found no collective difference in amygdala volume between depressed individuals and healthy controls. The discrepancies across amygdala volumetric studies suggest that presently there is no consistent relationship between amygdala volume and depressive illness.

Several studies have also found reduced hippocampal volume in depressed patients, but there are discrepancies with other studies. Interest in the study of the hippocampus in depressed populations lies in its involvement in episodic, declarative, contextual, and spatial learning and memory (Burgess, Maguire, & O'Keefe, 2002; Fanselow, 2000), deficits often evidenced in depression (Veiel, 1997; Ravnkilde, & Videbech, 2002). Some volumetric studies have found significant bilateral deficits in depression (MacQueen et al., 2003; Sheline et al.,1999). Other studies have found significantly lower volume in the right hemisphere (Bell-McGinty et al., 2002; Steffens et al., 2000) or in the left hemisphere (Bremmer et al., 2000; Mervaala et al., 2000), but numerous studies have failed to find any differences (Frodl et al., 2002; Posener et al., 2003; Vakili et al., 2000). Similarly, the inconsistencies are found between measurements of hippocampal volume and clinical characteristics (Mervaala et al., 2000; Steffens et al., 2000).

Insel (2007) argues that there is compelling evidence to suggest that attention should focus on the prefrontal cortex (PFC), particularly a site in the midline subgenual ACC, frequently referred to as Broadman area 25. Further, he is skeptical about studies that suggest a proposed link between the hippocampus and depression. In his view, none of the neuroimaging or postmortem studies has produced findings unique to the hippocampus or to MDD. Other authors agree that the PFC sites appear to be central to MDD (Coryell et al., 2005; Fales et al., 2008; Hastings et al., 2004; Johnstone et al., 2007).

Along these lines of research, Hastings et al. (2004) conducted a substantive test. They utilized MRI scans to simultaneously explore volumes in the PFC, hippocampus,

and amygdala in patients diagnosed with MDD. Their sample included ten women and eight men and a matched control group of healthy volunteers. A key aim of the study was to examine gender differences. An intriguing finding was that there was no difference in hippocampal volume between depressed and non-depressed subjects for either gender, which contradicted the majority of research findings thus far (e.g., Videbech & Ravnkilde, 2004). Neither were there significant differences in volume in the orbital PFC, despite the expectations with which Hastings et al. entered the study. Differences between depressed and non-depressed subjects emerged in the inferior anterior cingulate, demonstrating a 23% reduction in volume in depressed men and an 11% reduction in depressed women. Depressed women showed a smaller amygdala compared to the healthy controls but the same effect was not apparent in depressed men.

Despite significant advances in understanding depression from neuroimaging research, substantial discrepancies remain. Experts generally concede that 1. Neuropathophysiological studies of depression have resulted in contradictory findings; and 2. A major cause of these confusing findings is due to the weakness of the DSM-IV's diagnostic classification of depression, which produces heterogeneity within groups included in neuroscientific studies (Davidson et al., 2002; Drevets, 2007; Fountoulaksi et al., 2004; Pagani et al., 2006; Pizzagalli et al., 2002; Smith & Cavanagh, 2005).

At the most basic level, some inconsistencies are thought to be unique to the capabilities/limitations of the various types of imaging technologies (e.g., PET, SPECT, fMRI). However, more crucial is the issue of diagnostic criteria. For instance, Davidson, Pizzagalli, Nitschke, & Putnam (2002) state that:

> We wish to underscore at the outset that one of the crucial issues that plagues research in this area is the heterogeneity of depression….From an examination of the inconsistencies across studies, it is apparent that traditional methods for parsing heterogeneity based on descriptive phenomenology are not yielding clean separation of underlying neural circuitry. (p. 547)

Similarly, Smith and Cavanagh (2005) further highlight the inconsistency of these findings, and suggest reasons for these inconsistencies by noting the variance of depressive symptoms:

> As with many psychiatric diagnoses, the term ‘depression’ fails to capture the considerable variations in symptoms and signs that exist between different depressive subtypes….When we consider that some of the SPECT studies carried out to date have tended to use patients from several of these different subtypes in the same study, it is perhaps unsurprising that many of the findings reported so far have been inconsistent. (p. 197)

Pizzagalli et al, (2002) further echo this point with reference to depressive subtypes:

> Most importantly, our findings underscore the considerable heterogeneity of depression even within melancholic and nonmelancholic subtypes and underscore the need for better, more objective measures of affective dysfunction to systematically characterize the neural circuitry underlying affective processing deficits in depression. (p.83)

And more recently, Gotlib and Hamilton (2008) conclude:

> Above all, they underscore the fact that"depression" refers to a heterogeneous group of disorders that are not carved at their neurobiological joints in the DSM-IV. Perhaps the most pressing task for future research, therefore, is to begin more explicitly to conceptualize depression subtypes and symptom profiles that are related systematically to specific neural functional and structural abnormalities…. (p.162)

Akin to neuroscientific studies, pharmacological studies have been besieged with inconsistent findings across treatment studies utilizing different pharmacotherapy regimes. The most notable advances in the diagnosis and treatment of depression are generally recognized to have begun in the late 1950's. Roughly 50 percent of depressed individuals are successfully treated with pharmacotherapy (Rush, Trivedi, & Fava, 2003), and yet a notably high percentage -- the remaining 50 percent – continue to be symptomatic after initial treatment, and/or switching to a different class of antidepressants.

Clinical trials are not immune to the methodological flaws that plague depression research in general. Several studies have been heavily criticized due to the numerous methodological flaws inherent within them (e.g., lack of appropriate comparison groups, small sample sizes, ineffective dosing, short duration of studies, inadequate screening tools) and application of disparate definitions across studies, many of which were done prior to a formal classification to recognize depressive subtypes (Bielski & Friedel, 1976; Fiedorowicz, 2004; Geddes et al., 2007; Fava et al., 2003; Joyce & Paykel, 1989;

Liberman et al., 2005; Nierenberg et al., 2007; Quitkin et al., 1979, 1993; Thase et al., 1995) making it difficult to interpret findings. Acknowledging that many antidepressant trials have been heavily criticized, Geddes et al. (2007) declare, “This was possibly justifiable, or at least understandable, when depression was not so widely recognized as a highly prevalent disorder that is responsible for so much human suffering, however, this state of affairs is no longer acceptable.” (p. 544)

From the aforementioned areas of research, it is apparent that one of the most important conclusions, supported by evidence in all fields of depression research, is that real progress in the effective diagnosis and treatment of this disease is seriously hindered by the fact that MDD as presently conceptualized in the DSM-IV, represents a set of clinically heterogeneous disorders. As a result, all attempts to elucidate the underlying neuropathophysiology of depressive disorder, continue to yield inconsistent results when this criteria is applied to studies.

The DSM-IV task force, to address the issue of the clinical heterogeneity of MDD, recommended the definition revision of MDD to reflect symptom features of the various expressions of depression as depressive feature specifiers to be integrated into the diagnostic classification as a) endogenous depression, typically, known as melancholia and/or severe depression, and b) non-endogenous depression. Historically, a significant number of researchers have equated non-endogenous depression with atypical depression (Davidson, 2007), although others have referred to atypical depression as a biologically distinct subtype of depression.

Although the DSM-IV Task Force arrived at a formal classification for diagnosing MDD, which defined melancholia and Atypical forms of depression (AD)-- as

feature specifiers of MDD -- variations in symptom presentations continued in clinical studies. These distinctions not only remain a significant issue of controversy among depression researchers, but may even complicate the issue.

For instance, several researchers have suggested that this heterogeneity would decrease with the further re-definition of MDD into two distinct categories of endogenous and non-endogenous depression (Shorter, 2007; Stewart et al., 2007; Taylor & Fink, 2008). Shorter (2007) states that "it was the DSM-III in 1980 that committed the classic historical blunder of lumping the two depressions together in the form of 'major depression.' This has been a nosological catastrophe from which almost 30 years later the field has not recovered" (p.6). Other researchers have argued that the manner in which the DSM-IV portrays MDD with feature specifiers of AD and melancholia is far too narrow of a definition approach, and they suggest that the current DSM-IV criteria for both AD, as well as melancholia, both of which have yielded inconsistent neurobiological findings needs to be re-conceptualized (Angst et al., 2002, 2006; Matza et al, 2003; Parker et al., 2002; Silverstein, Cohen, & Kasen, 2006; Stewart et al., 2007).

The identification of AD has its genesis in the method of "pharmacological dissection" wherein the specificity of response to different antidepressants is used to help define particular disorders or subtypes of depression that are presumed to be associated with differing physiological substrates. Over the years, several studies have concluded that AD, which is characterized by reversed neurovegetative symptoms (e.g., weight gain, hyperphagia, hypersomnia) responds relatively well to monoamine oxidase inhibitors (MAOI) and shows a poorer response to tricyclic (TCA) antidepressants (Liebowitz et al., 1984, 1988; Quitkin, Rifkin, and Klein, 1979; Quitkin et al., 1984; Quitkin et al., 1993;

Sargant, 1961; Stewart et al. 1989; West and Dally, 1959). Based on these findings, predominantly from clinical trials conducted by the Columbia University Research Group, AD was entered into the DSM-IV as a feature specifier for MDD.

Interestingly, from a different body of research a concept similar to AD has arisen. Somatic depression (SD: non-endogenous form of depression) involves depression accompanied by a number of somatic symptoms such as disordered eating, poor body image, disordered sleep, fatigue, and body aches. Analyses of several databases, including both the Epidemiologic Catchment Area Survey (ECA) and the National Comorbidity Study (NCS), indicate that the gender difference in the prevalence of depression results because women exhibit much more SD than men but not much more pure depression (depression without somatic symptoms) (Silverstein, 1999; Silverstein, 2002; Silverstein et al, 2006). Respondents reporting SD, defined in the ECA and NCS as exhibiting all three categories of appetite disturbance, sleep disturbance, and fatigue, show a large gender difference in prevalence whereas respondents reporting depression without all three of these symptoms exhibit little gender difference in prevalence.

Additional differences between the two subtypes of depression relate to psychosocial measures of gender roles. Such measures, whether taken from female respondents themselves or from their parents, have been found to predict the extent of SD, but not of pure depression, of the female respondents (Silverstein, Perlick, Clauson, & McKoy, 1993;Silverstein, Caceres, Perdue, & Cimarolli, 1995; Silverstein & Blumenthal, 1997; Silverstein & Lynch, 1998).

A close examination of the symptoms of both AD and SD, which were derived from two very different lines of research, indicate that symptoms of SD overlap with

those of AD. This suggests the hypothesis that a definition of a depressive subtype (SD) that grew out of research on gender and gender roles and a definition of a depressive subtype (AD) that grew out of research on response to antidepressants might be two aspects of the same disorder. In support of this hypothesis, analyses of data from The Children in the Community Study found a strong relationship between AD and many of the additional symptoms included in the definition of SD (Silverstein et al., 2006).

Further, a preliminary investigation to examine whether a set of criteria made up of a combination of the symptoms of SD and AD may better define a distinct disorder than the current criteria used for AD demonstrates that SD as well as the combined criteria provide a stronger predictor of gender than does AD alone (Silverstein in preparation).

Based on this evidence of overlap between AD and SD, a valid test would be to compare the two criteria sets on a measure other than gender. However, it is notable that if the SD criteria set is a stronger predictor on a second measure, this would have implications for the endogenous type of depression melancholia. Specifically, it has been suggested that AD may not be restricted to the symptoms of overeating and oversleeping as traditionally thought, but expanded to include lack of appetite and insomnia as well, symptoms currently present in the criteria for SD. If in fact, AD does include lack of appetite and insomnia as a symptom, then it will be important to review and refine criteria for melancholic depression, which also includes similar symptoms.

In summary, given MDD's substantial human suffering and costs to society, the need for more effective diagnostic and treatment methods resonates throughout the literature. There are calls for improvement in virtually all aspects of areas that are

intrinsically interrelated to depression treatment including clinician care (Huynh & McIntyre, 2008; Kessler et al., 2003; Mischoulon, Nierenberg, Kizilbash, Rosenbaum, & Fava, 2000), clinical trials (Blier, 2007; Brown, 2007; Davis et al., 2006; Price, 2006; Rush et al., 2006, 2008; Sussman, 2007) diagnostic classification (Angst et al., 2007; Coryell, 2007; Fava et al., 2006; Fountoulakis, Fotiou, Iacovides, & Kaprinis, 2000; Geddes, Furukawa, Cipriani, & Barbui, 2007; Kessing, 2007; Malhi et al., 2005; Matza, Revicki, Davidson, & Stewart, 2003; Pagani et al., 2007; Parker, 2000; Parker et al., 2002; Stewart, McGrath, Quitkin, & Klein, 2007; Taylor & Vaidya, 2005;), neuroimaging research (Coryell, Nopoulos, Drevets, Wilson, & Andreasen, 2005; Drevets, 1998; Fales et al., 2008; Fountoulakis et al., 2004; Goldapple et al., 2004; Hastings, Parsey, Oquendo, Arango, & Mann, 2004; Hugdahl et al., 2007; Insel, 2007; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Moretti, Gorini, Villa, 2003; Pizzagalli et al., 2004; Videbech & Ravnkilde, 2004; Zipursky, Meyer, & Verhoeff, 2007), and psychopharmacology (Briley, 1998; Joyce, Mulder, Luty, McKenzie, & Rae, 2003; Mallinckrodt, Watkin, Liu, Wohlreich, & Raskin, 2005; Montgomery, 2006; Nemeroff, 2002; Nemeroff & Owens, 2002; Norman, 2006; Parker, 2002; Ressler & Nemeroff, 2000; Stahl, 2004; Stewart & Reid, 2002).

In line with the findings of Silverstein and Colleagues, both AD and SD are reasonable possibilities for delineating a distinct non-endogenous depressive subtype. A stronger case for defining a distinct depressive subtype would be to compare current criteria for AD to criteria for SD using the method of pharmacologic dissection, the very area of research from which the current criteria for AD were derived.

Study one examined through the method of pharmacologic dissection whether SD better predicts than do current AD criteria, treatment response to antidepressant medications. Specifically, it was hypothesized that the SD criteria would predict a poorer response to tricyclic antidepressants compared to the current DSM-IV criteria for AD. If the optimal criteria for the hypothesized non-endogenous form of what is currently termed “atypical depression” includes loss of appetite and sleep problems, this would have implications for the alleged endogenous form of “depression: melancholic depression”, the criteria for which include similar symptoms. In line with this, study two examined whether refining criteria for melancholic depression by eliminating appetite loss and sleep problems better predicts than do current criteria, treatment response to antidepressant medications. Melancholic depression has frequently been associated with a better response to TCAs (e.g., Bielski & Friedel, 1976; Kiloh, Ball, & Garside, 1962; Navarro, Gasto, Torres, Marcos, & Pintor, 2001; Perry, 1996; Schatzberg, 1998).

In addition to using the measure of pharmacologic dissection in study one and two, findings for changing criteria sets would be strengthened by using a different measure. Some studies examining the relationship between cognitive functioning and depressive subtype (e.g., Bruder et al., 1989; Bruder et al., 2002) have shown that compared to AD, melancholic depressives exhibit a right-hemisphere dysfunction on the cognitive measure of perceptual asymmetry (PA) in both the auditory and visual modality. Study three used the cognitive measure of PA to test whether current criteria sets for AD and melancholic depression would be a less discriminatory measure of PA compared to melancholic depression and SD defined in study one and two.

II. Literature Review

A. Definition of Major Depressive Disorder

As characterized in the field of psychiatry, depression is among the most prevalent of all psychiatric disorders (Gotlib & Hammen, 2002). There are currently two distinct types of depression: Unipolar Depression, which is also known as Major Depressive Disorder (MDD), and Bipolar Depression. MDD is the most severe and most studied of all of the depression syndromes (Wells, Stewart, & Hayes, 1989).

The DSM-IV, currently characterizes MDD by the following symptoms:

1. Depressed mood
2. Markedly diminished interest or pleasure in all, or almost all, activities
3. Significant weight loss when not dieting, or decrease/increase in appetite
4. Insomnia or hypersomnia
5. Psychomotor retardation or agitation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think, concentrate, or decide
9. Recurrent thoughts of death or suicidal ideation, without a specific plan; or a suicide attempt or specific plan for committing suicide.

A quick review of the foregoing symptoms clearly reflects that these symptoms are considerably heterogeneous, and in some instances, polar opposites of each other. Despite these incongruities, MDD is presently construed as a single nosologic entity.

This issue of heterogeneity is a major obstacle to effective diagnosis and treatment of depression.

In order to meet criteria for MDD, an individual must present with at least five of these symptoms, one of which must be either depressed mood or loss of interest or pleasure in previously enjoyed activities. Further, symptoms must persist for most of the day, nearly every day for at least two consecutive weeks and cause significant clinical distress or impairment in social, occupational or other important areas of functioning (American Psychiatric Association & American Psychiatric Association, 2000). Obviously, despite the requirements of this diagnostic guideline, substantial room for error remains. Variations in symptom presentations suggest heterogeneity of underlying neuropathology. This heterogeneity is thought to immensely contribute to the persistent discrepancies found across numerous channels of investigation in the depression literature. Some researchers have suggested that this heterogeneity would decrease by recasting the definition of MDD into two specific depressive disorders: a) melancholic disorder, and b) non-melancholic disorder (Shorter, 2007; Stewart et al., 2007; Taylor & Fink, 2008). Essentially, these two depressive subtypes define the issue of polarity, which is seen in symptomatology.

The remainder of this literature review will focus particularly on the aforementioned subtypes of endogenous and non-endogenous depressive disorders and how the redefining of MDD into these two distinct categories might serve more effective diagnosis and treatment of this complex and pernicious mental disease. For a review of the primary channels of investigation into the area of depression research (i.e., neurochemical basis, stress as a factor in the etiology of depression, and neuroanatomical

structures implicated in depression) and what these fields of study reveal about the current status of depression in general please refer to Appendix A, B and C, respectively.

B. Issues in Classifying Depression

The classification of depressive disorders has historically been, and continues to be, a controversial issue. The central question in this issue is whether there are one, two, or multiple types of depression (Parker, 2000). The unitary model is more commonly known as MDD, while the binary model is based on the idea that there are two main types of depression disorder: "endogenous/psychotic" and "neurotic/reactive" (p. 1195). According to Fountoulakis et al (2004) "it has been estimated that 198 different opinions on classification and nomenclature have been proposed" for depression (p. 5367).

Since the 19th century, there has been an echo of a dichotomy between distinctive types of affective illnesses captured in the contrast between 'neurasthenia' and 'melancholia'. The former conceptualization popularized by American electrotherapist Beard (1869) shortly after expanded from the mainstay concept of 'tired nerves' to represent garden-variety depression and anxiety (Tredgold, 1933, as cited in Shorter, 2007). Ballet (1911) contended there was melancholia, typified by motor and intellectual slowing and by 'a painful feeling of powerlessness that explains the sadness.' Yet, simultaneously, acknowledging that neurasthenia existed as well "a quite different phenomenon including pain, fatigue, and hypochondriac anxiety. Melancholia came on episodically; neurasthenia was more chronic" (Ballet, 1911, as cited in Shorter, 2007).

The influential works of classical nosologist Kraepelin (1899) still remains prominent today in the DSM. Kraepelin proposed the existence of Manic Depressive Illness (MDI), which was inclusive of all forms of melancholia, psychotic depression,

and serious depressive and manic illnesses indicating a philosophy of a unitary model of depression (Shorter, 2007).

However, Shorter points out a misinterpretation of Kraepelin's work and consequently, how his name has erroneously been associated with 'one depression' (p. 7). Specifically, Kraepelin in his writings mentioned 'psychogenic depression' which did not correspond to a 'simple depression,' the milder form of MDI. He made marked comparisons in symptomatology between MDI and psychogenic depression (e.g., unlike MDI it was responsive to changes in the patient's social situation, paucity of speech and anxious tension might have suggested a circular depression) suggesting that "in cases of this kind one will not be able to interpret the symptoms correctly without knowledge of the patient's history" (Kraepelin, 1913, as cited in Shorter, 2007, p.7). Shorter concludes that "Kraepelin's psychogenic depression, therefore, marks a reinforcement of the melancholic-non-melancholic distinction, one almost entirely ignored by historians of nosology" (p.7).

Some characterize the argument as beginning in 1926, when British psychiatrist Mapother wrote in support of the unitary model of depression and concluded that there only exists a single form of depression, which varies in terms of severity. He further challenged the binary model, arguing that "psychotic" and "neurotic" depression represent two points on a continuum as opposed to two distinct types (Boyce & Hadzi-Pavlovic, 1996).

This debate continued in Britain through the 1960s, but was largely academic (Parker, 2000). A parallel debate in North America gained momentum in the 1970s. In 1971, and in support of the binary model, Klerman noted that with increasing use of

antidepressants, many clinicians observed that patients with "the endogenous symptom patterns respond better to somatic therapies…than do psychoneurotic patients" (Klerman, as cited in Parker, 2000, p. 1196).

Klerman continued to be adamant that the unitary model of depression was incorrect, and, he worked extensively to prove his point in support of the concept of "endogenous" depression, despite results of his tests that were mixed. He deemed the status of endogenous "unsettled," constituting either "a well-defined group, clearly separated from other groups, or merely an issue of gradation on multiple dimensions" (Klerman, as cited in Parker, 2000, p. 1196).[4]

According to Parker, in retrospect three [practical] issues impede a resolution of the "unitary/binary debate" (p. 1196). First, dualism fails to consider that there is almost invariably a third alternative of some type. Research using cluster analyses produced heterogeneous groups with considerable comorbid features among depressed patients. However, statistical approaches to discerning different types of depression were not looked upon favorably and few such studies were replicated.

A second issue, which still continues, lies in the disparate profiles that emerge from research conducted in different settings with different population samples. The prevalence of different features of depression varies tremendously depending upon whether the subjects are drawn from the community, general practice, psychiatric

[4] Theoretically, Klerman's position was grounded in phenomenological and treatment response differences. The phenomenological distinction lay in the inability of individuals with "endogenomorphic" depression to feel pleasure, or what Klerman labeled an "inhibited pleasure mechanism" (p. 1196). In terms of treatment response, Klerman proposed that patients with melancholia would experience a delayed but superior reaction to TCAs while the same drugs would have minimal effect on those with "chronic neurotic depression" (p. 1196). Both groups would have minimal responses to a placebo.

inpatient or outpatient facilities, and other clinical settings including those that specialize in working with patients with treatment-resistant depression.

The third issue, which Parker considers the most basic, is the classification system itself. The most viable method for distinguishing "types" is on the basis of unique characteristics. Most of the "endogeneity systems" traditionally explored, to discern between melancholic and non-melancholic depression, are common across depressive types. Differences in prevalence are largely attributable to differences in depressive symptom severity. The greater severity of melancholic depression in general (a point widely accepted) would mean that those with melancholic depression are more likely to appraise common symptoms as more severe.

Parker argues that it is not possible to differentiate between "true" melancholic and non-melancholic subtypes on the basis of a severity index, given that core DSM-IV criteria for melancholic depression include loss of pleasure in virtually all activities, lack of response to pleasurable stimuli, pronounced psychomotor disturbance, as well as slowness of movement (APA, 2000). These symptoms "are virtually ubiquitous in clinical samples of significantly depressed patients," in contrast to the perspective that they are unique features of melancholia (Parker, 2000, p. 1197). In reviewing research on melancholia, Brown (2007) reiterates this point: "Most patients meeting qualitative criteria for melancholia are likely to be judged 'severe' according to rating scale scores and about half of severely depressed patients meet criteria for melancholia" (p. 126).

Furthermore, this overlap between severity and melancholia confounds understanding of treatment responses. Severely depressed patients show equivalent if not

superior responses to antidepressants, analogous to patients with melancholia.[5] Overall, findings indicate that subtype or symptom pattern rather than symptom severity influences treatment response (Fountoulakis et al., 2000; Malhi et al., 2005; Matza et al., 2003; Parker, 2000).

1. The Limitations of DSM-IV Criteria

The DSM-IV and its predecessors have described psychiatric disorders largely as syndromes (i.e., clusters of signs and symptoms). Although this approach was once well received, there has been a marked shift in recent decades in how the research community perceives the DSM. What was once thought of as a great step forward for its provision of operationalized diagnostic categories and a crucial tool for the study of mental disorders, criticism over the DSM has become more prevalent in its impact on research and pedagogy.

For instance, Keltner (2000) contends:

> Psychiatric diagnoses are imprecise and that imprecision flows from the current diagnostic criteria. Essentially, psychiatric conditions are viewed, reported, and studied from a syndromal perspective…..This relative "softness" contrasts with more pathophysiological-based diagnostic criteria used by our medical-surgical colleagues. (p.31)

Similarly, in their review of the current status of neuroimaging findings in the depression literature, Gotlib and Hamiltion (2008) strongly conclude that:

[5] Brown (2000) notes that while some early studies suggested that patients with more severe depression responded better to TCAs than SSRIs, other studies dispute that claim.

Above all, they underscore the fact that, “depression” refers to a heterogeneous group of disorders that are not carved at their neurobiological joints in the DSM-IV. Perhaps the most pressing task for future research, therefore, is to begin more explicitly to conceptualize depression subtypes and symptom profiles that are related systematically to specific neural functional and structural abnormalities…. (p.162)

Shorter (2007) comments on the existence of “other nosological guideposts that physicians in the past have relied upon in sorting out illnesses,” however, these have played a less significant role in the classification of depression over the past 40 yeas. He adds “we will not call them depression ‘subtypes’ because they are diseases as distinct as mumps and measles” (p. 7).

Taylor and Vaidya (2005) argue that reliance on DSM-IV criteria is an impediment to the practice of neuropsychiatry. Central to neuropsychiatry is the use of evaluation techniques that “extend beyond traditional psychiatric assessments and integrate concepts of brain driving the behavior” (p. 246). Neuropsychiatry also entails knowledge of certain neurological phenomena that are not included in the DSM checklist.

One aspect of DSM-IV that Taylor and Vaidya (2005) consider especially limiting is the fact that the “DSM does not consider patterns of features, but rather the number of features” (p. 247). A patient who exhibits a requisite number of clinical features is typically diagnosed as having a given disorder. However:

> The combination of features, their characteristic onset, the relationships among different patterns, the context in which the symptoms unfold is rarely addressed. Although the duration of a syndrome in days, weeks or months is a typical requirement to aid reliability, the more difficult assessment of the quality of

> symptoms onsets, the sequence of symptom appearances, and patterns is not incorporated. (p. 247)

To improve the classification of depression for the purpose of driving treatment, Parker (2000) calls for research contrasting findings derived from DSM-IV, ICD-10, and "categorical paradigm models into etiological and treatment outcome studies," with the ultimate goal of developing and operationalizing "an empirically driven diagnostic paradigm" (p. 1202).

2. Issues Related To The Accurate Diagnosis Of Atypical Depression

In the broadest sense, AD has referred to any depressive disorder that does not exhibit the classic signs of endogenous depression. According to Parker et al. (2002), the concept of "atypical depression" has three curious attributes: 1) the use of the term "atypical" to qualify it, 2) the mixture of personality and clinical features, and 3) the implications for treatment specificity (p. 1470).

Fountoulakis et al. (1999,2000, 2004) note that initially, the term "atypical depression" was used to denote patients whose depressive symptoms were resistant to treatment with TCAs but responded well to MAOIs. However, they concede that the "international literature is full of conflicting results, which complicates efforts to interpret and compare findings across studies" (p. 219). Ironically, "What seems to survive is worse than expected response of atypical depression to imipramine but not a favorable response to MAOIs" (p. 431, Fountoulakis et al., 1999).

Initial reports of West and Dally (1959) in London found that the MAOI Iproniazid appeared to be working for patients with "somewhat atypical states, somewhat

resembling anxiety hysteria with secondary depression" (p.1491) who previously failed to respond to TCAs and electroconvulsive therapy (ECT). They turned their attention to attributes distinguishing responders and non-responders to MAOIs. Responders had less guilt, were less predisposed to awakening early or feeling worse in the morning, responded poorly to ECT, had more phobias and panic in their histories, and were prone to feeling shaky or fatigued. However, West and Dally did not identify current DSM-IV atypical features of hypersomnia or hyperphagia. In general, the clinical manifestations departed from the features of endogenous depression (West & Dally, 1959; Sargant, 1961)

Other members of the "London group" built on the concept, systematically highlighting the superior response to MAOIs but diverging in their descriptions of atypical features (e.g., Parker et al., 2002; Sargant & Dally, 1962), producing heterogeneous samples in most earlier studies. Eventually diagnostic guidelines were developed distinguishing features of endogenous and atypical depressions. Such features included "psychic and somatic anxiety, somatic complaints, long-standing phobias, and hysterical personality style, and pain" which were far less common in endogenous depression (Parker et al., 2002, p. 1471). Since the term was introduced, AD has varied in its use to denote depression with characteristics of non-endogenous depression, anxiety state, reversed vegetative symptoms, chronic pain, bipolar disorder, and rejection sensitivity (Davidson, 2007).

Since the initial reports of West and Dally, several studies have demonstrated a relatively good response to MAOIs in AD and a poorer response to TCAs (e.g., Bieleski & Friedel, 1976; Davidson, Miller, & Turnbull, 1982; Joyce & Paykel, 1989; Liebowitz

et al., 1984, 1988; Quitkin, Rifkin, & Klein, 1979; Quitkin et al., 1988; Quitkin et al., 1993; Sargant, 1961).

The most widely used definition of AD was established by the Columbia University Research group (e.g., Liebowitz et al., 1984, 1988; Quitkin et al., 1988; Quitkin et al., 1990;Quitkin et al., 1993). In the first attempt to operationalize diagnostic criteria for AD, Liebowitz et al (1984) stated that " To validate a concept of a specifically MAOI-responsive depressive subtype, both MAOI efficacy and relative tricyclic unresponsiveness must be shown" (p.22). Referring to methodological limitations of the earlier studies (e.g., variations in diagnostic criteria, inadequate dosing), the Columbia group conducted a series of clinical trials. Overall, studies (using Columbia criteria) identified a greater response rate to a MAOI compared to a TCA (71% versus 50%, respectively) and a placebo response rate of 28%. This pattern of response was replicated in two additional studies. Patients that were unresponsive to placebo were reassigned to receive a MAOI or TCA. Results indicated a superior clinical response to MAOI (63% versus 35%, respectively). Similarly, non-responders to medication at 6 weeks were crossed-over in a double-blind design which further confirmed the preferential response of a MAOI over TCA (67% versus 41%, respectively). In terms of the predictive value of atypical features, one study found that the presence of the associated criterion features of AD predicted a selective response to MAOIs, while another study indicated that no one single feature was more predictive than any other. The group concluded that at least if one associated feature is present along side mood reactivity, then a MAOI is therapeutically superior to TCAs (Liebowitz et al., 1984, 1988; Quitkin et al.,1979, 1988, 1989 1990, 1991, 1993; McGrath et al., 1993).

Results of these studies have been pivotal to the inclusion of AD into the DSM-IV defined as MDD with atypical features. The Columbia criteria were adopted by the DSM-IV. Core criteria for AD are mood reactivity (criterion A) and at least two of the following (criterion B): 1) significant weight gain or appetite increase, 2) hypersomnia, 3) feelings of heaviness in the arms or legs, and 4) an enduring pattern of hypersensitivity to interpersonal rejection as defined by the Columbia group (APA, 2000).

However, the efficacy of MAOIs relative to TCAs in AD have produced conflicted findings (Fountoulakis et al.,1999, 2000, 2004). Some studies have not demonstrated a differential response between MAOIs and TCAs. For example, in an overview of pre-1980 studies, Davidson and Colleagues concluded that "while the 'London group' found MAOIs more effective than TCAs for AD, later studies showed class equivalence, a shift perhaps reflecting overenthusiastic early claims, insufficient doses of TCAs, or differing side effect profiles." Moreover, they point out that difficulties in data interpretation have largely been due to variable definitions of AD and variable comparator groups (p.1472 as cited in Parker et al. 2002).

Paykel and Colleagues (1982) using 4 definitions of AD found no differences between responders to TCAs and MAOIs. Further, Paykel states "…but the evidence that atypical depression in its current meaning is associated with good response to MAOI response is mainly limited to a single, very active US research group. Other evidence would point to anxious or phobic patients; but in general selectivity appears to be weak, and there is evidence that MAO inhibitors in a high enough dose are effective in quite a range of depressives" (p.98. Paykel, 2002).

Kayser et al (1988) examined response to phenelzine and amitryptline in 169 patients using structured symptom-based inventories. Analyses were conducted on the basis of both depressive subtypes (melancholic, non-melancholic, MDD, minor depression and AD and [symptom groups] depressive, somatic, anxiety, interpersonal sensitivity). In symptom-based analysis phenelzine was superior to amitryptline (phobic anxiety, general anxiety, interpersonal sensitivity symptoms) accounting for a significant overall superiority of phenelzine after 6 weeks of treatment. In contrast, response was statistically equivalent when patients were grouped by pre-defined subtypes including AD.

Davidson, Giller, Zisook, & Helms (1991) used a regression analysis to find predictors of response to MAOIs in a double-blind study of a MAOI versus placebo. Results identified interpersonal rejection sensitivity as predictive of clinical response to the MAOI, however, reversed vegetative symptoms were not found to be predictive. Treatment x predictor effects were found for distinct quality of mood and non-reactivity. The latter symptom was associated with a positive outcome in both study groups, however, the effect was significantly enhanced in the treatment group. Similarly, preserved mood reactivity also resulted in improvement compared to placebo. In light of these findings, Rosenberg, Davanzo, and Gershon (2002) suggest that a plausible explanation may be that “atypical symptoms predict a negative response to tricyclic agents, rather than a strong positive response to MAOIs” (p.326).

In further support of the findings by Davidson et al. the methodologically well-designed STAR*D study found no significant difference in treatment response to a

MAOI among any of the depressive groups including the AD group (McGrath et al., 2006).

Patients with AD are reported to differ in clinical and demographic features such as sex, psychiatric and medical comorbidity, and course of illness. Most studies report a greater preponderance of AD in females (2:1), however, some studies do not always support the sex split (Novick et al., 2005). Prevalence rates based on epidemiologic studies have varied depending on the criteria used. The ECA study found AD in 15.7% of person's with MDD using truncated criteria (2 of 4 symptoms). In the general population AD is reported to be between 0.7% to 4.0%. Among clinical populations, rates have ranged between 22% to 46% (McGrath et al. 2001; Novick et al. 2005).

In applying their own research findings to a review of studies exploring the validity of AD, Stewart et al. (2007) concluded that DSM-IV criteria for depression with atypical features delineates a valid albeit heterogeneous disorder. Based on their work, they propose certain changes to make diagnosis more concise. First, they propose reducing the requisite number of features in criterion B from two to one (Columbia group definition). Second, they recommend including early onset and very chronic illness as requisite features. Third, they favor retaining both significant mood reactivity and the absence of melancholic features.

Controversy over criteria of AD is not new, and differing perspectives over relevant criteria have existed for over 50 years in various forms and continue to persist. The inclusion of the atypical feature specifier in the DSM-IV has been controversial for several reasons: a) limitations of earlier pharmacological data (methodological

problems); b) lack of consistency in definitions and prevalence of AD; and c) varying demographic and clinical features identified.

Commonly, researchers have questioned the validity and reliability of mood reactivity (absent from earlier case studies) as a mandatory symptom for diagnosis (e.g., Angst et al., 2002; Benazzi 2002b; Henkel et al. 2004; Nierenberg et al. 1998 Parker et al. 2002, 2000), the number of requisite symptoms (five to two) and type (e.g. fatigue, appetite/sleep disturbance inclusive of both increased and decreased sleep and appetite) for a diagnosis (Angst et al., 2006; Benazzi, 2002a; Matza et al, 2003; Quitkin et al., 1990; Silverstein et al. 1999), the absence of anxiety, panic disorder and social phobia in current criteria (originally found by West and Dally, 1959), and the relevance of weight gain and hypersomnia (Parker et al., 2002). Some researchers have tried to further clarify the aforementioned issues pertaining to a diagnosis of AD.

Since there is a lack of consensus on the requirement for mood reactivity for AD, Sotsky and Simmens (1999) investigated the importance of mood reactivity and other related features as essential characteristics of AD using data from the NIMH Treatment of Depression Collaborative Research Program, a 16-week clinical trial. The objective was to assess whether the presence of atypical features predicts reduced responsiveness to a TCA and which features were of predictive value to the definition of AD. 3 definitions of AD: (1) mood reactivity plus hyperphagia, weight gain, or hypersomnia; (2) atypical vegetative symptoms and non-reactive mood; and (3) mood reactivity with associated features (hypersomnia, hyperphagia, weight gain, diurnal mood variation, fatigue or hostility) were applied. Findings showed that the presence of mood reactivity primarily predicted non-responsiveness to the TCA compared to placebo for the AD subgroup

(25.2%; mood reactivity plus one reverse vegetative symptom).[6] Sotsky and Simmens concluded that the inclusion of mood reactivity and the requirement of one additional symptom of either hypersomnia, hyperphagia, or weight gain, supports the inclusion of AD features, with these criteria, in the DSM-IV.

Parker et al (2002), in a reappraisal of AD hypothesized that if mood reactivity [to identify AD] is a mandatory symptom, prevalence of ancillary symptoms should be greater when mood reactivity is present than when absent. In Parker et al's study, validity of DSM-IV criteria for AD was evaluated by examining the occurrence of each individual symptom. Results failed to confirm strong internal consistency among the five clinical features of the DSM-IV atypical features specifier for a MDE. Moreover, mood reactivity did not demonstrate any specificity in relation to any of the four (criterion B) associated symptoms or the number of such symptoms as found by Sotsky and Simmens. Rather, weak associations were identified between interpersonal rejection sensitivity and hypersomnia, and between weight gain and leaden paralysis.

Based on their remodeling of the five AD features, the authors suggested that the DSM-IV symptom criteria set for AD should be reformulated to present AD as a spectrum disorder. Specifically, primacy should be given to the personality style descriptor of interpersonal rejection hypersensitivity and lifetime anxiety disorders (social phobia and panic disorder), higher-order determinants of AD unlike mood reactivity. In addition, they proposed that hyperphagia and hypersomnia may have adaptive homeostatic potential as previously suggested (e.g., Thase, Frank, Kornestien, &

[6] Results for the second definition were non-significant. Additional symptoms features of diurnal mood variation, leaden paralysis, and rejection sensitivity did not further differentiate an imipramine non-responsive subgroup. In contrast, imipramine did demonstrate significant effectiveness compared to placebo in a group on non-ADs.

Yonkers, 2000, as cited in Parker et al., 2002), therefore, they are not necessarily indicative of pathological symptoms. One consequence of hypersensitivity may be an increase in susceptibility to developing depression in response to life stressors, in turn, a response to this may be overeating and oversleeping as a compensatory mechanism.

Matza et al. (2003) used data from the NCS to investigate the features characteristic of AD. The analysis was limited to respondents who met DSM-III-R criteria for MDD the prior year and who never had a psychiatric disorder. Based on responses to specific questions, 304 respondents (36.4% of the depressed sample and 39% when weighted to reflect the general population) were identified as having AD. The assessment was based on "reverse vegetative symptoms," approach which other studies have found to be effective in defining a group with AD characteristics (e.g., early age onset, comorbid anxiety) without mood reactivity as central. Hypersomnia and appetite increase or weight gain, which are opposite to the insomnia and appetite loss routinely reported in individuals with melancholic depression were used in the study (p. 818). Hypersomnia was assessed on the basis of excessive sleep every day for a period of at least two weeks, and hyperphagia on the basis of increased appetite lasting at least weeks or a period marked by a weight gain of two pounds a week or 10 pounds total.

Respondents who experienced a MDE but did not meet the designated criteria for AD comprised the non-atypical comparison group. This group was composed of 532 relatively heterogeneous individuals in terms of depressive symptoms. Slightly more than half (53.1%) had melancholic features of awakening unusually early and weight loss. The remaining subjects were classified as possible atypical (overeating or over-sleeping; 7.8%), possible melancholic (undereating or undersleeping; 10.3%), mixed

(overeating/undersleeping or oversleeping/undereating; 26.7%), and non-vegetative (no vegetative symptoms, 2.2%).

Based on their analysis, Matza et al. concluded that individuals with AD represent a distinct group. Characteristics of this group included a higher proportion of women, earlier age of onset of depression, and a higher rate of attempted suicide. All these attributes are consistent with the cumulative body of research (e.g., Parker et al., 2002; Stewart et al., 2007).

In terms of comorbidity, the AD group exhibited relatively high concurrence of panic disorder, social phobia, and drug abuse. Compared to the non-atypical group, atypical individuals were more prone to suicidal thoughts, experienced more days of disability and restricted activity, and had higher probability of using antidepressants and visiting hospital emergency rooms for mental health concerns. They were also less likely to be married, which Matza et al. propose may reflect the combined effects of excessive mood reactivity and sensitivity to rejection. In the STAR*D study, being female was a positive predictor of remission but having a higher number of concurrent psychiatric and medical conditions, lower psychosocial functioning, and being single or living alone had the reverse effect on remission (Huynh & McIntyre, 2008).

In view of their findings, Matza et al. challenge the idea that AD is a “minor or mild form of depression” (p. 822). Rather, the manifestations can be severe in some cases and can have even more serious consequences than other forms of depression. That AD can be both distinct *and* severe directly contradicts the unitary model of depression. Certain background characteristics were also associated with AD specifically significantly higher rates of paternal depression (with a non-significant trend for mothers)

and childhood neglect and sexual abuse, along with a near significant trend for physical abuse. The high prevalence of childhood trauma led the researchers to speculate that some cases of AD represent a form of traumatic stress that differs qualitatively from post-traumatic stress disorder (PTSD). Depression is very common in individuals with PTSD and there is substantial overlap between DSM-IV criteria for depression and PTSD (APA, 2000).

Angst et al. (2007) examined AD and melancholia in the Zurich study using a sub-sample of 591 participants. The study was initiated in 1978 and six waves of interviews were conducted from 1979-1999. In addition to self-reported assessments, psychiatric disorders were drawn from algorithms based on DSM-III, DSM-III-R, and DSM-IV criteria depending upon the disorder. ICD-10 criteria were used to define neurasthenia. DSM-IV-TR criteria for melancholia and DSM-IV criteria were utilized to classify major depression, yielding four subgroups: 1) a “combined group” comprised of participants who were diagnosed with melancholia or AD at different interviews; 2) pure melancholia; 3) pure AD; and 4) unspecified MDE, without atypical and/or melancholic features.

Based on cumulative data, 4.1% of the sample was classified as combined, 7.1% as pure melancholic, 3.5% as atypical, and 8.2% as unspecified MDE (Angst et al., 2007). The most striking finding emerged from the longitudinal analysis. Over two decades, a sizable proportion (55% of 107 cases) of individuals displayed symptoms of melancholia and AD independently at different interviews. Angst et al. noted that this phenomenon was reported by two other studies. The combined group ranked as the most severe on measures of symptoms, treatment visits, and number of drugs prescribed. At

the same time they were quite similar to those with pure melancholia in terms of distress, days depressed, and chronicity. The unspecified group tended to have the least severe symptoms and 42% had only a single episode of depression.

As with other studies, a disproportionate number of women suffered from AD. In the Zurich study, this effect was especially pronounced in the combined group and AD group. An unexpected finding was that the gender difference in pure melancholia was small; men were only slightly over-represented. However, Angst et al. noted that the Danish University Antidepressant Group study had a similar balance. While participants with melancholic and AD were similar on several measures (socio-demographic profiles, self-esteem, quality of life, comorbidity, body mass index, and illness course), those with AD had higher scores on certain personality indicators, specifically aggression, neuroticism, impulsivity, and depressivity.

Due to the severity of depression observed in the combined group, Angst et al. call for greater research into this group. They also claim that their findings of the fluctuation of high proportion of individuals between atypical and melancholic depression calls into question cross-sectional findings on differences between the two.

In describing similarities between participants classified into different groups, Angst et al. emphasize that their study did not investigate treatment response. This research into AD highlights that the most popular assessment tools used in clinical trials of antidepressants, namely the HAM-D and the MADRS, focus mainly on the symptoms of melancholic depression but may fail to capture atypical features (Matza et al., 2003; Murck, 2003).

Demitrack (2005) comments that given the varied symptom profiles of patient's, symptom measurement is one of the crucial factors to be addressed in assessing symptom change in response to treatment interventions for MDD. Further, the HAM-D has been frequently criticized for being developed to assess symptom improvement with melancholic symptoms with the expectation of treatment with a sedating effect (based on response to TCAs at the time). Consequently, 3 of the 17 items on the scale assess sleep and grade positively for patterns of increased sleep duration and improved sleep continuity. In contrast, SSRIs are commonly associated with insomnia or sleep disruption, thus, may tend to score negatively on sleep items.

Dematrack states:

> The problem presented here is that any one scale may be constructed in a manner to favorably detect a treatment signal for a specific pharmacologic profile and clinical presentation (i.e., melancholic depression treated with tricyclic antidepressants), but appear to suggest a more modest treatment effect if used to assess symptom change in patients with slightly different clinical presentation treated with an agent having a novel pharmacologic profile (i.e., atypical depression treated with an SSRI.)(p.230)

As an alternative, Matza et al. (2003) propose the Inventory of Depressive Symptomology (IDS), which contains items addressing both atypical and melancholic features.

a. Biological Basis of Atypical Depression

In an attempt to validate AD as a distinct depressive subtype, some researchers have provided preliminary evidence for biologic differences in AD compared to non-AD. Levitan, Vaccarino, Brown, & Kennedy (2002) evaluated low-dose dexamethasone in females with AD and without AD to evaluate plasma cortisol levels in an effort to discern the relationship between AD and hypothalamo-pituitary- adrenal (HPA) axis function (see Appendix B for overview of HPA-axis). Findings indicated a reduced morning cortisol secretion of 92% in females with AD, compared to a 78% reduction in control subjects. As these results are opposite to those found in melancholic depression, the authors suggested that AD represents a biologically distinct form of depression. Further, this "super suppression" of cortisol in AD is similar to the profile of those with PTSD. Histories of childhood trauma are common in individuals with AD, leading to the proposal that some cases of AD may be a type of traumatic stress reaction but with different symptoms than PTSD (Matza et al., 2003).

Further evidence to suggest hyposecretion of corticotrophin-releasing hormone (CRH) in AD comes from studies on Cushings syndrome (CS) in which CRH levels are reported to be decreased (Gold, Licino, Wong, & Chrousos, 1995). As CS is associated with high rates of AD rather than melancholic depression, it may be a result of CRH hyposecretion. In pre-clinical animal models, hyposecretion is found to induce a hypoactive stress response characterized by hypersomnia, hyperphagia, irritability and social anxiety, characteristic of AD and CS (Gold et al., 1995). In addition, hyposecretion of CRH has been documented in seasonal affective disorder (Vanderpool et al., 1991 as cited in Gold et al. 1995), chronic fatigue syndrome (Demitrack et al.,

1991, as cited in Gold et al. 1995), and bulimia (Levitan et al., 1997, as cited in Gold et al. 1995), all of which are associated with higher rates of AD.

In neuroscientific investigations, recent research using PET and SPECT to examine brain activity has discerned differences according to symptom patterns, generating resurgence of the historical debate over appropriate classification of depressive disorders. Neurobiological differences have been observed in patients with atypical and non-atypical depression (Pagani et al., 2007). Fountoulakis et al. (2004) used SPECT to investigate distinctions between subtypes of major depression in a study involving 50 adults (aged 21-60 years) diagnosed with major depression on the basis of DSM-IV criteria. Analyses revealed that 82% of the participants had abnormal SPECT profiles. Across subtypes, the most consistent occurrence was a global brain hypoperfusion that did not include the frontal lobes. The most striking finding was that participants with AD showed a relative enhancement of the frontal lobe perfusion, contrasting with a relative decrease in the same area in those who were melancholic or classified as “undifferentiated.” This was reversed for the right occipital lobe.

According to Fountoulakis et al. these observations supported the historical theory that there are two distinct subtypes of depression, each with unique underlying pathology. Furthermore, the results provided visual evidence that AD, the subtype most congruent with the conception of “neurotic” depression and thought to be psychological in nature, is rooted in a neurobiological abnormality.

Pagani et al. (2007) focused on AD in an application of SPECT to the study of 23 outpatients with chronic MDD. Of the 23 patients, 11 met DSM-IV criteria for AD, while 12 did not meet criteria for AD (non-atypical group). The control group was comprised of

23 healthy volunteers. Voxel-based analysis showed significant reductions in tracer uptake in large areas of the frontal lobe and portions of the right parietal associative cortex in subjects with non-atypical depression compared to the healthy control group. Compared to subjects with non-atypical depression, those with AD had higher tracer uptake in the right hemisphere (involved in mood reactivity), the supplementary motor area involved in movement, the posterior frontal associative cortex, the somatosensory cortex, the parietal association cortex in the superior parietal lobule, and the multimodal association cortex.

The composite effect helps explain the mood reactivity central to diagnostic criteria for AD. The involvement of brain areas involved in motor and sensory motor activity would relate to the "leaden paralysis" present in all the atypical subjects (Pagani et al., 2007, p. 117). Pagani et al. concede that some of their results diverge from other studies, attributing this to different populations, symptom profiles, and modes of analysis.

b. Depressive Syndromes Similar to Atypical Depression

Syndromes thought to be similar to AD and/or sharing overlapping symptoms although not recognized officially by the DSM-IV have existed for several centuries now. Based on endocrine similarities, it has been hypothesized that AD may be related to disorders of somatic complaints without medical explanation (Murck, 2003). For instance, neurasthenia as proposed by Beard was a common disorder, particularly among women during the 19th century. Predominant symptoms involve a multitude of anxiety-related and somatic symptoms (e.g., heaviness of the limbs, chronic fatigue, lethargy, exhaustion, headaches, irritability, backaches, insomnia and depression) (Akiskal & Cassano, 1997; Perlick & Silverstein, 1994). Some of these symptoms overlap with those

in AD. Merikangas and Angst (1994), reported an association of neurasthenia with irritability and sensitivity to criticism, similar to that of AD. In addition, somatoform symptoms (e.g., headaches) were also frequent. However, neurasthenia is currently classified in the ICD-10, but not DSM-IV (Murk, 2003; Merikangas & Angst, 1994).

Similar to neurasthenia, the rubric of neurotic depression, still a popular diagnostic concept in Europe proposed by Kielholz (1982), was replaced in the DSM-III (APA, 1980) by dysthymic disorder. Key symptoms and descriptors are described as: somatic complaints, initial insomnia, mood reactivity, irritability, manipulative behavior, hostility, unhappiness, other-blaming, histrionic attitude and self-dramatization, (Klein, 1974; Roth & Montjoy, 1997).

A large body of evidence on endocrine similarities (e.g., reduced HPA axis function) supports the idea that AD may be associated with disorders of somatic complaints (e.g., CFS, somatization disorder). CFS, synonymously used with the term neurasthenia is characterized by symptoms such as muscle pain, headaches, unrefreshing sleep and sore throat. Hypersomnia in AD is thought to be phenomenological and etiologically related to the fatigue and “unfreshing” sleep seen in CFS. Further leaden paralysis as defined in AD is thought to be related to the muscle pain evidenced in CFS. Similar to AD, previous studies have reported higher tracer uptake in medial and upper frontal regions in patients with CFS in comparison to other depressed patients. Overall, epidemiological studies show an increased rate of depression in patients with CFS (Murck, 2003).

While studies have given considerable attention to the current criteria for AD, they have been limited in their scope. For instance, studies have been conducted to

determine what symptoms should or should not be mandatory (e.g., mood reactivity), or whether other course of illness specifiers should be added, but they have not investigated the need to expand criteria with additional symptoms. Significant is the fact that findings from early case reports have been the guiding force behind the research underlying AD. However, symptoms such as weight loss, insomnia, somatic-over-reactivity, and fatigue mentioned in these reports (e.g., Sargant, 1962; West & Dally, 1959) are currently omitted from the DSM-IV criteria. In addition, the studies included in the research review that lead to the criteria for AD also mentioned symptoms of insomnia and pain which are also absent (Quitkin, Rifkin, & Klein, 1979).

Somatization disorder is commonly reported to be comorbid with affective disorders (ranges from 30-84%). It's relation to AD is implied by the finding that 79% of patients with chronic pain exhibit a depressive disorder with approximately one-third of them having AD (Davidson, Krishnan, France, & Pelton, 1985). Moreover, patients with AD are reported to fulfill the criteria for somatization significantly more than those with typical features (Howarth et al, 1992). Further, comorbidity of AD is reported with body image disturbances, disordered eating (Angst, Gamma,Sellaro, Zhang, & Merikangas, 2002), and insomnia (Silverstein, Cohen, & Kasen, 2006). Currently, these are sometimes conceptualized under the heading of *atypical depression spectrum disorder*, a category that also includes somatic disorders that defy medical explanation such as CFS and fibromyalgia (Murck, 2003). Somatic complaints are extremely common in AD.

c. Somatic Depression

In a series of studies, Silverstein and Colleagues have suggested the existence of two different subtypes of depression. First, somatic depression (SD) is characterized by elevated levels of depression accompanied by a number of somatic symptoms including breathing difficulties, headaches, fatigue, body-image distortions, protracted periods involving trouble falling asleep, fatigue and eating problems (e.g., binging, purging, and intentional food restriction) (Silverstein et al., 1998; Silverstein et al., 2006). In contrast, "Pure" depression is depression unaccompanied by significant amounts of these symptoms.

Like AD, females exhibit a greater prevalence of SD than males. Analyses of several databases (e.g., ECA, NCS, The Children in the Community study) have shown that the gender difference in the prevalence of depression occurs because women exhibit higher rates of SD versus men, but not much more pure depression. For example, in two studies looking at the depressive criteria, SD was defined as people exhibiting all three depressive criteria of appetite disturbance, sleep disturbance, and fatigue and pure depression was defined as those who did not exhibit these criteria. Respondents reporting SD, show a large gender difference in prevalence whereas respondents reporting depression without all three of these symptoms exhibit little gender difference in prevalence (Silverstein et al., 1999; Silverstein, 2002). Other measures that were not from the depressive criteria (e.g., reports of body aches and anxiety) were strongly correlated with SD.

Another difference between the two subtypes emerge from psychosocial measures of gender roles. That is, women who report issues related to psychosocial measures

related to limitations inherent within gender roles tend to have SD but not pure depression. One good example of this finding was in a study of female high school students and their mothers. The mothers' reports of attitudes toward their own gender roles predicted the daughters' report of somatic, but not pure depression. In contrast, the mothers' self-reports of depression was shown to predict the daughters' reports of pure, but not somatic, depression.

Taken together, these findings imply two separate diseases, pure depression, perhaps associated with a more genetic component, and SD, which may be significantly influenced by psychosocial factors involving gender roles (Silverstein et al., 1993; Silverstein et al., 1995; Silverstein & Blumenthal, 1997; Silverstein & Lynch, 1998; Silverstein & Perlick, 1995).

The symptom criteria for SD overlap with those of AD. Of significance is that appetite, sleep disturbances and fatigue are common to both AD and SD. However, it should be noted that some symptoms either do not overlap at all, or the ones that do may not be entirely identical in both disorders:

(1) SD does not include the mandatory feature of mood reactivity required by the DSM-IV.

(2) Criteria for AD are short of the somatic symptom: breathing difficulty, headaches, and body image disturbance.

(3) Similar somatic symptoms differ in the way they are defined. Symptoms of AD (e.g., hypersomnia, hyperphagia, leaden paralysis) are present during a MDE. In comparison, sleep, eating disturbances, and fatigue in SD are not restricted to a MDE. Further, these symptoms are described in SD as being both reversed (increased) and typical (decreased), whereas AD is restricted to reversed vegetative symptoms.

Based on the overlap of symptoms between AD and SD, Silverstein and Colleagues hypothesized that a definition of a depressive subtype (SD) that has its origins in gender and gender roles research and a definition of a depressive subtype (AD) that originates from research on response to antidepressants may be two aspects of one larger distinct disorder. As such, they contend that the current DSM-IV criteria for AD are too narrowly defined and should be expanded to include symptoms of SD.

In an initial attempt at testing whether a set of criteria made up of a combination of the symptoms of SD and AD may better define a distinct disorder than the current criteria used for AD, re-analyses of data from The Children in the Community Study found a robust relationship between symptoms of AD and SD. Specifically, 68% of respondents with AD reported fear of fat vs. 36% without AD; 42% of respondents with AD reported taking at least 30 minutes to fall asleep (insomnia) vs. 21% without AD; and 47% with AD reported headaches/stomachaches vs. 12% without AD. Overall, 58% of respondents with AD reported at least two somatic symptoms that are currently not included in the DSM-IV criteria but are included in criteria for SD.

An important finding was that the proportion of respondents reporting loss of appetite during depression did not significantly differ between the two groups (26% vs. 25%), nor did reports of insomnia during a depressive episode (63% vs. 43%). Silverstein and Colleagues suggest that the items traditionally used to index non-AD vegetative symptoms related to appetite and sleep problems during a depressive episode do not effectively distinguish AD respondents from others. However, appetite and sleep items indicative of disordered eating and chronic trouble falling asleep do (Silverstein et al., 2006).

In a recent study, the extent to which the criteria for AD discriminated males and females were compared to criteria that combined symptoms of AD and SD using data from the Zurich Study of a representative sample of people living in the Swiss canton of Zurich {Silverstein, unpublished data). Respondents were divided into five groups: (1) those who did not meet criteria for depression; (2) those who met criteria for depression but did not meet criteria for either AD or SD; (3) those who met criteria for AD but not SD; (4) those who met criteria for SD but not AD; and (5) those who met criteria for both SD and AD.

Results weighted back to the original population indicated that both SD and AD showed significant gender differences. As shown in Table 1, it is of interest that the data indicates that respondents who met criteria for SD alone were overwhelmingly female (6%) than males (2%). In contrast, those who met criteria for AD alone showed no difference in gender (0%), and those who met criteria for both AD and SD actually had a slightly smaller difference in gender (5%), thus no more likely to be female than those who met criteria for SD alone. These results suggest that the gender difference in depressive prevalence is almost entirely explained by SD alone and not to AD (Silverstein and Angst in preparation, unpublished data).

Table 1
Gender Differences in the Prevalence of Depression in a Representative Sample of The Canton of Zurich

Non-Depressed		**Depressed**			
Somatic		No	No	Yes	Yes
Atypical		No	Yes	No	Yes
Male	79%	17%	1%	2%	1%
Female	68%	18%	1%	6%	6%
Female-Male	11%	1%	0%	4%	5%

Collectively, these studies based on gender differences in the prevalence of depression provide preliminary evidence that the current criteria for AD need to be reconsidered. The current criteria for AD include only the vegetative symptoms of hypersomnia related to sleep and hyperphagia related to eating, whereas SD criteria in addition to these symptoms also include insomnia and symptoms of anorexia. Given that the gender difference in depressive prevalence as found by Silverstein and Colleagues is almost entirely due to SD alone and not to AD, there is a chance that there could be better criteria to delineate a distinctive non-endogenous subtype of depression. As both AD and SD are similar and therefore are reasonable possibilities for a non-endogenous subtype of depression, a comparison of AD criteria with that of SD criteria could be a better way to define a distinctive subtype of depression. A more compelling study to investigate this, however, would not use gender as the standard for deciding which set of criteria better define a distinct subtype of depression, but instead the tool of pharmacologic dissection, the very area of research from which the current criteria for AD were derived. Reasonably strong support for defining a non-endogenous depressive subtype would be

derived if SD criteria better predict response to antidepressants than do the current criteria for AD.

If it can be concluded from such a study that criteria for SD better predict poorer response to antidepressants than does current DSM-IV criteria for AD, this finding would suggest that it is better to include the symptom of lack of appetite and insomnia (currently symptoms of SD) than being restricted to the current AD symptoms of hyperphagia and hypersomnia.

If this assumption is correct , the very results that led to the development and acceptance of AD are much stronger for SD reflected in a poorer response to a TCA antidepressant, it may be fair to conclude that SD is a better criteria set, reflective of a distinct type of non-endogenous depression Moreover, if items such as lack of appetite/anorexia belong to current criteria for non-endogenous depression, this finding would have implications for reviewing current criteria for endogneous- melancholic depression. Specifically, melancholic depression criteria include the symptom of lack of appetite/anorexia, which raises the question of how can a form of non-endogenous depression (AD) and a form of endogneous depression (melancholia) both include the symptom of lack of appetite/anorexia.

C. Issues Related to the Accurate Diagnosis of Melancholic Depression

Current research in neurobiology has renewed the debate over DSM criteria but the issue is not a novel phenomenon. Although there is general agreement in the field to support the existence of an endogenous depression that constitutes a distinct subtype, there is disagreement related to the validity of criteria, and, therefore, to successful treatment. Since the main purpose of defining a depressive subtype is to understand

underlying pathophysiology as well as to inform successful treatment decisions, it becomes imperative to resolve this crisis of definition.

Historically the term "melancholia" has subsumed several names such as "endogenous depression" (Roth, 1959), "endogenomorphic depression" (Klein, 1974) "vital depression" (VanPraag, et al., 1959), and "retarded depression" (Overall et al., 1966). Initially, the term was synonymous with what today is termed depression. Even today there is substantive research (Parker 2000) which reflects melancholic depression as virtually synonymous with severe depression. It is interesting to note here that Brown (2007) conducted a review of research on melancholic patients and their responses to different treatments, which emphasized that severe depression and melancholic depression are related but not identical. He further emphasized that a majority of patients who meet qualitative criteria for melancholia will probably be classified as "severe" according to rating scale scores and roughly half of severely depressed patients meet criteria for melancholic depression.[7]

The most up-to-date classifications of "melancholia" are provided by: 1) the APA, which identifies melancholia as a melancholic feature specifier, and 2) the WHO, which identifies melancholia as somatic syndrome.

To meet DSM-IV criteria for melancholic features specifier, core criteria of *either* loss of pleasure in all, or almost all, activities *or* lack of reactivity to usually pleasurable stimuli (criterion A) must be met, and at least three of the following (criterion B): 1) distinct quality of mood, 2) depression regularly worse in the morning, 3) early morning

[7] And, as well, the association between depressive symptom severity and treatment response has generated much more research attention than the association between melancholic depression and treatment response.

awakening (at least two hours before usual time of awakening, 4) marked psychomotor retardation or agitation, 5) significant anorexia or weight loss, and 6) excessive or inappropriate guilt (APA, 2000).

Over the years, the different definitions of endogenous depression/melancholia have been evaluated in numerous studies, which have tested the definitions for their association with numerous correlated factors, including: stressful life events, personality disorders, familial transmission of recurrent unipolar depression, and treatment response to antidepressants. However, as Khan et al (2006) point out, the validity of several of the earlier studies are questionable due to the utilization of significantly differing factors/criteria (e.g., Feinberg and Carroll, Research Diagnostic Criteria [RDC], Newcastle Scale, DSM-III, Autonomous Depression). These included: small sample sizes and not controlling for severity of depression. Similarly, the prevalence rate of melancholic depression has varied between 20%-80% depending on the source of the sample (Taylor & Fink, 2008). Consequently, the symptom pattern of melancholic and non-melancholic depression continues to be a matter of debate.

Treatment is, therefore, also a matter of debate. For instance, the broad DSM-II definition of "endogenous depression," or melancholia, facilitated prediction of response to treatment (Parker, 2000). However, a controversy arose several years after the publication of DSM-III when Zimmerman and colleagues observed that paradoxically, "all published studies examining the relationship between DSM-III melancholic subtyping and response to antidepressant medications or ECT were negative" (Zimmerman et al., as cited in Parker, 2000, p. 1197). The problem was resolved by the elimination of two problematic descriptors, as well as the inclusion of three non-symptom

criteria deemed to capture some of the clinical attributes of melancholia. The problematic descriptors were: 1) excessive or inappropriate guilt, and 2) distinct quality. The three non-symptom criteria included were: 1) no significant premorbid personality disturbance, 2) previous episodes followed by recovery, and 3) previous good response to antidepressant drugs and ECT (p. 1197). According to Parker (2000), the last item related to previous treatment responses "would clearly improve treatment prediction, and although scientifically valid, it is a pseudoprofound criterion" (p. 1197).

Despite this research, which seemed to resolve important aspects of the debate, DSM-IV continues to use basically the same criteria for melancholic depression as DSM-III, classifying it as a "feature specifier," rather than a distinct disease. The result is that "DSM-III and DSM-IV criteria sets have failed to generate any consistent neurobiological findings or to demonstrate any treatment specificity for DSM-distinguished melancholic and non-melancholic depression" (p. 1197).

Prior to the addition of melancholia as a separate subtype (DSM-III,1980), Klein (1974) described "neurotic depression" as a "chronic emotional or personality disorder related to low self-esteem, overly severe disappointment reactions, feelings of helplessness…" He compared this with melancholic depression, characterized by a loss of interest or pleasure, anorexia, suicidal preoccupation, retardation or agitation. Furthermore, he characterized melancholia as "endogenomorphic" depression (i.e. having the form or appearance of endogenous depression). Klein held that the true key feature of endogenous depression is persistent and severe anhedonia, thought to be due to inhibition of the brain's "pleasure mechanism" (p.488).

More recently, Parker (2000) argues that the best way to demarcate melancholic and non-melancholic depression is on the basis of features that are unique to one type. Parker, and others who share his position, contend that psychomotor disturbance meets this criterion, and it is a particularly advantageous feature, as it is a highly observable phenomenon. Parker notes that psychomotor disturbance was a feature of ancient Greek and Roman depictions of melancholia and is present in description of melancholia "across cultures and races," which "attests to its clinical utility" (p. 1197). The prospective value of psychomotor disturbance for assessing melancholic depression led Parker and his colleagues to develop the Clinical Outcomes Routine Evaluation (CORE) instrument, which Joyce et al. (2003) deem superior to DSM-IV.

Building on the study of Parker, Joyce et al. found that age and gender were key factors in responses to different classes of antidepressants by patients with melancholic depression. In a sample comprised of 191 patients, 113 were classified as melancholic. Nortriptyline (TCA) produced far superior results for melancholic patients aged 40 and older, particularly men. In contrast, fluoxetine (SSRI) was substantially more effective for melancholic patients aged 18-24, particularly women.

Because there is only partial overlap between the DSM-IV and CORE definitions of melancholia, Joyce et al. repeated their analysis utilizing DSM-IV criteria. A discrepancy emerged in the response rates depending upon the assessment used. The impact of age on medication effect was much stronger using the CORE definition. A prior study by Joyce and colleagues also found that melancholia defined by CORE but not DSM-IV criteria was linked with activation of the HPA axis, a finding also reported by Mitchell and colleagues. Based on the composite results, Joyce et al. propose that "the

CORE system" may be advantageous compared to DSM-IV for defining melancholia, "perhaps reflecting its focus on observable psychomotor disturbance" (p. 22).

In comparison to other assessments such as the DSM-IV and the Newcastle scales, CORE scores have proved superior in distinguishing melancholic depression across a spectrum of assumptions associated with melancholia including illness variables (such as older age of onset), psychosocial risk factors (such as lower prevalence of personality disorders, less exposure to childhood neglect or trauma), neuropsychological testing (higher incidence of cognitive processing problems), and treatment response.

Coryell (2007) concurs with Parker's conception that psychomotor disturbance is the observable marker of an "underlying neuropathological process" (p. 1198). He observes that there has been little attention given to examining the relative value of the Newcastle scale, the RDC, or DSM-III, DSM-III-R, and DSM-IV criteria for distinguishing melancholia. He attributes this to a dearth of efforts to compare definitions, and in some part, to the absence of widely recognized validators, emanating from vagueness in the traditional perspective of melancholia as "biological" in origin, and non-melancholic depression as a mix of personal and environmental factors.

This status of research events is especially troubling given that as early as 1970 clinicians observed that patients with melancholic depression responded better to antidepressants than neurotic/reactive patients, particularly TCAs (Bielski & Friedel, 1976; Kiloh, Ball, & Garside, 1962; Liebowitz et al.,1984; Raskin & Crook, 1976) and the theory underlying the observed phenomenon was that "melancholia is more 'biological' than non-melancholic depression and should thus require, or respond particularly well to a 'biological' treatment" (Brown, 2007, p. 125). Additionally, while

some early research comparing responses of patients with “endogenous” and “neurotic” depression supported that presupposition, the disparities in treatment response were small and were not consistently found.[8]

Coryel (2007) provides important clarification to the debate supporting Parker’s emphasis on psychomotor disturbance as an indicator of neuropathological activity, proposing that:

> A biological abnormality with specificity for depressive disorder would have particular value for the refinement of melancholic definitions given the historical presumption of a biological genesis. The abnormal escape of plasma cortisol from suppression by dexamethasone attracted considerable interest as just as much an abnormality and the number of studies that resulted in the 1980s allows for comparisons across definitions. (p. 32)

As in other areas of depression research, methodological disparities precluded comparison across studies**.** Coryell (2007) observed substantial variations of the dexamethasone test (DST) results across studies utilizing the same definition of melancholia, suggesting that factors such as differences in samples and possible differences in the way researchers apply the same criteria account for the contrasting results. Carroll (1981) initially proposed the DST test as a biological marker for the presence of melancholia when tests on normals indicated a suppression of cortisol, whereas non-suppression was found in melancholic patients, which suggested HPA-axis dysfunction. Later he commented on the high specificity of the test for melancholia “Our

[8] When SSRIs became a viable treatment option, patients with melancholic depression, especially older adults, responded less favorably to SSRIs than to TCAs.

results give unequivocal support to the view that melancholia is a categorically distinct entity from non-endogenous depression" (Carroll, 1982, p. 298). This line of research was generated by evidence that more than half of patients with melancholia have increased HPA activity and it is definitely more common in melancholic than non-melancholic depression (Brown, 2002). However, the DST as a diagnostic measure has been controversial due to negative and positive findings reported. Abnormal DST response has varied between 35%-60% in melancholic individuals (e.g., Rush et al., 1997, as cited in Leventhal et al., 2005). Other studies have failed to find differences between patients with high and low DST scores on measures associated with different types of depression such as dysphoria, anxiety, irritability, and initial insomnia. In contrast, other investigators have found no correlation between a diagnosis of melancholic depression and DST non-suppression (Leventhal et al. 2005). Brown (2007) concluded that while promising, the composite finding has been that there are no practical differences between suppressors and non-suppressors in terms of rate or extent of response to treatment.

The presence of a personality disorder, negative life events, and "serious" suicide attempts are generally accepted as being associated with non-melancholic, but not melancholic depression (Coryell, 2007; Kessing, 2007). However, these three factors elude precise definition. At the present time, the most reliable indicators are that individuals who meet accepted definitions of melancholia have lower probability of responding to a placebo, environmental changes, and psychotherapy. Indeed, the cumulative body of research on the treatment of patients who have been diagnosed with melancholic depression, confirms that these patients respond poorly to placebo and

psychotherapy (Brown, 2007), and further confirms that they do tend to respond to ECT and antidepressant drugs. Conversely, those with non-melancholic depression "often respond poorly to ECT and the tricyclics" (Shorter, 2008, p. 8)[9]

Zimmerman et al. (1986) have suggested adding features to the melancholic construct. Based on a literature review and an empirical examination of 152 patients with unipolar MDD, they found the following features to be relevant: lower prevalence of divorce/separations; fewer stressful life events; older age; better social support; less cognitive distortion; lower probability of premorbid personality disorder; higher frequency of neuroendocrine or other biologic abnormalities; higher scores on symptom severity indexes; and better response to somatic therapies.

Additionally, in a recent study by the STAR*D group investigating the clinical and demographic factors associated with DSM-IV melancholic depression, the authors concluded that among outpatients with MDD, melancholic features were less prominent in Hispanic patients; more likely in slightly younger patients, particularly in men; and associated with slightly shorter current episode. They summarize that their findings are consistent with the perception that external-socio-demographic factors do not play a significant role in the pathophysiology of melancholic depression (Khan et al., 2006).

[9] Brown emphasizes that these are conclusions drawn from *aggregate* data. The results of STAR*D (and indeed the design itself) highlight the wide variation in responses to different antidepressant drugs by patients with similar symptom patterns but different individual characteristics (Rush et al., 2006, 2008). No significant differences were found between treatment groups in their response to a TCAs (Fava et al., 2006).

According to Nelson and Charney (1980), as quoted in Shorter (2007), the symptoms of melancholic depression vary to the point that they lack much value as criteria:

> In 1980, Craig Nelson and Dennis Charney at Yale commented on the 'non-specific' nature of major depression: 'The signs and symptoms of a major depressive episode appear to define a heterogeneous group that may be further divided into those patients having an autonomous depression or melancholia and those who are responsive to environmental stimuli.' The following year, in 1981, Max Fink found the new DSM categories 'of limited usefulness in selecting a therapy for a depressed individual.' (p. 10)

Two large independent reviews of many factor analytical studies of endogenous symptoms, which reported similar findings, questioned the inclusion of some of the symptoms currently used to define melancholic depression (Nelson & Charney, 1981; Parker, Hadzi-Pavlovic, & Boyce, 1989). As indicated in Table 2 below, whereas most symptoms currently included in criteria for melancholia were found in studies to load highly on a single endogenous factor, vegetative symptoms including insomnia (and early morning awakening) as well as decreased appetite and eating disturbances, although with a positive loading, did not load highly on the endogenous factor. The symptom of weight loss produced conflicted findings between the two reviews. The relative weaker loading of symptoms in the category of sleep and appetite disturbance are supported by the hypotheses of Silverstein and Colleagues that maybe these items which are also in criteria for SD and strongly related to AD should be reconsidered for melancholic depression.

As reported previously, Silverstein and Colleagues found that the proportion of respondents reporting loss of appetite during depression did not significantly differ between the AD and non-AD groups (26% vs. 25%, respectively), nor did reports of insomnia during a depressive episode (63% vs. 43%, respectively). Silverstein and Colleagues suggest that the items traditionally used to index non-AD vegetative symptoms related to appetite and sleep problems during a depressive episode do not effectively distinguish AD respondents from others. However, appetite and sleep items indicative of disordered eating and chronic trouble falling asleep do (Silverstein et al., 2006). Unfortunately, despite the powerful quantitative evidence from the studies reviewed in Table 2, criticisms have largely been ignored when creating criteria for DSM-IV. As a result, it is fair to conclude that it is appropriate to call for a wholesale redefinition of melancholic depressive criteria. One way to test if there is a better definition for melancholic depression would be to use items that better discriminate sleep and appetite.

Table 2
Number of Factor Analytical Studies Where Symptoms Loaded > .40 on Endogenous Factor

Symptom	**Number of Studies**	**Loading** + ≥.40	**(%)**
Retardation	12	12	100
Lack of reactivity	10	9	90
Distinct Quality	9	8	89
Loss of interest	8	6	75
Guilt	14	9	64
Morning worsening	9	5	56
Early Morning awakening	13	4	31
Weight Loss	10	2	20
Difficult Falling asleep**	10	0	0

American Journal of Psychiatry, 1981

In conclusion, if in fact there is any indication to change criteria for AD and melancholic depression, to further strengthen this hypothesis would be to use a second measure in addition to pharmacologic dissection. One area of interest would be to use a neuropsychological predictor of depressive subtypes.

D. Neuropsychological Predictors of Depressive Subtype

Despite the assertion that cognitive measures are thought to index the integrity of brain functioning in particular areas, relatively few studies have examined the relationship between cognitive functioning and depressive subtype. Initial baseline identification through performance on cognitive tasks may provide insight into which areas are impaired relative to healthy individuals, and increase knowledge of the underlying neuropathophysiology of depression as well as inform treatment decisions.

One area of research that has attracted the interest of researchers is using the cognitive tool of perceptual asymmetry (PA) to further demarcate depressive subtypes. Generally, it has been suggested that right-hemisphere disorganization characterizes patients with unipolar depression (e.g., Paykel, 1982; Wexler, 1980). However, study findings continue to be contradictory in the depression literature. Some researchers propose that depressed patients exhibit more deficits in visuo-spatial than verbal tasks, implying right hemisphere dysfunction. However this hypothesis has only received limited support (Richards & Ruff, 1989; Silberman & Weingartner, 1986; Robertson & Taylor, 1985).

1. *Dichotic Listening Tasks*

Cerebral lateralization has frequently been used as a biological marker for several psychiatric disorders. PA (ear advantage/hemi-spatial bias) is a measure of preferential response to one cerebral hemisphere over another during dichotic listening or visual tasks. Auditory processing tasks typically involve the use of different stimuli (e.g., verbal and nonverbal stimuli). Similar but distinct stimuli are delivered simultaneously to the left and right ears. Differences in accuracy for which sounds or words are processed by each ear provide a measure of PA. As auditory information is processed contralaterally, PA favoring one ear as evidenced by more accurate reporting is indicative of the corresponding hemisphere being more actively engaged in the specific task. Healthy subjects tend to process nonverbal dichotic stimuli (musical tones, clicks) predominantly in the left ear (right hemisphere advantage), whereas, depressed subjects tend to exhibit a left hemisphere “shift,” reflecting right hemisphere dysfunction (Bruder et al., 1989).

Bruder et al. (1989) examined the influence of diagnostic subtype of depression on PA for a dichotic listening task. Subjects were administered two auditory tasks (verbal/nonverbal): (1) Consonant-Vowel (CV) discrimination task and; (2) Complex tone test. In the CV syllable task, subjects were presented simultaneously a different syllable to each ear and required to report the two syllables per trial. On the complex tone test, subjects were required to compare the pitch of a binaural complex tone to the pitches of a dichotic pair of complex tones presented 1 s earlier. Subjects responded "yes" when the probe tone was the same as either member of the dichotic pair or "no" when it differed from both.

Subject groups included an AD group, melancholic depression, and a normal control group. Analysis of asymmetry differences indicated a significant difference between the AD, melancholic and control groups on the dichotic CV syllable and complex tone tasks. As expected, the control group demonstrated a right-ear (left-hemisphere) advantage for the CV syllable task and a left-ear (right-hemisphere) advantage for complex tones. No significant difference in ear asymmetry was found between the AD and control group on both tasks. In contrast, melancholic depressives differed significantly from AD and control subjects demonstrating an abnormal right-ear advantage (poor left ear processing) for CV syllables when compared to either AD or controls, and a right-ear advantage for complex tones, opposite to that evidenced in controls. The authors noted that AD females had a high incidence of left-handedness compared to controls, and all melancholic females were right-handed. Further, analysis indicated that handedness did not account for the between-group differences in

asymmetry, rather, central nervous system disturbances and right hemisphere function vary with diagnostic subtypes.

2. *Affective Visual Stimuli*

Studies investigating perceptual processing of visuo-spatial stimuli have typically used affective faces. Perceptual processing of visuo-spatial stimuli in normals is frequently reported to show a left-visual field (i.e., right-hemisphere) advantage for the perception of both faces and facial affect. The Chimeric Faces Test (CFT: Heller & Levy,1981;Levy, Heller, Banich, and Burton, 1983) which is a free-vision chimeric face perception task has been used to investigate emotional processing in normal healthy participants. Findings have shown a highly significant lateralizing effect in normals. Stimuli are pairs of non-congruent chimeric faces in which one half of a poser's face is smiling, while the other half of the face consists of a neutral expression from the same poser. Two chimeric faces, an original and the mirror image is randomly positioned above or below on a single sheet of paper. Subjects are required to make an emotional judgment as to which face of each pair "looks happier". Favoring one side of the face as happier has been interpreted as increased activation of the contralateral side of the brain. A negative PA laterality quotient (LQ) score indicates a preference for right hemisphere processing. In contrast, an LQ of zero means that the smiles both on the left and right side are chosen equally.

A number of studies have shown that most right-handed individuals (approximately 75%) are reported to demonstrate a hemi-spatial bias for the face as happier on the left, indicative of a right parietotemporal advantage for processing facial and/or emotional content. This suggests that in most right-handers, the right side of the

brain is more adept at recognizing faces and emotional faces in expression and when activated, attention is biased toward the left side of space. Levy, Heller, Banich, and Burton (1983) in a sample of 111 normal right-handed subjects found a strong tendency to perceive the chimeric face with the smile on the left hemi-space as happier (mean laterality quotient -.28). Left-handers also showed a significant leftward bias on the CFT but to a significantly lesser degree (mean laterality quotient -.14) than in right-handers (Levy et al., 1983).

Given the evidence of left-hemisphere bias in normals for the perception of emotional stimuli as well as the relative ease of task administration, the CFT is a valuable measure for examining lateralization effects in clinical populations. Moreover, as depression is reported to be associated with cognitive deficits particularly sustained effort and attention (Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982), the minimal influence of these factors in performance on the CFT make it an ideal tool to use in this population.

In clinical populations deficits in the perception of faces has been associated with right hemisphere damage but results have varied. For instance, some studies have shown that people exhibiting depression and anxiety show opposing biases on the CFT. For example, depression is found to be more associated with decreased right hemisphere bias, whereas, anxiety with increased right hemisphere bias (Heller, Etienne, & Miller, 1995). Keller et al (2000) reported similar findings with the exception that participants in their study who did meet criteria for a MDE did not differ from healthy controls in their right hemisphere bias. Therefore, although there is support for reduced right parietotemporal

bias when perceiving emotional chimeric faces in depression, this is not evident in all patients.

Some researchers have hypothesized that in cases of comorbid anxiety, the effects of depression may be neutralized, resulting in normal parietal asymmetry, thus explaining the inconsistent findings in the depression literature (Heller & Nitschke, 1998). One study in support of this contention comes from electrophysiological measures. EEG obtained from depressed adults and adolescents having a comorbid anxiety disorder did not demonstrate reduced parietal activation. However, the opposite was true for those having "pure" MDD (Bruder et al., 1997). An alternative explanation has been that some subtypes of depression such as AD may not display evidence of right parietal hypoactivation. For instance, Heller (1993) proposed a right parietotemporal system hypothesized to be involved in the arousal component of emotion and regulation of autonomic activity. Because AD patients are characterized by the ability to have preserved pleasure capacity, mood reactivity, and rejection sensitivity, such symptoms may enhance activation of the right parietotemporal system during processing of emotional faces compared to patients have typical or melancholic depression (Heller, 1993 as cited in Bruder et al., 2002).

To date, only one study has assessed hemi-spatial bias for perceiving emotional chimeric faces between AD and melancholic depression. As PA differentiated AD and melancholic subtypes in the auditory domain, Bruder et al. (2002) predicted that this difference in lateralization would also apply to the visual domain using the CFT. Study outpatients were recruited from both the New York State Psychiatric Hospital and Connecticut Mental Health Center. Patient groups included in the study were AD

(Columbia Criteria), typical depression with or without melancholic features (DSM-IV criteria), dysthymic disorder (DSM-IV), and anxious depression assessed by meeting criteria for an anxiety disorder (DSM-IV).

As predicted, results indicated that the percentage of patients having a right hemisphere bias differed among the groups. Patients with AD were considerably more likely than healthy controls and typical depressives to report the left-sided smile to be happier (86% vs. 70% vs. 60%, respectively). However, no significant difference was found between the typical depressives and healthy controls. Moreover, despite the small sample of patients who met criteria for MDD with melancholic features (N=9), they demonstrated essentially no right hemisphere bias. Less than half of the patients (44%) had a negative asymmetry score, indicative of right hemisphere bias. No significant differences were found for depression with and without comorbid anxiety.

Overall, the findings in PA on the CFT among depressed patients are similar to those seen on the dichotic listening tests by Bruder et al. One main difference is that the AD group demonstrated greater right hemisphere bias than healthy controls on the CFT but did not differ significantly from controls on measures of dichotic listening. The authors suggest that this finding may be attributed to modality specificity of PA. Furthermore, the CFT differs from the dichotic listening tasks in its emotional and cognitive content. The selection of the face that looks happier involves both emotional and spatial processes not active during dichotic listening tasks (Bruder et al., 2002).

Collectively, the studies presented in this section are a further testament to the existence of distinct subtypes of depression that have differing underlying pathologies as indicated by differences in measures of PA in the auditory and visual domain.

E. Purpose of Study

The purpose of the three studies described herein was to examine whether both melancholic and non-melancholic depression may better define two distinct depressive subtypes than do current DSM-IV criteria sets. Specifically, the purpose of *Study one* was to examine whether criteria for SD would be a stronger predictor of treatment response to antidepressant medication than are currently-defined DSM-IV criteria of AD. *Study two* tests whether criteria for melancholic depression would better predict response to antidepressant medication if modifications were made in the eating and sleep criteria. Studies one and two were conducted via a secondary data analysis using the STAR*D study methodology.

The purpose of *Study three* was to compliment study one and two with cognitive data by examining whether the difference between performance on the CFT of probands with AD and melancholic depression as currently defined in the DSM-IV is strengthened when comparing SD with melancholic depression using the modifications defined in study two.

F. Study Hypotheses Testing

Study one hypothesis is based on the conclusion of several studies that indicate a relatively good response to MAOIs and poor response to TCAs in AD.

Predictor Hypothesis Study 1:

Poor response to a tricyclic antidepressant, and possibly good response to MAOI, will be better predicted by meeting criteria for Somatic Depression that includes both reversed and typical vegetative symptoms of appetite and sleep disturbance than by meeting criteria for Atypical Depression.

Predictor Hypothesis Study 2:

Good response to a tricyclic antidepressant, will be better predicted by meeting criteria for Melancholic Depression that eliminates the appetite or sleep criteria for respondents who meet the sleep or appetite criteria for Somatic Depression than by meeting current criteria for Melancholic Depression.

In addition to using the measure of pharmacologic dissection in study one and two, findings for changing criteria sets would be strengthened by using a different measure. *Study three* used the cognitive measure of perceptual asymmetry (PA) to test whether a measure of PA discriminated less well between disorders defined using current criteria sets for AD and Melancholic Depression than between disorders defined using the criteria for SD and modified criteria for Melancholic Depression.

Predictor Hypothesis Study 3:

The difference reported by Bruder et al (2002) between performance on the CFT of probands with Atypical and Melancholic Depression will be strengthened with use of the new operational criteria for Melancholic Depression compared to Somatic Depression.

III. Methods

A. Participants: Studies One and Two

The population and methods of STAR*D including enrollment, inclusion and exclusion criteria, and data collection are briefly summarized here as they relate to study one and two. For detailed description of STAR*D refer to Fava et al, 2003 and Rush et al, 2004 or www.star-d.org.

Participants for the clinical multi-centered STAR*D study seeking routine medical care were recruited from 23 psychiatric and 18 primary care settings in public and private sectors across the United States. Outpatients (male and female) 18-75 years of age, diagnosed with non-psychotic MDD as determined by a score of 14 or greater on the Hamilton Depression Rating Scale-17 Item (HAM-D_{17}) were eligible for study participation. Pre-screening established that 2876 were eligible for analysis. For a full description of baseline characteristics pertaining to various domains of the STAR*D study (demographic, social, and clinical), refer to Trivedi et al., 2006. Eligible participants for the present study were limited to those who were at baseline diagnosed as having MDD with or without atypical and/or melancholic features. A total of 107 patients receiving Nortriptyline (a tricyclic antidepressant) at treatment level three (refer to Table 5 for sub-sample demographic information) and a total of 43 patients receiving Tranylcpyromine (a MAOI antidepressant) at treatment level four (refer to Table 6 for sub-sample demographic information) were eligible for hypothesis testing. Inclusion and exclusion criteria for enrollment in STAR*D Study are given in Table 3 followed by general demographic information for all enrolled patients in Table 4.

Table 3
Inclusion and Exclusion Criteria for Participation in STAR*D Study

CRITERIA	METHOD OF ASCERTAINMENT
Inclusion	**Inclusion**
1. Age 18-75	1. Ask the patient (CRCs)
2. Meets criteria for DSM-IV nonpsychotic MDD	2. HAM-D_{17} rated by CRCs (score of $\geq$ 14)
3. Only patients seeking medical care or psychiatric outpatient treatment	3. Identified by CRCs or clinician
4. Signs informed consent and able to comply with study	4. By CRCs; Able to comply; Signature
5. 5. Patients with co-occurring psychiatric disorders.	5. Assessed by PDSQ
Exclusion	**Exclusion**
1. Person's with medical contraindications that precluded randomization to any treatment in levels 2 through 4.	1. Liason between CRCs and clinician
2. Pregnant women or those breast-feeding	2. Liaison between CRCs and clinician
3. Patients meeting DSM-IV diagnoses: schizophrenia; schizoaffective disorder; bipolar or psychotic disorder; primary diagnosis of anorexia nervosa, bulimia or obsessive compulsive disorder; substance dependence (inpatient detoxification required);	3. Liaison between CRCs and clinician
4. Clear history of intolerance (current MDE) to any protocol antidepressants in first two treatment levels	4. Liaison between CRCs and clinician

Note: CRC: clinical research coordinator

Table 4
Baseline Demographic Characteristics of 2,876 Outpatients with Non-psychotic Major Depressive Disorder

Characteristic	N	%	Mean	SD
Caucasian	2,180	75.8		
African American	506	17.6		
Hispanic	373	13.0		
Other	190	6.6		
Gender				
Male	1,043	36.3		
Female	1,833	63.7		
Age Group (years)				
18-30	754	26.2		
31-50	1,380	48.0		
≥50	741	25.8		
Age (years)			40.8	13.0
Education (years)			13.4	3.2

Adopted from Trvedi et al (2006)

Table 5
Baseline Demographic Characteristics of 106 Outpatients with Non-psychotic Major Depressive Disorder Receiving Nortriptyline at Treatment Level Three

Characteristic	%
Ethnicity	
African American	20
Hispanic	16
Asian	1
Gender	
Male	45
Female	55
Age Group (years)	
<20	1
20-29	8
30-39	21
40-49	25
50-59	21
60-69	7
>70	1

Table 6
Baseline Demographic Characteristics of 43 Outpatients with Non-psychotic Major Depressive Disorder Receiving Tranylcpyromine at Treatment Level Four

Characteristic	%
Ethnicity	
African American	16
Hispanic	12
Asian	0
Gender	
Male	39.5
Female	60.5
Age Group (years)	
20-29	14
30-39	9
40-49	30
50-59	46
60-69	9
>70	0

Instrumentation

Patient Characterization: For all patients, demographic, clinical, social and medical information was collected using a variety of measures at a baseline visit.

B. Mood and Psychiatric Rating Scales

Baseline and treatment outcome ratings for study one and two are summarized in Table 7.

Table 7
Flow Sheet of Relevant Mood and Psychiatric Rating Scales

Baseline
HAM-D-17 Item Total Score
IDS -C30 Item Score
PDSQ Selected Subscale Items
QIDS-C-16 Item Total Score
Treatment Outcome
HAM-D-17 Item Total Score (Primary measure of remission)
QIDS- C-16 Item Total Score (Secondary measure of remission)

1. Baseline Ratings (Pre-treatment)

a. Hamilton Depression Rating Scale-17 Item (HAM-D_{17})

The HAM-D (Hamilton, 1960) is a widely used observer-rater depressive symptom scale (Yonkers & Samson, 2000) with its total score as a measure of symptom severity. The 17-item checklist is used to characterize depressive symptomatology including vegetative, behavioral, cognitive and motivational symptoms. Symptom severity is quantified along scales from 0 to 4 or 0 to 2; higher numbers being indicative of greater severity. At baseline, patients clinically diagnosed with non-psychotic MDD had to meet an initial total score of $\geq$ 14 (moderate severity) as rated by a clinical research coordinator (CRC) to meet inclusion criteria.

b. Inventory of Depressive Symptomatology Clinician Rated (IDS-C_{30})

The IDS-C_{30} (Rush et al, 1996; Trivedi et al, 2004, as cited in Novick et al, 2005) has been widely used in diagnosing depression and is also available in a matched self-report (IDS-SR_{30}) format. The standard total score is obtained by summing the ratings of 28 of the 30 items. Either weight loss or weight gain, appetite loss or appetite gain is scored because only one member of each pair is applicable to any given respondent. Each of the 28 items is scored on a scale of 0 to 3 (0–the absence of pathology; 3–severe pathology). The total scores range from 0 to 84. Reliability of IDS-C_{30} scores has been compared and validated with scores using the clinician-rated Atypical Depression Diagnostic Scale (J.W.S; McGrath; Quitkin, unpublished data, 2004, as cited in Novick et al, 2005). In STAR*D, the IDS-C_{30} was used to identify which patients met criteria for MDD with atypical or melancholic features.

c. Quick Inventory of Depressive Symptomatology Self-Report /Clinician Rating 16 Item (QIDS-SR_{16}; QIDS-C_{16})

The QIDS is a brief 16-item symptom severity rating scale that was derived from the longer form (IDS-C_{30}). The scale assesses the nine diagnostic symptom domains of MDD and is available in matched clinician-rated (QIDS-C_{16}) and self-report (QIDS-SR_{16}) formats. The QIDS-SR_{16} and QIDS-C_{16}, as well as the longer 30-item versions, have been found to have highly acceptable psychometric properties and are treatment sensitive measures of symptom severity in depression (Trivedi et al, 2004). Initial baseline QIDS-SR_{16} and QIDS-C_{16} scores were obtained from patients to gauge depressive symptom severity. Thereon, both measures were administered at each treatment visit for each level

of treatment applicable (weeks 2, 4, 6, 9, 12) as part of the clinical decision support system for enhanced patient care and medication management.

d. Psychiatric Diagnostic Screening Questionnaire (PDSQ)

The PDSQ is a brief (Zimmerman, 2002) 126 item (yes/no questions) self-rated screening questionnaire for which patients rate the presence or absence of current and recent symptoms relevant to each of the most common Axis 1 major DSM-IV disorders presenting in outpatient settings (e.g., post-traumatic stress disorder, bulimia nervosa, somatization disorder, panic disorder, and hypochondrias among others). For study one and two, selected items on the PDSQ were used to determine which patients met criteria for Somatic depression and modified melancholic depression.

2. Treatment Outcome Measures

a. Hamilton Depression Rating Scale- 17 Item (HAM-D_{17})

The total HAM-D_{17} score at the last observed treatment visit per treatment level completed (scores collected at weeks 2, 4, 6, 9, 12) collected by research outcome assessors (ROA) was used as a primary outcome measure of treatment remission. Remission was defined as an exit score of ≤ 7. In the present study, the score obtained at the last treatment visit was used to assess remission at level three treatment exit for Nortriptyline (TCA) and at level four treatment exit for Tranylcpyromine (MAOI).

b. Quick Inventory of Depressive Symptomatology Clinician Rating 16 Item (QIDS-C16)

The QIDS-C_{16} score for the last observed treatment visit at each treatment level completed was utilized as a secondary outcome measure of treatment remission. Remission was defined as a score of ≤ 5 on the QIDS-C_{16}. QIDS-C_{16} scores were

collected at each clinic visit (weeks 2,4, 6, 9, 12). In the present study, the score obtained at the last treatment visit was used to assess remission at level three treatment exit for Nortriptyline (TCA) and at level four treatment exit for Tranylcpyromine (MAOI).

C. Operational Definition of Diagnostic Subtypes

1. DSM-IV Definition of Atypical Depression

Atypical depression was operationally defined by STAR*D using an algorithm applied to selected items of the IDS-C_{30} that addressed DSM-IV symptoms for depression with atypical features. The DSM-IV criteria for atypical features specifier is applied when these features predominate during the most recent 2 weeks of a current MDE in MDD or in Bipolar I or Bipolar II Disorder when a current MDE only is the most recent type of mood episode, or when these features predominate during the most recent 2 weeks of Dysthymic Disorder; if the MDE is not current, it applies if the feature predominates during any 2-week period.

The IDS-C_{30} items that most closely resembled DSM-IV criteria were chosen by consensus as indicated in Table 8.

Table 8
STAR*D Definition of Atypical Depression Matched with Items on the IDS-C_{30}

DSM-IV	**Related IDS-C30 Items**
Must have:	**Score 0,1, or 2** (0: highly mood reactive:3 highly non-mood-reactive)
(1) Mood reactivity (i.e., mood brightens in response to actual or potential positive events)	Reactivity of Mood responses: brightens only somewhat with few selected extremely desired events
Two or more of the following features:	**Score 2 or 3 on:**
(1) Significant weight gain or increase in appetite	Weight Gain: has gained 2 or more pounds; has gained 5 or more pounds **OR** Appetite Increase: regularly eats more often and/or greater amounts than usual; feels driven to overeat at and between meals
(2) Hypersomnia (oversleeping or spending more time in bed)	Sleeps no longer than 12 hours in a24 hour period (include naps); sleeps longer than 12 hours in a 24 hour period (include naps)
(3) Leaden paralysis (i.e., heavy, leaden feelings in arms or legs, or severe fatigue)	Feels physically weighted down(without physical energy) more than half of the time; feels physically weighted down (without physical energy) most of the time, several hours per day, several hours per week
	Score of 3
(4) Long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment	Often feels rejected, slighted, criticized, or hurt by others, but only that results in impaired social/ ccupational functioning

American Psychiatric Association. & American Psychiatric Association, DSM-IV, 2000.

2. Definition of Somatic Depression

Criteria for somatic depression was assessed by determining the presence or absence of required symptoms from patient responses obtained on the PDSQ at baseline. Specifically, items that most closely resembled criteria for SD were selected. To meet criteria, patients had to have symptoms in three (3) or more of the following categories: a. appetite (*either* binging, overeating, purging, intentional vomiting/food restriction (but credit not given for more than one symptom in this category); b. body image problems (unhappy with body shape). c. fatigue; d. breathing difficulties; e. sleep (trouble falling asleep); and f. headaches or pain. This method follows the identification of patients who meet criteria for somatic depression as defined by Silverstein and Colleagues. See Table 9 for corresponding somatic items on the PDSQ.

Table 9
Individual Symptoms of Somatic Depression Matched With Their Corresponding Items on the PDSQ

Symptoms of Somatic Depression	**Corresponding Items of the PDSQ**
Category	*During the Past two weeks:*
Eating	*One credit for one or more of the following*
Binging	Did you often go on binges during which you ate a large amount of food even when you didn't feel hungry? Did you feel that you could not control how much you were eating during an eating binge? Did you go on eating binges during which you ate so much that you felt uncomfortably full?
Purging	To prevent weight gain from an eating binge did you force yourself to vomit or use laxatives or Water pills?
Intentional Food Restriction	To prevent gaining weight from an eating binge did you go on strict diets or exercise excessively?
Body Issues	*One credit for:*
Desire to be Thinner	Was your weight, or the shape of your body, one of the most important things that affected your opinion of yourself?
Breathing	Did you get very scared because you were short of breath?
	During the Past 6 Months:
Trouble Falling Asleep	Did you often have problems falling asleep because you were worrying about things?
Pain	Have you been bothered by aches and pain in many different parts of the body?
Fatigue	Did you feel tired out on most days of the past 2 years?

D. Study Design

During the initial screening/pre-treatment (baseline) visit, participants were instructed on the risks, benefits, and potential adverse events associated with each treatment level. After patients provided written informed consent, an evaluation to obtain clinical and demographic information was conducted by CRCs using various instruments. A diagnosis of non-psychotic MDD was confirmed by a checklist based on DSM-IV criteria for which patients had to meet a score of $\geq$14 on the HAM-D_{17} at baseline for study inclusion. Further, the HAM-D_{17}, QIDS-C_{16}, and QIDS-SR_{16} were administered to assess for symptom severity. A 14-item Cumulative Illness Rating Scale (CIRS) was used to determine the severity/morbidity of general medical conditions relevant to different organ systems. A modified version of the PDSQ (Zimmerman, 2002) was completed at baseline to approximate the presence of 11 potential concurrent axis 1 (psychiatric) disorders. Eligible participants were registered for the telephone-based interactive voice response (IVR) system.

Within 72-hours of the baseline visit, trained ROAs by telephone interview obtained baseline scores on the: IDS-C_{30} to estimate the presence of atypical, melancholic, and anxious symptom features; the HAM-D_{17}; and the IPAQ (income questions). This same procedure is completed within 72 hours of each treatment level exit (30 minutes for IVR; 30 minutes for a telephone interview by the ROA). Participants who entered a 1-year naturalistic follow-up, applicable to all treatment levels, completed the aforementioned assessment package.

Overview of Protocol Treatment Procedures:

Patients were provided with a medication card for all study medications free of charge. In conjunction with self-reports of treatment side effects (side effect frequency, intensity, and burden) obtained at each clinic visit, a clinical procedures manual was used to assist in clinical decision-making with reference to: dosing levels (fixed vs. flexible); remission vs. response; intolerance to medication and entrance into the next treatment level. Depressive symptom severity over the previous week was assessed using the QIDS-SR16 and the QIDS-C16.

Overall, didactic instruction, clinical research coordinator support, and a centralized monitoring system with feedback were used to ensure that prompt dose increases were made as long as symptom reduction was inadequate and side effects were acceptable. Generally, dose adjustments were based on how long a patient had taken a specific dose, symptoms changes, and side effect burden. However, suitable flexibility was allowed (e.g., initiation of medication at a lower level or slower dose escalation to optimal target dose) to accommodate patients with GMCs, substance abuse/dependency and other psychiatric disorders for safety concerns.

The treatment protocol suggested that clinic visits take place at baseline and weeks 2, 4, 6, 9, and 12. When necessary, additional clinic visits could be scheduled if clinically determined. Treatment trials lasted for a duration of 12 weeks, however; participants could exit a trial due to intolerable side effects; remission maintained for 2 weeks; or if minimal symptoms reduction (QIDS-C16 total score >9) had occurred at 6 weeks at maximally tolerated doses. Participants who experienced symptom reduction ($\geq$ 50% in QIDS-C16 score at week 12) had the option of continuing treatment for 2

additional weeks to establish whether remission would occur with additional time. After an optimal treatment trial (based on dose and duration), remitters and responders could enter a 12-month naturalistic follow-up. However, all responders who did not achieve remission were encouraged to enter the subsequent randomized trial.

Following treatment level one, STAR*D utilized "equipoise-stratified randomization" as opposed to "forced randomization," whereby, patients' reported *a priori* what treatment option(s) they would be willing or not willing to accept in subsequent trials. Randomization to clinical trials was based on this information (for in-depth description of treatment protocol see Fava et al, 2003).

Treatment Levels:

Treatment levels relevant to the present study are described herein. However, it should be noted that at any given treatment level, the several treatment options available to patients are not described here (for a detailed description see Fava et al, 2003).

Level 3: Nortriptyline (NTP), a generic brand of TCA's (effects NE/5-HTP system) was one of two monotherapy options available to those study participants (N=107) who failed to achieve remission with two previous adequate trials with antidepressant therapy.

Level 4: Tranylcypromine (TCP) is a common MAOI used in the treatment of resistant depression as an alternative to ECT. Participants considered to have relatively high treatment resistant depression (48 weeks of illness during the protocol), with no remission at level one, two, or three were eligible to receive TCP (N= 43).

E. Statistical Analysis

The statistical analysis for study one was conducted using SPSS Version 15.0®. A 2 x 2 Chi-Square Cross-tabulation analysis with Yates Continuity Correction (or Fisher's Exact Test) was performed to test the study one hypothesis.

F. Results

Predictor Hypothesis Study 1: Poor response to a tricyclic antidepressant, and possibly good response to MAOI, will be better predicted by meeting criteria for Somatic Depression that includes both reversed and typical vegetative symptoms of appetite and sleep disturbance than by meeting criteria for Atypical Depression.

For hypothesis one, at level three, 15% of respondents met criteria for atypical depression while 61% of respondents met criteria for somatic depression. A Chi Square Cross-tabulation analysis was performed to discover any potential overlap between diagnostic groups. The analysis revealed that 8% of the total number of respondents (n =106) met criteria for both atypical and somatic depression. Specifically, 14% of all respondents with somatic depression (n = 64) also had atypical depression, whereas, 56% of all atypical depressives (n= 16) also met criteria for somatic depression. Of the total number of respondents at level three, 9% of respondents (n =10) also met criteria for both melancholic and somatic depression. Specifically, of all of the patients who met criteria for somatic depression (n =65), 15% also met criteria for melancholic depression.

As reported in Table 10, on the primary outcome measure of remission as assessed by the HAM- $D_{17,}$ 6.3% of the proportion of patients meeting DSM-IV criteria for atypical depression remitted on the TCA antidepressant medication in comparison to a 23.3% remission rate for the patients who did not meet criteria for atypical depression. A

2 x 2 Chi Square analyses revealed that this difference in remission rates when taking a TCA antidepressant medication is not significant, (P = .183; Fisher's Exact Test probability), suggesting that there was no relationship between depression subtype and treatment response to a TCA antidepressant medication.

However, although the results did not approach significance, when examining the data it is clear that they point to the predicted direction, that is, atypical depression showing a relatively poorer response to a TCA. A likely reason for the results not approaching significance is due to the limited sample size of patients meeting criteria for atypical depression. Although the STAR*D study began with a substantial number of eligible patients (N = 2876 of which 635 meet criteria for atypical depression), there were several treatment options that preceded level three (levels 1, 2A and 2B) during which time patients with atypical depression either remitted on another medication, exited the study or graduated to the follow-up phase of the study. As such, by the time the remaining patients reached level three and only those receiving nortryptline as their primary medication, the sample size decreased significantly with only 16 patients meeting criteria for atypical depression out of which only one patient remitted on the TCA antidepressant medication on the HAM-D_{17}. Had there been more patients at this level with atypical depression receiving the TCA, or if patients had first received a TCA at level one, it is likely that the results would reach significance resulting in a differential response to a TCA for atypical depression. In contrast, as reported below, patients with somatic depression did show a differential response to a TCA in the expected direction. However, of note is that in comparison to atypical depression, more patients met criteria

for somatic depression (N = 65) providing some support for somatic depression but not necessarily implying its superiority over atypical depression based on these results.

On the secondary outcome measure of remission as defined by a score of ≤ 5 on the QIDS-C_{16}, patients meeting DSM-IV criteria for atypical depression did not show the expected significant difference in remission rates to TCA medication compared to patients not meeting criteria for atypical depression, ($P = .739$; Fisher's Exact Test probability). As reported in Table 11, 25.0% of the proportion of patients meeting criteria for atypical depression remitted on the TCA antidepressant medication in comparison to a 20.0% remission rate for the proportion of patients who did not meet criteria for atypical depression, suggesting that there was no relationship between this depressive subtype and treatment response to a TCA antidepressant medication.

Table 10
Response to Nortriptyline (TCA) of Atypical Depression Patients Versus Non-Atypical Depression Patients on the HAM-D_{17}

Measure	**Atypical Depression**	**Non-Atypical Depression**
HAM-$D_{17} \leq 7$	1 (6.3 %)	21 (23.3%)
HAM-$D_{17} \geq 7$	15 (93.8%)	69 (76.7%)
		Total 106

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Table 11
Response to Nortriptyline (TCA) of Atypical Depression Patients Versus Non-Atypical Depression Patients on the QIDS-C_{16}

Measure	Atypical Depression	Non-Atypical Depression
QIDS-C_{16} ≤ 5	4 (25.0 %)	18 (20.0%)
QIDS-C_{16} ≥ 5	12 (75.0%)	72 (80.0%)
		Total 106

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Patients meeting criteria for somatic depression did not show the expected significant difference in remission rates on the HAM-D_{17} to the TCA antidepressant medication compared to patients not meeting criteria for somatic depression, χ^2 (1, N = 107) = .000, p = 1.000. As reported in Table 12, 20.0% of the proportion of patients with somatic depression remitted on a TCA antidepressant medication very close to 21.4% of patients who did not meet criteria for somatic depression. However, interestingly, on the secondary outcome measure of the QIDS-C_{16}, the difference in remission rates on the TCA antidepressant medication between patients meeting criteria for somatic depression relative to those patients not meeting criteria for somatic depression was of borderline significance on the χ^2 test, χ^2 (1, N = 107) = 3.584, p = .058, and significant on the more accurate Fisher's Exact Test (P = .049; Fisher's Exact Test probability). The p-value suggests a borderline significance in the predicted direction indicating that patients with somatic depression responded worse to a TCA antidepressant medication compared to those patients who did not meet criteria for somatic depression. As reported in Table 13, 31.0% of the proportion of patients with non-somatic depression remitted on a TCA

antidepressant medication versus 13.8% of the proportion of patients meeting criteria for somatic depression.

It is of interest to know that when you break down the data into groups by gender, there is either no difference or a difference in the opposite direction in every group between males and females and the only group in which depression is more common in females compared to males (59.2% vs. 38.9%, respectively) is the SD group with no remission on a TCA antidepressant medication.

A further interesting point to note is that depending on which outcome measure of remission is applied (HAM-D_{17} or QIDS-C_{30}), very different results are produced. Whereas atypical depression results in poorer response to a TCA on the HAM-D_{17} but not on the QIDS-C16, somatic depression produces a poorer response to a TCA on the QIDS-C_{16}, but not on the HAM- D_{17}. The possible reason for this will be discussed in the discussion section.

Table 12
Response to Nortriptyline (TCA) of Somatic Depression Patients Versus Non-Somatic Depression Patients on the HAM-D_{17}

Measure	**Somatic Depression**	**Non-Somatic Depression**
HAM-$D_{17} \leq 7$	13 (20.0 %)	9 (21.4%)
HAM-$D_{17} \geq 7$	52 (80.0%)	33 (78.6%)
		Total 107

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Table 13
Response to Nortriptyline (TCA) of Somatic Depression Patients Versus Non-Somatic Depression Patients on the QIDS-C_{16}

Measure	Somatic Depression	Non-Somatic Depression
QIDS-$C_{16} \leq 5$	9 (13.8 %)	13 (31.0%)
QIDS-$C_{16} \geq 5$	56 (86.2%)	29 (69.0%)
		Total 107

Note:Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

In hypothesis one, as several studies in the literature have concluded that AD responds better to MAOI antidepressant medication, it was also predicted that the SD criteria would predict response to a MAOI better than the AD criteria. Of the total number of respondents (n = 43) 9.3% met criteria for atypical depression, whereas, 58% of respondents met criteria for somatic depression. A Chi Square Cross-tabulation analysis to discover any potential overlap between diagnostic groups revealed that 89% of respondents who met criteria for atypical depression also met criteria for somatic depression, where as 50% of somatic depressives also met criteria for atypical depression.

As reported in Table 14, 15.4% of the patients not meeting criteria for AD remitted on the MAOI antidepressant medication as determined by the primary outcome measure of remission assessed by the HAM- $D_{17,}$ compared to 0% of the proportion of patients meeting DSM-IV criteria for atypical depression. A 2 x 2 Chi Square analysis revealed no significant difference between groups, (P = 1.000; Fisher's Exact Test probability). On the secondary measure of remission assessed by the QIDS-$C_{30,}$ as reported in Table 15, 15.4% of the proportion of patients that did not meet criteria for

atypical depression remitted on the MAOI antidepressant medication compared to 25.0% of patients meeting criteria for atypical depression. Although as reflected in the percentages the atypical depression group responded better than the non-atypical group to medication, this difference did not approach significance (P = .523; Fisher's Exact Test probability).

Table 14
Response to Tranylcypromine (MAOI) of Atypical Depression Patients Versus Non-Atypical Depression Patients on the HAM-D_{17}

Measure	**Atypical Depression**	**Non-Atypical Depression**
HAM-$D_{17} \leq 7$	0 (0 %)	6 (15.4%)
HAM-$D_{17} \geq 7$	4 (100.0%)	33 (84.6%)
		Total 43

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Table 15
Response to Tranylcypromine (MAOI) of Atypical Depression Patients Versus Non-Atypical Depression Patients on the QIDS-C_{16}

Measure	**Atypical Depression**	**Non-Atypical Depression**
QIDS-$C_{16} \leq 5$	1 (25.0 %)	6 (15.4%)
QIDS-$C_{16} \geq 5$	3 (75.0%)	33 (84.6%)
		Total 43

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

As reported in Table 16, 16.0% of the proportion of patients who met criteria for somatic depression compared to 11.1% patients who did not meet criteria for somatic depression achieved remission on the MAOI antidepressant medication as determined by the primary outcome measure of remission assessed by the HAM- D_{17}. Although the somatic depression group did respond somewhat better to a MAOI, a 2 x 2 Chi Square analysis resulted in no statistically significant difference between patients with somatic compared to patients with non-somatic depression, (P = 1.000; Fisher's Exact Test probability). On the secondary outcome measure of the QIDS-C_{30}, the proportion of patients with somatic depression that remitted on a MAOI antidepressant medication was 12.0% versus 22.2% of patients who did not meet criteria for somatic depression (see Table 17). The difference in the opposite direction than predicted was not significant, (P = .427: Fisher's Exact Test probability).

Table 16
Response to Tranylcypromine (MAOI) of Somatic Depression Patients Versus Non-Somatic Depression Patients on the HAM-D_{17}

Measure	**Somatic Depression**	**Non- Somatic Depression**
HAM-$D_{17} \leq 7$	4 (16.0 %)	2 (11.4%)
HAM-$D_{17} \geq 7$	21 (84.0%)	16 (88.9%)
		Total 43

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Table 17
Response to Tranylcypromine (MAOI) of Somatic Depression Patients Versus Non-Somatic Depression Patients on the QIDS-C_{16}

Measure	**Somatic Depression**	**Non- Somatic Depression**
QIDS-$C_{16} \leq 5$	3 (12.0 %)	4 (22.2%)
QIDS-$C_{16} \geq 5$	22 (88.0%)	14 (77.8%)
		Total 43

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Methods: Study 2

A. Participants

Participants for study two were those as described in the STAR*D methodology for study one. Specifically 106 patients at treatment level three receiving Nortriptyline (TCA) were eligible for data analysis to test the study two hypothesis.

B. Study Design

The STAR*D methodology described for study one was used for study two except that for study two in addition to DSM-IV melancholic depression, the refined criteria for melancholic depression was the measure of interest. The STAR*D definition of melancholic depression was developed by using selected items on the IDS-C_{30} to closely match the DSM-IV criteria for melancholic features specifier (applied to the most current or recent MDE in MDD and to a current MDE in Bipolar I or Bipolar II Disorder only if it is the most recent type of mood episode). The current DSM-IV criteria for melancholic depression include: 1) either loss of pleasure in all or most activities *OR* loss of reactivity to usually pleasurable stimuli during the most severe period or current MDE; and 2) three (3) or more of the following: a. distinct quality of depressed mood, b. depression regularly worse in the morning, c. early morning awakening (at least 2 hours before need to wake), d. marked psychomotor retardation or agitation, e. significant anorexia or weight loss, and f. excessive or inappropriate guilt. Table 18 indicates matched items on the IDS-C_{30} for DSM-IV melancholic depression.

Table 18
STAR*D Study Definition of Melancholic Depression

DSM-IV	**Related Items on IDC30**
Either of the following occurring during the most severe period or current episode:	*Must score a 2 or 3 on:*
(1) Loss of pleasure in all, or almost all, activities	Pleasure/Enjoyment (excluding sexual activities): rarely derives pleasure from any activities **OR** is unable to register any sense of pleasure/enjoyment from anything
(2) Loss of reactivity to usually pleasurable stimuli	Reactivity of Mood responses: mood brightens only somewhat with few selected extremely desired events **OR** mood does not brighten at all, even when very good or desired events occur
Three (or more) of the following:	
(1) Distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)	Quality of mood is qualitatively distinct from grief nearly all of the time
(2) Depression regularly worse in the morning	Mood variation (worse in morning): for most of the week, mood appears more related to time of day than to events **OR** mood is clearly, predictably, better or worse at a fixed time each day
(3) Early morning awakening	Early morning insomnia: awakens at least 2 hours before need be, more than half of the time
(4) Marked psychomotor retardation or agitation	Psychomotor Retardation: takes several seconds to respond to most questions; reports slowed thinking **OR** is largely unresponsive to most questions without strong

DSM-IV	Related Items on IDC30
	encouragement **OR** Psychomotor agitation describes impulse to move about displays motor restlessness **OR** unable to stay seated. Paces about with or without permission
(5) Significant anorexia or weight loss	Appetite Decrease: eats much less than usual and only with personal effort **OR** eats rarely within a 24-hour period, and only with extreme personal effort or with persuasion by others **OR** Weight Decrease: has lost five pounds or more in last two weeks
(6) Excessive or inappropriate guilt	Outlook (Self): largely believes that he/she causes problems for others **OR** ruminates over major and minor defects in self

American Psychiatric Association. & American Psychiatric Association. DSM-IV, 2000.

1. Procedure for Study 2 Modified Criteria for DSM-IV Melancholic Depression

Modified Melancholic depression for the purposes of the present study was determined by using responses to items on the PDSQ. All aforementioned symptoms presented in Table 18 for melancholic depression were applied to meet criteria (4 out of 6 symptoms) with the exception of changes made to two categories: sleep and appetite disturbances. As determined by patient responses to items on the PDSQ for categories of sleep and appetite: 1) patients defined in STAR*D as having melancholic depression who reported either prevention of weight gain from an eating binge by dieting or exercising excessively, or concerns about the shape of their body and self opinion were not given credit toward meeting the criteria for appetite loss; and 2) patients who reported insomnia

on the PDSQ specifically trouble falling asleep due to worrying about things were not given credit toward meeting the criteria for the criterion related to sleep in current criteria for melancholic depression, early morning awakening. See table 19 for matched items on the PDSQ.

Table 19
Matched Items on the PDSQ for Categories of Sleep and Appetite Disturbances

Category	**Matched PDSQ Item**
Appetite	To prevent gaining weight from an eating binge did you go on strict diets or exercise excessively?
	Was your weight, or the shape of your body, one of the most important things that affected your opinion of yourself?
Sleep	Did you often have problems falling asleep because you were worrying about things?

C. Statistical Analysis

The statistical analysis for study two was conducted using SPSS Version 15.0®. A 2 x 2 Chi-Square Cross-tabulation analysis with Yates Continuity Correction (or Fisher Exact Test) was performed to test study two hypothesis.

D. Results

Predictor Hypothesis Study Two: Good response to a tricyclic antidepressant, will be better predicted by meeting criteria for Melancholic Depression that eliminates the appetite or sleep criteria for respondents who meet the sleep or appetite criteria for SD than by meeting current criteria for Melancholic Depression.

For hypothesis two, at level three, 15% of respondents (n =16) met current criteria for melancholic depression while 8.5% of respondents (n = 9) met criteria for modified melancholic depression.

As reported in Table 20, on the primary outcome measure of remission assessed by the HAM- $D_{17,}$ 24.4% of the proportion of patients not meeting criteria for melancholic depression remitted on a TCA antidepressant medication versus 0% of patients meeting DSM-IV criteria for melancholic depression. Statistical analysis confirmed that patients with melancholic depression responded significantly worse to a TCA antidepressant medication compared to patients who did not meet criteria for melancholic depression, (P = .039; Fisher's Exact Test), which is in the opposite direction than would be expected. In contrast, on the secondary outcome of remission assessed by the QIDS-$C_{30,}$ as reported in Table 21, 31.3% of the proportion of patients meeting DSM-IV criteria for melancholic depression did remit on a TCA antidepressant medication compared to 18.9% of patients not meeting criteria for melancholic depression. Statistical analysis revealed no significant difference between groups (P = **.**316; Fisher's Exact Test probability).

Table 20
Response to Nortriptyline (TCA) of Melancholic Patients Versus Non-Melancholic Depression Patients on the HAM-D_{17}

Measure	**Melancholic Depression**	**Non- Melancholic Depression**
HAM-$D_{17} \leq 7$	0 (0 %)	22 (24.4%)
HAM-$D_{17} \geq 7$	16 (100.0%)	68 (75.6%)
		Total 106

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Table 21
Response to Nortriptyline (TCA) of Melancholic Depression Patients Versus Non-Melancholic Depression Patients on the QIDS-C_{16}

Measure	**Melancholic Depression**	**Non- Melancholic Depression**
QIDS-$C_{16} \leq 5$	5 (31.3 %)	17 (18.9%)
QIDS-$C_{16} \geq 5$	11 (68.8%)	73 (81.1%)
		Total 106

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

As reported in Table 22, of the proportion of patients meeting the modified criteria for melancholic depression, 0% remitted on the medication in comparison to 22.7% of patients not meeting criteria for melancholic depression. The statistical analysis revealed no significant difference between the two groups, (P = .199; Fisher's Exact Test probability). As reported in Table 23, when assessing remission as determined by the secondary outcome measure of the QIDS-C_{30}, the proportion of patients meeting modified criteria for melancholic depression was 44.4% versus 18.6% of patients not meeting the

modified criteria for melancholic depression. The difference was of borderline significance (*P* =.087; Fisher's Exact Test probability).

In an additional analysis comparing respondents who met criteria for modified criteria to those who met criteria for non-melancholic depression, a Chi Square Cross-tabulation analysis was performed to eliminate any respondents meeting current criteria for melancholic depression who also met criteria for non-melancholic depression. Of the 97 respondents who met criteria for non-melancholic depression, 7 of these also met current criteria for melancholic depression. A 2 x 2 level Chi Square analysis revealed that when respondents meeting criteria for current melancholic depression were eliminated from the comparison group (non-melancholic depression) and compared to modified melancholic depression on response to Nortriptyline, the analysis was essentially identical to the first analysis in which respondents meeting current criteria for melancholic depression were not eliminated from the comparison group.

Table 22
Response to Nortriptyline (TCA) of Modified Melancholic Depression Patients Versus Non-Melancholic Depression Patients on the HAM-D_{17}

Measure	**Modified Melancholic Depression**	**Non- Melancholic Depression**
HAM-$D_{17} \leq 7$	0 (0 %)	22 (22.7%)
HAM-$D_{17} \geq 7$	9 (100.0%)	75 (77.3%)
		Total 106

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Table 23
Response to Nortriptyline (TCA) of Modified Melancholic Depression Patients Versus Non-Melancholic Depression Patients on the QIDS-C_{16}

Measure	**Modified Melancholic Depression**	**Non- Melancholic Depression**
QIDS-$C_{16} \leq 5$	4 (44.4 %)	18 (18.6%)
QIDS-$C_{16} \geq 5$	5 (55.6%)	79 (81.4%)
		Total 106

Note: Numbers in parentheses indicate the percentage of respondents in each row exhibiting each type of symptomatology

Methods: Study 3

A. Participants

Participants were recruited from the undergraduate psychology subject pool at City College (CUNY). Data were collected on 142 participants, from which 49 participants (29 females and 20 males, mean age = 20. 8 years) met criteria for depression as determined by a score of ≥16 on the Center for Epidemiological Studies Depression (CES-D) rating scale. Participants were diverse in ethnicity. All participants were awarded extra credit for study participation. Study three received Institutional Review Board approval from City College (CUNY), and the Graduate Center (CUNY). Participants were treated in accordance with the "Ethical Principles of Psychologists and Code of Conduct" (American Psychological Association, 1992). Inclusion and exclusion criteria are given in Table 24 and general demographic information presented in Table 25.

Table 24
Inclusion and Exclusion Criteria for Study Participation

CRITERIA	METHOD OF ASCERTAINMENT
Inclusion	**Inclusion**
1. 18 years of age or older	1. Verbal report/demographic form
2. Have normal vision/corrective lenses	2. Visual Acuity Test
3. Sign written informed consent	3. Researcher
Exclusion	**Exclusion**
1. Participants currently taking antidepressant medication	1. Verbal self-report
2. Participants with neurological Impairment	2. Self-report on demographic form
3. Visual acuity below 20/20 without corrective lenses	3. Visual Acuity test

Table 25
Demographic Information for Subjects Meeting Criteria For Depression

	Number	Mean	S.D.	Percentage
Gender				
Female	29			
Male	20			
Age (Years)		20.82	3.11	
Ethnicity				
Caucasian	8			16.33
Hispanic	18			36.73
AA	4			8.16
Asian	13			26.53
Other	6			12.24
EHI		35.97	29.62	
CES-D		25.53	7.62	

Note: African-American (AA)

Subject/Control group Characterization: Demographic and clinical information was collected using the following measures:

B. Baseline Measures

a. Snellen Eye Chart

The Snellen eye chart (Snellen, 1862) is a common standard visual acuity test for normal and abnormal vision. Subjects were tested with the eye chart to rule out any significant visual acuity impairment that may have interfered with viewing the visual stimuli. The eye chart has a series of letters and numbers with the largest size at the top, gradually decreasing in size as one reads down the chart. As the individual being tested reads down the chart, the letters gradually become smaller. Testing requires one to remove contact lenses/glasses and to stand 20 feet in front of the chart and read out loud the smallest line of letters that one can read on the chart. If unsure of the letter, individuals are instructed to guess. This test is done on each eye, one at a time, and both eyes open together. Visual acuity is expressed as a fraction. The top number refers to the distance one stands from the chart (e.g., 20 feet). The bottom number indicates the distance at which a person with normal eyesight could read the line correctly. 20/20 is considered normal as the eye being tested can read a certain size letter at 20 feet.

b. Demographic Questionnaire

A standard questionnaire was developed to obtain basic demographic information from each participant (e.g., gender, age, handedness, visual acuity). In addition to basic demographic information, participants were asked if they had any pre-existing neurological problems or were currently taking any antidepressant medications. Based on

this information, it was determined whether a participant met inclusion criteria for study participation.

c. Edinburgh Handedness Inventory (EHI)

The EHI (Oldfield, 1971) is a measurement used to assess the dominance of a person's right or left hand in everyday activities (e.g., writing, drawing, cutting with scissors, holding a spoon). Participants were required to indicate which hand they typically use for certain activities. Responses to items are used to compute a handedness laterality quotient (LQ). A positive LQ score indicates an individual who tends to do more things with his/her right-hand in comparison to the left hand, whereas a negative LQ score is more frequently found in left-handed individuals. A score of +100 reflects full right-handedness, whereas, a score of –100 full left-handedness. People who are ambidextrous would have an LQ score near to zero. Scores on this measure were used to assess for handedness between experimental groups to ensure that potential differences did not interfere with a finding of difference in PA scores among subgroups.

C. Mood Rating Scales

a. Center for Epidemiological Studies Depression Scale (CES-D)

The CES-D is brief 20-item self-report symptom rating scale used to measure the current level of depressive symptomology among the general population (Radloff & Locke, 1986). The CES-D was administered to characterize subjects into groups of depressed and non-depressed. Items specifically chosen from previously developed scales (e.g., Beck Depression Inventory, Zung Self-Rating Depression Scale) represent the major symptoms of clinical depression. Specifically, the scale taps into areas of depressed

affect, positive affect, somatic and retarded activity, and an interpersonal factor. Respondents are required to rate (0-3) how closely each of the 20 statements best describes how often they felt a certain way during the past week. For all except 4 questions, higher scores indicate greater impairment. Total scores range from 0-60. The cutoff score to differentiate depressed from non-depressed persons is $\geq$16. Radloff and Locke (1986) have provided norms and psychometric properties. The CES-D is reported to be highly correlated with a number of other depression and mood scales, indicating good concurrent validity.

b. Inventory of Depressive Symptomology-Self Rated-30 (IDS-SR30)

Consistent with study one and two, the IDS-SR$_{30}$ was administered to assess whether participants met criteria for depression with atypical or melancholic features to test study three hypothesis. Diagnostic categories were formed using the same number of requisite symptoms defined in study one and two. However, it should be noted that a change in the pre-determined cutoff scores on the IDS-SR$_{30}$ to meet criteria for DSM-IV AD feature specifier and DSM-IV melancholic feature specifier consonant with the STAR*D methodology for study one and two was made. In study one, for a subject to meet criteria for AD they had to have: 1) a score between 0-2 on the mood reactivity item; and 2) have a score of 2 or 3 on two of the following items: a. hypersomnia, b. hyperphagia, or c. leaden paralysis, and a score of 3 on d. interpersonal rejection sensitivity (as defined by STAR*D study).

For melancholic depression, subjects had to score a 2 or 3 on either a. mood reactivity *or* lack of capacity for pleasure and a score of 2 or 3 on three of the following items: b. distinct quality of depressed mood, c. depression regularly worse in the

morning, d. early morning awakening (at least 2 hours before need to wake), e. marked psychomotor retardation or agitation, f. significant anorexia or weight loss, and g. excessive or inappropriate guilt.

Applying these cutoff scores for both AD and melancholic depression in study three yielded an insufficient number of subjects for statistical comparison. As a result, the cutoff scores had to be lowered in order for a comparison to be made possible. Applying the new cutoff scores, for subjects to meet criteria for AD on the IDS-SR30, they had to have: 1) a score between 0-1 on the mood reactivity item; and 2) have a score of 1 or more on two of the following items: a. hypersomnia, b. hyperphagia, or c. leaden paralysis, and d. interpersonal rejection sensitivity.

For melancholic depression, subjects had to score a 2 or 3 on *either* a. mood reactivity or lack of capacity for pleasure and a score of 1 or more on three of the following items: b. distinct quality of depressed mood, c. depression regularly worse in the morning, d. early morning awakening (at least 2 hours before need to wake), e. marked psychomotor retardation or agitation, f. significant anorexia or weight loss, and g. excessive or inappropriate guilt.

c. Psychiatric Diagnostic Screening Questionnaire (PDSQ)

Consistent with study one and two, the PDSQ was administered to determine which subjects met criteria for somatic depression, and the modified definition for melancholic depression. The same items selected on the PDSQ for study one and two was used in study three to create these criteria sets.

D. Cognitive Measures

a. Chimeric Faces Test (CFT:)

The CFT developed by Levy et al (1983), is a cognitive task assessing perceptual asymmetry that was administered to all participants. The CFT has been commonly used in research to investigate the processing of emotional stimuli in normal, healthy control subjects. The CFT uses split (chimeric) faces. Each face is a composite picture consisting of one half of a poser's face smiling and the other half of the poser's face with a neutral expression. Two faces, the original and its mirror image are mounted on a single page (one above the other), with the smiling half appearing either on the right side or the left side (see Figure 1 of sample pair). The paired faces are counterbalanced to control for order effects. Half of the time the chimera on the top appears with a smile to the left and the other half of the time with a smile to the right. The subject's task is to choose from the paired faces the face (top or bottom) that looks happier.

Sensitivity to properties of lateralized hemispheric functions have demonstrated that left-and right-handers were clearly differentiated on the CFT with respect to several aspects of performance that conform with known differences between handedness groups in hemispheric asymmetry. Further, highly reliable and stable individual differences in perceptual asymmetries within handedness have been shown. The outcome measure for study three was an asymmetry index (LQ: laterality quotient) for the CFT. To compute the asymmetry index (R-L)/36, the number of responses in which the smile is in the participant's left hemi-space (L) is subtracted from the number of responses in which the smile is in the participant's right hemi-space (R). The total score is divided by the total number of trials (36). Negative asymmetry scores reflect a left hemi-spatial (right

hemisphere dominance) bias, positive scores a right hemi-spatial bias (left hemisphere dominance) and a LQ of zero indicates that smiles to the left and right of the face were chosen equally. Perceptual asymmetry scores were calculated for each participant to determine hemispheric bias for perceiving emotion based faces.

Figure 1

FIG. 1. Item 1 from the free-vision task. The top face is a normal print and the bottom face is mirror-reversed print of the same negative. The same chimeric pair reoccurs in the test booklet with top and bottom positions reversed, and the same poser appears in two other pairs, but with the smile produced by the left half of the face and the neutral expression by the right half. Adopted from Levy et al., 1983.

E. Study Design

Participants were informed about the potential risks, benefits and confidentiality associated with study participation. Participants who provided informed consent were first administered the Snellen eye test to rule out any visual impairments that could preclude them from participating in the study. Following the vision test, the order of tasks administered were counterbalanced across participants to control for order effects. For the first part of the study, participants were either administered a battery of rating scales to obtain demographic and diagnostic information (demographic questionnaire, CES-D, IDS-SR$_{30}$, PDSQ) or the CFT cognitive perceptual asymmetry task.

Prior to administration of the CFT task, participants were given task instructions. The stimulus booklet was placed in front of them which contained 36 bound pages, each consisting of two chimeric face photographs with one half of the face smiling and the other half with a neutral expression with its mirror image placed on the top or bottom. Each participant was asked to look at each page and to identify which face they perceived to look happier. For each of the 36 pages, participants were required to mark their choice (top or bottom) on the answer sheet provided. Participants were instructed to work at their own pace carefully examining study stimuli before choosing their response. Study participants were not compensated financially for their time, however, they were awarded extra credit toward their psychology courses upon completion of study participation.

Data collected from the diagnostic measures was used to stratify participants into groups. Specifically, in accordance with study one and two, the same methodology was used to stratify subjects into: 1) depressed as established by a score of $\geq$16 on the CES-D; 2) meeting DSM-IV criteria for AD was determined by responses on the IDS-SR$_{30}$; 3)

meeting DSM-IV criteria for melancholic depression was determined by responses on the IDS-SR30; and 4) meeting criteria for SD and modified melancholic depression was determined by selected responses on the PDSQ.

F. Statistical Analysis

A Chi-Square Cross-tabulation analysis was performed to eliminate potential overlap between diagnostic groups (AD versus. melancholic depression; modified criteria for melancholic depression versus. somatic depression). Only participants in each group that did not overlap with the diagnostic group to which they were being compared were eligible for analysis. That is, participants meeting criteria for both diagnoses in each analysis were eliminated.

The cognitive measure of perceptual asymmetry as assessed by the CFT was used to test study three hypothesis. Differences between PA scores were assessed through an Independent Samples T-test with test performance as the dependent measure and diagnostic subtype (AD versus. melancholic depression; melancholic depression versus. somatic depression) as the between-subject factor.

G. Results

Hypothesis: The difference reported by Bruder et al (2002) between performance on the CFT of probands with Atypical Depression and Melancholic Depression will be strengthened with the use of the new operational criteria for Melancholic Depression compared to Somatic Depression.

The first step in the analysis of data was to conduct a Chi-Square Cross-tabulation analysis on groups of interest (AD, SD, melancholic, and modified criteria for

melancholic depression) to eliminate potential overlap between diagnostic groups. After controlling for overlap between diagnostic depressive subtypes, group comparisons were made. Of note is that the Chi-Square Cross-tabulation analysis for melancholic depression and the modified criteria for melancholic depression resulted in complete overlap of participants in both groups (N=9 in each group). As such, a direct comparison using the Independent Samples T-test on the CFT measure of PA between current DSM-IV criteria for melancholic depression compared to the modified criteria for melancholic depression could not be performed.

As reported in Table 26, the Independent Samples T-test comparing the AD group to the melancholic depression group on the cognitive measure of perceptual asymmetry assessed through the CFT yielded no significant difference in PA scores between the two groups ($t = .457$, $df = 33$, $p = 0.651$). For the second analysis, as indicated by the results in Table 27, although there were only 4 participants in the melancholic group versus 22 participants in the SD group, there was a trend toward significance suggesting differences in hemispheric processing of visuo-spatial affective stimuli between the two groups ($t = 2.021$, $df = 24$, $p = 0.055$). However, unexpectedly, the melancholic group demonstrated a more negative PA score than the somatic depression group, (-.72 vs. -.21, respectively) indicative of a right hemispheric bias. As SD is very similar to AD in criteria sets, it was expected that the SD group would demonstrate a stronger right hemisphere (more negative PA score) bias as reported by Bruder et al. for the AD group. Possible interpretations of these results will be discussed in the discussion section.

Table 26
Means, Standard Deviations, and t-tests for Atypical Depression Versus Melancholic Depression for the Measure of Perceptual Asymmetry

Depressive Subtype	Atypical (N=26)		Melancholic (N=9)			
Variable	Mean	S.D.	Mean	S.D.	T	*p*
PA[1]	-.33	.4506	-.41	.5576	.457	.651

[1]Perceptual Asymmetry Score

Table 27
Means, Standard Deviations, and t-tests for Melancholic Depression Versus Somatic Depression for the Measure of Perceptual Asymmetry

Depressive Subtype	Somatic (N=22)		Melancholic (N=4)			
Variable	Mean	S.D.	Mean	S.D.	T	*p*
PA[1]	-.21	.4823	-.71	.3544	2.021	.055

[1]Perceptual Asymmetry Score

IV: Discussion

The three studies described here were based on the conclusions of several studies conducted by Silverstein and Colleagues and the pressing issue of the clinical heterogeneity of depression as it is currently conceptualized which resonates throughout the depression literature. These studies were designed to investigate whether there may be better criteria sets to represent the current DSM-IV form of non-endogenous depression (AD) and endogenous depression (melancholia) which may help to reduce the clinical heterogeneity of these depressive subtypes in future studies**.** Since several studies in the depression literature have indicated a relatively good response to MAOIs and poor response to TCAs in the AD population, it was hypothesized in study one that poor response to a tricyclic antidepressant, and possibly good response to a MAOI, will be better predicted by meeting criteria for SD that includes both reversed and typical vegetative symptoms of appetite and sleep disturbance than by meeting criteria for AD.

Contrary to the hypothesized difference for the TCA antidepressant medication and treatment response, analyses indicated that for both the primary outcome measure of remission as assessed by the HAM- $D_{17,}$ and the secondary outcome measure of remission on the QIDS-$C_{16,}$ patients meeting DSM-IV criteria for AD versus non-AD did not significantly differ in remission rates for a TCA antidepressant medication, thus, suggesting that there was no relationship between depressive subtype and treatment response to a TCA antidepressant medication. However, as noted earlier, the data was in the predicted direction of a differential treatment response on the HAM- D_{17} measure of treatment outcome for the AD group. A reasonable explanation for this non-significant finding can be accounted for by the small sample size. A major advantage of using the

STAR*D data for re-analyses to conduct this study in addition to the careful methodology that improved upon earlier studies of response to antidepressants was the tremendously large sample size. However, when reaching the treatment levels relevant to the present study, a substantially large amount of the initial sample size had been lost due to numerous reasons (e.g., successful response to previous treatment options, entrance into follow-up phase, exit of study due to treatment side effects and/or failure to achieve remission). As a result, study one ended up with only 16 patients who met criteria for AD.

Similar to the results of the analysis of AD, it was found that patients meeting criteria for SD did not show the expected poorer response to a TCA antidepressant medication on the HAM-D_{17} compared to patients who did not meet criteria for SD. However, on the secondary outcome measure of the QIDS-C_{16}, there was a finding of borderline significance when applying the results of the Chi- Square analysis and a significant finding when using Fisher's Exact Test probability. The tradition in psychology has been to use the P-value for the Chi Square test to determine significance except in analyses with very small samples, however, recent statements contend that Chi-Square test results in P-values that are considerably lower than the Fisher's Exact Test, even for larger sample sizes (e.g., in the hundreds; McDonald, 2009). As such in the present study it was more logical to use the Fisher's Exact probability in determining whether the hypothesis was supported. Patients with SD did respond worse to a TCA antidepressant medication compared to those patients who did not meet criteria for SD suggesting that there is some indication of a differential treatment response for SD.

One of the interesting findings is that depending on which outcome measure is used, different treatment results are produced between the AD and SD group. That is, the AD group respond worse to a TCA when measured by the HAM-D17 (although the result was not significant), whereas, the SD group did respond significantly worse to a TCA on the QIDS-C16 measure but not on the HAM-D17. These are both well-know measures in the depression field, however, not equivalent as would be expected. As discussed previously, several researchers point out that a contributing factor to the inconsistencies found across depression studies is the measures used to assess symptom change. For instance, as Demitrack (2005) points out, given the varied symptom profiles of patient's, symptom measurement is one of the crucial factors to be addressed in assessing symptom change in response to treatment interventions for MDD. "The problem presented here is that any one scale may be constructed in a manner to favorably detect a treatment signal for a specific pharmacologic profile and clinical presentation (i.e., melancholic depression treated with tricyclic antidepressants), but appear to suggest a more modest treatment effect if used to assess symptom change in patients with slightly different clinical presentation" (Demitrack, 2005; Joyce et al., 2003). Upon closer examination of the items assessed on the HAM-D17 and QIDS-C16, the latter tends to address more of the criteria for SD and the former more of reversed vegetative symptoms characteristic of AD, which is likely to explain the difference in findings.

The result of a significant differential response for SD is particularly striking in light of the recent findings reported by Silverstein and Colleagues (in preparation). In their recent study examining gender differences in the prevalence of AD versus non-AD, it was found that there is approximately a 16% higher prevalence of depression among

females than males. It is well documented in the literature that AD has a higher preponderance in females than males. However, the gender difference found by Silverstein and Colleagues was almost entirely due to SD and not AD. AD was only found to exhibit any gender difference in prevalence because it is associated with SD. The results that SD has a poorer response to TCA than AD provides some support to the notion that SD may be an optimal criteria set for a distinctive form of non-endogenous depression than the current DSM-IV AD. Although both AD and SD are similar forms of non-endogenous depression, it is apparent from the results that AD defines too fewer people. As such, it may be better to replace AD with SD.

The definition of AD lies in reports of better response to MAOIs relative to TCAs and as AD and SD overlap in symptoms, it was thought that a better response to MAOIs may be pronounced for SD. However, the findings from study one did not support this. Patients with AD did not respond better to a MAOI on either outcome measure. Similarly, patients with SD did not respond significantly better than non-SD patients to a MAOI on the HAM-D$_{17}$. Moreover, on the QIDS-C$_{16}$, the result was in the opposite direction with SD showing a poorer response to a MAOI. As noted previously, the efficacy of MAOIs relative to TCAs in AD have produced conflicted findings (Fountoulakis et al,1999, 2000, 2004). Some studies have demonstrated a differential response between MAOIs and TCAs, while others have not. These results support the view of Rosenberg, Davanzo, and Gershon (2002) who suggest that maybe "atypical symptoms predict a negative response to tricyclic agents, rather than a strong positive response to MAOIs" (p.326).

Similar to these results, the methodologically well designed STAR*D study found no significant difference in treatment response to a MAOI among any of the depressive groups including the AD group (McGrath et al., 2006).

In study two it was hypothesized that a good response to a tricyclic antidepressant, will be better predicted by meeting criteria for Melancholic Depression that eliminates the appetite or sleep criteria if respondents meet the sleep or appetite criteria for Somatic Depression than by meeting current criteria for Melancholic Depression. Contrary to what was expected, patients with melancholic depression responded significantly worse to a TCA on the HAM-D_{17} measure and the difference on the QIDS-C_{16} was not significant.

Similar to the finding for melancholic depression, patients meeting criteria for modified melancholic depression did not show a differential treatment response to a TCA on the HAM-D_{17}. However, interestingly, despite the small sample size, patients with modified melancholic depression responded better to a TCA (but only at a borderline level of significance) as predicted. As with study one, the major limitation of study two is the sample size. Had the primary interest of the STAR*D study been on response to a TCA at level one, it is possible that with a much larger sample size, there would have been a significant finding in differential treatment response. However, distinguishing depressive subtypes should not be limited to the study of pharmacological dissection. Despite the significant advances in this area of study over the past half-century, the exact underlying mechanisms of antidepressant medication and their interactions with other neuroreceptor systems is not yet fully understood to make firm conclusions. Of particular note is, that the patients studied here were from levels three and four, and thus had

exhibited resistance to treatment in levels one and two. Thus, they may constitute a group of patients with treatment-resistant depression and so not be representative of all depressed patients. Future studies should explore pharmacologic responses of a more representative group of patients as well as investigate differences other than pharmacologic response among depressive subtypes that may further help to delineate depressive subtypes.

In study three, it was hypothesized that the difference reported by Bruder et al (2002) between performance on the CFT of probands with AD and Melancholic Depression would be strengthened with the use of the new operational criteria for Melancholic Depression compared to Somatic Depression. However, as mentioned previously, a direct comparison could not be made between the current DSM-IV criteria for melancholic depression and the modified criteria for melancholic depression for which changes to the categories of appetite and sleep were made. As described earlier, participants who met criteria for melancholic depression and who also reported trouble falling asleep on the PDSQ, as a symptom of SD were not given credit for early morning awakening. Additionally, participants who had symptoms of anorexia or weight loss but endorsed items on the PDSQ related to SD criteria (e.g., restricting food intake due to body image issues) did not receive credit for either of the former two items. However, in this small sample, no participants who met current criteria for DSM-IV melancholic depression failed to meet the redefined criteria. As such, the originally planned comparison between the modified melancholic criteria versus the current DSM-IV criteria for melancholic depression on perceptual asymmetry could not be made.

The results from an independent samples t-test for the first analysis comparing AD versus melancholic depression indicated that there was no significant difference in PA scores which contradicts the findings of Bruder et al. which reported melancholic depressives to essentially show no right hemispheric bias on the CFT when compared to AD. The second analysis comparing melancholic depression to SD did not yield a significant difference between the two groups on PA scores. However, interestingly, there was a finding of borderline significance suggesting differences in hemispheric processing of visuo-spatial affective stimuli between SD and melancholic depression. The melancholic group demonstrated a more negative PA score than the SD group, (-.72 vs. -.21, respectively) indicative of right hemisphere activation, opposite to the predicted difference. As SD is very similar to AD in criteria sets, it was expected that the SD group would choose more faces with the smile in the left hemi-space demonstrating a stronger right hemisphere bias as reported by Bruder et al. for the AD group. However, the results of study three need to be interpreted with caution due to the limitations of the study.

A major limitation to study three was the actual sample used. In contrast to a clinically depressed outpatient sample used by Bruder et al. participants in study three were relatively healthy college students recruited from an undergraduate psychology subject pool, therefore, unrepresentative of a clinically depressed population.

Furthermore, a small sample size was also a limitation in the study. From the original 142 participants included in the study, only 49 met the cutoff criteria for depression as assessed by the CES-D rating scale. Within the 49 subjects eligible for analysis, symptoms endorsed on the IDS-SR$_{30}$ administered to assess for AD and melancholic depression yielded an insufficient number of participants in each group for

statistical comparison. As a consequence, the more rigorous cutoff scores for participants to meet criteria for either subtype pre-determined by the STAR*D study methodology had to be substantially lowered in order to have enough participants in each diagnostic category for a statistical comparison. With a substantially lower cutoff score to meet diagnostic criteria for AD and melancholic depression, a plausible explanation for the lack of significant differences between the AD and melancholic group may be that the latter actually resembles healthy individuals who like the AD group are expected to show a stronger negative PA score indicative of a stronger right hemispheric bias for perception of emotional chimeric faces. This explanation also extends to the second analysis in which the mean PA score was more negative but for the melancholic group in comparison to the SD group.

Historically, the classification of depression has been contentious. However, what is not in dispute among experts in the field of depression is that the most important conclusions, supported by evidence in all fields of depression research, is that real progress in the effective diagnosis and treatment of this disease is seriously hindered by the fact that MDD as presently conceptualized in the DSM-IV, represents a set of clinically heterogeneous disorders, resulting in contradictory findings across studies (e.g., Davidson et al., 2002; Drevets, 2007; Fountoulaksi et al., 2004; Pagani et al., 2006; Smith & Cavanagh, 2005; Pizzagalli et al., 2002).

This weakness of the DSM-IV's diagnostic classification of depression has prompted several researchers to suggest that: (1) this heterogeneity would decrease with the further re-definition of MDD into two distinct categories of endogenous and non-endogenous depression (Shorter, 2007; Stewart et al., 2007; Taylor & Fink, 2008;); and

(2) that the manner in which the DSM-IV portrays MDD with symptom specifiers of AD and melancholia is far too narrow of a definition approach (Angst et al., 2002, 2006; Matza et al, 2003; Parker et al., 2002; Silverstein, Cohen, & Kasen, 2006; Stewart et al., 2007).

As discussed previously, several studies (e.g., ECA, NCS), indicate that the gender difference in the prevalence of depression results because women exhibit much more SD than men but not much more pure depression (depression without somatic symptoms) (Silverstein, 1999; Silverstein, 2002; Silverstein et al, 2006; Silverstein, 2009 in preparation). That is, respondents reporting more symptoms of SD (e.g., categories of appetite disturbance, sleep disturbance, and fatigue) show a large gender difference in prevalence whereas respondents reporting depression without significant somatic symptomatology exhibit little gender difference in prevalence. A further difference between the two subtypes of depression relates to psychosocial measures of gender roles. Specifically, depression involving symptoms of SD is significantly related to several measures of gender roles, whereas, depression not involving significant somatic symptomatology is not related to these psychosocial measures (Silverstein, Perlick, Clauson, & McKoy, 1993;Silverstein, Caceres, Perdue, & Cimarolli, 1995; Silverstein & Blumenthal, 1997; Silverstein & Lynch, 1998).

These findings suggest that SD may be a non-endogenous form of depression that is distinct from depression without significant somatic symptoms. The data distinguishing AD from other types of depression are based primarily on studies of response to antidepressants. But the results reported in the studies described here suggest that SD exhibits at least as much differential response to antidepressants as does AD.

Thus, compared to current criteria for AD, criteria for SD: 1. Defines a larger group of patients; 2. Better explains the gender difference in depressive prevalence (Silverstein, unpublished data). Furthermore, even though generally depression is more frequent in females than males, in study one the only time females exhibit a higher percentage of depression than males is in the SD group with no remission, suggestive of SD as a distinct subtype of non-endogenous depression; 3. Strongly relates to psychosocial measures of processes that might underlie the development of a non-endogenous depression; and 4. Predicts at least as well response to antidepressants. This pattern is support for the notion that the criteria for SD are more useful in defining a distinct disorder than are the criteria currently used for AD.

Further, of note is that if criteria for SD which include items such as lack of appetite/anorexia and insomnia are more useful in defining a distinct disorder than are the criteria currently used for AD, the current criteria for endogneous- melancholic depression need to be further studied which also includes similar symptoms. Not only have the vegetative symptoms including insomnia (and early morning awakening) as well as decreased appetite and eating disturbances been reported to have a relatively weaker loading on a single endogenous factor in the literature (e.g., Nelson & Charney, 1981; Parker, Hadzi-Pavlovic, & Boyce, 1989), patients with modified melancholic depression in study two responded better to a TCA antidepressant medication (although of a borderline significance level) whereas those with traditional melancholic depression did not respond better to medication. This finding provides some support for the notion that a clearer distinction needs to be made between the appetite and sleep criteria for SD and melancholic depression which can only be substantiated with further investigations.

In conclusion, the studies presented herein were the first attempt to identify whether using criteria for SD and modified criteria for melancholic depression are stronger predictors of response to antidepressant medications and at discriminating on the cognitive measure of PA compared to the current DSM-IV criteria. Despite the major limitations of the studies presented here, the results provide some support for a differential response to treatment as well as hemispheric bias for affective visual stimuli, both of which are more pronounced for SD. Nevertheless, although some evidence exists suggesting that SD defines a better set of criteria than AD for a distinct type of non-endogenous depression, given the weakness of the statistical findings reported here, one cannot be too firm in this conclusion. Until these findings are replicated on larger samples, it is best to consider these findings simply suggestive. Future studies are warranted in this area of investigation and may play a key role to a broader understanding of depression and its neuroscientific basis. Of particular importance would be to use both an appropriate sample (i.e., not a college sample as in Study three reported here) representative of a depressed population and an adequate sample size to detect a difference.

Better operationally defined diagnostic criteria within a more sophisticated division of depressive subtypes can 1) advance neuroimaging studies in systematically relating specific neural functional and structural abnormalities as well as isolating how these are associated with behavioral, cognitive and affective symptoms of depression; and 2) improve prospectively identifying sub-groups of depressed patients who are responsive (or conversely unresponsive) to specific medications. This would be significant because patients could then be matched to drugs that they are more likely to benefit from earlier

rather than later by trial and error. Furthermore, for those patients who are unresponsive to or have a history of being resistant to antidepressants, alternative therapeutic interventions can be sought out.

Appendix A

The Monoamine Hypothesis Model of Depression

Systematic study of the biological correlates of depression since the 1950s have lead to several lines of converging evidence that disturbances in one or more neurochemical systems within the brain cause depression. Dysfunction in various central nervous system (CNS) neurotransmitters has been implicated in the biological etiology of depression.

The monoamine hypothesis was the first developed cohesive theory of the neurochemical etiology of affective disorders and has been the driving force in depression treatment research since its inception. This hypothesis derived (accidentally) from the observation that reserpine, a drug effective in reducing high blood pressure, induces depression as a side effect in a large number of patients. Essentially, the drug acts by blocking the vesicular monoamine transporter, which normally transports the catecholamines norepinephrine (NE), Dopamine (DA), and indoleamine serotonin (5-HT) from the cytoplasm of the presynaptic nerve into vesicles for subsequent release into the synaptic cleft. The unprotected neurotransmitters are then metabolized by monoamine oxidase and therefore never reach the synapse, thus creating a deficient state; and (2) that antidepressant medications increase levels of NE, DA, and/or 5-HT within the synaptic cleft. These findings led to the the emergence of the hypothesis of catecholamine and indoleamine deficiencies in depression. These neurotransmitters in addition to acetylcholine (Ach) have been found in brain tracts and nuclie imperative for the regulation of sleep, reward, appetite, libido, psychomotor behavior, and emotional expression, which are frequently disturbed during depression. (It remains to be resolved

which neurotransmitter is the most important in the etiology of depression (Meyer & Quenzer, 2005).

Antidepressant Drugs: Mechanisms of Action

Antidepressant drugs are the most widely used means of treatment for all types of depression. However, possibly the only consensus about the efficacy of antidepressant drugs is that despite decades of progress since the introduction of imipramine (a tricyclic antidepressant) discovered serendipitously half a century ago, the advent of numerous new classes of drugs "has not produced a quantum leap in depression treatment" (Norman, 2006, p. 394).

Virtually all approved antidepressant drugs operate via the same principle: to block the reuptake of serotonin and/or noradrenaline. This therapeutic action is accomplished by one of three methods: 1) blocking presynaptic monoamine transporter proteins, which carry released neurotransmitters from the extracellular space, 2) inhibiting monoamine oxidase, which degrades monoamine neurotransmitters, or 3) inhibiting or stimulating pre- or postsynaptic receptors that regulate the release of monoamines and/the rate of neuronal firing activity (Nemeroff & Owen, 2002).

Tricyclics (TCAs)

TCAs, among the first generation of antidepressant medications were introduced in the early 1960s, and thereon have been the standard for antidepressant efficacy. However, TCA antidepressants are used less frequently at the present time, to treat depressive disorder, while antidepressant drugs of the SSRI class (selective serotonin reuptake inhibitors) and the SNRI class (serotonin-noreprinephirine reuptake inhibitors) are more frequently used. TCAs do not operate specifically on the monoamine oxidase

enzyme (MOA), but work to inhibit the reuptake of the monoamine neurotransmitters 5-HT and NE in varying degrees (Briley, 1998; Norman, 2006). At the same time, they interact negatively with other neurotransmitter systems, causing the blockade of alpha 1 adrenergic receptors, H1 histamine receptors and cholinergic muscarinic receptors, to produce significant side effects, including blurred vision, dry mouth, and drowsiness (Stahl, 2000). While TCAs have a known record of success in treating specific endogenous and/or severe depression, the presence of substantial, unpleasant side effects has promoted reliance on suboptimal dosages of the medication or the decrease in treatment adherence, thus diminishing their more positive treatment capabilities.

The advent of SSRIs has been viewed as a great improvement over TCAs, because while the SSRI neurotransmitter action is not devoid of side effects, they are not as severe as those associated with TCAs. However, SSRIs are not necessarily more effective. Several studies have found certain TCAs to be more effective than SSRIs to treat specific kinds of depression disorder. A meta-analysis found that TCAs significantly surpassed SSRIs in treating hospital inpatients, as well as patients assessed as having very severe depression as measured by a high Hamilton Depression Rating Score (Anderson and Tomenson, 1994, as cited in Briley, 1998). Additionally, some studies have found that older patients suffering from melancholic depression, especially women, tend to respond better to TCAs than SSRIs (Joyce et al., 2003; Parker, 2002).

Monoamine Oxidase Inhibitors

The discovery of mononamine oxidase inhibitors (MAOI) predates the same discovery of TCAs, therefore making them the oldest antidepressant medications. Like first generation TCAs, MAOIs increase the amount of NE and 5-HT in the synapse, but

MAOIs operate on the CNS differently than do TCAs. Specifically, MAOIs operate by inhibiting the target function of MAO in the CNS that serves to inactivate intracellular NE, 5-HT and DA. Given that MAO is bound to the outer surface of the plasma membrane of mitochondria, it is not able to break down amines that are stored in vesicles within the neuron, thus, only metabolizing amines that are present in the cytoplasm. In turn, MAO activity sustains a low cytoplasmic concentration of amines. Therefore, MAOIs through their inhibition raise the amine content within the cytoplasm, increasing the amount available for storage in vesicles allowing more amine neurotransmitters to be released into the synapse.

Given that DA is also a substrate for MAO, its intrasynpatic concentration is also increased. As in some brain regions DA is transported by the NE transporter into the presynaptic neuron for those regions rich in NE nerve terminals, MAOIs may act like a DA reuptake inhibitor but indirectly through inhibition of NE reuptake. Hence, the altered function may also be relevant to antidepressant effects (Wong and Bymaster, 2002).

MAOIs are typically considered as the third- or fourth-line of pharmacotherapy due to the grave side effects commonly associated with them which include: changes in blood pressure; sleep disturbances (e.g., insomnia); and overeating, particularly of carbohydrates, possibly leading to excessive weight gain. Additionally, due to the inhibition of MAO consequently elevating NE levels in peripheral nerves of the sympathetic branch of the autonomic nervous system, as well as the CNS, any over the counter drugs (e.g., nasal sprays, cold medications, anti-asthma drugs, cocaine,) that enhance NE function will produce unexpected, heightened effects, such as sweating, as

well as increased blood pressure, and increased body temperature (Beckham and Leber, 1995; Gotlib and Hammen, 2002). MAOIs can produce life- threatening conditions if dietary restrictions are not adhered to due to the inhibition of MAO in the liver and lining of the intestinal tract. For instance, since MAO in the liver deaminates tyramine, which is a naturally occurring amine produced as a by-product of fermentation in many foods (e.g., cheese, certain meats and pickled products), increased tyramine levels cause the release of higher than normal stores of NE at nerve endings, which results in such a dramatic increase in blood pressure that it may cause nausea, vomiting, headaches, and a possible stroke. At the same time, MAOIs also inhibit liver enzymes such as cytochrome P450 enzymes, which degrade drugs such as opiates, alcohol and barbiturates, thereby intensifying and prolonging the effect of these drugs in the presence of MAOIs (Beckham and Leber,1995; Gotlib and Hammen, 2002).

Earlier studies investigating MAOIs reported them to be less effective than TCAs for treating severe, classic depression. However, these findings were deemed to be due to inadequate dosing used in these studies. Later studies, utilizing higher doses found MAOIs to be just as effective as other antidepressants in treating severe depression (Davis, Wang, & Janicak, 1993, as cited in Gotlib and Hammen, 2002). In addition, MAOIs are also used to treat various anxiety disorders, and they have been found to have positive effects on the eating behavior and mood of patients with bulimia and anorexia nervosa.

SSRIs

As a class, the second generation of antidepressants, SSRIs have a common mechanism of action and have demonstrated comparable efficacy in treating depressive

disorders as well as a range of anxiety disorders (Stahl, 2004). However, like TCAs, SSRIs have affinity for non-target neurotransmitter sites ("secondary binding properties") thus causing side effects (p. 8). The secondary binding properties and hence the adverse side effects vary according to the drug and the individual patient. The importance of individualizing treatment is underscored by the fact that some patients who do not respond to a prescribed SSRI, or, who experience serious side effects, experience symptom remission and/or reduced side effects upon switching to another drug in the same class. This phenomenon is extremely common, and "suggests strongly that, despite broad class similarities, differences in secondary binding properties can have real clinical relevance" (Stahl, 2004, p. 4).

Serotonin plays a role in a myriad of psychological and physiological functions including mood and anxiety, appetite, sleep, sexual behavior, gastrointestinal activity, and thermal regulation (Stahl, 2004). Consequently, there are about 14 subtypes of 5-HT receptors spread across different areas of the brain affecting the various aspects of human functioning. Given the array of activities impacted by 5-HT, it is not surprising that its effects should be highly variable.

The success of SSRIs is the ability to fine tune treatment options to address different symptom patterns. For instance, SSRIs with mild CNS properties such as sertraline and fluoxetine can be especially efficacious for patients whose symptoms include drowsiness and fatigue. Conversely, SSRIs with mildly sedative and anxiety reducing properties can be advantageous for patients who experience anxiety, agitation, and insomnia. Citalopram and escitalopram, which have minimal secondary binding properties are thus recommended for patients who complain of unpleasant side effects.

The critical factor in the treatment of depression disorder with SSRIs is *balance.* It is important to consider that "Human energy and interactivity can be viewed as a continuum, with sedation, fatigue and listlessness at one end and agitation and mania at the other" (Stahl, 2004, p. 4). Serotonin, noradrenaline, and dopamine play a critical role in striking the proper balance of CNS activation in patients spanning the full spectrum of depressive symptomology. Broadly, this helps explain differences in response to TCAs or SSRIs by patients with AD or melancholic depression but there is virtual consensus that present understanding of individual treatment responses is seriously inadequate.

SNRIs

The recent trend in psychopharmacology has been the development of novel antidepressants that selectively inhibit the reuptake of NE and 5HT without acting on the receptors that produce the unpleasant side effects (Briley, 1998). These newer compounds are referred to as the third generation of antidepressant medications. The drugs in this class of specific serotonin and noradrenaline reuptake inhibitors (SNRIs) include duloxetine, milnacipran, and venlafaxine. A major advantage of these drugs is that they demonstrate the efficacy of TCAs but have fewer harsh side effects.

In clinical trials, venlafaxine and milnacipran seemed to be more effective than SSRIs for patients with more severe depression. Both types of drugs were equally well tolerated. In the clinical trials that included SSRIs, duloxetine (SNRI) was at least as effective as paroxetine and fluoxetine (Norman, 2006). The research analysis of Mallinckrodt et al. (2005) affirmed the efficacy of duloxetine for patients with melancholic depression.

Clinical trials are not immune to the methodological flaws that plague depression research in general. Acknowledging that many antidepressant trials have been heavily criticized, Geddes et al. (2007) declare, "This was possibly justifiable, or at least understandable, when depression was not so widely recognized as a highly prevalent disorder that is responsible for so much human suffering, however, this state of affairs is no longer acceptable" (p. 544). The authors view the enlarged sample size of the STAR*D study as a precursor to more efficient, higher quality trials.

*The Sequenced Treatment Alternatives To Relieve Depression Study (STAR*D*

The STAR*D study, funded by the National Institute of Mental Health, screened 4,041 participants, and is the largest study of treatment response in depression ever carried out. It was conducted as a five-year prospective study and has succeeded as the most innovative and far-reaching study investigating the effectiveness of treatments for depression and, it continues to provide analyses in the field.

STAR*D is unique for its use of "real-world patients experiencing a depressive episode" (Huynh & McIntyre, 2008, p. 91). The authentic design of the study is evident in the socio-demographic composition of the sample that paralleled the general U.S. population and the participants had very varied psychiatric profiles and treatment histories.

A focal point of STAR*D was remission following treatment versus response. The STAR*D group heavily criticized previous clinical trials in their lack of vigor toward striving for remission rather than symptom reduction or response. Remission is defined as "the virtual absence of symptoms" (Trivedi et al., 2006, p.28). According to Thase (2003), in a review of the definitions of response and remission, the two terms have been

inconsistently applied across studies. As a consequence, a task force in 1989 established a convention of 50% reduction in baseline depressive symptoms as measured by various scales (e.g., HAM-D: Hamilton Depression Rating Scale) to be indicative of antidepressant efficacy. However, as several studies have shown, symptomatic response without remission is associated with continuing functional disability and higher rates of relapse due to residual symptoms (Trivedi et al., 2006; Thase, 2003).

A major strongpoint of STAR*D was that the design allowed for analysis of differences and similarities within and between different subgroups of participants. For example, 29.4% of STAR*D participants had comorbid substance used disorder (Davis et al., 2006), which would exclude them from most clinical trials.[10] Furthermore, STAR*D reflected a broad inclusion criteria in terms of the many manifestations of depression (e.g., MDD, MDD with atypical /melancholic features specifiers, and anxious depression).

Among the initial group of 1,450 participants, 46 % met designated criteria for anxious depression (Fava et al., 2006). The final sample yielded a comparable figure (45.1%), similar to outpatient studies indicating a range of about 41% to 51% for lifetime concurrence of major depression and anxiety disorders. Of particular note, STAR*D participants with anxious depression were significantly more likely to endorse items related to melancholic depression such as distinct mood quality, slowed down movement, appetite decrease and/or weight loss. They were less likely to describe the appetite increase or weight gain commonly associated with AD.

[10] Although men were more prevalent among participants with concurrent substance use disorder, many of their characteristics overlap with AD. They tended to have early onset depression, hypersomnia, fluctuations in mood, suicidal tendencies and symptoms reflecting OCD, as well as, panic disorder, social phobia and PTSD.

In addition, more women than men were classified as having anxious depression (47% versus 40.7%). Socio-economically disadvantaged participants were over-represented possibly because the illness interfered with school and work productivity. Prolonged episodes of depression were characteristic of this group, as well as a tendency toward somatic complaints. Of particular concern to the researchers, this group reflected a high degree of suicidal thoughts and attempted suicides, and, therefore, researchers emphasized the high prevalence and illness severity of anxious depression and strongly recommended focusing greater attention on this disorder (Fava et al., 2006).

One group of patients that was a major focus of STAR*D, and which is excluded from most clinical trials, is a group of patients diagnosed with treatment-resistant depression. The methodology used for treating these patients was designed to have four treatment steps: Level 1 to Level 4, and to extend over a four-year period. All participants started at Level 1 by taking citalopram (Rush et al., 2006, 2008; Sussman, 2007). Rates of treatment response and symptom remission were 47% and 28%, respectively. Higher remission rates were observed in women and more educated and affluent participants. Remission was low in those with comorbid psychiatric and general medical conditions, longer duration of depressive episode, and poorer functioning and life satisfaction.

At Level 2, participants were offered seven treatment options: four offered the choice of switching from citalopram to another drug or cognitive behavior therapy (CBT); three provided the option of supplementing the citalopram regimen with another drug or CBT. Approximately half (51%) chose to switch, and those who chose medication were assigned to one of three common antidepressants (sertraline, bupropion,

or venlafaxine). Despite efforts at randomization, the participants varied considerably in their willingness to accept different treatments. Only 26% accepted CBT. (Rush et al. (2008) propose that patients preferring psychotherapy were discouraged from entering STAR*D.) Roughly one-third of the participants who chose augmentation, and one-quarter who switched, achieved remission.

Level 3 included two switch options (mirtazapine or nortriptyline) and two augmentation options (triidothyronine or lithium). Adverse side effects from lithium produced high attrition. Treatment with triidothyronine produced the highest rate of remission (25%), while switching produced modest results (12%-13%). Participants who entered Level 4 received either tranylcypromine or venlafaxine plus mirtazapine. Remission rates were 7% and 14%, respectively. The probability of remission declined with the number of steps required.

Researchers have responded to the STAR*D findings in a variety of ways. Rush et al. (2006) speculate that adherence to treatment protocols could produce remission in 70% of patients even if four steps were needed. However, attrition resulting from medication side effects was high. According to Price (2006), the most decisive finding of STAR*D is that successful intervention for depression entails more effective and easily tolerated treatment options. Rush et al. stress the need for better treatment for short-term and long-term results so that symptoms are alleviated in more severely depressed patients earlier in their treatment and the results sustained longer. According to Rush et al. a key implication of STAR*D is that, "The findings are suggestive that MDD is biologically heterogeneous such that different treatments differ in the likelihood of achieving remission in different patients" (p. 1913).

Given negligible differences between various treatments used in STAR*D and the outcome criteria, the results are difficult to interpret (Geddes et al., 1007; Price, 2006). In fact, Price (2006) asserts that without a placebo condition, the treatments could be construed as equally effective or equally ineffective. In the opinion of Geddes at al. (2007), in view of the "largely neutral results" it is "perhaps between seen as a pilot demonstrating the feasibility of large trials rather than the definitive item" (p. 544).

Overall, STAR*D has been simultaneously criticized, for lacking the rigor of a randomized controlled trial, and commended, for a design that more closely parallels real world clinical treatment. Blier (2007) succinctly states, "Clinical trials can only answer a limited number of questions" (p. 232). In defense of STAR*D, Blier points out that conventional trials almost invariably use "picture perfect" patients who are diagnosed with one specific psychiatric disorder and whose history is "uncomplicated" by repeated or chronic episodes or treatment resistance (p. 232). This does not mirror the profile of individuals in the community who are experiencing a depressive disorder. Additionally, patients in usual care have a choice of treatment options, as opposed to having a specific treatment imposed upon them. The selection of a treatment that is mutually satisfactory to the patient and the clinician can have a powerful impact on treatment adherence and consequent outcomes. Participants in STAR*D varied considerably in their preferences for different treatments. Only 1% of participants accepted all the treatments offered in Stage 2 (Rush et al., 2008). Blier notes that the placebo response is usually small in treatment-resistant patients.

Malhi et al. (2005) regard the term "treatment-resistant depression" (alternately, refractory depression) as a misnomer, more accurately described as depression that has

been *misdiagnosed* and *mismanaged.* In their study of 196 depressed patients referred to a tertiary referral Mood Disorders Unit, the researchers explored a wide array of clinical variables, gathering data over 32 months. The most striking finding was the significant over-representation of patients with melancholia in the group most resistant to treatment. The three groups of patients (defined in terms of "high," "low," and "no" treatment resistance) were similar on all demographic characteristics thus allowing "robust comparison of the features of depression" (p. 307).

Malhi et al. describe melancholia as "prototypic treatment-resistant depression subset" (p.302). They note that the predominance of patients with melancholic depression among those who are highly resistant to treatment concurs with their clinical observations but is "somewhat at variance with much of the literature." As possible explanations for the disparity they propose that, "depression subtyping has fallen out of favor" and that few studies have included such a "broad set of variables," therefore precluding comparisons (p. 307).

The sequencing intrinsic to STAR*D was designed for the precise purpose of investigating the phenomenon of treatment resistance (Blier, 2007; Huynh & McIntyre, 20008; Rush et al., 2006, 2008). Geddes et al. (2007) assert that future trials must be at least as large as STAR*D albeit more cost efficient. The authors envision a more active role in antidepressant trials by patients and clinicians so that participation becomes "the norm rather than an isolated academic activity" (p. 544). It is ironic that given the investment in research on depression, individuals with a subtype of depression can be defined by the drugs they do not respond to, while another group is defined as "treatment-resistant" (usually, melancholic).

Pitfalls of the Monoamine Hypothesis

The Neurotransmitter Receptor Hypothesis

Although to date there is no adequate or complete understanding of how antidepressant drugs work, it was initially thought that the enhanced neurotransmitter function was responsible for antidepressant action; however, those biochemical changes occur within hours, whereas, the actual antidepressant effects often takes as long as 10 weeks of persistent treatment to determine whether or not a patient is responsive to medication (conversely, unresponsive) (Quitkin et al., 2003). As a result, it is proposed that neuron adaptation involving changes in receptor density or second messenger function is likely to play a crucial role in these drug effects (Beckham and Leber, 1995; Gotlib and Hammen, 2002; Maisto, Galizio, & Connors, 2007).

Stahl (2000) suggests that a move from the monoamine hypothesis to a neurotransmitter receptor hypothesis better elucidates the effectiveness of antidepressant drugs. Specifically, it is not the increase in neurotransmitter availability intrasynaptically that better accounts for the symptom reduction in depression, but rather, effects or changes in receptor activity is a plausible explanation for the delayed therapeutic action of antidepressants. The hypothesis proposes that antidepressants, apart from their initial actions on receptors and enzymes, ultimately instigate a desensitization, or down regulation process, of fundamental neurotransmitter receptors in a time frame that is consistent with the delayed onset of antidepressant action.

For instance, extended inhibition of MAO-A has been shown to enhance serotonerigic neurotransmission in the brain by altering both the regulation of 5-HT neuronal firing and the release of 5-HT from nerve terminals (Stamford et al., 2000).

Evidence has demonstrated that the firing rate of these cells is regulated by 5-HT$_{1A}$ autoreceptors situated on cell bodies and dendrites of serotonergic neurons (somatodendritic receptors). Stimulation of these receptors by 5-HT consequently leads to inhibition of neuronal firing and a decreased release of 5-HT from the terminal fields in the hippocampus. Increased levels of 5-HT in the dorsal raphae nucleus as a result of MAO-A inhibition results in a decrease in density of 5-HT$_{1A}$ autoreceptors, lessening the inhibition of cell firing, with a consequent increase in neuronal firing and enhanced release of 5-HT. Simultaneous to changes in serotonergic neuronal firing due to down-regulation of 5-HT$_{1A}$ receptors is a similar desensitization of alpha-2 adrenoreceptors on the 5-HT terminal fields in the hippocampus that function normally to decrease the release of 5-HT. Increased synaptic concentration of NE from MAO-A inhibition has been shown to desensitize these receptors, resulting in enhanced release of 5-HT. Overall, MAO-A inhibition leads to adaptive changes in both 5-HT$_{1A}$ and alpha-2 receptors thought to contribute to enhanced serotonergic activity (Mongeau et al., 1994).

Influences of Neurotranmitters on Subtypes of Depression

Malhi et al. (2005) present a compelling case for a functional-structural model of depression that allows for intensive exploration of the respective influences of serotonergic, noradrenergic, and dopaminergic neurotransmitters on specific subtypes of depression, namely, melancholic, non-melancholic, and psychotic depression. They criticize the predominance of studies utilizing heterogeneous clinical samples that make no distinction between the three types. They acknowledge that monoamine loss plays a central role in the etiology and continuation of depression but at the same time see an advantage to their three-tiered model, which has empirical support. For example, the

psychomotor disturbances found in melancholia and psychotic depression result mainly from abnormalities in DA activity while other features of melancholic depression related to lack of energy and drive are also associated with neurotransmission of noradrenaline. Non-melancholic features of depression including disturbed mood, appetite, and sleep, which have common characteristics with anxiety disorders, obsessive-compulsive disorder (OCD), and eating disorders, which points to a more prominent role for disturbances in 5-HT transmission. This helps explain the therapeutic impact of SSRIs on these disorders.

Further, these researchers emphasize the role of stress in the etiology of depression (which is downplayed by the monoamine hypothesis), noting that long-term exposure to stress can result in cell damage in areas of the brain such as the hippocampus.

Stewart and Reid (2002) advance the perspective that functional neuroimaging techniques have the power to extend knowledge of the neurobiology of depression beyond the actions of the monoamine system, "charting not only molecular events within individual cells…but also exploring the structure and function of networks of neurons in an effort to develop a more integrated and enriched neurobiology of depressive disorder" (p. S15). The authors find the monoamine hypothesis alone to be remarkably similar to the "humors" proposed by the ancient Greeks for explaining melancholia. The excessive "black bile" of antiquity is the "serotonin imbalance" or even the "corticosteroid-mediated 5HT1A receptor dysregulation" of the 21st century (p. S15). The authors' point is that, "Clearly, this sort of neurohumoral conceptualization—chemistry equals disorder—fails to capture important relationships between brain functioning and the clinical construct that is depressive disorder" (p. S15).

Norman (2006) agrees that the development of new classes of drugs should be guided by knowledge gained from neuroimaging studies. A consistent finding in research using magnetic resonance imaging (MRI) is that patients with depression have reduced hippocampal volumes compared to healthy control subjects (Goldapple et al., 2004; Hastings et al., 2004; Moretti et al., 2003; Neumeister et al., 2005; Videbech & Ravnkilde, 2004). Other areas implicated in depression include the prefrontal cortex and amygdala.

In summation, there have been several modifications of the monoamine hypothesis suggesting that there as yet is not a simple relationship between biogenic amines and depression. A plausible explanation for this may be that the subtypes of MDD are most likely a group of disorders differing in their underlying pathologies. Secondly, disturbances in one or several neurotransmitter systems can result in depression. Thirdly, various modulatory systems of the brain do not function independently of each other but interact at several levels. For instance, 5-HT and NE may coexist on the same neurons. Investigators are looking beyond direct dysfunction of these systems.

Some researchers suggest that the pathophysiology of depression may not be at the receptor level, but related to signals beyond the receptors. Alterations in second messenger systems and other intracellular events, including gene expression are also being examined for sites of dysfunction. For instance, lithium, commonly used for bipolar disorder works by blocking certain second messengers, dampening excessive neural activity in mania (Stahl, 2000). Therefore, although it is apparent that monoamine systems are significantly involved in the mechanism of action of antidepressants, the

underlying mechanism of damage may be related to pathology of other factors that are modulated by the monoamines.

Appendix B

Stress As a Factor in the Etiology of Depression

The significance of stress in the etiology of depression has received considerable attention in the field of neuroscience. According to Gotlib and Hammen (2002) a review of the literature suggests that: (1) a substantial number of depressed persons relative to non-depressed controls experience severe stress; (2) severe stress foretell's the clinical course of depressed persons; and (3) severe stress predicts greater levels of depressive symptoms, specificity of symptoms, and potentially symptom profiles. However, the authors also point out that congruent with the depression literature as a whole, one possible barrier to identifying a distinct stress-induced depressive subtype is the immense heterogeneity of the signs, symptoms, and presentations of MDD. They state "Different people diagnosed with major depression often display considerably different permutations of the requisite criterial features- indeed stretching the boundaries of the syndrome concept." {p. 327). The authors reference Brown et al. and Frank et al. in suggesting that prevalence of severe life events may be analogous for patients diagnosed with endogenous and non-endogenous symptomatic criteria for a first episode. In contrast, for those who experience recurrences of depression, severe events may be more prominently related to subsequent non-endogenous presentations of depression (Brown et al., 1995; Frank et al., 1994, as cited in Gotlib & Hammen, 2002).

Approximately 20-40% of depressed outpatients and 60-80% of inpatients exhibit one or more signs of elevated cortisol secretion in response to stress (Gotlib & Hammen, 2002). Hypercortisolism is reported to be one of the most consistent neuroendocrine abnormalities in depressed persons, distinguishing between milder forms of MDE versus

the more restricted subtypes (e.g., endogenous depression). Several hypotheses have been proposed to explain the relationship between stress and depression.

Glucocorticoid Cascade Hypothesis

Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation in Depression is a key to understanding the glucocorticoid cascade hypothesis (Sapolsky et al., 1985) where changes in monoamine activity associated with depression are thought to be linked to a broader pattern of effects related to the brain's response to sustained stress. It has long been established that increased HPA activity is the trademark of mammalian stress responses. Partially under the control of phasic NE (activating) and tonic 5-HT (inhibitory) neurotransmission, the HPA stress response system functions to maintain equilibrium and serves as a coping mechanism for acute stress.

In response to stress, the hypothalamus is reported to communicate messages to the endocrine glands via two major pathways which work simultaneously in their response: (1) the sympathetic division of the autonomic nervous system (SNS) for "fight" or "flight" increases heart rate and blood pressure, resulting in the release of epinephrine and NE from the inner part of the adrenal glands; and (2) the hypothalamic corticotrophin-releasing hormone (CRH) neurons which are normally controlled by other areas of the CNS, namely the amygdala key to emotional responses stimulates the CRH circuit, while the hippocampus rich in glucocorticoid receptors provides inhibitory control in the presence of increased glucocorticoid levels (Wade & Tavris, 2006).

Specifically, the hypothalamus generates increased levels of CRH in response to activating NE, cholinergic, and glutaminergic inputs (to perceived threat). CRH then stimulates the release of adrenocorticotropin-releasing hormone (ACTH), which travels

from the anterior pituitary gland via the bloodstream to the cortex of the adrenal glands where glucocorticoids are synthesized. Upon stimulation by ACTH, glucocorticoid hormones (cortisol) are released into the bloodstream facilitating short-term survival in response to stress. Taken together, glucocorticoids and secretions from the SNS account for an array of physiological and behavioral responses.

The entire HPA axis is regulated by a system of inhibitory control through negative feedback loops to the pituitary, the hypothalamus, and the hippocampus. As acute stress is resolved, elevated plasma cortisol levels normalize within minutes or hours (Gotlib & Hammen, 2002). According to the *glucocorticoid cascade hypothesis* of depression, high levels of glucocorticoids due to prolonged stress cause significant damage to the hippocampus, namely, alterations in hippocampal morphology such as reduced synaptic plasticity, cell loss, atrophy of dendrites and a reduction in neurogenesis which may account for the frequent cognitive deficits seen in depression. As such hippocampal dysfunction may contribute to over-activity of the HPA axis.

Neurotrophic Hypothesis

Researchers investigating the possible mechanisms underlying hippocampal cell loss following stress have proposed the *Neurotrophic Hypothesis.* Neurotrophic factors are key proteins needed during brain development and for regulating changes in cells and their survival in adult brains. The hypothesis proposes that low brain-derived neurotrophic factor (BNDF) may be culpable for the loss in dendritic branches and spines and that antidepressants may be able to protect cells by preventing the decrease in BNDF. Evidence in support of this hypothesis derives from studies conducted on both animal models and humans. For instance, chronic stress is shown to reduce BNDF in the

hippocampus of rats. Moreover, chronic but not acute antidepressant treatment increases BNDF in both humans and animals, suggesting that perhaps depression is related to a downregulation of neurogenesis which can be reversed with antidepressant treatment (Meyer & Quenzer, 2005).

The Neurogenesis Hypothesis

Related to the neurtrophic hypothesis is the *neurogenesis hypothesis*. Neurogenesis is described as the process by which cells proliferate, survive and differentiate into different neurons. Until recently, this was only thought to occur at birth, as the majority of granule neurons are produced during the first two postnatal weeks of life. However, recent studies indicate that neurogenesis does in fact occur in the adult brain with the hippocampus as one of two primary sites. Hippocampal neurogenesis and its potential cause and cure of depression is gaining momentum among neuroscientists. As mentioned previously, alterations in hippocampal morphology have been demonstrated in both humans and animal models of depression (D'Sa & Duman, 2002).

Manev, Uz, Smalheiser, & Manev, (2001) and Malberg, Eisch, Nestler, & Duman (2000) have linked neurogenesis to the beneficial actions of certain antidepressants, suggesting a relationship between decreased hippocampal neurogenesis and depression. Santarelli et al (2003) demonstrated that behavioral effects of antidepressants in mice did not transpire when neurogenesis was prevented with x-irradiation techniques. Further, adult-born neurons were shown to be more excitable versus older neurons due to a differential expression of GABA receptors. The authors suggest that a possible model is that these neurons enhance the role of the hippocampus in the negative feedback mechanism of the HPA-axis, and potentially in inhibiting the amygdala. This idea is

consistent with a number of findings relating stress-relieving activities to amplified levels of neurogenesis. Increased glucocorticoid levels during stress may reduce neurogenesis. Furthermore, animals exposed to physiological stress or psychological isolation exhibit noticeably decreased levels of adult-born neurons (Santarelli et al., 2003).

Studies have hypothesized that learning and memory deficits are associated with depression, and have proposed that neurogenesis may promote neuroplasticity. For instance, Castren (2005), has proposed that mood may be regulated at a base level by plasticity, and therefore not chemistry, and that the effects of antidepressant treatment are only secondary to this.

In summation, if there is reduced hippocampal size due to inhibited neurogenesis as found in several studies, this may consequently lead to reduced inhibitory feedback, increased coritsol release, and further hippocampal damage, in essence a snowball effect. However, what is not definitive is the direction of causality- does depression cause hippocampal volumetric reductions or do small hippocampi predispose an individual to depression. Hippocampal volumes do correlate significantly with the duration of the depressive episodes, suggesting that stress and/or depression may lead to hippocampal volume loss as evidenced in neuroimaging studies (Videbech, 2005).

Appendix C

Functional Neuroimaging in Depression

In recent years, a combination of neuroimaging techniques (PET, SPECT, MRI, fMRI) has significantly advanced our knowledge of MDD, because they graphically illuminate both the complex underpinnings of depression and the divergent manifestations of depressive symptoms. A common application of these tools in depression research has been to measure during resting state and/or active conditions, regional cerebral blood flow (rCBF) and glucose metabolism (Gm) in depressive patients during various phases of illness. However, there is no consensus as to the specific locations and directions of abnormalities in rCBF and Gm in depressed samples (Drevets,1998; Drevets et al, 2002).

Drevets (1998) deems MDD particularly conducive to functional neuroimaging techniques aimed at revealing underlying pathology, because neuroimaging reflects abnormalities in brain function, but does not reflect gross neuropathology. Drevets presented a detailed review of neuroimaging studies, extolling the promise of this line of research while calling attention to flaws in many existing studies. As in other areas of depression research, there is frequent reliance on small heterogeneous samples. Other issues are unique to the application of neuroimaging techniques. One is the failure of most studies to control for the effects of medication on blood flow and metabolic activity. This is somewhat ironic since the impact of medication on neurotransmitter activity is the mechanism of action of antidepressants. This problem might be addressed in future studies by taking baseline data from subjects who are beginning medication. Thus far, few studies provide this control. Therefore, Drevets's critique that the findings of

imaging studies vary considerably continues to hold true (Fountoulakis et al., 2004; Hastings et al., 2004; Pagani et al., 2007; Pizzagalli et al, 2002; Pizzagalli et al., 2004; Videbech & Ravnkilde, 2004; Zipursky et al., 2007).

At the most basic level, some inconsistencies in test findings may be due to differences in terminology used to denote the anatomical structures of the brain. (This, in itself, is a compelling argument to promote clarifying and standardizing the body of knowledge surrounding this topic.) Small sample sizes, differences in age, gender, and symptom patterns of subjects across studies, as well as technical issues related to imaging techniques and analysis, and failure to control for medication effects have all been cited as explanations for the conflicting results. Drevets (2001) further highlights the vast diversity of symptoms found in depressive disorders to account for incongruities in imaging studies.

Smith and Cavanagh (2005) further highlight the inconsistency of these findings, and suggest reasons for these inconsistencies by noting the variance of depressive symptoms:

> As with many psychiatric disorders, the term “depression” fails to capture the considerable variations in symptoms and signs that exist between different depressive subtypes….When we consider that some of the SPECT studies carried out to date have tended to use patients from several of these different subtypes in the same study, it is perhaps unsurprising that many of the findings reported so far have been inconsistent”. (p. 197)

A key issue unique to this research model hinges on the capabilities/limitations of the various types of imaging technologies (PET, SPECT, and fMRI) to be used, and the gradual resolution of the problems associated with each. Further to this issue of technical limitations, while Insel (2007) considers functional neuroimaging techniques valuable for identifying brain regions associated with depression, he questions whether present PET and fMRI techniques can effectively "capture the real-time dynamics of brain function that are most relevant to mood and cognition" (p. 1). Additionally, few investigators have carried out longitudinal studies that would allow for observation of changes over time, for example during episodes of depression and remission of symptoms (Hugdahl et al., 2007; Videbech & Ravnkilde, 2004).

However, Drevets' (1998) vision of the future of neuroimaging research is embodied [in positive findings] from studies conducted within the last few years. For example, Drevets envisioned the use of PET and fMRI to examine brain activity *during* the performance of cognitive and emotional tasks, and Hugdahl et al. (2007) recently examined changes over time in patients whose symptoms were in remission, and, as well they were able to observe patients while they performed real-time calculation tasks.

Despite problems, neuroimaging studies provide valid evidence that both supports and challenges entrenched theories of depression (for example, the monoamine hypothesis), and, as well poses questions, which advance future research guidelines into the mechanisms of major depression, along with their resulting treatment implications.

Neuroanatomical Structures Implicated in Depression

As elucidated by neuroimaging studies, significant involvement of the limbic system, a complex of structures including the amygdala, hippocampus, and parts of the anterior cingulate cortex (ACC) has been implicated in the pathophysiology of mood disorders. Investigators have also examined cortical structures of which the prefrontal cortex (PFC), particularly the dorsolateral prefrontal cortex (DLPFC) has gained much interest in its regulation of emotion in depression and cognitive control (Davidson et al.,2002).

Hippocampus

In recent years, the hippocampus has increasingly been implicated as a key structure involved in depression, as it plays a significant role in many of the functions impaired in depressed persons, including declarative, contextual, and spatial learning and memory (Burgess, Maguire, & O'Keefe, 2002; Fanselow, 2000; Ravnkilde, & Videbech, 2002; Veiel, 1997), adverse reactions to stress, and altered neuroendocrine functions.

Since 1993, MRI scans have been used to explore alterations in the volume, density, and water content of the hippocampus in patients with unipolar depression (Videbech & Ravnkilde, 2004). These studies have yielded contradictory results. For instance, some volumetric studies have found significant bilateral deficits in depression (MacQueen et al., 2003; Sheline, Sanghavi, & Mintun, 1999). Alternatively, some studies have reported significantly lower volume in the right hemisphere (Bell-McGinty et al., 2002; Steffens et al., 2000) or in the left hemisphere (Bremmer et al., 2000; Mervaala et al., 2000), but numerous studies have failed to find any differences (Frodl et al., 2002; Posener et al., 2003; Vakili et al., 2000). Similarly, inconsistencies are found

between measurements of hippocampal volume and clinical characteristics (Mervaala et al., 2000; Steffens et al., 2000).

Drevets (1998) attributes some of these discrepancies to limitations in the scope and sensitivity of the technology and the techniques used by researchers to compensate for these limitations. Differences in scanning techniques, even under optimum conditions, make comparisons difficult. Other reasons for discrepancies involve differences in subject selection, with many studies failing to control for variables such as subject age, age of onset of depressive symptoms, and course and duration of illness.

Videbech and Ravnkilde (2004) undertook an extensive research review and meta-analysis of MRI studies of hippocampal volume in patients with unipolar and bipolar depression. A total of 12 studies of unipolar depression met the researchers' inclusion criteria, yielding a sample of 351 subjects with depression and 270 healthy control subjects. The overall subject pool was extremely diverse in terms of gender, age, age of onset of depression, average number of depressive episodes, and treatment responses. Analysis of the aggregate data revealed significantly decreased hippocampal volume in the presence of depression. According to the weighted average, patients with depression had reduced hippocampal volume of 10% in the right hemisphere and 8% in the left hemisphere. The most striking finding was the strong correlation between the number of depressive episodes and reduced volume in the right hemisphere only. Videbech and Ravnkilde note that this phenomenon is consistent with the "so-called glucocorticoid cascade hypothesis" suggesting that elevated levels of cortisol frequently observed in patients with severe depression promote neuron loss via apoptosis

(programmed cell death) or by impeding neurogenisis (p. 1964). At the same time, the authors do not rule out other possible explanations.

Videbech and Ravnkilde further emphasize that the cross-sectional studies that predominate in neuroimaging research cannot illuminate the causes of hippocampal damage. They consider longitudinal studies essential for drawing any reasonable conclusions. They also recommend future research into the impact of childhood trauma on hippocampal volume, noting the overlap between depression and PTSD. Some studies have found reduced hippocampal volume in patients with PTSD. This line of research is consistent with the theory of Matza et al. (2003) regarding AD and PTSD.

Similarly, Neumeister et al. (2004) built on the theory that high levels of cortisone in depression are related to decreased hippocampal volume. Observations of this phenomenon have generated conjecture that elevated cortisol might induce changes that affect cognitive performance. The investigators find support for this theory from research, which demonstrated the most marked decrease in hippocampal volume in cases of depression characterized by: early onset, numerous depressive episodes, prolonged periods of untreated depression, and histories of childhood abuse. The reduction is most apparent in the posterior hippocampus, which is congruent with evidence, which reflects learning and memory disturbances in episodes of major depression. Using MRI scans to scrutinize targeted hippocampal areas, Neumeister et al. averaged the volumes of these hippocampal areas in non-medicated depressed patients and compared them to normal control subjects. As anticipated, the depressed subjects had lower hippocampal volumes limited to the parameters of the posterior hippocampus. They surmise that this effect

reflects cellular alterations in serotonin receptor and neurotropin mechanisms, possibly associated with excessive cortisol levels.

Amygdala

The amygdala has been shown to play an important role in emotionally mediated attention, in the perception of and assigning emotional significance to stimuli, and in remembering significant events (Phelps, 2008). Studies examining amygdala volume in depression have yielded contradictory findings. In a number of structural neuroimaging studies, researchers have examined differences in amygdala volume between depressed and non-depressed individuals. Some studies have reported depressed individuals to be characterized by smaller amygdala volume than non-depressed individuals (e.g., Caetano et al., 2004; Sheline, Gado, & Price, 1998; Sheline, Sanghavi, Mintun, & Gado, 1999). Alternatively, studies have reported greater amygdala volume in depressed individuals (e.g., Lange & Irle., 2004), while others have reported no differences in amygdala volume between depressed and non-depressed individual (e.g., Munn et al., 2007).

In a review of the literature on amygdala volumetric studies, Hamilton, Siemer, and Gotlib (2008) point out that discrepant findings across studies may be better accounted for by several different factors across studies (e.g., antidepressant medications, chronic stress, age and gender composition of samples studied). Taking these factors into consideration, the authors conducted a meta-analysis on 13 MRI studies investigating volumetric abnormalities in the amygdala. Specifically, based on the literature, they predicted that: (1) there would not be a reliable difference between depressed and non-depressed individuals given the inconsistent findings thus far in volumetric studies; (2) variation in antidepressant use and chronicity of depressive illness, but not age and

gender would predict significant variation in amygdala volume differences. Specifically, from evidence that antidepressant medication supports neurogensis, it was predicted that average amygdala volume in depressed, relative to non-depressed control samples would increase with the proportion of medicated individuals in depressed samples; and (3) in line with studies showing volumetric decreases in the hippocampus associated with recurrence of depression, it was predicted that amygdala volume in these samples would decrease relative to controls as a function of increasing chronicity of depression.

The authors found no collective difference in amygdala volume between depressed individuals and healthy controls. However, a significant inter-study variability in the difference between depressed and non-depressed groups in amygdala volume was reported. Specifically, as the proportion of medicated participants across studies increased, amygdala volume in depressed participants significantly increased relative to control participants. In contrast, for studies with only un-medicated depressed participants, amygdala volume was found to be significantly lower in depressed relative to control participants. In addition, chronicity of depression did not predict variability between groups in amygdala volume across studies.

In light of these findings, the authors note that their findings are consistent with studies reported in the literature showing decreased hippocampal volume in depression. Moreover, they suggest that the stress-induced glucocorticoid excitotoxicity that is hypothesized to underlie hippocampal atrophy in depression (e.g., Sapolsky, 1985) may serve as a potential moderator of amygdala volume loss in depression, given that like the hippocampus, the amygdala is rich in glucocorticoid receptors. Furthermore, the results support the notion that an antidepressant mediated increase in levels of BDNF promotes

neurogenesis and protects against glucocorticoid toxicity in the amygdala in medicated but not in un-medicated depressed individuals (Hamilton Siemer, and Gotlib, 2008).

Evidence for anomalies in amygdala functioning comes from functional neuroimaging studies. For instance, PET studies have documented elevated baseline amygdala activity in depressed persons compared to non-depressed individuals. Furthermore, within depressed persons, elevated baseline amygdala activity is found to be positively correlated with symptom severity, and reported to return to normal with antidepressant medication (e.g., Drevets, Bogers, & Raichle, 2002).

Studies have also reported heightened amygdala reactivity to emotional stimuli in depressed relative to non-depressed individuals, and particularly to negatively valenced stimuli (e.g., Sheline et al., 2001). However, some researchers have also found abnormal amygdala reactivity to positively valenced stimuli, but these findings are less consistent in their direction (i.e., increased or decreased) of amygdala reactivity (Canli et al., 2004; Sheline et al., 2001).

Prefrontal cortex

Insel (2007) argues that there is compelling evidence to suggest that attention should focus on the PFC, particularly a site in the midline subgenual ACC, frequently referred to as Broadman area 25. Further, he is skeptical with studies that suggest a proposed link between the hippocampus and depression. In his view, none of the neuroimaging or postmortem studies has produced findings unique to the hippocampus or to MDD. In addition to the presence of abnormalities revealed by structural and functional scans, the PFC is rich in 5-HT transporters and is a target site for many

antidepressant agents. Other authors agree that the PFC sites appear to be central to MDD (Coryell et al., 2005; Fales et al., 2008; Hastings et al., 2004; Johnstone et al., 2007).

Along these lines of research, Hastings et al. (2004) conducted a substantive test. They utilized MRI scans to simultaneously explore volumes in the PFC, hippocampus, and amygdala in patients diagnosed with MDD. Their sample included 10 women and eight men and a matched control group of healthy volunteers. A key aim of the study was to examine gender differences. An intriguing finding was that there was no difference in hippocampal volume between depressed and non-depressed subjects for either gender, which contradicted the majority of research findings thus far (e.g., Videbech & Ravnkilde, 2004). Neither were there significant differences in volume in the orbital PFC, despite the expectations with which Hastings et al. entered the study. Differences between depressed and non-depressed subjects emerged in the inferior anterior cingulate, demonstrating a 23% reduction in volume in depressed men and an 11% reduction in depressed women. Depressed women showed a smaller amygdala compared to the healthy controls but the same effect was not apparent in depressed men. Given the different patterns observed in depressed men and women, Hastings et al. recommend further investigation of gender differences, which may have implications for better targeting pharmacological treatment of depression.

Coryell et al. (2005) have also conducted tests to examine the PFC as a primary location for depression. They used MRI techniques to examine the PFC in 10 subjects, who had been diagnosed with MDD with psychotic features and who were recruited from a longitudinal study of recent onset psychosis. Comparisons were conducted with 10 matched subjects, who had been diagnosed with schizophrenia and 10 healthy control

subjects. No significant group differences emerged in the volume of the anterior subgenual PFC. However, subjects with psychotic depression had the smallest volumes in the left side of the posterior subgenual PFC. In addition, the depressed subjects were more likely to exhibit increases in volume of the posterior subgenual PFC at the six-month follow-up than those with schizophrenia. Coryell et al. found their observations consistent with evidence that hyperactivity of the HPA axis is most prevalent in patients with psychotic depression than any other depressive subgroups.

One of the most consistent findings reported in depression research has been abnormalities of function within the DLPFC region. Consonant with the high levels of rumination evidenced in depression, researchers have proposed that this may reflect difficulties in cognitive control, and that consequently depression is typified by low levels of activity in the DLPFC. Several researchers have reported lower-resting-state DLPFC activity in depressed persons relative to healthy individuals (Gonul, Kula, Bilgin, Tutus, & Oguz, 2004; Mayberg et al., 2005). Further support of lower DLPFC activity comes from tryptophan depletion studies. In PET studies of induced depressive relapse through tryptophan depletion, individuals who relapse are reported to have lower DLPFC activity during relapse in comparison to individuals who do not relapse (Bremner et al., 1997). Similar to these findings, studies have shown depressed individuals to show evidence of less DLPFC reactivity to negative affective stimuli compared to healthy controls. For example, one study found that depressed individuals failed to activate the DLPFC while listening to taped criticisms from their mothers unlike healthy controls (Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005). This finding was has also be shown for positive affective stimuli. For example, Schaefer, Putnam, Benca, and

Davidson (2006) reported reduced reactivity of the DLPFC in depressed subjects in response to erotica and positive emotions faces. Collectively, these studies support the functional abnormalities in the DLPFC in depression.

Given the decreased reactivity of the DLPFC, Mayberg et al. (1999) proposed a neural model in which the normal reciprocal relationship between the limbic system and dorsal cortical structures are thought to be imbalanced, or skewed in depression. The authors depict a "vicious" circle in which hyperactivation in limbic structures (e.g., amygdala and subgenual ACC) dampens activation of in dorsal structures, impeding the ability of the latter to regulate limbic activation (Mayberg et al., 1999, as cited in Gotlib & Hamiltion, 2008, p.161).

Neurotransmitter Activity

Drevets (1998) predicted the increasing use of PET and SPECT to analyze and quantify neuroreceptor binding and neurotransmitter activity, which would allow for greater elaboration of neurochemical disturbances implied by studies of neuroendocrine activity, bodily fluids, and postmortem tissue.

Zipursky et al. (2007) conducted a research review of studies using PET and SPECT to investigate the neuropathology and treatment of depression, schizophrenia, and dementia. The authors note that recent evidence, which suggests that the loss of monoamines in major depression varies across individuals and is greater with the severity of depression, contradicts the original theory that the three monoamines, 5-HT, NE, and DA, are comparably lower in individuals diagnosed with the disorder. According to the original monoamine theory, untreated individuals with depression should register increased 5-HT receptor density due to an increase in density that occurs when

extracellular 5-HT is low. But, two PET studies conducted to measure serotonin receptors in untreated subjects of fairly large sample sizes found no difference during episodes of depression. However, higher 5-HT binding potential (an indicator of serotonin receptor density) was observed in individuals who exhibited pessimism as a character trait.

Zipursky et al. note that other imaging studies have shown a relationship between 5-HT binding potential and pessimism, suggesting that low extracellular 5-HT intensifies feelings of pessimism, which is congruent with findings that serotonin plays a role in altering levels of pessimism. They add that fenfluramine, a drug that increases 5-HT, can quickly decrease pessimism. According to Zipursky et al. "These findings suggest that particular symptoms of depression, rather than the diagnosis of depression per se, reflect lowered levels of different monoamines in the brain" (p. 151).

Additional findings from PET studies offer support for the idea that the 5-HT transporter and DA transporter contribute to the loss of monoamines during untreated episodes of MDD thus intensifying the symptoms (Zipursky et al., 2007). As to their respective roles, regional 5-HT transporter binding potentials are increased during depressive episodes characterized by more severe pessimism, and regional DA binding potential is increased during depressive episodes characterized by greater psychomotor retardation. Given that "these transport sites remove their respective monoamines from functionally relevant extracellular locations…these results may be interpreted to argue that greater monoamine density facilitates monoamine loss, which in turn contributes to greater severity of depressive symptoms" (p. 151).

Supplementing this theory, Meyer (2007) conducted a detailed analysis of studies focusing on the 5-HT transmission system. He notes two reasons there is no direct

evidence of low 5-HT in patients with major depressions. First, it is impossible to measure 5-HT directly in vivo; and, using animal simulations it is probable that 5-HT levels are destabilized within a relatively short time after death.

Second, postmortem examinations of 5-HT levels have not included non-medicated subjects who were experiencing MDE. As a result, the assumption that extra-cellular 5-HT is low during depressive episodes is based on the remission of symptoms after taking 5-HT increasing antidepressant medication, depressed mood following lower 5-HT levels, and alterations in indicators of serotonin 2 receptor density in major depression and suicide. In explanation the evidence linking low 5-HT and suicide, Meyer invokes the studies of pessimism analyzed by Zipursky et al. (2007). In effect, the more intense feelings of hopelessness are associated with lower levels of 5-HT (Meyer, 2007).

Further, based on existing research, Meyer concluded that low 5-HT does not adequately explain treatment resistant depression. He speculates that future research will be concentrated on the development of novel antidepressants that bind to the 5-HT transporter and other potentially therapeutic sites with high binding properties.

Cognitive Functioning and Symptom Remission

Atchley and Ilardi (2007) single out the study of Hugdahl et al. (2007) as an excellent example of research exhibiting "a good fit between the theoretical goals, empirical questions, and the research tools applied" (Atchley & Ilardi, 2007, p. 143). In an innovative application of functional neuroimaging to depression, Hugdahl et al. (2007)

explored changes in brain activation in nine patients who had experienced recurrent MDD over a period of two years.[11]

Hugdahl et al. used fMRI measuring the BOLD contrast to record neuronal activity in nine patients with MDD while they carried out a simple mathematical task. The task was selected on the rationale that it synthesizes key elements of attention, working memory, and executive functions and represents a real world activity. The depressed participants were five women and four men under treatment at outpatient and inpatient clinics. They were taking different antidepressants, primarily SSRIs. Nine non-depressed participants served as a control group. The scans were conducted at the beginning and end of a two-year period.

At the second MRI session, the depressed group showed significantly enhanced activation in the inferior frontal gyrus and the superior and inferior parietal lobule compared to the initial images. The areas involved were Broadman 40, 44, 45, in the frontal lobe and area 7 in the parietal lobe. Enhanced activation was also observed in the posterior cingulate. Hugdahl et al. propose that the changes observed in the inferior frontal gyrus may be a direct manifestation of changes in information processing ability as a result of clinical remission. They also suggest that the increased activations may indicate enhanced ability for both mental calculation and working memory. The overall

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[11] The researchers note that the vast majority of MRI and PET studies were cross-sectional in design thus providing a "snapshot" into the neuronal underpinnings of depression. However, no prior study "investigated brain activation in response to cognitive challenges in depressed patients over time as correlates of clinical improvement" (p. 148). From one perspective, neuronal activity in brain regions involved in depression could be normalized as depression remits. Alternatively, clinical recovery could be contingent on the normalization of blood perfusion and activation in key brain regions.

implication is that “patients experienced restored aspects of effortful and cognitively demanding processing associated with clinical remission” (p. 157).

Overall, the correlation with neuronal activation showed a negative correlation particularly in the inferior frontal and parietal lobe areas, which overlapped with similar areas activated in the healthy control participants. This may indicate a tendency towards normalization of brain activation in the patients as a function of time from an illness phase to a remission state. (p. 157)

Scores on the HDRS showed that seven of the nine depressed subjects had significant clinical improvements over the two-year period. All were assessed as “severe” at the onset of the study; at the second session, two patients were still in the “severe” range, five were “mild” and two were fully recovered (Hugdahl et al., 2007). Given that this was the first neuroimaging study to use a longitudinal design, the small sample size is understandable. Future studies would be enhanced by larger sample size, especially to further investigation of participants with different responses to treatment.

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