Chapter 3

Differential Risk for Emotion Processing Difficulties by Gender and Age in Major Depressive Disorder

Sara L. Wright1,2 and Scott A. Langenecker1, 3
1University of Michigan Medical School, Department of Psychiatry
2Ann Arbor Veterans Affairs Medical Center, Geriatric, Research, Education, and Clinical Center (GRECC)
3 Depression Center, Molecular and Behavioral Neuroscience Institute, University of Michigan

Abstract

Background: Differences in emotion processing during Major Depressive Disorder (MDD) have not been well explored as a potential explanation for age and gender disparities in rates of depression and depressive symptoms. Early studies by our group demonstrated that those with MDD underperform in emotion processing of faces, although recently we showed a selective decrement in young women with MDD. We now extend this study of gender differences in facial emotion processing during MDD to the full age spectrum. We assessed emotion processing performance using posed facial emotional expressions in those with early (age < 36) and late (age > 35) MDD as well as in women and men to determine if there was differential impact of MDD in these four groups. We hypothesized that knowledge about gender, age, and emotion processing performance differences might increase understanding of risk for and expression of MDD in women and in those with later onset MDD.

Methods: Participants included 161 young adults (123 women, 38 men) and 150 adults (100 women, 50 men) diagnosed with MDD, as well as 97 young adult (60 women, 37 men) and 35 adult (24 women, 11 men) healthy controls. A conservative age classification ≤ age 35 was used to separate young adult and adult control and MDD groups in order to be confident that potential causes of late onset MDD (e.g., cardiovascular) were less likely to be present in the young adult MDD groups.

Results: There was an interaction between age, gender, and MDD status for response time, with slower response times in young MDD patients compared to their age-matched control groups. This effect of slower response time was not detected in the comparisons
between adults with and without MDD. Young adult and adult women and adult men with MDD made significantly more errors than did their same-age, same-gender control counterparts (p < .05), whereas young men with MDD performed similarly to same-age control men (p > .26). Further, although adult women and men with MDD performed more poorly in facial perception relative to same age control cohorts, older men with late onset MDD performed worse than older men with early onset MDD, in contrast to no difference between performance of women with late and early onset MDD.

Conclusions: These findings suggest that young men with MDD may have a different neurobiological etiology of depression compared to young women. In contrast, older men and all women with MDD appear to have similar difficulties with emotion processing, suggesting comparable neurobiological mechanisms of illness. Notably, older men with late onset MDD appear to have a greater burden of emotion processing deficit compared to other depressed groups.

Keywords: psychiatric disorders, affect perception, gender differences

Introduction

Women are nearly twice as likely as men to be diagnosed with Major Depressive Disorder (MDD; American Psychiatric Association, 2000). These gender differences persist into middle and older adulthood (Weissman, Bruce, Leaf, Florio, and Holzer, 1991), despite that the mechanisms underlying depression during older age likely broaden to include medical illness, cerebrovascular and cardiovascular events, dementia, hypercortisolemia, and loss of a spouse relationship through death (Blazer and Hybels, 2005; Goldstein and Gruenberg, 2007; Holley and Mast, 2007; Wright and Persad, 2007). While rates of MDD during middle and old age are similar to those observed in young samples, and even decline in the oldest age groups, prevalence of clinically significant depressive symptoms increases (Weissman et al, 1991). These numbers are often difficult to capture due to increased primary and secondary morbidity in older adults with MDD, yet it does appear that a gender bias in the prevalence of depression is continuous throughout the lifespan. Various biological, cognitive, and interpersonal hypotheses have been offered and tested to explain gender (Geerts and Bouhuys, 1998; Grigoriadis and Robinson, 2007; Joiner, 2000; Lara and Klein, 1999) and age (Blazer and Hybels, 2005) differences in prevalence rates and characteristics of depressive symptoms. This chapter will explore facial emotion processing ability as a possible variable underlying age and gender differences in depression.

Emotion Processing Construct and Neuroanatomical Correlates

Emotion processing and categorization are necessary for successful communication and adaptive social behavior. Indeed, those with the most adaptive social behavior are often the most successful, and attempts to integrate the concept of emotional intelligence into cognitive and affective neuroscience predate these terms themselves (Thorndike, 1920). In a recent
Emotion Processing in MDD

formulation, Phillips, Wayne, Drevets, Rauch, and Lane (2003a) contend that emotion processing entails a three-step process, including 1) identifying and appraising the emotional significance of the stimulus; 2) producing autonomic, neuroendocrine, somatomotor, and affective responses to the stimuli; and 3) regulating the affective response, which can involve inhibitory and modification processes. We add that the individual can make adaptive social and behavioral responses only with accurate emotion perception. Behaving in accord with accurate perceptions can help ameliorate any potential social discord. For example, those with higher non-verbal decoding ability in communication are more likely to be successful in their professions, particularly those that rely on social interaction for success (e.g., foreign service workers, teachers, and therapists, Rosenthal, 1979). As such, it is reasonable to conclude that an interpersonal basis for depression could be the end result of poor emotion perception, poor control of one’s emotional responses, or inability to execute corrective behaviors and strategies in social relationships. We have focused largely on emotion perception accuracy as a critical mediating factor in the etiology of depression, and have, along with others, repeatedly demonstrated emotion processing decrements in individuals with depression, described in greater detail below.

Cognitive and affective neuroscience studies exploring the neurophysiology of facial emotion perception and processing have burgeoned in the last decade. Indeed, early work with tumor and lesion patients demonstrated a right hemisphere bias in the processing of facial characteristics, particularly the emotional aspects of faces (Bowers et al., 1985; Ley and Bryden, 1979). More, specifically, the fusiform face area (FFA) has been specifically linked to face recognition and identification (Grill-Spector, Knouf, and Kanwisher, 2004), and the amygdala and ventral striatal regions have been implicated in the processing of specific types of emotions (Adolphs, Tranel, Damasio, and Damasio, 1994; Gur, Skolnick, and Gur, 1994). Emotion discrimination is a complex cognitive process that involves multiple cortical and limbic areas. Phillips and colleagues (2003a) propose that a ventral system (i.e., amygdala, insula, ventral striatum, ventral anterior cingulate gyrus, ventral prefrontal cortex) is responsible for identifying and generating an emotional response and a dorsal system (i.e., hippocampus, dorsal anterior cingulate cortex, dorsal prefrontal cortex) is accountable for planning an appropriate behavioral response and regulating affect.

The early research into the laterality of facial emotion processing suggested a more critical role for the right hemisphere in emotion processing (e.g., Borod, Koff, Perlman, Lorch, and Nicholas, 1986; Bowers et al., 1985; DeKosky, Heilman, Bowers, and Valenstein, 1980). More recent functional imaging studies, however, have also shown activation of the left hemisphere, especially during processing of sad and fearful faces (e.g., Blair, Morris, Frith, Perrett, and Dolan, 1999; Iidaka et al., 2001). It has been suggested that the left hemisphere is involved in the analytic tasks associated with facial emotion processing, while the right hemisphere may be responsible for holistic processing (Sergent and Bindra, 1981). Further, as most of the emotion processing task literature studies facial emotion processing, one might suspect that the right hemisphere dominance for emotion may be in part mediated by this factor. Even so, there is one study that controlled for visual spatial acuity that still showed a relative, greater deficit in those with right hemisphere damage (Bowers et al., 1985). Further, a recent study by our group demonstrated no difficulty on visual perception and categorization of animals by patients with left or right hemisphere damage, whereas the
left hemisphere damage group performed worse than published norms and the right hemisphere damage group performed worse than the left hemisphere damage group on categorization of faces (Paradee, Rapport, Lumley, Langenecker, Hankes, and Whitman, in press).

Depression and Emotion Processing

The present line of research follows from the premise that the etiology of depression in at least some individuals is secondary to deficient emotion processing skills. Indeed, interest in this line of inquiry has expanded greatly in recent years, including behavioral and functional imaging studies. Individuals with MDD tend to remember events more negatively than controls (see Matt, Vazquez, and Campbell, 1992 for review). Further, those with depression generally perceive environmental stimuli as more negative than do individuals who are not depressed (Hollon and Kendall, 1980). One study reported that subjects with MDD recognize angry facial expressions better than happy expressions (Gilboa-Schechtman, Erhard-Weiss, and Jeczemien, 2002), although we have shown a bias in young women with depression to overendorse anger as the emotion expressed (Wright et al., submitted). This is in the context of decreased accuracy in categorizing sad and fearful expressions; an effect that was not present in young men with depression.

Inaccuracies in classification of emotional facial expressions are also more frequent among depressed than non-depressed individuals, both during their categorization (e.g., Deldin, Keller, Gergen, and Miller, 2001; Gotlib and Hammen, 1992; Gur, Erwin, Gur, Zwil, Heimberg, and Kraemer, 1992; Langenecker, Bieliauskas, Rapport, Zubietal, Wilde, and Berent, 2005; Langenecker et al., 2007a; Mikhailova et al., 1996; Rubinow and Post, 1992; Surguladze, Young, Senior, Brébion, Travis, and Phillips, 2004) and when self-simulated (Jaeger, Borod, and Peselow, 1986). However, the kinds of errors reported as characteristic of depressed patients varies across the literature. For example, Gur and colleagues (1992) found that depressed patients made more false negative categorizations for positive stimuli, more true positive categorizations for negative stimuli, and more frequently interpreted neutral faces as sad than did controls. The bias toward over-interpretation of neutral faces as sad has been replicated and was related to risk of relapse in one study (Bouhuys, Geerts and Gordjin, 1999). In contrast, other studies have found that depressed patients are more likely than controls to classify sad faces incorrectly and are no different from controls in identifying neutrally posed expressions (Mikhailova, Vladimirova, Iznak, Tsusulkovskayo, and Sushko, 1996; Rubinow and Post, 1992), or that controls make more errors in classifying happy expressions (Langenecker et al., 2005; Surguladze et al., 2004). Still others have found no evidence that depressed patients perform more poorly in recognizing any particular types of emotional expressions (Persad and Polivy, 1993).

Inconsistencies in the reported literature about the error patterns of participants with MDD may be explained in part by sample differences (e.g., inpatient as opposed to outpatient samples), differing diagnostic criteria, inclusion/exclusion of comorbid illness, and methodological variability across studies. For example, some studies have presented facial expressions for very brief periods of time (80-300 ms) using a computer (Langenecker et al.,
Emotion Processing in MDD

2005, Mikhailova et al., 1996), whereas others have asked participants to match expressions with key photographs that most closely resemble the posed expressions (Rubinow and Post, 1992). The one study that detected no differences between groups (Persad and Polivy, 1993) gave no categorization time limit to participants, which may account for the null findings. It is critically important to attempt to simulate as much as possible the real-time demands of processing emotions in experiments with depression, as these studies are more likely to reflect the real-life challenges of those who suffer from depression (Langenecker et al., 2005).

Few studies of facial emotion processing deficits among patients with MDD have specifically examined differences in reaction time to faces among individuals with and without MDD and those that have asked this question have yielded equivocal findings. Langenecker and colleagues (2005) found no differences between depressed and non-depressed individuals in reaction time to faces in one study, but found the opposite pattern in a larger study (Langenecker et al., 2007a). Surguladze and colleagues (2007) showed that individuals with MDD were slower than controls to respond to sad, but not happy faces. Participants in the latter study were somewhat older than participants in the former study, possibly explaining disparate findings.

Neurophysiological Correlates of Emotion Processing Abnormalities in MDD

In their seminal review of emotion processing abnormalities among patients with psychiatric disorders, Phillips, Drevets, Rauch, and Lane (2003b) provide a convincing argument for disruptions in both dorsal and ventral emotion processing systems among patients with MDD. Within the ventral system, important for identifying and responding to emotional stimuli, volume reductions have been shown in the amygdala, ventral striatum, and subgenual cingulate gyrus. Within the dorsal system, crucial to planning and regulating responses to emotional stimuli, volumetric reductions have been shown in the prefrontal cortical regions and hippocampus. Functional studies, too, support increased activation in regions important for identifying and responding to emotional stimuli and partially reciprocal deactivations in areas crucial for regulating affective states, with increased activation found in the subgenual cingulate gyrus, ventrolateral prefrontal cortex, amygdala, anterior insula, ventral striatum, and thalamus (Keedwell, Andrew, Williams, Bramner, and Phillips, 2007; Siegle, Thompson, Carter, and Thase, 2002). There are mixed reports of decreased activity in the dorsomedial and dorsolateral prefrontal cortices depending upon whether there is equivalent or enhanced performance (higher activation in MDD, Harvey et al., 2005; Holmes, Macdonald, Carter, Barch, Stenger, and Cohen, 2005; Langenecker et al., 2007b; Wagner et al., 2007) decreased performance (decreased frontal and increased limbic, Siegle et al., 2007), or no performance required (decreased frontal and increased limbic, Mayberg et al., 1999). Further decreased activation, blood flow, and electrical activity in medial frontal regions is linked to a decreased probability of successful treatment response (Langenecker, Kennedy et al., 2007; Mayberg et al., 1997; Pizzagalli et al., 2001; Siegle, Carter, and Thase, 2006).
Age and Emotion Processing

Studies have rather consistently found that as people age, they become less adept at recognizing negative facial expressions, such as anger, sadness, and fear. At the same time, the ability to recognize relatively more positive emotions displayed in facial expressions, including happiness and surprise, has been found to be similar in younger and older adults (Calder et al., 2003; Keightley, Winocur, Burianova, Hongwanishkul, and Grady, 2006; MacPherson, Phillips, and Della Sala, 2002; Malatesta, Izard, Culver, and Nicolich, 1987; McDowell, Harrison, and Demaree, 1994; Phillips, MacLean, and Allen, 2002; Sullivan and Ruffman, 2004). This could be due to the relatively few positive emotion expressions available compared to the complexity of more possible negative emotion expressions available. For example, of the “eight” primary emotions reported by Ekman, happiness is the only positive emotion that is readily distinguished across cultures, and there is some difficulty in distinguishing surprise from fear (Ekman and Friesen, 1976; Ekman, 1984). In comparison, disgust, fear, sadness, and anger are equally well recognized across cultures. Therefore selection of a negative emotion is inherently more difficult as a result of having more potential choices from which to choose.

A recent exception highlighting this potential bias in complexity for positive emotions was conducted by Isaacowitz and colleagues (2007), who found that older adults were less accurate than younger and middle-aged adults in recognizing posed facial expressions of happiness and less accurate than younger adults in recognizing anger, but equivalent in recognizing neutral expressions and expressions of disgust, fear, happiness, sadness, and surprise. They contend that previous studies finding no age differences in the detection of happiness may have been confounded by ceiling effects or emotion specific response biases. To test the latter hypothesis, scores were adjusted for the number of correct responses for a specific type of expression that would be expected by chance, and this was incorporated into a formula that included number of correct responses and the total number of items per task. The resultant value for this equation for each participant was then used as the dependent variable for all analyses. Results demonstrated that younger adults were significantly better than middle-aged but not older adults at recognizing expressions of disgust and happiness. Older adults performed more poorly than the other two groups in recognizing facial expressions of fear. There were also age differences for anger, but none of the pairwise-comparisons reached significance. Recognition of expressions of sadness and surprise were equivalent among the three groups.

Very few studies that have examined age-effects of facial emotion processing have assessed reaction time group differences. Those that have analyzed such data have found that older adults are also slower than younger adults, overall, in identifying emotions in posed facial expressions, and this is especially true for negatively-valenced expressions (Keightley et al., 2006; Sullivan and Ruffman, 2004). Some portion of the differences in processing speed between older and younger adults is likely explained by known age-related declines in general processing speed (Salthouse, 1996), although this does not explain the relatively greater declines in processing negatively-valenced expressions. Socioemotional Selectivity Theory may provide some insight into this finding. This theory postulates that during older age, emotional information becomes more salient and emotion regulation increases
Emotion Processing in MDD

Carstensen and Turk-Charles (1994; Kliegel, Jäger, and Phillips, 2007). The latter may be explained by older adults' tendency to selectively inhibit negative stimuli (e.g., Charles, Mather, and Carstensen, 2003), and this would be consistent with findings of changes during older age in the ability to process negative emotions. However, this has been an equivocal finding across studies (see Mather, 2004 for review).

Neurophysiological Changes with Age

Changes in emotion processing with age might also be related to age-related changes in brain structure and function. Normal aging has been associated with overall reduction in brain volume (Raz, 2000; Resnick, Pham, Kraut, Zonderman, and Davatzikos, 2003), though different subregions demonstrate disparate rates of decreasing volume. The lateral prefrontal cortex shows the greatest reduction in volume with age (Raz, 2000, 2004; Tisserand et al., 2002), with corresponding decreases in regional cerebral blood flow (De Leon et al., 1987; Garraux, Salmon, Degueldre, Lemaire, Laureys, and Frank, 1999). Likewise, cognitive functions mediated by the prefrontal cortex, especially ventrolateral and dorsolateral regions, are especially likely to decline during old age. Hippocampal, amygdala, and neostriatal volume also demonstrate a moderate negative relationship to aging (Raz and Rodrigue, 2006; Langenecker, Briceno, Hamid, and Nielson, 2007) and these are known to be involved in processing and categorizing emotion. Findings of increases in white matter lesions are also generally unequivocal across studies, particularly in periventricular and frontal areas (for review, see Raz, 2006). That age-related regional structural and functional changes occur in some of the same regions as are important for emotion processing, including the amygdala, ventral prefrontal cortex, hippocampus and dorsal prefrontal cortex may provide an explanation for age-related emotion processing changes reported in the literature.

Functional neuroimaging studies may also illuminate the etiology of the age differences found in the ability to detect emotions in facial expressions. A study by Gunning-Dixon and colleagues (2003) found that during a facial emotion discrimination task involving displays of happiness, sadness, anger, fear, disgust, and neutrality, younger adults activated limbic regions, including the amygdala and temporo-limbic areas, to a greater extent than did older adults, who were more likely than younger adults to activate left-frontal regions. These findings are consistent with those of Liadaka and colleagues (2002) who found greater bilateral amygdala activation among younger adults, as compared to older adults during sex discrimination of angry and disgusted faces. Finally, a study by Fischer, Sandblom, Gavazzeno, Fransson, Wright, and Bachman (2005) sought to separate possible age-related emotion processing differences from age-related cognitive-processing differences by constructing a task that involved only passive viewing of blocks of angry and neutral faces. They found that while viewing angry faces, older adults activated right anterior-ventral insula cortex to a greater extent than did younger adults, while younger adults demonstrated greater activation in the right amygdala/ hippocampus region. Unlike the other aforementioned functional imaging study, this study did not find differences in frontal activation between younger and older adults, potentially because the emotion processing task did not require emotion discrimination. Although age differences in the ability to classify facial emotion
expressions may help in explaining increased prevalence of depressive symptoms during middle- and old age, no study thus far has examined whether age contributes to facial emotion processing ability independently of MDD status.

Gender and Emotion Processing

Gender is also an important area of inquiry in understanding the experience and sequela of MDD. Of note, we use the term gender here as opposed to sex. While sex refers to the biological differentiation of man from woman, gender encompasses the sociocultural implications of being a woman or a man. We can make no assumptions about the etiology of the relationships between brain and behavior differences in emotional processing between women and men, and thus choose the broader term, gender, for use throughout this chapter. Differences in treatment-seeking behavior do not account for the large discrepancies observed in the prevalence of MDD among women and men (Kornstein, 1997). A multitude of explanations have been offered to explain this gap in prevalence of MDD, including gender differences in perceived self-efficacy (Nolen-Hoeksema and Jackson, 2001), general life stress (Hammen, 2005), poverty (Brown and Moran, 1997), rumination (Nolen-Hoeksema, Parker, and Larson, 1994), and biological (Robert et al., 2006) and hormonal (Kravitz et al., 2006) factors.

Differences in how emotions are processed and relative experience with emotion processing might help to explain some of the disparities in the prevalence of MDD between women and men. Gender may also be an important moderating variable in emotion processing and categorization during MDD. Gender differences in facial emotion processing of a wide variety of emotions have consistently favored healthy women when compared to healthy men, both in terms of speed of processing and accuracy in qualifying emotional information (Hall and Matsumoto, 2004; Montagne, Kessels, Frigerio, de Haan, and Perrett, 2005; Mufson and Nowicki, 1991; Thayer and Johnsen, 2000). Men tend to be less emotionally expressive in relation to women overall, and women demonstrate stronger physiological responses to emotional stimuli (Kring and Gordon, 1998).

Neuroimaging studies of gender differences, in both anatomical structure and functional activation, have been marshaled to help explain differences in emotion processing. Gender differences have been found in the volume of structures related to emotion processing, as well as in functional activation patterns in response to emotion stimuli, although the significance of these differences is still unclear. Women have larger orbital frontal cortices (Gur, Gunning-Dixon, Bilker, and Gur, 2002), an area important for cross-hemispheric integration in emotion processing. Women also show greater overall activation in the basal ganglia (Wager, Phan, Liberzon, and Talor, 2003) and more bilateral activation during emotion processing than men (Kline, Allen, and Schwartz, 1998; Sutton and Davidson, 2000; Wager et al., 2003). Others have demonstrated lateralization of amygdala activation differences between women (left) and men (right) in response to recognizing previously presented aversive stimuli, although the region of interest analysis did not allow for comparisons of limbic and cortical regions by gender (Mackiewicz, Sarinopoulos, Clevan, and Nitschke, 2007). Schneider, Habel, Kesslou, and Posse (2000) showed a
Emotion Processing in MDD

relationship between level of sad mood induction and blood flow in the right amygdala for men but not women (Schneider et al., 2000).

Gender differences in emotion processing have not been specifically addressed in a uniform fashion with a large enough sample and behavioral correlates to understand functional and structural relationships with emotion processing. Nonetheless, the presence of these anatomic and functional findings in the context of differential emotion processing ability can certainly generate reasonable hypotheses about how they may be related. Increased activation and a more bilateral activation pattern may suggest greater resource availability or utilization in emotion processing for women, although other hypotheses may be equally valid. Emotion processing skills may develop and mature differently in women and men, supported by the behavioral, as well as brain volumetric and functional activation findings available at present. In addition, the impact of differences in social expectations and learning as they affect brain development can not be ignored. Given our inability to retrospectively tease apart neurobiological, social learning, and interactive developmental processes, we can not distinguish among these mechanisms. This may explain, in part, why it is unclear whether and how emotion processing differences between women and men are relevant to the increased prevalence of MDD in women.

With the exception of one recent study (Wright, et al., submitted), we are not aware of any research to date exploring gender as potentially moderating the relationship between depression and facial emotion processing, and some studies have been composed primarily or exclusively of women (Gur et al., 1992; Langenecker et al., 2005; Persad and Polivy, 1993; Rubinow and Post, 1992) or only of men (Jaeger et al., 1986; Mikhailova et al., 1996). The recent study by our group found that gender and MDD status in young adults (< 35) interact in predicting facial emotion processing errors. Specifically, women with MDD made substantially more errors and had significantly slower reaction times than did non-depressed women; especially to negative stimuli. Men with MDD, on the other hand, performed similarly to their non-depressed man counterparts. These results suggest that depression in young adults differentially affects emotion processing symptoms in women as compared to men. Reasons for these findings are not entirely clear at this time, although we discuss these results in the context of gender differences in neurobiological, socioemotional, and social cognitive processing. Concomitant studies of functional activation among young women and men with and without MDD will help to provide some support for these hypotheses.

Few studies have explored the interaction of age and gender in predicting facial emotion processing accuracy. Calder and colleagues (2003) asked participants falling into five different age groups to identify six different morphed facial expressions, primarily expressing surprise, happiness, fear, sadness, anger, or disgust. Results suggest that men performed more poorly than women in classifying fear, but the same linear reduction with age was shown for both genders.

The Present Study
The present study was designed to address the effects of age, gender, and MDD status in predicting facial emotion processing accuracy and speed. First, we hypothesized that 1) older adults would perform more poorly than young adults; 2) that individuals with MDD would perform more poorly than non-depressed controls; and 3) that men would perform more poorly than women on a task of facial emotion processing. Second, we were interested in learning whether the women-specific emotion processing decrement that we have observed in young adults with MDD is also present in older adults with MDD. We hypothesized that the interaction of MDD status and gender would persist into older adulthood, such that women with MDD would exhibit emotion processing deficits, when compared to their same-age counterparts, but that men with MDD would not be similarly affected. As we knew there was an interaction between gender and MDD status, we collected additional information that we believed might be pertinent to explaining this interaction, including depression chronicity, severity, and age-of-onset.

Methods

One-hundred-, thirty-two healthy control (HC) subjects were recruited in three separate studies. Seventy-one participants were formally screened by licensed and trained clinicians with the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, and Gibbon, 1995) or the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) and 61 participants were screened with a semi-structured psychiatric and neurologic interview (Langenecker et al., 2005; Langenecker and Nielson., 2003). The semi-structured interview (by SAL) includes rule out diagnoses for neurologic conditions, psychosis, and substance abuse as taken from the DSM-IV/SCID-IV.

Three hundred eleven patients with MDD were recruited through three separate mechanisms, two prospective studies and retrospective collection of patients from inpatient psychiatry (IP) clinics at the University of Michigan Comprehensive Depression Center. Twenty-eight completed the SCID-IV and 251 completed interviews by a licensed psychologist and/or licensed psychiatrist, with diagnosis and exclusion criteria confirmed by chart review. Those patients retrospectively collected also had diagnoses achieved by consensus group discussion after the clinical interview, by more than one member of the outpatient psychiatry teams. Thirty-two completed the semi-structured interview (by SAL). Those with MDD alone (n = 211) as well as comorbid MDD and anxiety disorder (n = 70) or MDD and dysthymia (n = 30) were included in the study.

Prospective participants had documented informed consent and informed consent was waived for retrospectively included subjects (between the years of 2001-2007), each as approved by the IRB of the University of Michigan and consistent with the Declaration of Helsinki. Some was retrospectively collected from the University of Michigan Comprehensive Depression Center clinics. General exclusion criteria included past or current psychotic symptoms, bipolar disorder, dementia, head injury, schizophrenia, history of ECT, or conditions that might affect cognitive functioning (e.g., epilepsy).

Facial Emotion Perception Test
The Facial Emotion Perception test was designed by our group using the Ekman faces (Ekman and Friesen 1976; Langenecker et al 2005; Rapport et al 2002). Participants were asked to categorize faces into one of four possible categories (happy, sad, fearful, angry) and animals from each of four categories (dogs, cats, primates, and birds). Each event began with a briefly presented orienting cross (500 ms), followed by a brief presentation of the stimulus (300 ms), a visual mask (100 ms), and a response window (2600 ms). Index through pinky fingers were used to respond to the choices presented (e.g., types of facial expressions and animal categories). Choices were always presented and did not need to be remembered. The task took seven minutes to complete. There were four primary dependent variables: animal accuracy, faces accuracy, response time for animals, and response time for faces. There were also secondary measures of the number of errors for each of the stimulus types, and also the types of error choices made by participants (including the four emotions and no responses).

Depression Measures and Diagnosis

As participants were selected from several clinical and research samples, measures to assess depression were not similar across clinical (Patient Health Questionnaire, Kroenke, et al., 1997) and research (Hamilton Rating Scale for Depression, Hamilton, 1960) settings. Minimum severity of depression symptoms was not used for inclusion in the study. Means and standard deviations for both measures in Table 1.

Age of Onset and Chronicity

Age of onset was derived from the semi-structured clinical interview, SCID-IV, or from clinical records when available. This information was available for 281 patients. Age of onset was used in posthoc analyses to assess differential gender by age effects based upon early or late age of onset. To conservatively capture late age of onset, we used those having first onset after age 36 or later as late onset MDD subjects. Chronicity was measured as number of years of illness. Age of onset and chronicity are reported in Table 1. Total number and duration of MDD episodes was not available for enough participants to conduct adequately powered analyses.

Medications

Some participants with MDD were taking psychotropic medications at the time of the evaluation. As there are reports of psychotropic effects on cognitive functioning, we ran analyses to ascertain the nature of these effects, if present. To this end, we classified medication effects as SSRI or SSRI-like (n = 112), which would also include Wellbutrin (n = 33), into one group. We also combined those taking SSRI-like medication plus combinations of neurontin (n = 7), mood stabilizers (n = 10), opiates (n = 14), stimulants (n = 5), tranquilizers (n = 12), and/or anxiolytics (n = 27) as well as a primary SSRI-like medication
Those in the SSRI-like plus group were on average four years older ($F(2,296) = 3.68, p = .03, M = 39.1 SD = 12.0$) than the non-medicated ($M = 35.0 SD = 12.0$) and SSRI-like groups ($M = 34.5 SD = 11.9$). In addition, as might be expected, those with comorbid MDD and anxiety were more likely to be in the SSRI-plus group (22/64) compared to the MDD alone (40/199) and comorbid MDD and dysthymia (4/30) groups ($X^2 = 9.46, p = .05$). The effects of medication class and MDD comorbidity will be explored in specific posthoc analyses, as we can not tease apart potential medication by diagnosis and age interactions in a naturalistic study.

**Statistical Analyses**

Two repeated measures multivariate analyses of variance (rmANOVA) were computed with depression status (yes or no), age group (<36 or >35), and gender as factors. The first rmANOVA was conducted with response time for animal categorizations and emotion choices, while the second analysis was conducted with accuracy for animal categorizations and emotion choices. Planned posthoc analyses addressed our previous findings of emotion perception decrements that are specific to young women, but not men participants with MDD, but were expanded to include older adults. Further, posthoc analyses also explored effects of age of onset, chronicity, symptom severity, and medication group on dependent variables of interest.

**Results**

**Demographic Analyses**

Analysis of demographic variables indicate a significant interaction between age group, MDD status, and gender for years of formal education ($F(1, 435) = 4.46, p = .035$), with the young HC men having fewer years of formal education relative to the older groups and the young women with MDD. The adult groups also had significantly more years of formal education compared to the young adult groups ($F(1, 435) = 5.51, p = .019$). When comparing the groups on age, the interaction between age group and MDD status was significant ($F(1, 435) = 21.58, p = .0001$), as was the interaction between age group and gender ($F(1, 435) = 13.83, p = .0001$). The young MDD group was on average four years older than the corresponding HC group, whereas the older MDD group was on average two years younger than the corresponding HC group. Whereas there was no difference between men and women in the younger age group, the older men were on average four years older than the older women. Men were 1.7 years older than women ($F(1,433) = 5.1, p = .02$) and MDD patients were one year older than healthy HCs ($F(1,433) = 2.66, p = .10$). Although these modest differences would be expected to have no impact on cognitive function, we ran the analyses with education as a covariate throughout. Age was not entered as a covariate, as it would undermine the age group comparisons planned for the study. Further, the age differences
described herein would be more likely to result in slightly poorer performance in the HC
groups.

**Table 1. Demographic and Clinical Information for Groups by Age Group, Gender, and MDD status**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control &lt;=35, n = 37</td>
<td>&gt;35, n = 11</td>
<td>&lt;=35, n = 60</td>
</tr>
<tr>
<td>Age ^a</td>
<td>20.7 (3.4)</td>
<td>51.5 (9.1)</td>
</tr>
<tr>
<td>Education ^b</td>
<td>14.2 (2.4)</td>
<td>16.6 (2.1)</td>
</tr>
<tr>
<td>HDRS ^c</td>
<td>0.8 (1.8)</td>
<td>0.9 (1.2)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD &lt;=35, n = 38</td>
<td>&gt;35, n = 50</td>
<td>&lt;=35, n = 123</td>
</tr>
<tr>
<td>Age ^a</td>
<td>26.8 (5.0)</td>
<td>48.3 (7.9)</td>
</tr>
<tr>
<td>Education ^b</td>
<td>15.5 (2.7)</td>
<td>15.6 (3.0)</td>
</tr>
<tr>
<td>Age of Onset ^d</td>
<td>18.1 (7.3)</td>
<td>28.2 (14.0)</td>
</tr>
<tr>
<td>Chronicity ^e</td>
<td>8.9 (7.3)</td>
<td>19.7 (15.3)</td>
</tr>
<tr>
<td>HDRS ^c</td>
<td>20.3 (0.6), n = 3</td>
<td>18.1 (1.6), n = 7</td>
</tr>
<tr>
<td>PHQ-8</td>
<td>13.3 (6.4), n = 28</td>
<td>16.7 (5.3), n = 38</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>n = 16</td>
<td>n = 18</td>
</tr>
<tr>
<td>SSRI-Like</td>
<td>n = 14</td>
<td>n = 15</td>
</tr>
<tr>
<td>SSRI-plus</td>
<td>n = 6</td>
<td>n = 13</td>
</tr>
<tr>
<td>Comorbidity ^f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD alone</td>
<td>n = 21</td>
<td>n = 32</td>
</tr>
<tr>
<td>MDD and Anxiety</td>
<td>n = 13</td>
<td>n = 11</td>
</tr>
<tr>
<td>MDD and Dysthymia</td>
<td>n = 4</td>
<td>n = 7</td>
</tr>
</tbody>
</table>

^aYoung MDD subjects were older than young HC subjects \(F(1,433) = 14.6, p = .0001\), and older men were older than older women \(F(1,433) = 8.2, p = .004\). ^bThe young HC subjects had fewer years of formal education compared to the MDD subjects \(ps < .036\) and the older men HC group \(p = .007\). ^cMDD subjects had higher HDRS (Hamilton Rating Scale for Depression) scores compared to the healthy controls \(p < .0001\). ^dOlder MDD subjects had later age of onset compared to young MDD subjects \(F(1,277) = 45.9, p = .0001\). ^eOlder MDD subjects had more years of illness (chronicity) compared to young MDD subjects \(F(1,277) = 54.7, p = .0001\). ^fYoung men with MDD were less likely to be diagnosed with MDD alone and more likely to be diagnosed with MDD and anxiety \(X^2, 160, = 6.4, p = .04\) compared to young women. No gender effect by MDD interaction was present in diagnoses for the older groups \(X^2, 3.45, = 3.5, p = .18\)

**Assessment of Interaction between Age Group, Gender, and MDD Status on Emotion and Animal Processing**

The first analysis was a rmANOVA assessing the factors of age group, gender, and MDD status with response time in either facial emotion perception or animal categorization as the dependent variables. Here, education was a significant covariate \(F(1, 430) = 4.23, p = .04\) and there was a significant effect of age group \(F(1, 430) = 44.91, p = .0001\), with slower response time with increasing age. There was also a main effect of gender, with faster
response times observed in women ($F(1, 430) = 7.52, p = .006$). The interaction between MDD status, gender, and age group was significant ($F(1, 430) = 5.14, p = .02$). Furthermore, there was a significant interaction between MDD status, gender, age group, and response time ($F(1, 430) = 5.18, p = .02$). This interaction is displayed in Figure 1. Reaction time was generally slower in MDD groups compared to HC groups, including both young groups ($t(73) = -2.73, p = .004$, one tailed for men, and ($t(181) = -2.20, p = .015$), one tailed for women). The difference was in the same direction, but not significant in older women ($t(122) = -0.85, p = .20$, one tailed), and non-significant in the opposite direction in the older men ($t(59) = 0.53, p = .30$, one tailed).

The second analysis was a rmANOVA assessing the relationship of age group, gender, and MDD status to accuracy in either facial emotion perception or animal categorization as the dependent variables. The effect of MDD status was significant ($F(1, 434) = 16.57, p = .0001$), with poorer performance in MDD groups relative to the other groups. Older adult
Figure 2. Interaction between Stimulus Category, Accuracy, Gender, Age Group, and Depression Status. The older MDD groups were worse in animals accuracy compared to the young HC group, and the older men HC group. The older men MDD group was worse in animals accuracy compared to the young MDD groups. The older women HC group had significantly worse animals accuracy compared to the young women HC and older men HC groups. The older women group was significantly better in faces accuracy compared to the young women MDD group. The older MDD groups were worse than all other groups for faces accuracy.

groups also performed more poorly than the young adult groups ($F(1, 434) = 7.44, p = .007$). The interaction between MDD status, gender, age group, and accuracy was not significant ($F(1, 434) = 0.78, p = .38$), but is displayed in Figure 2 for comparison with Figure 1.

The critical hypotheses of interest were related to whether the women-specific emotion processing accuracy decrement that we have observed in young adults with MDD is also present in older adults with MDD. As expected, there was better performance among HC women as compared to women with MDD in both young ($t(181) = 2.41, p = .008$, one tailed) and older age cohorts ($t(122) = 3.01, p = .002$, one tailed). Contrary to expectation, older men with MDD exhibited significantly worse performance relative to older HC men for face perception ($t(59) = 1.74, p = .043$, one tailed), whereas we extended our previous finding of no difference in emotion processing in young men with MDD in comparison to their HC cohort ($t(73) = 0.65, p = .265$, one tailed).

We explored this gender by age disparity in further analyses, taking into consideration the stimulus properties of the faces (e.g., happy, sad, angry, fearful), the specific choices the participants made during errors (happy, sad, angry, fearful, no response) and finally in posthoc analyses examining the relationship of age of onset, chronicity, depression severity,
and medication class to performance. First, we wished to replicate our findings of specific types of difficulty in emotion processing of emotional stimuli. For example, we previously demonstrated that young women with MDD had difficulty in categorizing facial expressions of sadness and fear, and that they were more likely to erroneously indicate that these facial expressions were angry (Wright et al., submitted). We suspected that this pattern would hold in a larger young cohort of MDD patients, and we were interested to see what patterns might be evident in older adults with MDD. We also hypothesized that in the absence of preserved emotion perception, as noted in the young men cohorts, older men with MDD may have dysfunction in emotion processing through secondary mechanisms (e.g., vascular).

Posthoc Exploration of Stimulus Properties, Response Biases, and Clinical Variables that Might Explain Differential Performance by Gender, Age Group, and MDD Status

Facial Stimulus Characteristics. To assess the potential difficulty of processing certain types of stimuli in MDD, we ran a posthoc rmANOVA with specific types of emotional stimuli (happy, sad, anger, fear) as the dependent variable, and MDD status, age group, and gender as independent variables. The interaction between MDD status, age group, and gender was significant (F(1, 344) = 5.30, p = .02). The interaction between stimulus type and age was also significant (F(3, 1032) = 2.61, p = .05). Further posthoc analysis indicated that older men with MDD had significantly more errors than their older men HC counterparts in the number of errors for fearful stimuli (t(45) = -2.23, p = .015, one tailed), but not angry (t(45) = -1.23, p = .111, one tailed), happy (t(45) = -0.31, p = .33, one tailed), or sad (t(45) = -1.43, p = .08, one tailed) stimuli. Consistent with our prior study, young women with MDD made more errors for fearful stimuli (t(136) = -1.81, p = .036, one tailed), but not for sad stimuli (t(136) = -1.36, p = .088, one tailed). There were also no differences in errors between young women with and without MDD for happy (t(136) = -0.79, p = .215, one tailed) or angry (t(136) = -0.49, p = .485, one tailed) stimuli. There were no differences between older women with and without MDD for any specific stimulus type (ts(98) < |0.66|, ps > .255, one tailed).

Error Response Choices to Facial Stimuli. As we had done previously, we further explored the specific choices (e.g., biases) that individuals were making with a MDD status, by age group, and gender rmANOVA with choices of fear, anger, happiness, sadness, or no response as the dependent variables. The interaction between MDD status, age group, gender, and response choice was significant (F(4, 1376) = 2.37, p = .05). In posthoc t-tests, there were no differences in response choices in comparing young men with and without MDD (t(66) < |0.49|, ps > .285, one tailed). Older men with MDD were more likely to choose happy when making an error in comparison to older men without MDD (t(45) = -3.00, p = .0025, one tailed), whereas there were no difference in choices of anger (t(45) = -1.41, p = .084, one tailed), fear (t(45) = -1.29, p = .103, one tailed), sadness (t(45) = 0.24, p = .406, one tailed), or no response (t(45) = -1.08, p = .143, one tailed). As we had shown in the previous study (Wright et al, submitted), young women with MDD were more likely to choose anger erroneously compared to young HC women (t(136) = -2.23, p = .014, one tailed), but not fear (t(136) = -0.65, p = .263, one tailed), happiness (t(136) = -0.46, p = .325, one tailed), sadness
Age of Onset. To assess age of onset effects in explaining the gender by age group and MDD status interaction, a posthoc rmANOVA was computed for the effects of gender and (categorical) age of onset on face and animal processing, this time only in older adults with MDD. Age was used as a covariate given that age of onset and age were significantly correlated ($r = .50$, $p = .0001$). The effect of age of onset was not significant ($F(1,124) = 3.24$, $p = .074$), although the interaction between gender and age of onset was significant ($F(1,124) = 5.05$, $p = .0326$).

Specifically, the older men with later age of onset ($n = 15$) showed specific decreased performance in face perception accuracy relative to older adults from the three other groups (older men early onset $n = 28$ ($t(41) = 1.78$, $p = .041$, one tailed), older women early onset $n = 62$ ($t(75) = 1.93$, $p = .028$, one tailed), and older women late onset $n = 28$, ($t(41) = 1.79$, $p = .04$, one tailed),). Older men with later age of onset also demonstrated slowed response time for faces relative to the two early onset groups ($t(41) = 2.78$, $p = .006$, one tailed) and ($t(41) = -2.54$, $p = .007$, one tailed), for men and women with early onset MDD, respectively, (Figure 3), but not compared to the late onset women with MDD. ($t(41) = -1.59$, $p = .06$, one tailed). There was a similar pattern for animal response time compared to faces response time for these groups, but not for accuracy in animal perception. Due to space limitations, these effects are not reported here.

Chronicity (Years of Illness). To assess for chronicity effects, we used the entire MDD sample where age of onset was available ($n = 281$) in another rmANOVA posthoc analysis, here again with older adults with MDD only. We conducted a median split of chronicity ($md = 9.0$, $M = 12.5$, $SD = 11.3$) and created high and low burden chronicity groups. Subsequently, we conducted another rmANOVA with the four dependent variables, with gender and chronicity status as the independent variables. Age was used as a covariate, as it is strongly correlated with chronicity ($r = .51$, $p = .0001$) and age of onset ($r = -.49$, $p = .0001$). The effect of chronicity was not significant ($F(1,127) = 2.18$, $p = .141$), nor was the interaction between gender and chronicity ($F(1,127) = 3.12$, $p = .079$).
Figure 3. Interaction between Age of Onset and Gender for Accuracy and Response Time. Older men, late onset, performed slower than older men and women, early onset, in response time for faces and animals. Older men, late onset performed more poorly in faces accuracy compared to all other older groups, including women, late onset.

To rule out more general effects of age of onset and chronicity on performance, we ran partial correlations with these two variables and the four dependent variables, covarying age, as age was significantly correlated with both MDD severity variables. Only one correlation
was significant, that of chronicity with face response time ($r(148) = -.15, p = .015$), whereas none of the other seven correlations was significant ($|r| < .09, ps > .13$).

**Symptom Severity.** We also assessed whether the interaction between age, gender, and MDD status might be explained by symptoms of depression severity. As we had both HDRS and PHQ-8, we could not rerun a rmANOVA with severity as a covariate. Thus, we split the MDD group into high and low symptoms by median split for each variable ($md$ HDRS = 16.0, $SD$ = 4.9, $md$ PHQ-8 = 14.6, $SD$ = 5.9). There was no significant effect of symptom severity ($F(1,254) = 1.28, p = .26$), nor were any of the interactions significant ($Fs(1,254) < 1.90, ps > .169$). We then ran correlations of these measures with the four dependent variables (accuracy and response time for faces and animals), again covarying the effects of age. The HDRS ($n = 56$) was significantly correlated with response time for faces ($r = .28, p = .036$), but not with the other three variables ($|r| < .21, ps > .12$). The PHQ-8 ($n = 88$) was significantly correlated with animals accuracy ($r = .25, p = .013$), but not with the other three variables ($|r| < .09, ps > .38$).

**Medication Effects.** We also completed posthoc evaluations to analyze any potential effects of medication upon the interaction of age and gender within the MDD group. This rmANOVA used age group, gender, and medication class as independent variables and the four dependent variables of interest. The effect of medication class was significant, with slower performance in the unmedicated and SSRI-plus groups compared to the SSRI-like group ($F(2,283) = 4.46, p = .012$). Posthoc analyses suggest that the non-medicated group was slower compared to the SSRI-like group for animal categorization response time ($t(229) = 2.18, p = .03$), but not for faces response time ($t(229) = 1.44, p = .15$). The SSRI-plus group was slower than the SSRI-like group in faces ($t(173) = -3.00, p = .003$) and animals ($t(173) = -2.76, p = .006$) response time. There were no significant effects of medication class on performance accuracy ($F(2,287) = 0.02, p = .98$).

**Comorbid Illness.** Finally, we completed a similar rmANOVA with the MDD group, this time investigating effects of comorbidity upon performance. This rmANOVA used age group, gender, and MDD diagnostic class (MDD alone, MDD plus anxiety, or MDD plus dysthymia) as independent variables and the four dependent variables. The interaction between gender and MDD diagnostic class was significant ($F(2,289) = 6.29, p = .002$) for both faces and animals response time. Posthoc analyses indicated slower response time for animals in men with either comorbid condition relative to MDD alone ($t(72) = -2.14, p = .006$ and ($t(60) = -2.11, p = .04$ for MDD plus anxiety and MDD plus dysthymia, respectively). Women with comorbid MDD and dysthymia responded more rapidly to faces ($t(173) = 3.43, p = .002$) and animals ($t(173) = 3.79, p = .001$), as compared to the women with MDD only. The interaction between accuracy for faces and animals with MDD diagnostic class, gender, and age group was significant ($F(2,293) = 3.39, p = .035$). Older women with MDD and dysthymia performed significantly better for faces ($t(69) = -2.27, p = .026$) and animals ($t(69) = -3.09, p = .014$) accuracy as compared to women with MDD alone.
Discussion

In this large study across the age spectrum, we studied whether previous findings of an interaction between gender and presence of MDD could be extended to those above the age of 35. We expanded the young MDD and HC samples and added older healthy HC and MDD samples for a total of over 400 participants. To our knowledge, this is the largest study to address the complex interplay among gender, MDD, and age on facial emotion processing. We replicated findings of women-specific emotion perception decrements in young MDD subjects. More specifically, in this larger sample of young adults with and without MDD, we again showed relatively equivalent performance in depressed and non-depressed young men and in young women with MDD. Yet, the healthy young women outperformed their same-gender MDD group in accuracy. We failed to extend findings of a women specific emotion processing deficit in MDD participants under the age of 35 to those in the age spectrum over age 35. In fact, we illustrated that men with MDD over age 35 are equally poor in emotion perception accuracy of faces when compared to women with MDD over age 35. Both groups were worse than respective healthy HC groups of similar age.

Consistent with our prior study, young women with MDD were more likely to make incorrect responses choices for fearful stimuli and were more likely to incorrectly choose anger, when compared to their same-gender and age counterparts. Older women with MDD did not show these emotion specific processing deficits, however, and in fact, were more likely not to respond to stimuli, as compared to their same-gender and age counterparts. Similar to our previous work, young men did not demonstrate specific stimulus or response biases, however, older men with MDD made more errors for fearful stimuli and were, interestingly, more likely to choose happy when making an error as compared to their same gender and age counterparts.

In an attempt to explain the lack of a gender by MDD status interaction in older adults, we explored clinical variables in posthoc analyses that might contribute to this finding. The most robust of the clinical variables in explaining decrements in older men with MDD was age of onset. Those men with later age of onset (after age 35) demonstrated poorer performance than men with early age of onset and than older women with MDD, including those with early and late onset. Chronicity of MDD, severity of MDD symptoms, and category of psychotropic medications prescribed did not contribute to the differences found between young and older women and men with MDD in emotion perception accuracy of faces. Intriguingly, and with admittedly smaller numbers, we demonstrated that comorbidity of MDD with anxiety and dysthymia may have different emotion processing sequela for women and men. For example, young men with comorbid MDD and anxiety performed worse than young men with MDD alone, whereas older women with comorbid MDD and dysthymia performed better than older women with MDD alone.
Mechanisms for Early Disruption of Emotion Processing Circuits in Women but not Men

A number of explanations, including neurobiological, socioemotional, and sociocultural may account for the disparate findings of emotion processing skills in young women and men with MDD. We will briefly summarize these mechanisms here, but for a fuller discussion, please refer to Wright and colleagues (resubmitted). First, with regard to neurobiological explanations, it is feasible that women’s and men’s ability to process emotions relies on different neurodevelopmental circuits. Research on gender differences in functional activation during emotion processing suggests that women rely on limbic and paralimbic circuits to a greater degree than do men during both euthymic and sad states (George, Ketter, Parekh, Herscovitch, and Post, 1996; Hall, Wittelson, Szechtman, and Nahmias, 2004), while men are more likely to activate unilateral frontal regions (Hall et al., 2004) associated with inhibitory control (Langenecker et al., 2007b). While women rely less on inhibitory emotional repair strategies than do men (Bjorklund and Kipp, 1996), during depressed states, increased limbic activation (Frodl, Scheurecker, Albrecht, Kleemann, Müller-Schunk, Koutsouleris, Möller, Brückmann, Wiseman, and Meisenzahl, 2007) may abrogate emotional repair strategies in women, leading to greater emotion perception inaccuracy. At the same time, given that men already rely heavily on frontal regions to process emotions (Hall et al., 2004), decreased modulation of limbic signals during depressed states in response to emotional stimuli might sustain their ability to sufficiently process emotions.

Second, socioemotional development is known to differ between women and men from very early in life. Interpersonal relations are accorded greater value for women than for men, while men are taught to strive for individualism (Jack, 1991; Miller, 1976). As a consequence, interpersonal skill is strongly related to self-esteem in women (Nolen-Hoeksema and Girgus, 1994; Stein, Newcomb, and Bentler, 1992), and when self-esteem is degraded, risk of developing MDD is heightened (Kendler, Gardner, and Prescott, 2002; Kernis et al., 1998; Roberts and Kassel, 1997). These findings of competence in interpersonal relationships suggest that deficits in emotion processing, which is an essential component of interpersonal skills, place women, but perhaps not men, at greater risk for MDD.

Finally, women and men are known to process emotions differently during non-depressed states, suggesting that social cognitive mechanisms might also be important in explaining the emotion processing difficulties detected in women, but not in men with MDD. Non-depressed women have consistently shown superiority over men in recognizing, expressing, and interpreting emotional stimuli (Barrett, Lane, Sechrest, and Schwartz, 2000; Johnsen, Thayer, and Hugdall, 1995; Kring and Gordon, 1998; Thayer and Johnsen, 2000). During depressed states, however, women and men are known to engage in different cognitive strategies that may affect emotion processing skills in disparate ways. Specifically, during depressed states, women are more likely to ruminate, whereas men are more likely to distract themselves (Nolen-Hoeksema, Larson, and Grayson, 1999). Given that rumination has been shown to influence appraisal of the past, present, and future (Lyubormirsky, Caldwell, and Nolen-Hoeksema, 1998; Lyubormirsky and Nolen-Hoeksema, 1995), it is likely to lead to distorted perceptions of events, including those that arouse emotion. Rumination has also been shown to disrupt problem solving (Nolen-Hoeksema, 1991, 2001),
and processing emotional stimuli such as facial expressions might be considered to engage problem-solving resources.

Mechanisms for Equal Disruption of Emotion Processing Circuits in Older Men and Women with MDD

Neurobiological explanations may help to account for the finding that during older age, both women and men with MDD demonstrate decrements in facial emotion processing relative to their same age and gender counterparts. This finding runs counter to the finding that in young adults there are gender specific decrements in facial emotion processing skills among women with MDD only. The neurobiological circuits disrupted during MDD and during normal aging overlap, and both are involved with emotion processing skills. Specifically, prefrontal and medial temporal regions are known to be affected during both aging and MDD (De Leon et al., 1987; Garraux et al., 1999; Phillips et al., 2003b; Raz, 2004; Tisserand et al., 2002). It is possible that in young adulthood, men’s tendency to activate frontal, but less so limbic regions (George et al., 1996; Hall et al., 2004), allows them to compensate for the increased limbic activation seen during depressed states (Frodl et al., 2007).

At the same time, the lateral prefrontal cortex demonstrates the greatest volumetric reduction during older age (Raz, 2000, 204; Tisserand et al., 2002), with corresponding decreases in regional cerebral blood flow (De Leon et al., 1992). Given that HC women and men did not demonstrate a change in facial emotion processing accuracy with age, these data would suggest that age-related neurobiological changes alone do not lead to emotion processing deficits. Instead, it is possible that a “double burden” of MDD and age impedes the ability of these men to successfully perceive emotional expressions in faces. The neurobiological disruptions that are evident in women with MDD at a young age are now apparent in older men with MDD, likely resulting in increased risk for MDD.

Despite that older women and men with MDD demonstrate similar difficulties with facial emotion processing, they make errors on different types of stimuli and display different response biases. While older women showed no tendency to respond incorrectly to any specific types of stimuli, older men were more likely to respond incorrectly to fearful stimuli. Older men also demonstrated a proclivity to erroneously perceive faces as expressing happiness, while older women were more likely to make no response. These findings are different from the specific kinds of errors found in young MDD groups, whereby young women were found to be likely to respond erroneously to fearful stimuli and to incorrectly choose anger when compared to young women controls. These age and gender differences in the types of errors made for specific kinds of facial expressions suggest that disparate processing biases or skill deficits are present in young adult and adult women and adult men with MDD. Further research might explore mechanisms behind such age and gender specific differences in emotion processing during MDD. For example, it may be that older adults’ superiority in emotion regulation (Carstensen and Turk-Charles, 1994; Kliegel et al., 2007) translates to their misperceptions of facial emotions during MDD, such that they either ignore the emotion altogether, and thus make no response, as was shown for older women with
MDD or misperceive the emotion as happy, as was found in older men with MDD. Further, MDD in older adults, and the accompanying underlying neurological disruption, may also circumvent emotion regulation skills.

Age of Onset as A Mechanism for Disproportionate Disruption in Emotion Processing Circuits in Older Men with MDD

Age of MDD onset is an important variable to consider in exploring the emotion processing decrements detected in older adults with MDD. Specifically, why is this significant in older men with MDD, but not in older women? In the present study, older men with later age of onset were less accurate and slower to process emotional stimuli than were older men with early age of onset and older women with early age of onset, suggesting a “triple burden” in men with late onset MDD. Late onset MDD has been hypothesized to stem from cerebrovascular changes in frontostriatal circuits, and has even been termed vascular depression, by some authors (Alexopoulis, Meyers, Young, Campbell, Silbersweig, and Charlson, 1997). Individuals with late-onset MDD are also known to exhibit cognitive difficulties mediated by frontostriatal circuits, including in the domains of executive functioning and processing speed (Herrmann, Goodwin, and Ebmeier, 2007; Wright and Persad, 2007). While we did not assess executive functioning skills in this study, findings of slowed reaction time in older men with late onset MDD to both face and animal stimuli suggest that these men might be experiencing the consequences of cerebrovascular pathology, possibly explaining the “triple burden” hypothesis.

It is interesting that age of onset was a significant finding for older men, but not older women. That older women with MDD show emotion processing difficulties regardless of age of onset is consistent with a finding of early age decrements, and late onset difficulties of a potentially different etiology. At the same time, it is not altogether surprising that men with later age of onset show far greater decrements, given that men are known to show higher rates of cardiovascular risk factors than are older women, although this sex difference becomes smaller with age (Jousilahti, Vartiainen, Tuomilehto, and Puska, 1999). Our findings here suggest that emotion processing skills might be an important domain to assess in older adults with MDD that may have a vascular or heretofore unknown origin. This incidental finding deserves further investigation in a study that can specifically assess and relate white matter hyperintensities in these regions to emotion processing deficits.

Other Incidental Yet Pertinent Findings in the Study of Emotion Processing in MDD

In post-hoc analyses, we found that MDD severity, as measured by the Hamilton Rating Scale for Depression (Hamilton, 1960) is predictive of speed of face recognition processing for all depressed groups studied. Thus, no matter the age or gender of the depressed individual, as depression symptoms worsen, facial processing is slowed. This is consistent with previous findings of slowed reaction time to faces during depression (Surguladze et al.,
2005), but not Langenecker and colleagues (2005). That MDD severity was correlated with face, but not animal processing speed suggests a selective processing speed deficit for faces with increasing depression severity, inferring that the processing speed decrement found in facial emotion processing during MDD is not fully explained by general slowed processing.

We also found medication effects for face and animal processing speed, with slower performance exhibited by unmedicated and SSRI-plus groups as compared to the SSRI-like group. This finding might be explained in a number of ways. First, patients taking SSRIs in addition to other psychotropic medications, such as benzodiazepines or mood stabilizers, may be more likely to experience cognitive slowing as a result of medication side effects and/or interactions including increased somnolence (Gray, Lai, and Larson, 1999). This group was older and had significantly greater symptoms of depression compared to the SSRI-like groups, which may also explain the medication effect. This would not explain the slower processing exhibited by unmedicated patients, however. Instead, depression severity might account for slowing in both groups, as it is feasible that unmedicated patients are untreated by choice or due to economic hardship, which may be a corollary to depression severity. Further, patients taking more than one medication for depression might experience a more severe form of depression. Future studies specifically designed to examine the consequences of these factors on processing speed of faces and animals might be helpful in parsing out these discrepancies.

Finally, we found significant effects of comorbidity for processing speed of faces and animals. Men with comorbid diagnoses exhibited slower performance for faces and animals than did men with MDD alone. In contrast, women with comorbid MDD and dysthymia processed visual information faster than those with MDD alone. There were no differences detected in diagnostic subgroups of women. We have not performed analyses that could assist us in directly understanding the reason for this discrepancy between women and men with MDD because of the relatively small sample sizes, particularly in the comorbid MDD and dysthymia group.

Importantly, it is possible that the biological and socioemotional development of men and women interact with diagnostic subtypes in such a way that would explain these discrepancies. As this was a posthoc analysis, we suggest that future studies with planned subgroup analyses can fruitfully exploit these findings. One potential hypothesis to explore is actual symptoms of anxiety as they relate to emotion perception skill. It is possible that those with higher anxiety have hyper-alertness to stimuli, and thus faster processing speed. This would be consistent with research demonstrating a positive relationship between anxiety and higher alertness to faces (Dennis, Chao-Cheng Chen, and McCandliss, 2007). In addition, we did not assess for the presence of melancholic subtype of MDD, which in turn might be more common in the men in this sample, resulting in greater psychomotor retardation (Naismith et al., 2003; Parker, 2000).

**Conclusions**

This is a complex study with a number of variables addressed toward understanding biological, social, and cultural explanations for increased prevalence of depression in women compared to men. Whereas we attempted to be comprehensive in the analyses that we
performed toward this end, it is inevitable that some were overlooked. There are a number of limitations that restrain the conclusions that might be drawn from this study.

First, the use of age 35 as a cut-off for adult versus young adults, to assess for age effects, is not ideal. This was necessitated in part by the small number of healthy adults recruited to date over the age of 35. This was beneficial in some respects, as it converged with evidence that late 30s and early 40s would be the upper extreme of a “traditional” onset for MDD (American Psychiatric Association, 2000). Thus, those studied under age 35 are very likely to have a developmental form of MDD, while those over age 35 were roughly evenly split between those who could recall onset of depression and episodes of MDD prior to age 35 and those who denied any such illness until after age 35. Ideally, a middle-age group of both MDD and HC adults would be added to this comparison to better gauge effect of age of onset and chronicity, and we encourage future studies with this goal.

The relatively small size of the older healthy adult groups does limit confidence in the age-related findings. In fact, we showed general age effects of slowing for both face emotion and animal categorization response time, and of decreasing accuracy for animal categorization. This could be a reflection of the limited power of the small sample sizes in the older adults, or it may suggest that facial emotion perception of emotion is a relatively preserved skill set for older adults. Of course, the rigorous screening criteria that healthy older adults must meet in order to be eligible for this study may by itself render these “control” subjects non-representative of the general population of older adults. Planned studies of the cumulative effects of depression in elders are underway by our group and others and we encourage the exploration of gender effects in this age group.

Another weakness of the present study that must be considered is the use of retrospective clinical data in the diagnosis of some patients with MDD. While this is clearly not ideal in a prospective study, it is a common limitation of a retrospective study. On a positive note, many of these patients were followed clinically for a number of visits, and we confirmed the initial diagnosis with later clinical records. We were able to exclude some patients with psychotic symptoms and/or bipolar illness who at first reported symptoms of and were diagnosed with MDD or MDD and a comorbid illness. There were no marked differences in MDD comparisons between those who had clinical data used when compared to those collected in prospective research studies, so this concern may only be modest in nature. The differential diagnostic tools render the MDD comorbidity analyses weaker, however. We did not take great lengths to explore or interpret these findings, particularly as the comorbid dysthymia group was small and the reliability of our clinical diagnostic procedures is not described in the scientific literature. Heartening to these findings, though, was the relative severity of MDD symptoms in our clinical and research samples, with depression on average in the moderate range.

In summary, the present study extends our previous findings of a gender-specific mechanism for increased incidence of MDD in young women that can be measured with a six minute test of facial emotion perception accuracy. We accentuate this finding with now a substantially larger sample in the young age group. Furthermore, we show that with age, particularly in those older men with a late age of onset, there are significant decrements in emotion processing accuracy among depressed individuals. Older women with MDD continue to have emotion processing difficulties, though they misperceive facial emotional
stimuli differently from young women with MDD. Neurobiological changes are thought to strongly contribute to the presence of late onset MDD (e.g., Alexopoulos et al., 1997) and our findings suggest that these disruptions in neurological function are not additive for women. This suggests that the neural circuitry disrupted in late onset MDD is the same as that involved in poorer emotion processing accuracy in young women with early onset MDD and in those older women with late and early onset MDD. Young men with early onset MDD do not appear to have disruptions in this circuitry, or are able to compensate for it in some fashion. Older men with early onset MDD do show decrements in emotion processing accuracy equivalent to that seen in older women with MDD regardless of age of onset. In contrast, older men with late onset MDD, appear to have a similar neural network that is disrupted to a far greater degree than the other older depressed groups. These stimulating findings may lead to better understanding of the different risk for depression by gender and by age and toward more effective and efficacious treatments of the underlying neurobiological disruptions.

Acknowledgements

This research was supported in part by Rachel Upjohn Clinical Scholars Awards (to SAL and SLW), K-12 Mentored Career Development Award (to SAL), NIH grant P01 MH 42251 (to Elizabeth Young, M.D. and Jon-Kar Zubieta, M.D., Ph.D.), internal support from the Depression and Neuropsychology Sections of the Department of Psychiatry, University of Michigan Medical Center, and the Department of Psychology, Marquette University (to Kristy A. Nielson, Ph.D.) and we thank these sources for support in completing this project. The present study is a further exploration of findings reported previously with a larger sample and there is some overlap \((n = 124)\) in participants across both studies (Langenecker et al., 2007a in this edition). A subset of these data \((n = 151)\) was presented at the annual meeting of the Cognitive Neuroscience Society, 2007. The aid of a number of students and assistants was invaluable in completing this project: Ami S. Antonucci, Ph.D., Erich Avery, Andrew Benway, Emily M. Briceno, Rachel Burns, Korey Cantrell, Luis Casenas, Stephen Crocker, Karla Felske, Caroline Freitag, Kristen Grabar, Leslie M. Guidotti, Najat M. Hamid, Melissa R. Hill, Thomas A. Hooven, Nicole Huby, Psy.D., Allison M. Kade, Jessica Layne, Hadia Leon, Benjamin D. Long, Justin B. Miller, Rebecca Reiten, Michael-Paul Schallmo, Maureen Schrock, Megan Shaheen, Simrat Singh, Karendeep Singh, Clare Tyson, Naalti Vats, Lesley Weitekamp, Yahong Yang, and Naomi Yodkovik. We thank Michael Ransom, Ph.D. for his review of this chapter and helpful comments.

References


Raz, N., Torres, I. J., and Acker, J. D. (1995). Age, Gender, and Hemispheric-Differences in Human Striatum - A Quantitative Review and New Data from In-Vivo MRI Morphometry. *Neurobiology of Learning and Memory, 63*, 133-142.


