

Perspective

Translational Research in Late-Life Mood Disorders: Implications for Future Intervention and Prevention Research

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Clinical and epidemiological studies have consistently observed the heterogeneous symptomatology and course of geriatric depression. Given the importance of genetic and environmental risk factors, aging processes, neurodegenerative and cerebrovascular disease processes, and medical comorbidity, the integration of basic and clinical neuroscience research approaches is critical for the understanding of the variability in illness course, as well as the development of prevention and intervention strategies that are more effective. These considerations were the impetus for a workshop, sponsored by the Geriatrics Research Branch in the Division of Adult Translational Research and Treatment Development of the National Institute of Mental Health that was held on September 7–8, 2005. The primary goal of the workshop was to bring together investigators in geriatric psychiatry research with researchers in specific topic areas outside of geriatric mental health to identify priority areas to advance translational research in geriatric depression. As described in this report, the workshop focused on a discussion of the development and application of integrative approaches combining genetics and neuroimaging methods to understand such complex issues as treatment response variability, the role of medical comorbidity in depression, and the potential overlap between depression and dementia. Future directions for integrative research were identified. Understanding the nature of geriatric depression requires the application of translational research and interdisciplinary research approaches. Geriatric depression could serve as a model for translational research integrating basic and clinical neuroscience approaches that would have implications for the study of other neuropsychiatric disorders.

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INTRODUCTION

In the recent commentary entitled ‘Psychiatry as a Clinical Neuroscience Discipline’, Insel and Quirion, 2005 discuss the importance of ‘applying the revolutionary insights from neuroscience to the care of those with brain disorders.’ In understanding the neurobiology of geriatric depression and developing more effective prevention and intervention strategies, the integration of basic and clinical neuroscience research is critical. Geriatric depression is characterized by substantial variability in treatment response and long-term

illness course, as well as heterogeneity in the extent of cognitive dysfunction and structural and functional brain alterations (as reviewed by Lebowitz *et al*, 1997). The importance of understanding the neurobiology of geriatric depression is underscored by the association between depression in late-life and functional disability, the increased rate of completed suicide in older depressed patients, greater mortality associated with depression in the medically ill, and the increased risk for the development of Alzheimer’s Disease (AD) as suggested by the epidemiological literature (Alexopoulos *et al*, 1996a, b; Henriksson *et al*, 1995; Conwell *et al*, 1996; Bruce and Leaf, 1989; Arfken *et al*, 1999; Jorm *et al*, 1991; Meyers and Bruce, 1998). Factors related to aging processes, medical comorbidity, cerebrovascular, and neurodegenerative disease must be considered in understanding the variability observed.

These considerations were the impetus for a workshop, sponsored by the Geriatrics Research Branch in the Division

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of Adult Translational Research and Treatment Development of the National Institute of Mental Health (NIMH) that was held on September 7–8, 2005. The primary goal of the workshop was to bring together investigators in geriatric psychiatry research with researchers in specific topic areas outside of geriatric mental health to advance translational research in geriatric depression. Investigators in the fields of genetics, neuroimaging, psychopharmacology, neuropsychology, and neuropathology presented their research. The discussion focused on integrating research findings across disciplines and identifying future directions for research. The workshop was also designed to encourage dialogue between basic and clinical researchers and to broaden crosstalk among junior, mid-career, and senior investigators. The workshop focused on developing and applying integrative approaches to understand such complex issues as treatment response variability, the role of medical comorbidity in depression, and the depression-dementia continuum. The meeting concluded with a discussion of the role of genetics and neuroimaging research approaches in the drug discovery and drug development process. It is important to note that the meeting focused on the study of unipolar major depressive disorder in the elderly, including both recurrent depression with an onset throughout the lifespan, as well as late onset depression. The meeting did not focus on the important areas of psychotic depression or bipolar disorders in the elderly that are currently the focus of large-scale, multi-center trials (eg, Meyers *et al*, 2005; Young *et al*, 2004), nor late-life anxiety disorders, which are extremely common in the elderly and represent challenges in clinical management (Flint, 1994, 1998). The following sections will focus on a summary of the status of research in genetics, structural, functional, and neurochemical imaging relevant to geriatric depression. The decision to focus on genetics and neuroimaging for the purposes of this report is that these methods best represent the interface between clinical and basic neuroscience research. Future directions for research were discussed and will be outlined at the end of the report.

THE NEUROBIOLOGY OF GERIATRIC DEPRESSION

Neuropsychological, neuroimaging, and neuropathological studies in geriatric depression have revealed deficits consistent with the normal aging process, cerebrovascular, and neurodegenerative disease processes. The integration of these data have led to the development of multifactorial models of pathophysiology (eg, Kumar *et al*, 2000; Alexopoulos, 2005). This section will summarize the status of research on the clinical course of geriatric depression, profiles of cognitive impairment, and neuropathological studies to provide a basis for the following discussion of neuroimaging and genetics research.

Studies characterizing the *clinical course and outcomes of antidepressant treatment* in geriatric depression have observed greater variability in response, increased rate of relapse, and a significant impact of age at onset, stress, and anxiety symptoms on treatment response (Reynolds *et al*, 1996, 1998, 1999; Dew *et al*, 1997; Mazure *et al*, 2002; Lenze *et al*, 2000; Flint and Rifat, 1999). Significant variability in the trajectories of acute and long-term treatment response

have been observed, in addition to the observation of significant numbers of patients who are treatment resistant (about 25% across studies; Dew *et al*, 1997; Little *et al*, 1998). It is noteworthy that geriatric patients respond as well if not better than younger patients do to electroconvulsive therapy (ECT; Tew *et al*, 1999; O'Connor *et al*, 2001). The neurobiological substrates of the differences in treatment trajectories are not well understood and are beginning to be investigated by serial cognitive and neuroimaging studies performed during the course of treatment (Nebes *et al*, 2003; Smith *et al*, 2002a, c). Clinical and epidemiological studies have identified some of the psychosocial and medical factors associated with depression, vulnerability, and prevention strategies have been evaluated in some instances (eg, bereavement, post-stroke depression, and interferon induced depression; Shear *et al*, 2005; Narushima *et al*, 2002; Whyte *et al*, 2004; Musselman *et al*, 2001). Although the choice of therapeutic agents for these prevention studies have focused on standard pharmacological and psychosocial interventions, emerging neurobiological data will potentially inform the development of novel therapeutic strategies. These strategies will be more focused on specific aspects of symptoms and cognitive deficits that are less responsive to standard pharmacotherapy.

Several domains of *cognitive impairment* have been reported in geriatric depression. As will be reviewed in subsequent sections, the cognitive deficits observed in geriatric depression using standard neuropsychological tests have informed the design of neuroimaging studies to visualize changes in functional neural circuitry associated with these deficits. These neuroimaging studies have used validated cognitive neuroscience approaches that are based on specific cognitive constructs. The most consistent cognitive deficits observed in depressed patients who do not meet criteria for early AD or other dementias, are slowed speed of processing, deficits in executive function, and memory (Kramer-Ginsberg *et al*, 1999; Lockwood *et al*, 2000, 2002; Nebes *et al*, 2003; Butters *et al*, 2000, 2004; O'Brien *et al*, 2004). A major focus of neuropsychological study in geriatric depression has been executive dysfunction, given the reproducibility of findings and the observation that executive function deficits often persist, despite remission of mood symptoms (Alexopoulos *et al*, 2002; Elderkin-Thompson *et al*, 2003; Lockwood *et al*, 2002; Nebes *et al*, 2001; Butters *et al*, 2000; Nebes *et al*, 2003). Executive dysfunction and/or slowed processing speed, both putative indices of fronto-striatal dysfunction, mediate other cognitive weaknesses in geriatric depression including poor visual spatial skills, and episodic memory (Butters *et al*, 2004; Elderkin-Thompson *et al*, 2004). It has been suggested that measures of executive function, compared to other cognitive domains, may have good prognostic value regarding response to treatment, whereas measures of global cognitive function and memory may identify patients 'at risk' for dementia (Lockwood *et al*, 2000).

Neuropathological studies are extremely important to understanding the pathophysiology of geriatric depression, interpreting the findings from clinical and neuroimaging studies and identifying new areas of *in vivo* mechanistic studies and therapeutic targets. The initial, preliminary neuropathological studies of patients with geriatric depres-

sion that have been clinically well characterized before death have been published (Sweet *et al*, 2004; Rajkowska *et al*, 2005). In a sample of patients, many of whom (70%) demonstrated cognitive deficits before death, evidence of cerebrovascular alterations, neurofibrillary tangles, amyloid plaques, and diffuse lewy bodies was observed (Sweet *et al*, 2004). To follow-up on reports of decreased orbitofrontal cortex volume identified on magnetic resonance scans (Lee *et al*, 2003), Rajkowska *et al* (2005) demonstrated a decreased packing density of pyramidal neurons and reductions to a greater extent in cortical layers IIIc and V, the source of prefrontal-striatal, prefrontal-cortical, and prefrontal-amygdala projections. These neuropathological studies have provided support for the observations of cerebrovascular and neurodegenerative pathology as observed with neuroimaging methods. The neuropathology of major depression with respect to neurochemical abnormalities has been reviewed extensively (Arango *et al*, 2002; Schatzberg *et al*, 2002). The majority of these studies have been performed in younger patients and the extension of these observations into older patients represents an important area of investigation. Future studies of the neuropathology of late-life depression will extend the observations made by these initial studies (Sweet *et al*, 2004; Rajkowska *et al*, 2005) to larger sample sizes and further integrate the post-mortem findings with clinical and neuroimaging methods.

TRANSLATIONAL RESEARCH

The application of an interdisciplinary research approach is critical to understanding of such issues in geriatric depression as treatment response variability, the increased morbidity, and mortality associated with depression in late-life and the role of depression as a possible risk factor for dementia. Future mechanistic research in geriatric depression is influenced by methodological developments in genetics, affective, and cognitive neuroscience and neuroimaging, by the ability to integrate information across different research modalities and by using the information obtained to generate new hypotheses and therapeutic strategies. The following sections will summarize the existing literature in structural, functional, and neurochemical brain imaging and genetics, as well as the integration of these approaches. Future directions for translational research studies will be described. It is important to note that in some areas, the data reviewed will focus on studies in geriatric depression. In other areas, in which limited data in older subjects is available, the discussion will include the identification of methodological issues relevant to the study of geriatric patients and the identification of directions for research based on data obtained in younger depressed patients.

Neuroimaging Research

Converging evidence from clinical, neuroimaging, and neuropathological studies suggest that biological susceptibility to geriatric mood disorders is likely mediated by compromise in fronto-striatal-limbic functions with contributions from genetic, vascular, neurochemical, neuro-

degenerative, and other aging-related factors. Structural and neurochemical imaging methods, in addition to neuroimaging studies using cognitive and affective neuroscience approaches can be used to investigate the relationship among potential contributing factors to neural network abnormalities, and relate these findings to the clinical features and course of geriatric mood disorders. The following sections will provide a review of the literature concerning the application of structural, functional, and neurochemical imaging methods, comments regarding the findings in these three areas and the identification of future research directions for geriatric depression.

Structural brain imaging.

Introduction: Structural magnetic resonance (MR) imaging studies of geriatric depression have emphasized two lines of research: the evaluation of gray matter volumes and cortical and subcortical gray and white matter hyperintensities (Krishnan, 2002; Alexopoulos, 2005). Structural alterations have been observed in many components of the cortico-striatal limbic networks implicated in depression that have been described in the literature (eg, Mayberg, 2003; Adler *et al*, 2006).

The consistency of such findings as white matter hyperintensities and hyperintense areas in subcortical gray matter structures has drawn attention to the role of cerebrovascular disease in geriatric depression (Greenwald *et al*, 1996, 1998; Krishnan *et al*, 1997; Taylor *et al*, 2005a). These observations have led to the 'vascular depression hypothesis' (Krishnan *et al*, 1997; Alexopoulos *et al*, 1997a, b). This hypothesis is supported by the observations that there is a high rate of depression in patients with hypertension, diabetes, and coronary artery disease. There is also a high rate of depression in patients who have had strokes and/or silent strokes. White matter hyperintensities frequently occur in late onset depression. Vascular features in geriatric depressed patients are associated with greater overall cognitive impairment, greater impairments in word fluency, and naming, more psychomotor retardation, less agitation, less guilt feelings and greater lack of insight. These symptoms were observed to be similar to a frontal lobe syndrome that would result from disruption of cortico-striato-pallido-thalamo-cortico pathways (Alexopoulos *et al*, 1997a).

Summary of the literature: The primary volumetric findings in geriatric depression compared to comparison subjects include decreased gray matter volumes in prefrontal, anterior cingulate, and orbitofrontal cortex hippocampus, amygdala, and basal ganglia (O'Brien *et al*, 2004; Ballmaier *et al*, 2004; Bremner *et al*, 2002; Lai *et al*, 2000; Lee *et al*, 2003; Ballmaier *et al*, 2004; Krishnan, 1993; Kumar *et al*, 1998; Sheline *et al*, 1996, 1998, 1999; Ashtari *et al*, 1999). With respect to clinical correlates of these findings, the primary observations are the association between reduced hippocampal volume and later age-of-depression onset (Steffens *et al*, 2000, 2002), vascular risk factors, such as coronary artery disease (Koschack and Irlle, 2005), and repeated episodes of depression (Bell-McGinty *et al*, 2002; Butters *et al*, 2000; Sheline *et al*, 1996, 1999, 2003) and greater degree of atrophic changes associated with poorer

treatment outcome (Pillay *et al*, 1998; Young *et al*, 1999). It has been suggested that antidepressant treatment may reverse some of these volume reductions (Jacobs *et al*, 2000; Vythilingam *et al*, 2004).

Gray and white matter hyperintensities, particularly in the deep gray matter, in geriatric depressed patients have been associated with poorer performance compared to depressed patients without such lesions or normal elderly subjects with or without deep white matter changes in multiple domains of cognition including general and delayed recall memory measures (Wechsler Memory Scale-general memory index, delayed recall index), executive functioning (animal naming test), and language testing (Boston Naming Test) (Lesser *et al*, 1996; Kramer-Ginsberg *et al*, 1999). Several studies have also demonstrated that poorer treatment outcome is associated with greater subcortical and white matter hyperintensities (Fujikawa *et al*, 1996; Hickie *et al*, 1995; Leuchter *et al*, 1997; Simpson *et al*, 1997; Steffens *et al*, 2001).

Comment: Several recent methodological developments with respect to MR sequence development and analytic methods will have an important impact on the evaluating of volumetric alterations, the detection of white matter changes and the ability to visualize connectivity. Higher-resolution images acquired at higher magnetic field strengths, new methods of shape analysis (Posener *et al*, 2003; Styner *et al*, 2004) and the use of data-driven, voxel based approaches, may yield novel observations of structural brain alterations and the relationship to course of illness.

More sophisticated methods have been developed to evaluating white matter lesions quantitatively (Firbank *et al*, 2004) and with improved regional localization (Macfall *et al*, 2005). Diffusion tensor imaging has been used to examine the biophysical characteristics of white matter and for fiber tract mapping (Pierpaoli and Basser, 1996; Wakana *et al*, 2004). In patients with geriatric depression there is preliminary evidence to demonstrate frontal and temporal cortical differences in white matter structure in older depressed subjects (Nobuhara *et al*, 2006; Taylor *et al*, 2004), as well as alterations in specific anterior regions that were associated with poorer antidepressant response (Alexopoulos *et al*, 2002). Magnetization transfer is a method that may be particularly sensitive to detecting changes in myelin-related proteins and hence of great use in demyelinating disorders. This technique may reveal areas that may be compromised in normal-appearing regions in older depressed subjects (Kumar *et al*, 2004). The development and implementation of these new MR sequences has the potential to contribute unique pathophysiological information with respect to cerebrovascular and neurodegenerative mechanisms underlying white matter pathology in geriatric depression.

Future directions: The observations of structural changes in the brains of patients with geriatric depression should be further integrated with clinical and cognitive measures, genetics and functional imaging data to understand the significance of the structural changes and to address such questions as: (1) are structural brain changes

related to differential treatment response or cognitive deficits; (2) what is the relationship between structural brain alterations and genetic polymorphisms that have been associated with antidepressant response, cognitive function, and neurotrophic factors; (3) how do structural changes relate to a differential functional response to cognitive or pharmacological activation? Another critical aspect of future MR research is studies to correlate the neuroimaging findings with post-mortem data. The objectives of such studies are to identify the pathophysiology underlying the alterations in gray matter volumes and in the white matter hyperintensities, addressing whether these white matter changes are owing to cerebrovascular compared to demyelinating processes, an issue that has been debated for over two decades (George *et al*, 1986a,b; Thomas *et al*, 2002).

Functional imaging: cognitive, and affective neuroscience approaches.

Introduction: As described in the introduction deficits in executive function, speed of processing, and memory have been the major findings of neuropsychological studies in geriatric depression. Thus, the integrity of fronto-striatal and fronto-limbic circuitry hypothesized to underlie these deficits has been the major focus of cognitive and affective activation studies in geriatric depression. The following section will briefly summarize these findings, in addition to other promising areas of research in younger patients that may have important applications to the study of older depressed patients.

Summary of the literature:

1. With respect to affective processing, neuroimaging studies in young and middle aged individuals with major depression have most consistently shown abnormal activation in fronto-limbic regions specifically hyperactivation of ventral limbic regions. In contrast, executive processing is usually accompanied by hypoactivation of dorsolateral prefrontal and dorsal anterior cingulate regions (eg, Canli *et al*, 2004; Davidson *et al*, 2003; Elliott *et al*, 2002; Surguladze *et al*, 2005; Rose *et al*, 2006).
2. Preliminary studies in patients with late-life depression using executive (standard Stroop task) and affective (emotional Stroop task) tasks suggest that relative to comparison subjects, elderly depressed patients show less activation of the dorsal anterior cingulate during executive processing and greater activation of the subgenual cingulate and dorsomedial prefrontal cortex in response to negatively valenced words (Gunning-Dixon *et al*, 2005).
3. Verbal fluency tasks (eg, phonemic word generation) demonstrated bilateral hypoactivation of the dorsal anterior cingulate and the hippocampus in severely depressed geriatric patients relative to comparison subjects (de Asis *et al*, 2001) with the disruption in hippocampal activation in depressed patients predicting poor memory performance.
4. Explicit sequence learning tasks have shown in patients, compared to age-matched comparison subjects, decreased prefrontal activation in addition to increased caudate activation (Aizenstein *et al*, 2005b).

5. With respect to episodic memory, patients with geriatric depression demonstrate decreased activation of temporo-limbic structures relative to control subjects, but a greater response of these regions and potentially a greater capacity for compensation compared to AD patients (Gron *et al*, 2002).

Comment: The systematic evaluation of the activation response in normal aging and the comparison of the activation responses in younger compared to older depressed patients represent two priorities for functional neuroimaging studies. Such studies would have implications for the understanding of the contribution of age-related changes in brain function to the pathogenesis of geriatric depression, as well as the understanding of abnormalities or compensatory mechanisms that may be associated with the onset of depression in late life, as well as the impact of repeated depressive episodes. Results from fMRI studies of non-depressed older adults provide evidence for the vulnerability of fronto-limbic regions to the influence of aging. While processing affective stimuli, older adults reveal diminished activation of the amygdala relative to younger adults (Gunning-Dixon *et al*, 2003; Lidaka *et al*, 2002; Tessitore *et al*, 2005), within the context of the older adults demonstrating greater activation of prefrontal regions than the young comparison groups (Gunning-Dixon *et al*, 2003; Tessitore *et al*, 2005). Activation results from both episodic memory and executive function studies indicate that older adults often recruit additional frontal regions when compared with young adults (Cabeza *et al*, 2000, 2002, 2004; Lamar *et al*, 2004; Nielson *et al*, 2002, 2004). Thus, these data suggest that the activation patterns in older depressed individuals may differ from the patterns observed in young and middle-aged depressed patients and the direct comparison of these groups may provide important information about the influence of aging-related brain changes on the pathophysiology of geriatric depression.

With respect to the application of recent methodological advances, correlating the time course of the blood oxygen level-dependent response between brain regions can be used as a measure of functional connectivity and is a promising technique that has only recently been applied to the study of geriatric mood disorders. In a study of geriatric depression, Aizenstein *et al* (2005a) used an executive probe in an event-related fMRI paradigm to activate the dorsolateral prefrontal cortex and the dorsal anterior cingulate. During baseline scanning, depressed patients revealed hypoactivation of the dorsolateral prefrontal cortex and the anterior cingulate as well as decreased functional connectivity between these regions relative to comparison subjects. Hypoactivation in these regions resolved following 12 weeks of treatment with paroxetine, but the decreased functional connectivity persisted (Aizenstein *et al*, 2005a). Furthermore, preliminary evidence suggests that abnormal activation of some regions may resolve with treatment, whereas a lack of functional connectivity between regions may persist. Coupled with the findings summarized above, this study suggests that not only specific regions of fronto-striatal and fronto-limbic networks exhibits abnormal activation, but a disconnection syndrome affecting these systems may exist in geriatric depression.

Future directions: Although traditional neuropsychological tests have contributed valuable data about the general cognitive domains affected in geriatric depression, these tests assess complex cognitive functions that are not ideal for studies of specific neural networks. In contrast, simpler cognitive tests, in some cases originating from non-human primate studies of neural circuitry should be used to study of specific cerebral network abnormalities in geriatric depression. Examples of such assessments are the tests included in the Cambridge Neuropsychological Test Automated Battery (Sahakian and Owen, 1992). This battery includes tests developed to evaluate the neural substrates of cognition in non-human primates that were adapted to the study of human subjects. Some of the tests have been evaluated using fMRI and psychopharmacologic interventions to characterize further the neural circuitry and neurochemical mechanisms underlying task performance. One example of the application of a well-characterized cognitive paradigm to geriatric depression is the study by Murphy and Alexopoulos (2006) who have used the well-established Attention Network Test (Fan *et al*, 2002) to assess the efficiency of the executive, orienting, and vigilance attention networks and their association to treatment response in older patients with major depression. Preliminary evidence indicates that executive-related performance, but not orienting- or vigilance-related performance, was correlated with time to remission.

In addition to characterizing changes in cerebral activation patterns following treatment, functional MRI should be used to identify cerebral network abnormalities that predict treatment outcomes, including core depressive symptoms, as well as cognitive deficits. An example of such a study in younger depressed patients, greater activation in the amygdala in response to emotional facial expressions predicted better treatment outcome several months following treatment, even after controlling for depression severity and medication status (Canli *et al*, 2005). The use of cognitive and affective fMRI paradigms within the context of controlled treatment trials for geriatric depression would not only advance our knowledge of the pathogenesis of geriatric depression, but also allow us to identify biomarkers of individuals who are at risk for poor treatment responses.

Further studies comparing cognitive and affective activation responses in patients with geriatric depression and AD (especially longitudinal studies in subjects who decline cognitively compared to those who do not) may be useful in identifying whether there are overlapping or independent patterns of neurodegeneration in geriatric depression compared to AD. The evaluation of medication effects would address the issue of whether antidepressant agents improve function and whether treatment with cognitive enhancing agents may be indicated.

Our understanding of the nature and role of fronto-striatal-limbic network anomalies in the presentation and course of geriatric depression may be enhanced significantly by the combination of fMRI with other imaging modalities. For example, rapid advancements in imaging processing and analysis techniques should enable combination of data across fMRI and DTI-imaging modalities allowing a more comprehensive analysis of functional connectivity in geriatric depression.

Neurochemical imaging approaches.

Introduction: The major emphasis of neurochemical imaging studies using positron emission tomography and single photon emission computed tomography in major depressive disorder has been the evaluation of the monoamine hypothesis of affective disorders (Schildkraut, 1965). Advances in radiochemistry over the past two decades have made possible the visualization of monoamine metabolism, transporter and receptor binding, as well as other potentially relevant neurochemical mechanisms (as reviewed by Fowler *et al*, 2003; Smith *et al*, 2004). There are other approaches for evaluating neurochemical function including the combination of pharmacologic challenges with the measurement of cerebral blood flow and glucose metabolism in the resting state or during cognitive or affective processing tasks. MR spectroscopy studies can potentially complement the PET and SPECT imaging methods and permits the evaluation of concentrations of amino acids (GABA, glutamate) and membrane lipids in the brain. For example, studies conducted in patients with geriatric depression have demonstrated increased myo-inositol/creatinine ratios in frontal white matter (Kumar *et al*, 2002).

Summary of the literature: The PET and SPECT studies performed thus far have been conducted mainly in patients with midlife depression. The major findings of the studies comparing depressed patients to demographically matched comparison subjects are (1) reduced serotonin precursor uptake and synthesis (Agren *et al*, 1991; Rosa-Neto *et al*, 2004); (2) modest or no reductions in serotonin transporter, 5-HT_{1A}, and 5-HT_{2A} binding (Malison *et al*, 1998; Meyer *et al*, 2004, 2001a, c; Parsey *et al*, 2006; Drevets *et al*, 1999; Sargent *et al*, 2000; Meltzer *et al*, 1999; Zanardi *et al*, 2001; Yatham *et al*, 1999); (3) modest changes in dopamine metabolism, dopamine transporter, and D₁ and D₂ receptor binding (Agren and Reibring, 1994; Meyer *et al*, 2001b; Suhara *et al*, 1992) and (4) most recently, a significant (average 34%) elevation of monoamine oxidase A concentrations in depressed patients compared to comparison subjects (Meyer *et al*, 2006). Thus, studies of monoamine transporter and receptor binding have shown limited sensitivity in differentiating depressed patients from comparison subjects. Studies evaluating the PET measures relative to symptom and genetic measures have observed (1) increased serotonin transporter and 5-HT_{2A} binding associated with negative dysfunctional attitudes (Meyer *et al*, 2003, 2004); and (2) higher 5-HT_{1A} binding associated with no previous antidepressant treatment, poorer antidepressant outcome and homozygosity for the functional 5-HT_{1A} G(-1019) allele of the promoter polymorphism (Parsey *et al*, 2006). Thus, the variability in transporter and receptor binding may be explained by symptom or genetic factors.

Comments: As described above, relatively modest changes in transporter and receptor binding in patients compared to comparison subjects have been observed. In addition, a lack of correlation between the magnitude of occupancy of a drug to the initial target site of action with clinical response has been observed across a variety of disorders, including SSRIs in patients with depression, antipsychotics in patients with schizophrenia, cholinester-

ase inhibitors in Alzheimer's disease (eg, Meyer *et al*, 2004; Wolkin *et al*, 1989; Farde *et al*, 1992; Kuhl *et al*, 2000). These observations suggest that measuring the dynamic aspects of monoamine function may be more revealing of pathophysiology and treatment mechanisms than measures of transporter or receptor binding.

On the basis of these observations, methodology development was initiated over a decade ago to evaluate dynamic measure of monoamine function and interactions between monoamine systems. The early focus of this work was on the measurement of striatal dopamine concentrations (eg, Dewey *et al*, 1993; Volkow *et al*, 1994) and modulation by other neurotransmitter systems (eg, serotonin, glutamate; as reviewed by Smith *et al*, 2004). Thus far, studies have not observed differences in striatal dopamine concentrations in midlife depressed patients (Anand *et al*, 2000; Parsey *et al*, 2001). However, developments in the imaging of extrastriatal D₂/D₃ receptor in cortical and limbic related areas (including the ventral striatum; Willeit *et al*, 2006) may have important implications for imaging dopamine function in brain regions that may be more relevant to depression and reward circuitry. The potential role of dopamine as a therapeutic target has been suggested by recent methylphenidate augmentation studies (Lavretsky and Kumar, 2001).

More recent studies have focused on the development and application of a method to measure serotonin function *in vivo* (Meyer *et al*, 1999; Hume *et al*, 2001; Smith *et al*, 1999, 2002b, 2004). Studies conducted thus far in geriatric depression combining acute and chronic SSRI treatment (citalopram) with measures of cerebral glucose metabolism have shown a differential lateralized pattern of acute metabolic effects in the patients in contrast to comparison subjects that are similar to the response in normal subjects who have a *s allele* of the serotonin transporter promoter polymorphism compared to those normal subjects with a *l allele* (Smith *et al*, 2004).

Thus, in the case of depressive disorders the combination of rCBF or glucose metabolism measures with a pharmacologically selective intervention may further enhance the predictive value of these measures with respect to identifying the functional differences between treatment responders and non-responders. After identifying the functional neuroanatomic changes, mechanistic studies using neuroreceptor radiotracers can be designed based on the functional circuitry altered to identify the neurochemical substrates underlying the metabolic effects. Similar pharmacologic intervention studies could be conducted with fMRI methods and would be extremely informative, especially with respect to monoamine regulation of the neural circuitry involved in cognition.

Future directions: The application of neurochemical imaging methods has focused on the investigation of monoamine transporters and receptors in depression and occupancy by antidepressant medications. Much of this work has been performed in younger patients. Some of the most intriguing results obtained thus far have involved integrating the neurochemical imaging measures with clinical variables and genetic polymorphisms.

The question embedded in this discussion is why these transporter and receptor measures are not more sensitive to

identifying pathophysiology, especially in brain regions that have shown glucose metabolic alterations. The limited data available in geriatric patients suggest that these effects are even more modest in older compared with younger patients (eg, Meltzer *et al*, 1999). Is the lack of a more dramatic effect telling us something about the adaptive function and compensatory mechanisms of these systems? As described, dynamic measures of monoamine function may be more sensitive than static measures such as transporter or receptor availability. Regarding other potentially relevant neurochemical systems, radiotracers development for both adrenergic and glucocorticoid systems are active areas at the present time, and development of radiotracers for these systems would have important implications for mechanistic studies in geriatric depression. Another important area of investigation would be to understand further the mechanism of action of antidepressant medications relative to promoting trophic responses in geriatric depressed patients as has been shown in laboratory animals (Duman *et al*, 1997).

PET methods can be applied to examine specific neurodegenerative processes *in vivo* that have been characterized in the post-mortem brain in patients with depression and with AD. *In vivo* imaging can be applied to evaluate when the neuropathologic process emerges in the illness and how it relates to the course of the illness with respect to treatment response and onset of cognitive impairment. As amyloid deposition has been observed in the brains of geriatric depressed patients, amyloid imaging agents would be important to evaluate in patients relative to cognition dysfunction (Sweet *et al*, 2004; Klunk *et al*, 2004). In addition, given the reports of increased neuroinflammatory markers in post-mortem brain and increased concentrations of pro-inflammatory cytokines in plasma (Thomas *et al*, 2000, 2005), the use of the peripheral benzodiazepine radiotracer [¹¹C]-PK 11195 (Groom *et al*, 1995) would be extremely interesting to evaluate in patients with and without cerebrovascular disease and also to evaluate the impact of antidepressant medication and other pharmacologic interventions. Another aspect of understanding neurodegeneration and cognitive impairment in geriatric depression is the application of radiotracer-binding methods to elucidate a potential cholinergic deficit. Preliminary post-mortem studies in geriatric depression report pathological changes in both monoaminergic and cholinergic neurons in geriatric depression (Sweet *et al*, 2004). The cholinergic system in depression is very much understudied. On the basis post-mortem studies in mild cognitive impairment and AD, there may be evidence of a compensatory cholinergic process early in the course of cognitive impairment and an actual cholinergic deficit may not appear until the later stages of impairment (DeKosky *et al*, 2002). The cholinergic system may similarly be involved as substrate of cognitive deficits in geriatric depression.

Other aspects of geriatric depression research that merit further neurochemical imaging studies include the comparison of younger depressed patients to older depressed patients to determine whether the initial onset of depression in mid-life compared to late-life patients involves the same neurochemical substrates and to determine the impact of repeated depressive episodes on neurochemical function. Such studies are critical in addressing such fundamental

questions as to whether depression in late-life is a distinct neurochemical entity, whether there are distinct neurochemical alterations that occur in patients who develop dementia, whether depression is a neurobiological prodrome of dementia or a consequence of neuronal loss. The mechanism of action of interventions that are effective in treatment-resistant patients such as ECT should be further investigated. The neurobiological effects of such treatments remain poorly understood (Mann, 1998; Szuba *et al*, 2000). Mechanisms such as greater enhancements of monoaminergic function and increased trophic responses have been suggested to underlie the greater efficacy of ECT compared to antidepressant medications. Finally, neurochemical imaging studies in psychosocial (bereavement; Shear *et al*, 2005) and medical (interferon induced depression; Musselman *et al*, 2001) circumstances, in which depressive symptoms occur in a subset of vulnerable individuals would be extremely interesting in terms of identifying neurobiological markers of vulnerability. Similar considerations apply to geriatric bipolar disorder and psychotic depression. These disease entities are studied conditions that are clinically challenging and associated with cognitive deficits and increased mortality in the case of psychotic depression (Vythilingam *et al*, 2003).

Genetics research.

Introduction: Genetic influences may be associated with vulnerability to both psychosocial and medical triggers of depression, as well as variable phenotypic expression and treatment sensitivity. As the data regarding candidate gene studies and pharmacogenetic studies have been reviewed extensively (eg, Nemeroff and Vale, 2005; Hattori *et al*, 2005; Paez-Pereda, 2005; Craddock and Forty, 2006; Binder and Holsboer, 2006; Lesch and Gutknecht, 2005; Serretti *et al*, 2005; Wong and Licinio, 2004; Levinson, 2006), this section will primarily focus on observations relevant to future genetic association studies of geriatric depression.

Summary of the candidate gene selection literature: In one of the few studies conducted in elderly subjects, the serotonin transporter promoter has been associated with depression following a hip fracture in the elderly (Lenze *et al*, 2005), consistent with the interaction of this polymorphism with psychosocial stress (Caspi *et al*, 2003). However, most candidate genes have been primarily examined in younger populations. These include enzymes for serotonin synthesis (Zhang *et al*, 2005; Zill *et al*, 2004), serotonin transporters and receptors (5-HT_{1A} and 5-HT_{2A} receptors, Lesch *et al*, 1996; Arias *et al*, 2005), the norepinephrine transporter (as reviewed by Leonardo and Hen, 2006), second-messenger systems (eg, Zubenko *et al*, 2002), glucocorticoids (Van Rossum *et al*, 2006; van West *et al*, 2006), neuroendocrine hormones (Binder *et al*, 2004) and brain-derived neurotrophic factor (BDNF: eg, Rybakowski *et al*, 2003; Strauss *et al*, 2004). These genes may have either much weaker or more predominant roles in older adults, hypotheses that await testing.

Previously unsuspected candidate genes are also being identified using genomic micro-arrays, animal studies, and genome-wide searches (Bunney *et al*, 2003), with potential sources of messenger ribonucleic acid (mRNA) from post-

mortem brains (Evans *et al*, 2004; Erraji-Benchekroun *et al*, 2005; Sibille *et al*, 2004), brain tissue from animal models of depression (Yamada *et al* 2001, 2000; Landgrebe *et al*, 2002; Alfonso *et al*, 2004), peripheral sources such as lymphocytes in living depressed subjects (Gladkevich *et al*, 2004), and cell cultures (Chen *et al*, 2003). Fibroblast growth factor gene expression was shown to be dysregulated in post-mortem brain tissue from depressed patients (Evans *et al*, 2004). Growth associated protein mRNA was increased in hippocampal cultures following desipramine treatment (Chen *et al*, 2003). Electroconvulsive stimulation in rodents identified potential roles for BDNF, second-messenger systems involving cAMP and related neurotrophic factors (Altar *et al*, 2004). In combination, studies such as these provide possible clues, regarding which gene systems, such as those involved in neurogenesis, to examine further in associational analyses. However, an important consideration is that many mRNA transcripts may change either with healthy aging or with other age-related disease processes (Lukiw, 2004; Ricciarelli *et al*, 2004; Toescu *et al*, 2004). Thus, it will be crucial to consider the aging process and associated disease processes in interpreting data specifically related to geriatric depression.

Whole genome associational studies are utilizing dense maps of genetic variation to examine the entire genome for possible candidates (Craig and Stephan, 2005; Ehm *et al*, 2005). A recently completed haplotype map of the human genome (Altshuler *et al*, 2005) has provided a dense array of SNPs for use in several different populations. The technology for this whole genome approach is nascent but should also provide a complimentary approach to hypothesis-based studies of genetic association.

Pharmacogenetic studies performed thus far in patients with geriatric depression have observed associations between speed of response and antidepressant side effects and the serotonin transporter promoter polymorphism (slower speed of response and greater side effects response associated with the *s allele*; Pollock *et al*, 2000; Murphy *et al*, 2004). Future pharmacogenetic studies will require controlling for differences in exposure to the pharmacologic stimulus (Lotrich *et al*, 2006). In particular, there can be large variability in exposure to medications, which may be an important confound to address, as different genotypes may be associated with dissimilar concentration-response relationships (Lotrich *et al*, 2006). This is particularly salient in the elderly who can have substantial variations in drug concentrations as well as markedly different sensitivities to medications (Lotrich and Pollock, 2005b).

Comment: Future genetic association studies should include (i) an explicit account of the selection of candidate genes and haplotypes, with appropriate statistical control for multiple testing, (ii) a comprehensive description of the psychiatric phenotype including course, pattern, and comorbidity, given the likely complexity of geriatric depression, (iii) statistical attention to the potential for population stratification, an issue that can be particularly problematic in neuroimaging studies with small sample sizes, and (iv) an analysis of linkage between polymorphisms within a gene and the potential for intra-genetic epistasis.

In geriatric depression, many co-morbidities are frequently present, most notably vascular disease and inflammation. For example, consistent with proposed theories that inflammatory cytokines induce a subtype of geriatric depression, late-life depression is associated with increases in interleukin 1b (Thomas *et al*, 2005), elevated interleukin 6 (Tiemeier *et al*, 2003), and an enhanced inflammatory response (Glaser *et al*, 2003). These co-morbidities may influence the relative role of genes in late life. Several possible causal genetic pathways have been suggested: (i) genes influence co-morbid illness that subsequently causes depression, (ii) genes moderate the ability of co-morbid illness to cause depression, (iii) genes directly influence depression that subsequently triggers co-morbid illness, (iv) genes moderate the ability of depression to cause a co-morbid illness, and (v) similar genes simultaneously influence both depression and co-morbid illness. Prospective studies will be needed to dissect the role of genetic vulnerability in these bi-directional pathways. The observation that comorbidity with depression is the rule rather than the exception suggests that these complex diagnostic issues should not be ignored in neurobiological studies of late-life mood disorder. Several of these hypotheses may be addressed in future studies that integrate neuroimaging studies with genetics, a technique reviewed in later sections.

For interpreting forthcoming associational studies, genetic influences on protein expression and function will require characterization. For instance, a common single nucleotide polymorphisms (SNP) in the upstream regulatory region for tryptophan hydroxylase 2 (TPH2) has recently been associated with changes in amygdala reactivity (Brown *et al*, 2005) during midlife, and may affect binding for several transcriptional regulators such as MSX-1 and MSX-2. However, whether this polymorphism is functional, whether this functionality changes with age, or whether it is in linkage disequilibrium with another functional variant requires determination. Moreover, functional effects may depend upon cell type. For example, a variant in the upstream promoter region of the 5-HT1A receptor has been associated with impaired regulation by NUDR/Deaf-1, major depression (Lemondé *et al*, 2003), and altered sensitivity to an acute challenge with a 5-HT1A receptor agonist (Lesch and Gutknecht, 2004). However, the genetic influence on expression may differ between pre-synaptic and post-synaptic cells in the raphe nucleus (Lemondé *et al*, 2003). Strategies for assessing intra-gene epistasis are also needed. For example, within the dopamine transporter (DAT), particular combinations of polymorphisms, both upstream and downstream, may interact to influence DAT expression (Greenwood and Kelsoe, 2003).

Future directions: Late-life depression has many characteristics that potentially distinguish it from earlier onset depression. Included are the numerous medical, inflammatory, and vascular co-morbidities, as well as the potential relationship to dementia. Changes in receptor levels and mRNA expression patterns with aging may also result in differences from midlife depression, as well as differential sensitivity to pharmacologic agents. These differences provide challenges in extrapolating results of genetic studies using younger adults to older subjects. However, these differences may also provide the opportu-

nity to understand more fully the etiology of depression and its consequences.

Additionally, although cross-sectional studies are informative, prospective longitudinal designs may ultimately be necessary for answering causal questions. Geriatric depression represents a unique opportunity for the conduct of prospective studies of specified depression subtypes and possibly for characterizing patients before the onset of depression. For example, vulnerability factors that may place euthymic individuals at high risk include loss of spouse (Vinkers *et al*, 2004), caregiver burden (Gallagher *et al*, 1989; Schulz *et al*, 1995), medical comorbidity (Cole and Dendukuri, 2003), cancer (Illman *et al*, 2005), and stroke (Antai-Otong, 2004). Another example is interferon-induced depression, in which many euthymic patients develop psychiatric symptoms including depression following the initiation of treatment (Valentine *et al*, 1998; Musselman *et al*, 2001). Longitudinal studies of these 'at-risk' populations may help inform how genetic vulnerability and resilience mechanistically influence the onset and development of depression. Relatedly, the interaction of genes and environment will be enhanced by studies that are focused on specific populations that are exposed to potential depressogenic triggers.

Guided by differences in patterns of drug response in the geriatric population (Lotrich and Pollock, 2005a), as well as medical triggers (eg, cardiac disease, menopause) of depression, other biologically plausible candidates for further investigation include the dopamine system, NMDA receptor subunits (eg, NR1), apolipoprotein E, vasopression and angiotensin receptors, inflammatory cytokine receptors (eg, TNF- α receptor), glucocorticoid receptors and chaperones (eg, FKBP5), nitric oxide (eg, nitric oxide synthetase), thyroid hormone receptors, estrogen, testosterone, G-proteins subunits (eg, α and β 3 subunits), adenylyl cyclases (eg, PKA regulatory subunit IIb), phospholipases (eg, PLC γ 1) phosphodiesterases isoforms (eg, phosphodiesterase 4), protein phosphatases (eg, PP2A and PP2B), and regulatory proteins that influence intracellular transduction (eg, A kinase anchoring protein 79/150; Lotrich and Pollock 2005b). Specifically guided by studies of menopause, a gene involved in estrogen metabolism has been implicated in perimenopausal depression (Kravitz *et al*, 2006). Similarly, the relative roles of these other systems in other potential subtypes of geriatric depression will require further evaluation.

The identification of multiple and varied 'at risk' elderly populations may provide useful cohorts to examine prospectively the interaction of genetic variation and various triggers of depression. Interactions between genetic risk and other potential sources of risk (including cardiovascular, inflammatory, psychosocial losses, early dementia) may provide meaningful insights into the pathophysiologic pathways leading to depression. Results from micro-array studies and from preliminary association analyses in midlife depression, have provided numerous plausible candidates for biologically guided future research. Moreover, although genetic studies in geriatric depression are only now beginning, statistical solutions to multiple testing, population stratification, and haplotype phasing are being addressed and will be feasible and appropriate to implement for the next generation of studies.

Potential causal mechanisms of genetic variation can be investigated using functional and structural neuroimaging. In this regard, the length polymorphism in the serotonin transporter promoter (5-HTTLPR) has been connected to glucocorticoids and cytokines (Glatz *et al*, 2003; Mossner *et al*, 2001), and this polymorphism has been associated with altered sensitivity to serotonergic challenges and functional differences in frontal-limbic pathways following both pharmacologic and affective challenges (eg, Smith *et al*, 2004; Hariri *et al*, 2002, 2005). These investigations are converging on an answer to the question of how this polymorphism may functionally influence the etiology of depression and the response to treatment. This single example illustrates how greater integration of genetics, neuroimaging, and pharmacologic challenges will be important in characterizing the functional consequences of other polymorphisms. In summary, genetics and its integration with other techniques appears to hold great promise in delineating the underlying pathways that influence the development, as well as the treatment of geriatric depression.

Integrating Neuroimaging and Genetics

Introduction. The majority of studies combining genetic and neuroimaging methods have focused on several genetic polymorphisms including the serotonin transporter promoter, apolipoprotein E (ApoE), catechol-O-methyltransferase (COMT), disrupted-in-schizophrenia (DISC1) and BDNF polymorphisms (as reviewed by Roffman *et al*, 2006; Meyer-Lindenberg and Weinberger, 2006; Hariri *et al*, 2006; Scarmeas and Stern 2005; Lehtovirta *et al*, 2000; Heinz and Smolka, 2006). The following summary of the literature will highlight the findings potentially relevant to the study of geriatric depression.

Summary of the literature. In normal subjects, the *s allele* of the 5HTTLPR gene has been associated with structural brain alterations such as reduced perigenual cingulate and amygdala gray matter volumes and functional uncoupling of the amygdala-prefrontal circuitry (Pezawas *et al*, 2005; Heinz *et al*, 2005). The *s allele* has also been associated with alterations in functional brain responses such as an increased amygdala activation response to fearful or anxiety-producing stimuli or a differentially lateralized cerebral metabolic response to serotonergic challenge (Hariri *et al*, 2002, 2005; Smith, *et al*, 2004). In patients with depression, the *ll genotype* has been associated with smaller hippocampal volumes (Frodl *et al*, 2004). In older patients with the *ll genotype*, later depression onset is associated with smaller hippocampal volumes, whereas earlier age of onset was associated with smaller volumes in individuals homozygous for the *s allele* (Taylor *et al*, 2005b). BDNF polymorphisms have also been associated with memory deficits and smaller hippocampal volumes (Egan *et al*, 2003; Hariri *et al*, 2003; Pezawas *et al*, 2004). Other genetic polymorphisms, such as COMT (Ho *et al*, 2005), DISC1 (Callicott *et al*, 2005), and myelination-related polymorphisms (Hakak *et al*, 2001) may also be related to structural alterations in gray and white matter. The COMT polymorphisms have been shown to be associated with differences in the processing of affective (greater amygdala

response to unpleasant stimuli associated with the met158 allele) and cognitive tasks (a more focused activation response in working memory and attention control tasks associated with the val158 allele; as reviewed by Heinz and Smolka, 2006). At the present time, the transition from identifying a genetic polymorphisms related to a particular behavior and activation response and evaluating a medication targeted at the particular mechanism is best evidenced by the evaluating of the COMT inhibitor tolcapone for augmenting working memory and attentional control processes in normal subjects (Apud *et al*, 2006).

With respect to genetic and neuroimaging studies of monoamine receptor or transporter polymorphisms, the 5-HTTLPR and several dopamine (D2) polymorphisms have been the focus of study (Willeit *et al*, 2001; Heinz *et al*, 2000; Shioe *et al*, 2003). With respect to the 5-HTTLPR, an association between the polymorphisms and *in vivo* binding has not been shown in normal subjects (Shioe *et al*, 2003; Willeit *et al*, 2001), but an association has been shown in subjects who abuse alcohol (Heinz *et al*, 2000). With respect to the D2/D3 receptor, decreased D2/D3 receptor availability associated with the A1 allele of the TaqIA polymorphism has been reported in a study with [¹¹C]-raclopride (Hirvonen *et al*, 2004), as observed previously in a post-mortem autoradiographic study (Thompson *et al*, 1997). The variability in the magnitude of change in D2 receptor availability induced by smoking a cigarette was shown to be associated with COMT, the dopamine transporter and D4 receptor variable nucleotide tandem repeats and the D2 receptor Taq A1/A2 polymorphisms (Brody *et al*, 2006). The subjects with polymorphisms associated with low dopamine tone were related to greater changes in D2 receptor availability.

Vascular risk genes such as methylenetetrahydrofolate reductase (*MTHFR*) (Chen *et al*, 2005; Naismith *et al*, 2002) and potentially the *5HTTLPR* (Ramasubbu, 2003) genotype may be associated with increased severity of cerebral hyperintense lesions and associated cognitive impairment (eg, psychomotor speed). With respect to the ApoE4 allele, Reiman *et al* (1998, 2001) initially demonstrated an association between the ApoE4 allele and low rates of glucose utilization, in addition to lower hippocampal volumes and worse long-term memory performance in cognitively normal subjects. These findings have been replicated by other groups and have been extended to aspects of pathophysiology associated with aging such as white matter structural integrity and hyperintensities and functional activation responses (as reviewed by Scarmeas and Stern, 2005).

Comment: Genetic associations of candidate genes in future neuroimaging experiments will involve the same challenges and caveats as those reviewed in the genetics section. In addition to these issues, there are several statistical issues with respect to appropriate statistical control for multiple testing and the fact that the sample sizes in neuroimaging studies are typically smaller than studies that involve less invasive and costly clinical outcome measures. In neuroimaging studies that involve drug challenges, attention to differences in drug exposure are critical (Lotrich *et al*, 2006). Moreover, although the

majority of studies conducted thus far are cross-sectional, prospective longitudinal designs may ultimately be necessary for answering mechanistic and causal questions.

With respect to the structural and functional neuroimaging studies, intriguing observations have been reported with respect to several genetic polymorphisms as described above and the findings are generally internally consistent. With respect to the neurochemical imaging literature, the data are more limited. The available data suggest that dynamic measures of neurotransmitter function may be more informative with respect to understanding the functional neurochemical significance of genetic polymorphism than more static measures of neuroreceptor availability or number of binding sites. Thus, employing the dynamic imaging methods described in the neurochemical imaging section to combine acute pharmacologic intervention paradigms and measures of cerebral metabolism or blood flow or neuroreceptor availability represents a potentially important line of investigation and may lead to the elucidation of compensatory mechanisms.

As described in the genetics section, the identification of previously unsuspected genes is critical for advancing mechanistic and therapeutic research. Approaches to identifying potentially relevant genes include the study of animal models of aging, depression, and cognitive impairment, as well as the application of proteomic approaches to the study of post-mortem brain tissue of elderly subjects and patients with mood and neurodegenerative disorders (as reviewed by Vercauteren *et al*, 2004). The identification of new potentially relevant genes may also inform the development and evaluation of neurobiological targets for pharmacologic intervention studies and radiotracer development, as well as for therapeutics.

Future directions: The integration of genetic with neuroimaging methods may provide important information regarding the significance of specific genetic polymorphisms with respect to structural and functional neural circuitry and neurotransmitter pathways, as well as an understanding of between-subject variability in the neuroimaging measures and whether the same associations are observed in normal function and in disease. The integration of genetic and neuroimaging data may provide a better delineation of neurobiological subtypes of depression that might relate to different patterns of disease course or treatment response.

Several priorities for neuroimaging and genetics research have been articulated consistently in previous sections. These themes include the importance of understanding the neurobiological mechanism underlying heterogeneity in normal aging, depression vulnerability, medical comorbidity (cerebrovascular disease and neuroinflammation, in particular) variability in treatment response and the pathophysiology of cognitive impairment. In this section, the potential contribution of integrating genetics and neuroimaging methods to addressing these themes will be discussed.

With respect to the *normal aging* process, substantial variability in cognition, as well as in brain structure and the functional integrity of neural circuitry and neurochemical pathways has been observed. The evaluation of the

neuroimaging measures relative to genetic polymorphisms is critical to identifying, which genes are associated with changes in the brain that result in cognitive impairment, and which genes are associated with compensatory processes identified by functional imaging methods to maintain cognitive function in the presence of brain structural and neurochemical alterations. The comparison of the associations between genes, cognition and brain structural and functional integrity in the normal aging process and the contrast with depressive disorders with onset across the lifespan could provide important neurobiological and therapeutic information. With respect to *depression vulnerability*, the study of depression in late life provides a unique opportunity to study vulnerability as the result of change in life circumstances and stress (eg, bereavement, caregiver burden, recovery from medical illness). The investigation of the neurochemical processes associated with genes related to depression risk may identify targets for more effective prevention and treatment strategies.

With respect to understanding *variability in treatment response*, the integration of genetic and neuroimaging measures may identify neurochemical subtypes of depression that may be associated with different speeds and rates of treatment response to different classes of antidepressant medications or to interventions, such as ECT, deep brain stimulation or transcranial magnetic stimulation. With respect to understanding mechanisms and developing interventions for *cognitive impairment* and the consequences of *medical comorbidity* (eg, hypertension, diabetes), serial neuroimaging studies could be used to monitor whether patterns of alterations are associated with specific genetic polymorphisms over time to determine whether the longitudinal course of geriatric depression could be altered in individuals depending on genotype with a particular class of agents (eg, antidepressant, cholinesterase inhibitors, diabetogenic agents or antihypertensives), who are potentially at greater risk for depression relapse and cognitive impairment.

For the goals of delineating the etiologies of depression, the mechanisms underlying vulnerability and resilience, the relationships between depression and other co-morbidities, and specific targets for individualized treatment and prevention, the inclusion of genetic analyses in neuroimaging is an exciting new direction.

FUTURE DIRECTIONS

Several directions for future research follow from the discussion above:

- The study of specific *subject samples* to ask questions about (1) the neurobiological differences in the early vs late onset of depression and the impact of repeated depressive episodes across the life span; (2) the neurobiology of treatment-resistant depression, including psychotic depression; (3) neurobiological vulnerability markers and prevention strategies by studying such 'at-risk' subject samples, including patients with depression secondary to significant psychosocial stressors (bereavement, caregiver burden, as reviewed by Arean and

Reynolds, 2005) medical illness (cardiovascular disease, hip fracture or stroke), or medical interventions (interferon-induced symptoms, β -blocker-induced depressive symptoms).

- The application of *genetic methods* using candidate gene and micro-array strategies in patients and animal models (1) to characterize the genetic basis of treatment response variability and genetic polymorphisms related to specific cognitive deficits; (2) to identify the significance of genetic polymorphisms related to the structural neuro-anatomic, functional and neurochemical alterations identified by neuroimaging studies (eg, white matter hyperintensities, hippocampal atrophy, decreased monoamine receptor binding, altered brain response to pharmacologic interventions); (3) to characterize genetic polymorphisms related to vulnerability to depression in the 'at-risk' samples as described above, and (4) to identify novel targets for radiotracer development and therapeutics.
- The development and application of *affective and cognitive neuroscience* approaches to characterize further the neural circuitry underlying deficits in speed of processing, affective processing, executive function, and memory using validated tasks combined with fMRI methods; (2) to characterize the domains of cognitive function that improve with antidepressant treatment, compared to those that remain impaired after remission of mood symptoms and, in addition, the cognitive domains that show decline longitudinally; (3) to evaluate the impact of novel acute and chronic pharmacologic interventions on the functional activation responses to inform the development of effective treatments to target these symptoms; and (4) to evaluate the variability in the functional activation response relative to structural brain changes and to genetic polymorphisms.
- The development and application of *neurochemical imaging* methods (1) to identify the acute and chronic neurochemical consequences of antidepressant treatment; (2) to characterize the neurochemical deficits that persist after antidepressant treatment and are related to residual mood and cognitive symptoms; (3) to develop and apply new radiotracers to target the same neurochemical systems, for which genetic polymorphisms have been shown to be related to treatment response variability and specific symptom domains; and (4) to understand the variability observed in the neurochemical measurements relative to relevant genetic polymorphisms for neurotransmitter metabolism, transporter or receptor availability.
- The directions for future research involving the integration of basic with clinical neuroscience research, include the following.
- The important area of *post-mortem studies* include (1) the further characterization of the pathophysiology of geriatric depression to inform the design of genetic, neuroimaging and neuropsychological studies; (2) the correlation of post-mortem data with cognitive and neuroimaging findings to understand the substrates of persistent mood and cognitive symptoms such as anhedonia and executive dysfunction; and (3) the correlation of postmortem and imaging findings to understand the underlying pathophysiology of volu-

metric loss, white matter hyperintensities and neurochemical imaging findings.

- The development of *animal models* of geriatric depression has not been a focus of research, given the challenges in developing an animal model of depression and the practical constraints of studying aged animals. Models developed in younger animals could potentially be applied to aged animals (Cryan *et al*, 2005). Specific strains of rodents (eg, spontaneously hypertensive rats, cognitively impaired aged rats) could be used to mimic some aspects of pathophysiology. Knockout mice for the genetic targets that have been identified in the human studies as important to treatment response or cognitive impairment should be evaluated with respect to the functional or neurochemical response to pharmacologic agents for mood and cognitive symptoms. Conversely, the study of knockout mice that display similar behavioral or neurobiological features as geriatric depressed patients should be informative as well (Cryan and Holmes, 2005).

CONCLUSION

Understanding the complex nature of geriatric depression requires a translational and integrative approach. Neurobiological studies in geriatric depression represent unique opportunities for the identification of mechanisms of depression pathophysiology and vulnerability, which could potentially inform the development of intervention and prevention strategies. Such strategies may have relevance to the treatment of younger depressed patients, as well as to patients with depression secondary to other neuropsychiatric or medical illnesses (eg, Alzheimer's disease, Parkinson's disease, cerebrovascular disease), and to the development of integrative, conceptual models that could be applied to the study of other neuropsychiatric disorders. The translational research studies needed to address such neurobiologically complex questions require an integration of basic and clinical neuroscience approaches, including genetic and neuroimaging methods. Although the workshop and this report focus on unipolar major depression, the importance of research into psychotic depression, and bipolar disorder in late-life should be underscored. Two large scale multi-center trials in psychotic depression and bipolar disorder have been undertaken in the past few years, with an emphasis on the study of geriatric patients (Meyers *et al*, 2005; Young *et al*, 2004). The results of these clinical trials and the ancillary genetic and neuroimaging studies will provide important information to inform the design of neurobiological studies for these disabling disorders in the future. For hypothesis-driven, mechanistic research to evolve, continued interaction between investigators across disciplines (including geriatric psychiatry, genetics, neuropsychology, neuroimaging, and neuropathology) is critical.

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