Habilitationsschrift

Structural Neuroimaging Research in Elderly Depression: Findings and Possible Implications for Development and Progression of the Illness

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1. Introduction

The bulk of the literature on neuroimaging investigations into the pathophysiology of major depression have revealed a complex set of abnormalities in multiple limbic and prefrontal cortical structures. Only in recent years, research has also begun to intensively focus on the neurobiological correlates of major depression in older age. Indeed, major depression is a common disorder in the elderly associated with substantial morbidity and mortality.

1-4% of the general elderly population has major depression (Blazer 2003), equivalent to an incidence of 0-15% per year. Twice as many women are affected. Both the prevalence (Palsson et al. 2001) and incidence (Teresi et al. 2001) of major depression double after age 70-85 years. In old age, depressive syndromes often affect people with medical illnesses, cognitive impairment, or disability (Alexopoulos et al. 2002; Blazer 2003). Beyond personal suffering and family disruption, depression worsens the outcomes of many medical disorders and promote disability (Alexopoulos et al. 2002). Although progress has been made in characterizing the presentation of late-life depression and in improving treatment, it continues to have detrimental consequences with a high risk of suicide (Charney et al. 2003).

For a diagnosis of major depression to be made, ICD-10 or DSM-IV state that depressed mood, loss of interest or pleasure must be present. Although not part of the diagnostic criteria, elderly depression is often associated with peripheral body changes and cognitive impairment. Changes to the body include hypercortisolemia, increased abdominal fat, decreased bone density, and increased risk for type II diabetes and hypertension (Brown et al. 2004). Non-demented elderly people with major depression often have difficulties with concentration, speed of mental processing, and executive function (Lockwood et al. 2002; Elderkin-Thompson et al. 2003). These deficits improve but may not completely solve after remission of elderly depression (Butters et al. 2000; Nebes et al. 2002).

Importantly, major depression, especially in the elderly, may be considered a heterogeneous disorder. Elderly individuals with depression may have had multiple episodes of depression, starting earlier in life; alternatively, they may have had no psychiatric history, becoming depressed for the first time later in life. Several distinctions between these groups have been identified, such that subjects with early-onset depression are more likely to have a family history of psychiatric illness, while subjects with late-onset
depression are more likely to have greater subcortical ischemic disease. Some evidence links late-onset depression to increased risk of developing dementia. These findings have been interpreted to be signs of different causes or risk factors for depression based on age at depression onset.

Elderly depression is accompanied by clinical, neuropsychological and neuroimaging findings pointing to specific brain abnormalities. Several recent methodological developments and analytic methods have played a major role in examining brain structure abnormalities and their implications in older people with major depression. Volumetric region of interest analyses of specific brain regions still have an important impact on the evaluating of volumetric alterations. However, reductions of morphometric results into a single volume may overlook regional specificity that may add insight into the pathophysiological mechanisms underlying elderly depression. Highly sophisticated computational image methods, known as cortical pattern matching and surface-based mesh modeling, enable the measurement and visualization of subtle and anatomically selective brain changes most vulnerable to disease processes.

*Highly sophisticated computational image methods*

Cortical mapping methods allow data from each individual to be analyzed with a series of manual and automated procedures that carefully match cortical anatomy across subjects and measure local proportions of gray matter at each of the 65,536 anatomically matched points on the cortical surface.
In addition, surface-based mesh modeling techniques are able to identify changes of specific brain structures, such as the hippocampus, at a very local level. Shape abnormalities are identified by comparing distances, measured from homologous surface points to the central core of each individual’s surface model, between groups that allow for changes in surface deformation/expansion to be examined at high spatial resolution in three dimensions. Importantly, damage to particular subregions may produce different functional and clinical consequences, because different cortical projections may be involved. Identifying regional local changes in a given brain structure may therefore point to disturbances in the neural network subserving functions that may be differentially affected based on age at illness onset. Moreover, these brain mapping techniques can identify how local changes correlate with cognitive function, which may yield novel observations of structural brain alterations and their relationship to course of illness. In addition, they may offer new perspectives for defining risk profiles and appropriate interventions.

In the work presented here, these sophisticated techniques were applied to shed light on the neuroanatomical correlates and neural network abnormalities of elderly depression. Specifically, differences in morphometry were assessed in the cortex, the hippocampus and the corpus callosum based on age at onset of depression, which have not been specifically addressed in the literature. Relations of these structural brain abnormalities to cognitive measures, treatment response and gender were also examined. These approaches allowed us to generate new hypotheses for a more comprehensive understanding of the complex nature of elderly depression.
3. Discussion

Brain structure abnormalities in elderly depression involve frontal and temporal/parietal cortices, as well the hippocampus and the corpus callosum, which may be differentially affected based on age at illness onset. Abnormalities in more than one region might predispose to depression. There are at least two reasons for this assumption. First, abnormalities in one brain region might influence other functionally connected regions. Second, elderly patients might have vulnerabilities in more than one brain region with complex interactions, leading to vulnerability to depression.

**Prefrontal cortex:** Structural imaging research in elderly depression has provided evidence for reduced gray matter (Kumar et al. 1997, 1998) and white matter abnormalities in the frontal lobe (Nobuhara et al. 2006), including the dorsolateral prefrontal cortex (Thomas et al. 2002, Taylor and Krishnan, 2003, Taylor et al. 2004), the orbitofrontal cortex (Lai et al. 2000; Taylor et al. 2003) and the anterior cingulate (Alexopoulos et al. 2002, Kumar et al. 2002; Bae et al. 2006). Using a detailed volumetric MRI-based parcellation of the prefrontal cortex, we have shown for the first time significant differential patterns of abnormalities in gray matter, white matter and cerebrospinal fluid volumes of the orbitofrontal cortex, the gyrus rectus and anterior cingulate, implying that distinct etiopathological mechanisms may underlie the structural changes in these regions. Whether and to what extent length of depression history contributes to frontal abnormalities is yet to be clarified. In a further study on elderly depression with an early-onset, we mapped morphologic abnormalities to the entire cortical surface and showed highly significant decreased brain size along with complex cortical abnormalities in the orbitofrontal cortex, supporting previous post-mortem observations (Rajkowska et al. 2005) and the role of this region as a critical target of depressed mood (Drevets et al. 2000; Liotti et al. 2002). On the contrary, investigating elderly depression with a late onset by using computational cortical surface mapping, we could not detect any differences in frontal regions. Future longitudinal studies are needed to support this observation, and to examine how frontal lobe abnormalities are related to age of illness onset and to what extent they progress over time.

**Temporal/parietal cortices:** Whereas the prefrontal cortex has been a primary area of neuroimaging studies, the involvement of temporal/parietal cortices in elderly
depression is less well established. Prior findings from structural MRI research implied mixed evidence for whole temporal lobe involvement in elderly depression (O'Brien et al. 1994; Kumar et al. 1998; Nobuhara et al. 2006). Using computational methods that map morphologic abnormalities to the entire cortical surface, we detected apparent gray matter increases in temporal cortices in early-onset depression, whereas patients with a late-onset of illness exhibited pronounced decreases of temporal gray matter. Similar differences based on age at illness onset were seen in parietal cortices. Apparent gray matter increase might reflect axonal myelin reduction (that diminishes white matter signal values, thus increasing gray matter appearance), whereas gray matter decrease might occur when degeneration of neuronal cell bodies overtakes reduced myelin formation.

In my two studies using the sensitive computational cortical pattern matching methods, early- and late-onset depression groups were compared to controls. In these studies, disease groups were not directly compared between each other. Nevertheless, our findings suggest that late-onset depression may present with more advanced atrophic or neurodegenerative processes.

**Hippocampus:** Structural imaging studies have reported decreased volumes of the hippocampus in major depression, including elderly patients (Steffens et al. 2000; Bell-McGinty et al. 2002, Janssen et al. 2004; Frodl et al. 2004; O’Brien et al. 2004, Hickie et al. 2005). These changes may be more pronounced in key clinical subgroups (e.g. early- or late-onset groups) and in subjects with genetic risk factors (Kim et al. 2002; Taylor et al. 2005). Using novel surface-based mesh modeling methods, we identified the hippocampal subregions most vulnerable to disease processes in elderly patients with early- and late-onset depression. Regional atrophy patterns were significantly more pronounced in late-onset than early-onset depression, with concentrated volume reductions in anterior aspects of the subiculum and lateral-posterior aspects of the CA1 subfield. In addition, significant shape differences were observed bilaterally in anterior CA1-CA3 subfields and the subiculum in all depressed patients compared to controls, results that were similar when each disease group was compared to control subjects separately.

Since projections to and from the prefrontal cortices occur in a gradient concentrated in anterior hippocampal regions (Barbas and Blatt, 1995; Cavada et al. 2000), these findings are in line with our previous investigations in elderly depression showing bilateral gray matter abnormalities in distinct subregions of the prefrontal cortex. We also found that late-onset depression may be associated with greater cortical atrophy.
than early-onset depression, especially in temporal and parietal regions. This may offer a potential explanation as to more pronounced local volume reductions in both hippocamal head and tail of late-onset compared to early-onset depressed subjects. In addition, greater CA1 involvement in late-onset depression may suggest that these patients might be at higher risk to develop dementia over time. Indeed, lateral edge atrophy in regions corresponding to CA1 has been found in patients with mild cognitive impairment who later developed Alzheimer's disease (Apostolova et al. 2006). Therefore, identifying regional abnormalities in hippocampal structure may help elucidate which neural systems are most vulnerable to the disorder and may prove useful for dissociating early-onset from late-onset depression.

**Corpus callosum:** The question of callosal abnormalities in elderly depression has not been specifically addressed in the literature. Our study was the first to examine regional alterations of callosal morphology in elderly depression and to shed light on the hypothesis that late-onset depression may present certain unique disease effects on callosal morphology that may differ from elderly patients with an early onset of illness.

Interestingly, subjects with late-onset depression showed callosal thinning in the splenium compared to subjects with early-onset depression. In addition, greater callosal thinning in the genu and the splenium were observed in all depressed patients compared to controls. Comparison between the early-onset depression group and controls revealed callosal thinning restricted to the genu, while the late-onset depression group exhibited reductions in both the genu and the splenium relative to controls.

The anterior part of the corpus callosum is composed by fibers connecting prefrontal, premotor and motor areas, whereas the caudal part is composed by fibers connecting temporal, parietal and occipital areas (de Lacoste et al. 1985; Pandya and Rosene 1985; Pandya and Seltzer 1986).

In light of these connectivity patterns, our observation of callosal thinning in the genu in the early-onset group could be an indicator of altered prefrontal connections, which is in accordance with our previous results of structural prefrontal alterations in depressed elders with an early onset of illness. On the other hand, callosal thinning in both the genu and the splenium in late-onset depression relative to controls may be suggestive of more diffuse changes in cortico-cortical connectivity. This may support our findings of cortical temporal and parietal gray matter reductions in late-onset depression.
Furthermore, greater splenium thinning in late-onset compared to early-onset depression might point to more prominent atrophic or neurodegenerative processes in temporal connections, in accordance with studies showing greater temporal lobe (Greenwald et al. 1997; Kumar et al. 1998) atrophy and hippocampal volume reductions (Steffens et al. 2000; Lloyd et al. 2004; Hickie et al. 2005) in late-onset than early-onset depression. In addition, splenium thinning supports our own findings of more pronounced local surface deformations in the hippocampus in late-onset depression, which may place these patients at higher risk for dementia.

**Cognitive measures and brain correlates:** Although a variety of studies found different clinical characteristics to be associated with impaired cognition, including depression severity (Boone et al. 1995; Barnes et al. 2006; Sheline et al. 2006), history of depression (Beats et al. 1996; Ownby et al. 2006), age (King et al. 1995; Lyness et al. 2002), late age of depression onset (van Ojen et al. 1995; Salloway et al. 1996; Geda et al. 2006), and vascular disease (O’Brien et al. 2003; Sheline et al. 2006), relatively little is known about the relationship between cognitive measures and structural abnormalities in specific brain regions.

We observed that apathy, a key component of executive dysfunction (Lockwood et al. 2002), is preferentially associated with structural abnormalities in distinct frontal regions, including the anterior cingulate. On the other hand, structural brain abnormalities can also correlate with neuropsychological measures when they are still in the normal range. This association may reflect an early indicator of cognitive impairment becoming clinically evident only with further illness progression. Indeed, our research on callosal abnormalities in elderly depression suggested a strong relationship between reduced genu and splenium volumes and normal learning and attention functioning, respectively, in late-onset depression, but not early-onset depression or controls. In addition, our study in the hippocampus found a strong correlation for the CA1 subfield and the subiculum and normal verbal as well as nonverbal memory performance in late-onset but not early-onset depression or controls.

Future longitudinal studies may be needed to clarify how the associations between local callosal and hippocampal abnormalities and neuropsychological functioning may predict later cognitive decline and whether late-onset depression is more vulnerable to dementia conversion.
**Effects of antidepressant treatments:** Research on treatment of elderly depression has yielded mixed results. This may be, at least partly, related to concomitant cognitive impairments (Alexopoulos et al. 2000; Butters et al. 2000; Nebes et al. 2003; O’Brien et al. 2004). Patients with poor response to antidepressant treatment appear at increased risk of developing dementia (Modrego and Ferrández 2004). On the other hand, antidepressant treatments, if effective, could contribute to counteract cognitive decline (Steffens et al. 2006).

We found that elderly depressed patients with prior history of antidepressant exposure had larger gray matter volumes of the orbitofrontal cortex than those without such an exposure. Interestingly, the drug-naïve group had the smallest orbitofrontal gray matter volumes, followed by the antidepressant-exposed group, and by normal controls. This effect warrants further investigation, also in light of a more recent study in elders by Geda et al. (2006) who found that prior history of depression rather than a late onset of illness may protect against mild cognitive impairment, relating this interaction to possible protective effects of antidepressant medications in subjects with recurrent depressive episodes during lifetime.

**Influence of gender:** Twice as many women as men are affected by major depression among elders. In all my studies, approximately two thirds of the subjects were women. We appropriately corrected for potential interindividual differences in brain size that might be associated with gender. However, the contribution of gender to structural abnormalities in elderly depression may deserve attention. We specifically addressed gender differences in brain structure in one study and found smaller frontal gray matter volumes in older men than women in both groups (patients and controls). In addition, the diagnosis x gender interaction became only significant after controlling for medical burden. This might imply that there are gender differences in the patterns of medical burden that may affect brain atrophy and may increase the risk of elderly depression. Frontal gray matter reductions might be one of the underlying mechanisms that may predispose older men to depression. Interestingly, our study on gender differences reported a greater proportion of men with late-onset depression than women, in line with earlier investigations (Krishnan et al. 1995). Therefore, exploring gender differences directly in future studies might add further valuable insight to the pathophysiology of elderly depression based on age at illness onset.
4. Summary

Findings from our MRI studies in elderly depression employing traditional volumetric region of interest analyses as well as sophisticated brain mapping methods have enabled us to identify complex morphological changes in frontal and temporoparietal cortical gray matter, as well as highly localized abnormalities in functionally relevant subregions of the hippocampus and the corpus callosum, which may reflect differential patterns of atrophic or neurodegenerative processes, possibly influenced by age at illness onset. We have also observed that apathy, a crucial component of executive dysfunction commonly observed in depressed elders, relates to structural changes in distinct frontal regions, such as the anterior cingulate.

Furthermore, we have shown that memory and attention performances correlate with regional hippocampal and callosal abnormalities among late-onset but not early-onset depression or controls. Since neuropsychological measures were in the normal range in this elderly depressed population, these results may suggest that regional hippocampal and callosal atrophy patterns and their associations with memory and/or attention could become apparent prior to clinical evidence of cognitive decline. Exploring abnormalities at a very local level may thus help identify risk profiles by dissociating possible neuroanatomic vulnerabilities to illness progression based on age at onset. Moreover, we have provided preliminary evidence for gender differences in critical brain regions involved in elderly depression. Finally, we have shown that antidepressant exposure may be neuroprotective against frontal gray matter loss in depressed elders.

Although cross-sectional studies are informative, prospective longitudinal designs may ultimately be necessary for answering questions about (1) the neurobiological differences in early-onset versus late-onset depression and the impact of repeated depressive episodes across the life span; (2) the neurobiology of treatment-responsive and treatment-resistant depression with focus on the domains of cognitive function that improve with antidepressant therapy compared to those that remain impaired after remission of mood symptoms; (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), medical illness (cardiovascular disease or stroke), or medical interventions (interferon-induced depressive symptoms, beta-blocker induced depressive symptoms). In addition, future investigations will integrate multimodal imaging approaches (diffusion tensor imaging,
functional neuroimaging including positron emission tomography) with genetic methods, thereby providing important information regarding for example the role of specific genetic polymorphisms with respect to altered neural circuitry and neurotransmitter pathways. The integration of genetic and neuroimaging data will ultimately foster a more comprehensive delineation of neurobiological subtypes of depression that might relate to different patterns of age at onset, disease course or treatment response.
4. Zusammenfassung


Des Weiteren wurde gefunden, dass Verhaltensstörungen wie Apathie, die zu den wichtigsten exekutiven Funktionseinschränkungen gehören, mit strukturellen Veränderungen in spezifischen frontalen Regionen, insbesondere im Gyrus cinguli anterior, einhergehen. Ferner haben wir gezeigt, dass Veränderungen in spezifischen Subregionen des Hippocampus und des Corpus callosum mit bestimmten Gedächtnis- und Aufmerksamkeitsfunktionen bei Menschen mit spätem Krankheitsbeginn, aber nicht bei Individuen mit frühem Krankheitsbeginn korrelieren. Da die in dieser Studie eingeschlossenen Patienten keine klinisch zu erkennenden kognitiven Defizite aufwiesen,

5. References


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ERKLÄRUNG

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