Depression is a common psychiatric disorder and one of the leading causes of loss of life quality and reduction in life years world-wide. The prevalence of depression in Denmark is estimated to be about 3%, corresponding to roughly 150,000 people. The prevalence is twice as high in women than in men.

**Cerebral white matter lesions**

Increasing evidence suggests that cerebrovascular disease may be an important factor in the pathogenesis of a subtype of depression occurring late in life, termed “vascular depression”2,3. Vascular disease is thought to contribute to the impairments in late-life depression through cerebral white matter changes such as white matter lesions (WMLs). WMLs are identified as white matter signal hyperintensities on proton-density or T2-weighted magnetic resonance imaging (MRI) of the brain and are believed to reflect underlying cerebrovascular disease4,5 (see Figure 1). The presence and severity of WMLs increase with age and have been shown to correlate with vascular risk factors, such as hypertension and smoking6,7.

Imaging studies using MRI have reported an increased frequency of these WMLs in late-life major depression8. WMLs are believed to affect the mood-regulating pathways, either by single, localized lesions or by an accumulation of lesions exceeding a certain threshold2. However, the relation between lesion characteristics, their interference with specific neuronal pathways, and the disease remains largely unknown.

**Diffusion tensor imaging**

Over the past decade, advances in MRI, such as diffusion tensor imaging (DTI), have enabled us to study the microstructural integrity of the brain tissue in vivo by reconstructing white matter trajectories - a technique known as tractography. In my PhD research project, we used DTI tractography to assess which pathways were affected by WMLs. The aim of my studies were to describe the localization and impact of WMLs on cerebral white matter structure in patients with late-onset MD and non-depressed controls (see Figure 2).

Our results showed no difference in the number or volume of lesions between patients and controls9. However, among the subjects with WMLs, patients showed a significantly higher white matter lesion density in brain areas essential for cognitive and emotional functions. We also showed a significant correlation between depression severity and WMLs affecting pathways involved in mood and cognition10. By combining measures of diffusion and magnetization transfer, we showed that WMLs have a marked effect on measures of white matter integrity both within the lesion site itself and along the neuronal pathways they intersect10.

The use of DTI tractography as a segmentation tool to map pathways that are intersected by WMLs enables the identification of specific white matter tracts potentially affected by WMLs. This allows for future, integrative approaches that combine cognitive and microstructural measures in order to address the functional impact of WMLs on tissue integrity in neuropsychiatric disease.

**Neural growth factors**

The prevalence of WMLs and the high comorbidity of depression and vascular disease, such as stroke or...
ischemic heart disease\textsuperscript{11}, calls for reflections on a possible interaction between neural and vascular growth factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). The neural growth factors are important regulators of neural survival, development, function, and plasticity. An increasing body of literature suggests an important role for BDNF in the pathophysiology and treatment of mood disorders\textsuperscript{12}. In a recent study, we examined the possible relationship between plasma BDNF and VEGF levels, WMLs, and white matter integrity in patients with late-onset depression and non-depressed controls, with respect to vascular risk factors\textsuperscript{13}. We demonstrated a positive association between plasma BDNF level and prefrontal white matter lesion load, the latter measured as the number and volume of prefrontal WMLs, in both patients and controls. This association suggests an important role for BDNF in the repair mechanisms of neural damage due to WMLs, reflecting underlying small vessel disease that primarily affects prefrontal regions in both normal aging and late-onset depression. Future focus on neurotrophic factors, their interactions with vascular risk factors, and their impact on white matter integrity, may help us to a better understanding of the neural and vascular pathophysiologic mechanisms underlying WMLs, and eventually lead to new treatment and prevention strategies.

Cerebral perfusion

Perfusion parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and mean capillary transit time are mutually dependent of cerebral autoregulation and perfusion pressure, and changes in these parameters reflect microvascular changes, such as regional hypoperfusion and reduction of capillary density. A recent physiological model combines the effects of CBF, CBV, capillary transit time heterogeneity (CTTH) on cerebral metabolic rate for oxygen (CMR\textsubscript{O$_2$}), and oxygen extraction fraction (OEF) in order to describe the regulation of oxygen supply by the cerebral bloodstream to meet changing metabolic needs in the brain\textsuperscript{14}. CTTH may be a crucial part of the hemodynamic response to increased metabolic demand. However, conditions with disturbed capillary flow due to e.g. ischemia, may disturb CTTH and thereby the normal flow-metabolism coupling and oxygen metabolism in the brain.

Depression has been associated with changes in CBF and metabolism in a network of structures involving the frontal lobes, limbic system and basal ganglia. We are currently investigating the association between blood flow changes, changes in the hemodynamics of the cerebral microvasculature, and structural changes such as WMLs, in depression. Increased knowledge on perfusion changes in depression may help future application of perfusion MRI as a diagnostic tool and a tool for monitoring treatment in depression.

Perspectives

The use of vascular depression as possible future independent entity of major depression calls for more refined diagnostic approaches in future psychiatry\textsuperscript{15}, including increased focus on vascular risk factors and the use of advanced cerebral imaging techniques such as perfusion MRI and DTI.

References