diabetic type 1and 2 compared to non-depressed in a meta-analysis of 24 studies. Frequency of diabetes complications as diabetic neuropathy, nephropathy, retinopathy macro vascular complications and sexual dysfunction have been found to be higher in depressed diabetic patients (De Groot et al 2001). Improved glycemic control has been found with antidepressant treatment in depressed diabetic patients Functional status of other chronic disease as chronic pain, rheumatoid is further impaired with the addition of depressive symptoms with biased negative perception of the disorder, passive coping and belief of uncontrollability. The actual nature of the impact of depression in cancer patients is still a matter of debate. Some studies have found a modest negative effect on actual survival in breast cancer. However in a recent review the follow-up of about 5000 patients with mostly breast cancer up to 15 years did not find an impact of hopelessness/helplessness on survival or recurrence. Nonetheless a detrimental effect for 5-year event-free survival has been observed in breast cancer patients with helplessness/hopelessness and depression as defined with high HAD score. Relationship between depression and cardiovascular diseases has received much attention in recent years following the seminal finding of an increased mortality for post-myocardial infarction patients with symptoms of depression. While these results have been confirmed in subsequent studies it has been found that even minimal symptoms of depression could increase mortality risk after acute myocardial infarction. Moreover depression has been found to represent an independent risk factor for cardiovascular morbidity and mortality in patients with and without previous cardiovascular diseases (Penninx et al 2001). Interestingly the increased risk has been observed with major depression but also with minor depression. There are some suggestions that specific treatment of depression could reduce this risk. Conversely cardiovascular conditions appear to have a significant impact on mood (Paterniti et al 2000). Various hypotheses have been forwarded to explain this consistent association. Neurovegetative cardiovascular changes linked to parasympathetic tone have been observed in depressed patients mostly reduced heart rate variability, and baroreflex sensitivity. These changes could be related to brain function alterations observed in depressed patients with brain imaging techniques. Both cardiovascular function changes have been found to have a negative predictive value for myocardial infarction outcome. They could also be modified with antidepressant treatment. Recent evidence have also indicated that immune alterations could be associated with depression. Depression has been associated with elevated pro-inflammatory cytokines and leukocyte levels increase in platelets aggregation. Major depression could modify immune system and conversely immune system abnormalities may play a role in the etiology of depression. Patients treated with interleukin 2 or interferon alpha for cancer or viral disease such as hepatitis C develop depressed mood. Change in the immune system activity might be involved in the cardiovascular disease as atherosclerosis via inflammatory like processes. It is possible that immune dysfunction may serve as a common pathophysiological mechanism for both altered mood and cardiovascular dysregulation (Grippo and Johnson 2003). Deleterious impact of depressive symptoms on a variety of somatic disease have been evidence. This effect might be related to a general impact of depression on self-care including poor compliance and lack of activity. However recent findings suggest that these effects could result from the complex interplay of biological mechanisms involved in the expression or and the pathophysiology of depression and somatic diseases. The positive impact on somatic disease outcome observed with efficient treatment of associated depression is further emphasized the need to improve diagnostic and treatment of depression in primary care setting.

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S.02.05 The pathophysiology of pain in depression

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Pain is a multi-dimensional process involving the physical, emotional and perceptual integration of noxious information. The emotional aspect of pain is encoded by the limbic system and involves the relationship between pain and mood. Chronic pain induces chronic stress, and a large proportion of patients with chronic pain also present clear symptoms of depression. In addition, clinical reports indicate that depressed patients, who do not suffer from chronic pain, exhibit alterations in their perception of pain. Thus, these two phenomena could be sequential. Data from imaging studies of the forebrain have shown that noxious stimulation activates neurons in cortical areas, as the insular and anterior cingulate cortex, in addition to areas of the limbic system including the amygdala, hippocampus, and hypothalamus. These ascending pain pathways and their supraspinal targets contribute towards two distinct, but yet related, aspects of pain: the sensory-discriminative and the affective-cognitive aspects, the first involving the perception and detection of a noxious stimulus, and the second the relationship between pain and mood, including pain memories. Nevertheless, although these different aspects of pain responses involve specific pathways and regions, it is believed that the basis of the conscious experience of pain is finally regulated by the overall activity of these regions (Blackburn-Munro and Blackburn-Munro, 2001). Given the diverse origins of chronic pain, controversy surrounds the relationship it bears to the depression with which it is often co-expressed. It has been estimated that over 50% of patients suffering from chronic pain also express clinically diagnosable symptoms of depression. Five major hypotheses have been proposed: (a) the "antecedent hypothesis", in which depression precedes the development of chronic pain, (b) the "consequence hypothesis", in which depression is a consequence of the chronic pain, (c) the "scar hypothesis", in which episodes of depression occurring before the onset of chronic pain predispose the patient to a depressive episode after the onset of pain, (d) the "cognitive mediation" hypothesis, in which psychological factors such as poor coping strategies are considered to mediate the reciprocal interactions between chronic pain and depression, and (e) the "independent hypothesis", in which depression and chronic pain

are considered to share some common pathogenetic mechanisms but remain distinct diseases without causal interaction (Blackburn-Munro and Blackburn-Munro, 2001). Several clinical studies have suggested that pharmacotherapies used to treat depression may be also effective analgesics in chronic pain sufferers. Detailed meta-analyses of multiple antidepressant trial studies indicate that antidepressants are associated with pain relief. In these studies, antidepressants are over 74% more effective than placebo in chronic pain patients. However, there are some difficulties in studying the effects of antidepressants on chronic pain. The issue of organic vs unexplained psychogenic or somatoform pain has to be resolved, as patients suffering from affective disorders are more likely to develop idiopathic chronic pain than those who do not. To address this, some studies utilizing only nondepressed patients suffering from chronic neuropathic pain of nerve injury, degeneration, or post-herpetic neuralgic origins, demonstrated 50% pain relief in response to antidepressants. Meta-analyses designed to control "masked depression", have also demonstrated that antidepressants act in chronic pain patients through an analgesic effect rather than through an effect to improve undiagnosed depression. Although the analgesic effect of antidepressants is to some extent independent of their antidepressant properties, clinical studies have shown that mixed inhibitor of serotonin and noradrenaline reuptake have greater analgesic potency than serotonin selective drugs (Rojas-Corrales et al., in press). Evidently, not all drugs with antidepressant profiles will provide adequate pain relief in the clinical situation. Regardless of the credibility of the above hypotheses, the importance of accurate diagnosis and reporting of chronic pain should not be underestimated. If chronic pain is excluded as a diagnostic tool for depression, the apparent prevalence of depression in a given patient population may be reduced (Ohayon and Schatzberg, 2003). However, the clinical consequence of ignoring patients' complaints of chronic pain may be the failure to receive appropriate treatment for their depression. Thus, classical pain targets may prove useful in the generation of novel antidepressants (Briley, 2003). On the other hand, regarding the neurobiological correlates between pain and depression, clear evidence exists about the relationship between the opioid system, noradrenaline and serotonin. It seems clear that the opioid system influences pain and depression. In fact, endogenous opioids (Tejedor-Real et al., 1995) and opiate analgesics have demonstrated antidepressant-like effects (Rojas-Corrales et al., 2002). In conclusion, it appears that pain and depression are two entities clearly related. Neurobiologically, the close relationship between the opioid system and the noradrenaline and serotonin system account for the analgesic effect of the antidepressants and the antidepressive-like effects of some opiates. Supported by FIS 01/1055.

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S.03. Alzheimer's disease: New insights into the pathophysiology

S.03.01 *In vivo* and *in vitro* models of AD demonstrate a role of distinct phosphorylation sites of tau in neurofibrillary tangle formation

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Alzheimer' s disease (AD) is characterized by beta-amyloid-containing plaques and neurofibrillary tangles (NFT). NFT are composed of hyper-phosphorylated tau and are abundant in additional neurodegenerative diseases including frontotemporal dementia (FTDP-17). The discovery of mutations in the tau gene in FTDP-17 established that dysfunction of tau in itself can cause neurodegeneration (Gotz, 2001). To model the tau pathology of AD *in vivo*, we expressed wild-type and P301L mutant human tau in transgenic mice. Expression of P301L tau in neurons of transgenic mice caused NFT formation as shown by Gallyas stainings. The presence of tau filaments was further confirmed by electron-microscopy. Next, we tested in mice the amyloid cascade hypothesis, that claims a central role of beta-amyloid in NFT formation. We injected Abeta42 fibrils into brains of P301L mice and non-transgenic littermate controls as well as human wild-type tau transgenic mice. Eighteen days following the Abeta42 injections, Gallyas impregnations revealed fivefold increases of NFT, along with neuropil threads and degenerating neurites in P301L, but not wild-type mice. To determine whether the Abeta42-induced NFT formation was associated with altered tau phosphorylation, we applied immuno-histochemistry. Whereas several phosphorylation-dependent antibodies including AT8 (directed against phospho-epitope Ser202/Thr205) detected tau throughout the brains of P301L mice independently of the injections, the use of antibodies specific for phosphorylated Ser422 and Thr212/Ser214 revealed a tight association of the phosphorylation of these epitopes with NFT formation (Gotz et al., 2001). The serine/threonine-specific phosphatase PP2A is highly abundant in brain. It binds to tau and microtubules, and FTDP-17 mutations cause a significant decrease in the binding affinity of tau for PP2A. We expressed the dominant negative PP2A mutant L199P in neurons of transgenic mice (Kins et al., 2001). In brain homogenates, PP2A activity was chronically reduced to 66%. Endogenous tau protein was hyperphosphorylated at epitopes AT8 (shown by immunohistochemistry) and Ser422 (shown by Western blotting). With age, phosphorylation of S422 increased significantly and was detected in selected neuronal populations. Aberrant tau phosphorylation was accompanied by activation of the ERK and JNK signaling pathways, suggesting an additional, indirect role of PP2A in tau hyperphosphorylation. To circumvent the limitations of *in vivo* models, we established a tissue culture system of beta-amyloid-induced tau filament formation. Mutagenesis of Ser422 prevented tau filament formation. Together, our data support the hypothesis that beta-amyloid is an important pathogenic factor in NFT formation, and that PP2A can contribute to tau hyperphosphorylation. In addition, our studies identified epitopes Thr212/Ser214 and Ser422 as pathological phospho-epitopes of tau linked to NFT formation.