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Pain Sensitivity in Patients With Major Depression: Differential Effect of Pain Sensitivity Measures, Somatic Cofactors, and Disease Characteristics

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Abstract: Patients with depression often report pain. Evidence regarding altered pain sensitivity in depressed patients remains, however, inconclusive. In a large cross-sectional study we investigated the association between depression and pain sensitivity with regard to 2 different dimensions of pain sensitivity, as well as the effect of somatic cofactors, symptom severity, and subtype of depression. In 735 patients with a current episode of major depression and 456 never-depressed control participants pain thresholds (pressure pain thresholds, PPTs) were measured at the index finger pad and self-rated suprathreshold pain intensity ratings were obtained using the Pain Sensitivity Questionnaire (PSQ)-minor subscore, an instrument that assesses pain intensity in daily life situations. Additionally, lifestyle factors, medical, and psychiatric conditions were assessed. Unadjusted, patients with depression had lower PPTs and higher PSQ-minor scores indicating increased pain sensitivity. After adjusting for potential mediators, such as poor sleep quality and physical inactivity, patients did not differ from control participants regarding PPTs, but still had significantly higher PSQ-minor ratings. Among patients with depression, severity of anxiety symptoms predicted higher PSQ-minor scores. In conclusion, we found a differential effect of depression on the 2 pain sensitivity dimensions: Decreased experimentally obtained pain thresholds were explained by depression-associated somatic factors whereas increased self-rated suprathreshold pain intensity ratings were associated with increased anxiety symptoms.

***Perspective:** Because increased pain intensity perception is hypothesized to be a risk factor for the development of chronic pain, our findings may contribute to understanding the high incidence of chronic pain in depressed patients. They also encourage clinicians to consider the role of anxiety in treatment programs for pain in patients with depression.*

***Key words:** Depression, pain sensitivity, pain intensity, pain threshold, anxiety.*

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Pain and depressive symptoms co-occur frequently.[27,55] Epidemiological studies suggest that up to 75% of patients with depression complain of pain.[2,5,33] Likewise, chronic pain is associated with an increased risk of having or developing depression.[33] With regard to this reciprocal association between pain and depression and their effect on physical, social, and occupational activities,[9] the investigation of potential linking factors is of utmost importance. Both depression and chronic pain are related to a dysfunction of serotonergic and noradrenergic pathways.[50] Depression and chronic pain also share frequent comorbidities such as sleep disturbances and increased stress levels.[37,40,41] Altered pain sensitivity might be another link between the 2 diseases. Increased pain sensitivity, possibly induced by the effect of depressive mood on endogenous pain inhibition,[57] is a hallmark of chronic pain[38] and might explain the increased frequency of pain complaints in depressed patients. Indeed, induction of depressive mood leads to increased experimental pain perception.[52,56] In contrast, patients with major depression have often shown reduced experimental pain perception.[7,12,31] Facing this apparent paradox, it is important to note that several factors may affect the measurement and interpretation of pain perception in depressed patients. First, most studies finding hyposensitivity in patients with depression relied on pain thresholds, measuring pain perception at just perceivable levels.[6,12] In contrast, perception of suprathreshold pain intensity, which is more similar to clinical pain, is a largely independent[4,44,45] dimension of pain sensitivity. Indeed, the few studies assessing suprathreshold pain intensity ratings in depression have either shown equal or enhanced pain perception compared with control participants.[8,26,39] Second, timing of assessment and antidepressant medication might play a role. Most studies showing hyposensitivity to pain were conducted in acutely, severely depressed patients before starting treatment, which hopefully only represents a short period in the course of the disease.[31,32] One study showed normalization of enhanced pain thresholds after 6 weeks of antidepressant treatment.[8] Moreover, depressed patients during treatment have sometimes shown increased experimental pain perception.[19,26,39] Third, the clinical diagnosis of depression usually comprises more aspects than depressive mood. Patients with depression often suffer from somatic conditions, such as sleep disturbances, arterial hypertension, obesity, and chronic pain, all of which have been associated with altered experimental pain perception[18,30,38] and might account for differences in pain sensitivity between patients with depression and control subjects.

In conclusion, the relationship between depression and pain sensitivity, although important from a pathophysiological and clinical point of view, is not yet completely understood. Thus, in the present study, we aimed to investigate different dimensions of pain sensitivity as well as potential moderating and mediating factors of altered pain sensitivity in patients with depression receiving routine clinical care: We assessed pain thresholds and self-rated suprathreshold pain intensity ratings of daily life situations in a large cohort of patients with a current episode of major depressive disorder (MDD) and compared them with healthy control participants, while taking into account comorbidities and somatic features of depression. We further aimed to investigate the effect of disease characteristics, such as depression subtype and severity of depressive and anxiety symptoms, on pain sensitivity.

To differentially assess the pain threshold and the pain intensity rating dimensions of pain sensitivity, experimental pressure pain thresholds (PPTs) and the self-report Pain Sensitivity Questionnaire (PSQ)-minor subscore were used, respectively. The PSQ-minor is composed of intensity ratings of painful daily life situations and has shown high correlations with experimental pain intensity perception but not with experimental pain thresholds.[44] However, it has to be kept in mind that an additional difference between PPTs and PSQ-minor scores is that one involves an experimental pain stimulus and the other is a self-rating measure.

Methods

Study Design and Participants

The present study is on the basis of 2 cohorts from the longitudinal BiDirect study[53] conducted at the University of Münster, Germany. The primary aim of the BiDirect study was to investigate the associations between depression and subclinical atherosclerosis on the basis of a 3-cohort design: 1) patients with a present episode of depression under current in- or outpatient treatment, recruited at the Department of Psychiatry and the Department of Psychosomatics and Psychotherapy at the University hospital of Münster and via cooperating local psychiatric clinics and psychiatrists; 2) outpatients with a recent manifestation of cardiovascular disease; and 3) population-based control subjects, randomly recruited using the population register of the city of Münster. Participants from all 3 cohorts were investigated in parallel. In total, 2,258 subjects aged between 35 and 65 years were enrolled in the baseline phase of the study, which was carried out from 2010 until 2013. All participants underwent an extensive examination program consisting of a face-to-face interview including sociodemographic background, medical history, health behavior, and medication intake, as well as a diagnostic workup.[53] In the present study we only included population-based control participants and patients with a clinical diagnosis of MDD corresponding to a diagnosis of F32 (depressive episode) or F33 (recurrent depression) in the *International Classification of Disease, Tenth Edition* (Fig 1). Participants with depression were recruited during an acute episode of depression. All patients, in- and outpatient, received some kind of psychological counseling during that episode. Most of the patients also received antidepressant medication at the time of the study examination and many of them also other psychotropic medication. In case of inpatient treatment, patients were examined