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Increased nuclear Olig1-expression in the pregenual anterior cingulate white matter of patients with major depression: A regenerative attempt to compensate oligodendrocyte loss?

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ABSTRACT

Background: Structural and functional oligodendrocyte deficits as well as impaired myelin integrity have been described in affective disorders and schizophrenia, and may disturb the connectivity between disease-relevant brain regions. Olig1, an oligodendroglial transcription factor, might be important in this context, but has not been systematically studied so far.
Methods: Nissl- and Olig1-stained oligodendrocytes were quantified in the pregenual anterior cingulate (pACC)/dorsolateral prefrontal cortex (DLPFC), and adjacent white matter of patients with major depressive disorder (MDD, $n = 9$), bipolar disorder (BD, $n = 8$), schizophrenia (SZ, $n = 13$), and matched controls ($n = 16$). Potential downstream effects of increased Olig1-expression were analyzed. Antidepressant drug effects on Olig1-expression were further explored in OLN-93 oligodendrocyte cultures.
Results: Nissl-stainings of both white matter regions showed a 19–27% reduction of total oligodendrocyte densities in MDD and BD, but not in SZ. In contrast, nuclear Olig1-immunoreactivity was elevated in MDD in the pACC-adjacent white matter (*left*: $p = 0.008$; *right*: $p = 0.018$); this effect tended to increase with antidepressant dosage ($r = 0.631$, $p = 0.069$). This reactive increase of Olig1 was confirmed by partly dose-dependent effects of imipramine and amitriptyline in oligodendrocyte cultures. Correspondingly, MBP expression in the pACC-adjacent white matter tended to increase with antidepressant dosage ($r = 0.637$, $p = 0.065$). Other tested brain regions showed no diagnosis-dependent differences regarding Olig1-immunoreactivity.
Conclusions: Since nuclear Olig1-expression marks oligodendrocyte precursor cells, its increased expression along with reduced total oligodendrocyte densities (Nissl-stained) in the pACC-adjacent white matter of MDD patients might indicate a (putatively medication-boosted) regenerative attempt to compensate oligodendrocyte loss.

1. Introduction

During the past years, oligodendrocyte pathology has become an important focus of research in major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ) (Bernstein et al., 2009; Edgar and Sibille, 2012; Rajkowska and Miguel-Hidalgo, 2007; Schmitt et al., 2011; Schnieder and Dwork, 2011; Schroeter et al., 2010; Tham et al., 2011). In frontal brain regions, reduced

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oligodendrocyte densities have been observed in the pregenual anterior cingulate cortex (pACC, Brodmann Area 32) of patients with MDD and BD, as well as in the dorsolateral prefrontal cortex (DLPFC, Brodmann Area 9) of patients with MDD, BD, and SZ (Farkas et al., 2010; Ongur et al., 1998; Uranova et al., 2004). These cell deficits may result from impaired gliogenesis, disturbances in oligodendrocyte maturation or an increased degeneration of oligodendrocytes (Bernstein et al., 2009; Rajkowska and Miguel-Hidalgo, 2007; Uranova et al., 2001). In parallel, reduced expression of key oligodendrocyte- and myelin-related genes, such as proteolipid protein 1 (PLP1), myelin basic protein (MBP), and myelin oligodendrocyte glycoprotein (MOG) has been observed in the DLPFC of patients with BD and SZ (Honer et al., 1999; Tkachev et al., 2003). To our knowledge, the pACC has not been systematically studied regarding oligodendrocyte gene expression in patients with MDD.

An intact function of oligodendrocytes is important for the myelination of axons, ensuring the maintenance of rapid saltatory axonal conductance and communication between distant brain areas. Thus, the above described oligodendrocyte pathology may cause disconnectivity of the pACC and DLPFC with other cortical and subcortical brain regions, causing functional network disturbances in patients suffering from MDD, BD, and SZ.

The pACC is crucial for cognitive emotional interaction and conscious self-reflection in higher primates and humans (Yu et al., 2011). Anhedonia, the inability to experience pleasure, was further related to functional and metabolite changes in this subregion in severely depressed patients (Walter et al., 2009). It also seems to have specific integrative functions considering the extensive connections with other affective and cognitive related cortical and subcortical networks, including the insula, thalamus, caudate, putamen, and other cingulate cortex subregions (Yu et al., 2011). Decreased corticolimbic functional connectivity has been observed in mood disorders. For instance, significantly decreased pACC connectivity to the mediodorsal thalamus was detected in BD and MDD patients (Anand et al., 2009). Additionally, BD patients had decreased pACC connectivity with the amygdala and pallidostriatum (Anand et al., 2009).

The dorsolateral prefrontal circuit modulates mood regulation and cognitive ability (Taylor et al., 2004). It originates in the DLPFC, projects to the dorsolateral head of the caudate nucleus, then continues to the lateral dorsomedial globus pallidus and, finally, to the ventral anterior and mediodorsal thalamus. The mediodorsal thalamus then sends fibers back to the DLPFC (Tekin and Cummings, 2002). This specific region is highly important for working memory and responsible for motor planning, organization, as well as regulating intellectual function and action (Bunge et al., 2000; Zhang et al., 2003). Alterations in volume and metabolic activity have been found in MDD (Drevets, 2000). However, working memory disruption is also considered as core cognitive dimension of SZ (Goldman-Rakic, 1994). Anatomical connectivity in SZ has been examined using diffusion tensor imaging (DTI). These DTI studies consistently reported reductions in fractional anisotropy, a measure of fiber density, axonal diameter and myelination (Basser and Pierpaoli, 1996), primarily within the DLPFC and in its connections with the ACC, subcortical (thalamus) and posterior cortical regions (Ellison-Wright and Bullmore, 2009).

Based on the particular importance of the pACC and DLPFC in the pathophysiology of MDD, BD, and SZ, the present study focused on the cellular and intracellular distribution pattern of the important oligodendroglial transcription factor Olig1, which has not been systematically studied in these psychiatric disorders so far. Our study aimed to assess Olig1-immunoreactive cell densities in cortical pACC/DLPFC and adjacent white matter brain regions. Olig1 is evolutionary well conserved, regulates the oligodendrocyte lineage and plays an important role for oligodendrocyte development and differentiation (Ligon et al., 2006) (see Supplementary Table). Thus, changes in its expression could have a significant impact on the maintenance of white matter integrity in major psychiatric disorders. We aimed to determine the subcellular distribution pattern of Olig1, which is considered as an indicator of oligodendrocyte activity and maturation: nuclear Olig1 marks oligodendrocyte precursor cells while cytoplasmic localization is associated with mature oligodendrocytes (Ligon et al., 2006) (see Supplementary Table). Potential downstream effects of increased Olig1 expression, such as an upregulation of myelin basic protein (MBP) or a potential inhibition of glial fibrillary acidic protein (GFAP) expression were analyzed separately in the brain regions where diagnosis-related differences in Olig1 expression were observed. Further statistical analyses aimed to consider the interference of potential confounding factors, such as age, gender, duration of disease, autolysis time, and medication dosage on the relevant diagnosis-related findings.

2. Materials and methods

2.1. Human brain tissue

Postmortem brains were obtained from the Magdeburg brain bank. Analyses were performed in accordance with the Declaration of Helsinki and the local institutional review board with written consent from the next of kin. The patients were diagnosed according to DSM-IV-criteria which were verified by two independent experienced psychiatrists (JS and BB) by carefully studying the patients' clinical records and structured interviews with physicians involved in patient treatment or family members (APA, 2000). The studied collective consisted of 17 patients with depression (mean age 51 years; 6 males, 11 females) which had been diagnosed with either MDD ($n = 9$) or BD ($n = 8$). Additionally the brains of schizophrenic patients (SZ; $n = 13$; mean age 54 years; 8 males, 5 females) and healthy control subjects ($n = 16$; mean age 55 years; 8 males, 8 females) were examined. These cases were matched with respect to age, gender, and autolysis time (Table 1).

Brains with lifetime reports of dementia, neurological illness, or severe trauma were excluded. Furthermore, cases with neuropathological changes due to neurodegenerative disorders, tumors, inflammatory, vascular, or traumatic processes were eliminated. As summarized in Table 2, the mean daily doses of psychotropic medication taken by patients during the last 90 lifetime days were established according to the clinical files (Bollini et al., 1999; Perry and Alexander, 1986; Rey et al., 1989). The brain bank has been established about 25 years ago. Therefore, patients received tricyclic antidepressants instead of selective serotonin or noradrenalin reuptake inhibitors.

Tissue preparation was performed as described previously (Steiner et al., 2008a, 2011b). Briefly, brains were fixed in 8% phosphate-buffered formaldehyde (pH 7.0) for three months. Subsequently, after separation of the brainstem and the cerebellum, the hemispheres were divided by coronal cuts into three bihemispherical coronal blocks comprising the frontal lobe anterior to the genu of the corpus callosum ("anterior" block), the fronto-temporo-parietal lobe extending the entire length of the corpus callosum ("middle" block) and the occipital lobe ("posterior" block). After embedding the brains in paraffin, serial coronal whole brain sections were cut 20 μm in width and mounted.

The exact thickness of each section was determined by focusing on the upper and lower surfaces of the section and subtracting the z-axis coordinate of the lower surface from that of the upper surface. The movements in the z-axis were measured with a