



# Astrocyte pathology in the ventral prefrontal white matter in depression

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## ABSTRACT

Astrocyte functions in white matter are less well understood than in gray matter. Our recent study of white matter in ventral prefrontal cortex (vPFC) revealed alterations in expression of myelin-related genes in major depressive disorder (MDD). Since white matter astrocytes maintain myelin, we hypothesized that morphometry of these cells will be altered in MDD in the same prefrontal white matter region in which myelin-related genes are altered. White matter adjacent to vPFC was examined in 25 MDD and 21 control subjects. Density and size of GFAP-immunoreactive (-ir) astrocyte cell bodies was measured. The area fraction of GFAP-ir astrocytes (cell bodies + processes) was also estimated. GFAP mRNA expression was determined using qRT-PCR. The density of GFAP-ir astrocytes was also measured in vPFC white matter of rats subjected to chronic unpredictable stress (CUS) and control animals. Fibrous and smooth GFAP-ir astrocytes were distinguished in human white matter. The density of both types of astrocytes was significantly decreased in MDD. Area fraction of GFAP immunoreactivity was significantly decreased in MDD, but mean soma size remained unchanged. Expression of GFAP mRNA was significantly decreased in MDD. In CUS rats there was a significant decrease in astrocyte density in prefrontal white matter. The decrease in density and area fraction of white matter astrocytes and GFAP mRNA in MDD may be linked to myelin pathology previously noted in these subjects. Astrocyte pathology may contribute to axon disturbances in axon integrity reported by neuroimaging studies in MDD and interfere with signal conduction in the white matter.

## 1. Introduction

The pathology of astrocytes in the white matter in major depressive disorder (MDD) is less well understood than in gray matter. White matter astrocytes are morphologically and functionally differentiated from gray matter astrocytes, although both types are associated with the blood brain barrier and glucose metabolism (Sofroniew and Vinters, 2010). Functionally, astrocytes in white matter have specific roles in myelination and impulse conduction (Black and Waxman, 1988; Ishibashi et al., 2006; Liedtke et al., 1996). Thus, one of the main functions of white matter astrocytes is promotion of myelination and myelin maintenance (Lundgaard et al., 2014). These functions are supported by gap junction-based coupling of astrocytes to myelin-forming oligodendrocytes (Nualart-Marti et al., 2013). Defects in myelination or in saltatory impulse conduction could impair propagation of action potentials and neural connectivity. Altered connectivity in ventral prefrontal cortex (vPFC) and elsewhere is reported in patients

with MDD, as determined with diffusion tensor imaging of white matter fiber tracts or with functional magnetic resonance imaging (Jalbrzikowski et al., 2017; Murphy and Frodl, 2011; Nobuhara et al., 2006; Rolls et al., 2017; Sexton et al., 2009; Shimony et al., 2009; Tham et al., 2011).

Our recent study in the white matter of postmortem vPFC revealed changes in the expression of myelin-related genes and a reduction in the size of oligodendrocyte cell bodies in MDD (Rajkowska et al., 2015), which may be related to white matter pathology detected using neuroimaging methods. Other molecular changes such as shortened telomere length or increased oxidation and DNA repair enzymes have been observed in white matter oligodendrocytes or astrocytes in Brodmann's area 10 of the prefrontal cortex in MDD (Szebeni et al., 2014, 2017). Additionally, reductions in gray matter in immunohistochemically labeled astrocytic gap junctions and in the density and area fraction of astrocytes immunohistochemically labeled for glial fibrillary acidic protein (GFAP) have been observed in the vPFC in subjects with MDD

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(Miguel-Hidalgo et al., 2010, 2014). However, in white matter, 3-dimensional quantification of GFAP-immunoreactive (-ir) astrocytes has not been reported in vPFC from subjects with MDD.

Of the few studies that have examined pathology of white matter astrocytes in depression, only Torres-Platas et al. (2011) reported hypertrophy of fibrous astrocyte processes in the white matter that underlies the anterior cingulate cortex in subjects with a mood disorder who died by suicide. In studies using a two-dimensional sampling method, Williams et al. (2013, 2014) found no significant difference in the density of GFAP-ir astrocytes in the white matter of the subgenual cingulate cortex in subjects with MDD vs. controls. In another two-dimensional study, there was a reduction in immuno-autoradiographic labeling of GFAP in white matter of the anterior cingulate cortex of subjects with a mood disorder (Gittins and Harrison, 2011). In a qualitative study, Webster et al. (2001) reported that fewer subjects with MDD than controls had any astrocytes immunolabeled for phosphorylated GFAP in association with blood vessels in white matter lining the dorsolateral PFC.

Thus, the present study sought to determine whether there are alterations in the density of GFAP-ir astrocytes and the area fraction covered by GFAP-ir astrocytic cell bodies and processes in the white matter of vPFC in subjects diagnosed with MDD as compared to age-matched controls. The subjects with MDD used in the present study for GFAP-ir astrocyte morphometry were all used in our study of oligodendrocyte and myelin pathology in vPFC white matter (Rajkowska et al., 2015). We also compared the levels of expression of GFAP mRNA in white matter of the vPFC between MDD and control groups in a mostly different cohort of subjects from the same brain collection. Finally, using rats exposed to chronic unpredictable stress (CUS) as a model for the induction of depression-like behaviors (Willner, 2016), and control animals, we investigated the density of GFAP-ir astrocytes in a region of the rat white matter homologous to the human vPFC.

## 2. Methods

### 2.1. Human subjects

Brain tissue was collected at autopsy at the Cuyahoga County Medical Examiner's Office (Cleveland, OH). Legally-defined next-of-kin provided written informed consent for tissue collection, medical histories, and diagnostic interviews administered to knowledgeable informants. The institutional review boards of University Hospitals Case Medical Center, Cleveland, OH, and the University of Mississippi Medical Center, Jackson, MS, approved the protocol for recruitment, tissue collection, and interviews. Tissue samples from the left ventral prefrontal white matter were collected from 25 subjects that met diagnostic criteria for MDD and 21 psychiatrically-normal control subjects that were matched for age and postmortem interval. The Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995) was administered by a trained interviewer to a knowledgeable informant for all subjects, as described (Cobb et al., 2013). Lifetime and recent psychopathology was determined by a board-certified psychiatrist and board-certified clinical psychologist according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed.) (DSM-IV; American Psychiatric Association, 1994). Information was also collected from informants or medical records about psychoactive substance use and medication history. No subjects had evidence of head trauma, neurologic or neuropathological disease. Twenty four subjects met criteria for MDD in the last month of life and one other diagnosed with MDD was in remission for one year. Subjects with MDD were comorbid with delusional disorder ( $n = 1$ ), dysthymic disorder ( $n = 1$ ), generalized anxiety disorder ( $n = 1$ ), panic disorder with agoraphobia ( $n = 1$ ), and anxiety disorder (not otherwise specified,  $n = 1$ ). Only one subject with MDD had a psychoactive drug use disorder at the time of death (benzodiazepine abuse). None of the 21 control subjects met criteria for a DSM-IV diagnosis at the time of death, although three

**Table 1**  
Characteristics of Control and MDD Subjects used for GFAP morphometry.

Parameter	Controls (n = 8)	MDD (n = 8)
Age (years) (range)	57 ± 7 (27–80)	58 ± 7 (34–82)
Gender (F:M)	3:5	4:4
PMI (hrs) (range)	22 ± 2 (15–29)	24 ± 3 (12–44)
Tissue pH (range)	6.7 ± 0.1 (6.3–7.1)	6.5 ± 0.1 (6.1–6.9)
TF (months) (range)	104 ± 11 (38–131)	102 ± 16 (24–141)
Cause of death	Cardiovascular disease $n = 7$ ; hemorrhagic pancreatitis $n = 1$	Suicide $n = 6$ (CO poisoning $n = 2$ ; hanging $n = 2$ ; drowning $n = 1$ ; fall from height $n = 1$ ) Natural causes $n = 2$ (cardiovascular disease)
Duration of MDD (years) (range)	not applicable	15 ± 3 (0.2–62)
Antidepressant or psychotropic drugs present postmortem	none	none

Data represent the mean ± S.E.M. AD – antidepressant; CO - carbon monoxide; MDD - major depressive disorder; PMI - Postmortem interval; TF - Time in formalin. The mean age ( $t = 0.117$ ,  $df = 14$ ,  $p = 0.91$ ), PMI ( $t = 0.438$ ,  $df = 14$ ,  $p = 0.67$ ), brain tissue pH ( $t = 1.575$ ,  $df = 14$ ,  $p = 0.14$ ), and TF ( $t = 0.092$ ,  $df = 14$ ,  $p = 0.93$ ) of subjects with MDD were not statistically different from the control subjects.

subjects met criteria for alcohol dependence at 6, 8, and 30 years prior to death. Eighteen of the 25 MDD subjects died by suicide (Tables 1 and 2). Postmortem samples of urine and blood were evaluated by the medical examiner for the presence of psychotropic medications or psychoactive substances. An antidepressant drug was identified postmortem in four of the 25 subjects with MDD (Tables 1 and 2). Control and MDD subjects were yoked for all procedures and matched for age and gender, and these values plus postmortem interval, tissue pH, and storage time in formalin are noted in Tables 1 and 2.

A total of 25 subjects with MDD and 21 control subjects were examined, with 8 MDD and 8 control subjects used for GFAP morphometry (Table 1) and 17 MDD and 13 control subjects used for mRNA expression (Table 2). One control subject and 4 subjects with MDD were used in both studies. Tissue frozen at autopsy was examined for mRNA expression, while other vPFC tissues were fixed in 10% phosphate-buffered formalin and used for GFAP immunohistochemistry and morphometry.

There were more subjects for expression of GFAP mRNA than for morphometry because there were more subjects in the brain collection with frozen than with fixed tissue. In addition, fixed tissue was chosen for morphometry of GFAP-ir astrocytes because there is minimal shrinkage of celloidin-embedded fixed tissue and it is ideally prepared for 3-D cell counting.

### 2.2. Rodents

To determine if any changes in the density of GFAP-ir astrocytes in white matter of the prefrontal cortex in MDD are a consequence of potential risk factors for depression such as stress, a rat model of depression-like behavior, namely CUS, was used. Body weight, sucrose preference, and novelty-suppressed feeding were examined in CUS-exposed and control rats. All procedures were approved by the Institutional Animal Care and Use Committee and conformed to the guidelines of the National Institutes of Health. Twenty male Sprague-Dawley rats (Charles River, Wilmington, MA, USA) weighing 200–250 g were housed two per cage in a temperature and humidity-controlled colony room. Rats were assigned to one of two groups ( $n = 10$  per group) and were either exposed for 35 days to CUS or handled to serve as controls, and then behavioral tests were administered as described by investigators naïve to treatment group (Riaz et al.,

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