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# Lower plasma total tau in adolescent psychosis: Involvement of the orbitofrontal cortex

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ABSTRACT

Schizophrenia is thought to be a neurodevelopmental disorder with neuronal migration, differentiation and maturation disturbances. Tau is a microtubule-associated protein with a crucial role in these processes. Lower circulating tau levels have been reported in adults with schizophrenia, but this association has not been investigated in adolescent psychosis. We aimed to test the hypotheses that a) adolescents with early-onset psychosis (EOP; age of onset <18 years) display lower plasma tau concentrations compared to healthy controls, and b) among patients with psychosis, tau levels are linked to structural brain measures associated with the microtubule-associated tau (MAPT) gene and psychosis. We included 37 adolescent patients with EOP (mean age 16.4 years) and 59 adolescent healthy controls (mean age 16.2 years). We investigated putative patient-control differences in plasma total tau concentrations measured by a Single molecule array (Simoa) immunoassay. We explored the correlations between tau and selected structural brain measures based on T1-weighted MRI scans processed in FreeSurfer v6.0. We found significantly lower plasma tau concentrations in patients compared to healthy controls ($p = 0.017$, partial eta-squared = 0.061). Tau was not associated with antipsychotic use or the antipsychotic dosage. Among patients but not healthy controls, tau levels were positively correlated with the cortical orbitofrontal surface area ($p = 0.013$, R-squared = 0.24). The results are suggestive of a tau-related neurodevelopmental disturbance in adolescent psychosis.

## 1. Introduction

Schizophrenia affects roughly 1% of the human population and is a major cause of health burden and disability (Kahn et al., 2015; Salomon et al., 2012). Up to one fifth of patients develop their first psychotic episode before reaching adulthood, termed early-onset psychosis (EOP; age of onset <18 years) (Werry et al., 1991), and they may have a more adverse outcome than patients with the adult-onset type of the disorder (Diaz-Caneja et al., 2015). Based on a series of scientific evidence, it has been suggested that schizophrenia has neurodevelopmental origins (Howes and Murray, 2014; O'Shea and McInnis, 2016; Owen et al., 2011; Rapoport et al., 2005) with environmental and genetic insults

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conferring risk occurring already during early phases of brain development (Kahn et al., 2015).

In the context of the neurodevelopmental hypothesis of psychosis, neuronal migration, differentiation and maturation disturbances have been suggested (Glausier and Lewis, 2013; Hagihara et al., 2013, 2014; Muraki and Tanigaki, 2015; Torkamani et al., 2010). During brain development, the neuronal cytoskeleton coordinates cell proliferation, differentiation and migration (Lasser et al., 2018). One of the main elements of the neuronal cytoskeleton is the microtubule assembly (Lasser et al., 2018). Tau, discovered in 1975 (Weingarten et al., 1975), is an intracellular protein mostly present in nerve cells and in smaller amounts in glial cells (Wang and Mandelkow, 2016). It is a key microtubule-associated protein that binds to the microtubule network, regulates its organization and shields it against depolymerization (Barbier et al., 2019; Lasser et al., 2018; Wang and Mandelkow, 2016). Adolescence represents the second period of major neurodevelopment with abundant ongoing maturation processes (Arain et al., 2013) and is proposed to be a second window of vulnerability to psychosis (Patel et al., 2020). If psychotic disorders are neurodevelopmental in nature, and circulating (plasma or serum) tau reflects early (pre- and perinatal) or later (during adolescence) developmental brain processes, we would expect lower circulating tau levels in patients with psychosis.

In psychotic disorders, increasing symptom load over time, cognitive deterioration and progressive brain changes suggest a progressive trajectory/neurodegeneration (Goodwin et al., 2008; Lieberman, 1999; Vieta et al., 2018), but data also shows a high functional recovery rate, lack of cognitive deterioration and stability of brain changes over time (Barth et al., 2020; Haukvik et al., 2016; Zipursky et al., 2013). Tau is the best studied microtubule-associated protein in neurodegenerative disorders known as tauopathies, including Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration and Pick's disease (Wang and Mandelkow, 2016; Williams, 2006). In tauopathies, tau is detached from the neuronal microtubular network and aggregated into paired neurofibrillary tangles (Medina and Avila, 2020; Wang and Mandelkow, 2016). Tau phosphorylation is pivotal for tau functionality, microtubular binding and stabilization, whereas tau hyperphosphorylation might contribute to the tau aggregation found in tauopathies (Wang and Mandelkow, 2016). In Alzheimer's disease both circulating and cerebrospinal fluid (CSF) total tau and phosporylated tau levels are increased (Olsson et al., 2016; Zetterberg and Blennow, 2020) establishing tau as a useful diagnostic biomarker. In case there is a major neurodegenerative component in psychotic disorders as in Alzheimer's disease and other tauopathies, we might expect tau circulating levels to be increased in psychosis. However, it is not likely that such major neurodegenerative processes are present already in adolescence. Elevated tau has not only been reported in neurodegenerative disorders, but also in traumatic brain injury, hypoxic states and epilepsy. In particular, circulating total tau (and phosporylated tau) levels have been reported increased after acute traumatic brain injury (Rubenstein et al., 2017) while transient hypoxia related to breath-holding diving has been associated with elevated circulating total tau levels among healthy individuals (Gren et al., 2016). Tau has also been implicated in epilepsy where patients with a non-idiopathic disorder have shown elevated CSF total tau levels (Matsui et al., 2007; Palmio et al., 2009).

Taken together, we hypothesized lower circulating total tau levels in patients with EOP compared with healthy controls (HC) indicative of an abnormal neurodevelopment. To the best of our knowledge, there is one previously published study on circulating tau concentrations among adults with schizophrenia, and none in adolescent psychosis, showing lower circulating tau levels compared to HC (Demirel et al., 2017) which is in line with our hypothesis.

Psychotic disorders are characterized by brain structure alterations, and a series of evidence suggests that the key to their development is early or late neurodevelopmental disturbances involving migration and differentiation disturbances during gestation and increased dendritic pruning during adolescence (Brent et al., 2013). As described above, the microtubule assembly and the tau protein are implicated in these processes. The cortical gray matter volume can be disintegrated into two components, the cortical surface area (SA) and the cortical thickness, considered to have different developmental trajectories (Houston et al., 2014; Tamnes et al., 2017). Numerous microtubule-associated tau gene (*MAPT*) mutations have been linked to frontal atrophies (Ghetti et al., 2015), while in a recent large population-based study, participants with psychotic symptoms had significantly smaller frontal (orbitofrontal and precentral) SAs (Jalbrzikowski et al., 2019). We therefore tested the hypothesis that circulating tau levels are linked to these frontal SAs.

## 2. Material and methods

### 2.1. Participants

We recruited patients from outpatient and inpatient psychiatric units in Oslo, Norway, as part of the Thematically Organized Psychosis Study for Youth (Youth-TOP). HC were recruited from the same catchment area using the national population register. We applied the following exclusion criteria for all participants: previous moderate or severe head injury, a neurological disorder or medical conditions that could affect brain function and previous or current substance use disorder (including alcohol use disorder). We excluded HC with previous or current psychiatric disorders or with first-degree relatives with a severe psychiatric disorder.

We included for analysis 37 adolescent patients with EOP and 59 adolescent HC with mean age (standard deviation) 16.2 (1.4) years. Specifically, we included patients with the following diagnoses: schizophrenia (n = 19), schizoaffective disorder (n = 1), brief psychotic disorder (n = 1), psychotic disorder not otherwise specified (n = 12) and affective disorder (bipolar I disorder or major depressive disorder) with psychotic features (n = 4). Medical doctors and clinical psychologists evaluated the patients and HC for diagnosis using the Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Regional Committee for Medical Research Ethics (REC South East Norway) and the Norwegian Data Inspectorate. Written informed consent was obtained from participants or parents/legal guardians if age was less than 16 years.

### 2.2. Tau

Blood sampling was performed between 8.10 and 11.20 a.m. after an overnight fast. Blood was taken using EDTA vials and the plasma was isolated and stored at −80 °C. Plasma total tau was measured using the Single molecule array (Simoa) Tau Advantage kit on an HD-X Analyzer (Quanterix, Billerica, MA) (https://www.quanterix.com/simoa-assay-kits/tau/). The assay uses a combination of monoclonal antibodies and measures total tau, i.e., both phosphorylated and non-phosphorylated forms. The antibodies recognize epitopes in the midregion of the molecule (which are not phosphorylated) and recognize all tau isoforms. The measurements were performed in one round of experiments using one batch of reagents by board-certified laboratory technicians. Intra-assay coefficients of variation were 4–13%.

### 2.3. Measures

We evaluated the patients with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). We defined the age of onset as the age of first emergence of psychotic symptoms (persistent psychotic symptoms for more than a week qualifying for a score ≥4 on any of the following

PANSS items: P1, delusions; P3, hallucinatory behavior; P5, grandiosity; P6, suspiciousness; or G9, unusual thought content). We calculated the duration of illness (DOI) defined as the time passed since the age of onset. We assessed the current use (yes/no) of antipsychotic medication and calculated current chlorpromazine equivalent doses (CPZ) in mg/day and lifetime CPZ (CPZ years) (Andreasen et al., 2010). Finally, we assessed the intelligent quotient (IQ) using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007) for patients and HC.

### 2.4. MRI acquisition and processing

T1-weighted MRI scans obtained with two 3T General Electric platforms were available for a subset of the participants, altogether 84 subjects of which 29 were patients and 55 HC. For 47 scans we used a GE 3T Signa HDxt scanner with an 8-channel head coil. A 3D fast spoiled gradient echo (FSPGR) sequence was acquired using the following parameters: 170 sagittal slices, slice thickness = 1.2 mm, voxel size = 1x1x1.2 mm, inversion time (TI) = 450 ms, echo time (TE) = MinFull, repetition time (RT) = 7.8 ms, flip angle = 12°. For 37 scans we used a GE 3T Discovery 750 scanner with a 32-channel head coil. A 3D ultrafast gradient echo (BRAVO) sequence was acquired using the following parameters: 188 sagittal slices, slice thickness = 1 mm, voxel size = 1x1x1 mm, TI = 450 ms, TE = 3.18 ms, TR = 8.16 ms, flip angle = 12°.

MRI scans were processed using the FreeSurfer v6.0 (Fischl, 2012). Quality inspection and editing were performed by trained research assistants following standard FreeSurfer procedures (McCarthy et al., 2015). SA measures were based on the Desikan-Killiany FreeSurfer Atlas (Desikan et al., 2006). In the hypothesis-driven MRI analysis, SAs were calculated as the sum of left and right measures. The orbitofrontal SA was calculated as the sum of the lateral and medial orbitofrontal SA. In the extended MRI analysis, all 34 regional SAs by hemisphere were obtained (Desikan et al., 2006).

### 2.5. Statistics

The distribution of the plasma tau concentrations was right-skewed and we used logarithmic transformation ($log_{10}$) to normalize the data (Suppl. Fig. 1). The logtau concentrations were normally distributed as assessed by the Shapiro-Wilk test of normality (p = 0.720). In the bivariate analysis, we assessed group differences in sex, age, IQ and mother's education years as a proxy for socioeconomic status, as well as the correlations of these variables with logtau (Table 1). In the multivariate model (analysis of covariance; ANCOVA), we explored the putative association between disease status (EOP vs. HC) and logtau concentrations, whilst controlling for variables that differentiated patients from HC or were correlated with logtau in the bivariate analysis. Among patients, we also investigated the putative correlations between age of onset, DOI, medication variables, PANSS total score and YMRS score, and logtau.

In our hypothesis-driven MRI analysis, among patients and HC separately, we searched for partial correlations between logtau and the orbitofrontal and precentral SAs whilst controlling for sex, age and scanner (Table 2). Further, we investigated putative patient-control differences in these two regional SAs.

In our extended MRI analysis, among patients and HC separately, we searched for partial correlations between logtau and all 34 regional SAs by hemisphere (Desikan et al., 2006) whilst controlling for sex, age and scanner. In both the hypothesis-driven and the extended analysis we applied a false discovery rate (FDR) of 5% by diagnostic category to correct for multiple testing (Benjamini and Hochberg, 1995). We conducted all the analyses with IBM SPSS Statistics 25.

**Table 2**
Partial correlations controlling for sex, age and scanner between plasma $log_{10}$tau (logtau) concentrations and the selected cortical surface areas (SAs) in adolescent patients with early-onset psychosis (EOP) and healthy controls. Unadjusted means and standard deviations (SD) of the SAs are also shown. P values < 0.05 shown in bold.

| | EOP patients (n = 29) | | | Healthy controls (n = 55) | | |
|---|---|---|---|---|---|---|
| | | Correlation with logtau | | | Correlation with logtau | |
| | Mean (SD) | R | P value | Mean (SD) | R | P value |
| Orbitofrontal SA | 9345 (958) | +0.489 | **0.013**[a] | 9965 (1137) | −0.001 | 0.992 |
| Precentral SA | 9672 (1057) | +0.195 | 0.339 | 10160 (1106) | +0.086 | 0.543 |

[a] Survives FDR correction.

**Table 1**
Group differences between adolescent patients with early-onset psychosis (EOP) and healthy controls in sex, age, maternal years of education and intelligent quotient (IQ). Among patients, the age of onset, the duration of illness (DOI), the percentage of patients on antipsychotics, the chlorpromazine equivalent doses (CPZ), the lifetime CPZ (CPZ years), the Positive and Negative Syndrome Scale (PANSS) total score and the Young Mania Rating Scale (YMRS) score are presented. Two and one patients were on antidepressants and antiepileptics, respectively. Correlations with plasma $log_{10}$tau (logtau) are shown. P-values < 0.05 are shown in bold.

| | Patients with EOP | | Healthy controls | | Test statistics | Correlation with logtau | |
|---|---|---|---|---|---|---|---|
| | N[a] | Mean (SD) or % | N[a] | Mean (SD) or % | P-value[b] | Direction (+or -) | P value[c] |
| Sex (females %) | 37 | 70.3 | 59 | 54.2 | 0.118 | – | 0.297 |
| Age (years) | 37 | 16.4 (1.3) | 59 | 16.2 (1.5) | 0.431 | – | **0.039** |
| Education years mother | 34 | 12.9 (5.3) | 57 | 13.5 (5.2) | 0.571 | + | 0.854 |
| IQ | 37 | 100 (13.6) | 59 | 104.1 (12.2) | 0.130 | + | 0.852 |
| Age of onset (years) | 34 | 14.6 (2) | | | | – | 0.345 |
| DOI (years) | 34 | 1.1 (1.3)[d] | | | | + | 0.420 |
| On Antipsychotics (%) | 33 | 57.6 | | | | – | 0.076 |
| CPZ (mg/day) | 19[e] | 255.9 (165.4) | | | | + | 0.469 |
| CPZ years | 22[f] | 4.3 (16.4)[d] | | | | – | 0.578 |
| PANSS total score | 31 | 71.2 (16.2) | | | | – | 0.867 |
| YMRS score | 29 | 2.8 (3.8) | | | | – | 0.953 |

[a] Number of participants with data in each variable.
[b] Chi-square test or *t*-test.
[c] Point-biserial correlation for binary variables; Spearman's correlations for quantitative variables.
[d] Median (interquartile range).
[e] Patients currently on antipsychotics.
[f] Non-antipsychotic-naïve patients.

## 3. Results

### 3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the participants are shown in Table 1. Patients and HC did not significantly differ in sex, age, mother's educational years or IQ. The percentage of females among patients was 16% higher relative to HC, and it was considered reasonable to include sex in our multivariate model. Age was negatively correlated with logtau and was also accounted for in the multivariate model. Among patients, age of onset, DOI, antipsychotic medication variables, PANSS total score and YMRS score were not significantly correlated with logtau (Table 1).

### 3.2. Lower plasma tau levels in EOP

In the multivariate model (ANCOVA), we determined the main effect of disease status (EOP patients vs. HC) on logtau whilst controlling for age and sex. We found a significant main effect of disease status on logtau, $F = 5.933$, $p = 0.017$, partial eta-squared = 0.061 with patients having lower logtau than HC, whereas sex ($p = 0.553$) and age ($p = 0.087$) were not associated with logtau. The back-transformed adjusted marginal tau means were 2.95 pg/ml (95% CI, 2.57 to 3.39) and 3.63 pg/ml (95% CI, 3.24 to 3.99) for patients and HC, respectively (Fig. 1).

### 3.3. Hypothesis-driven MRI analysis

The results of the partial correlations between logtau and the selected SAs controlling for sex, age and scanner are shown in Table 2. Among patients, there was a significant positive correlation between logtau and the orbitofrontal SA ($n = 28$, $r = 0.489$, $p = 0.013$, R-squared = 0.24) (Table 2). No significant correlations were found among HC. Among patients, we ran the analysis on the orbitofrontal area by hemisphere; logtau was positively correlated with both left ($n = 28$, $r = 0.513$, $p = 0.009$) and right ($n = 28$, $r = 0.399$, $p = 0.048$) orbitofrontal SA, whilst controlling for sex, age and scanner.

To determine if patients and HC differed in orbitofrontal and precentral SAs, we ran ANCOVAs investigating the main effects of patient-control status on these regional SAs whilst controlling for sex, age and scanner. There was a significant main effect of patient-control status on the orbitofrontal SA, $F(1,78) = 6.442$, $p = 0.013$, partial eta-squared = 0.076, with patients having significantly smaller orbitofrontal SA (mean = 9430 $mm^2$, 95% confidence interval (CI): 9072–9789) compared to orbitofrontal SA of HC (mean = 10001 $mm^2$, 95% CI: 9745–10257). There was no significant patient-control difference in the precentral SA, $F(1,79) = 3.510$, $p = 0.065$. The patients had (non-significantly) smaller precentral SA (mean = 9796 $mm^2$, 95% CI: 9463–10129) relative to precentral SA of HC (mean = 10188 $mm^2$, 95% CI: 9946–10431).

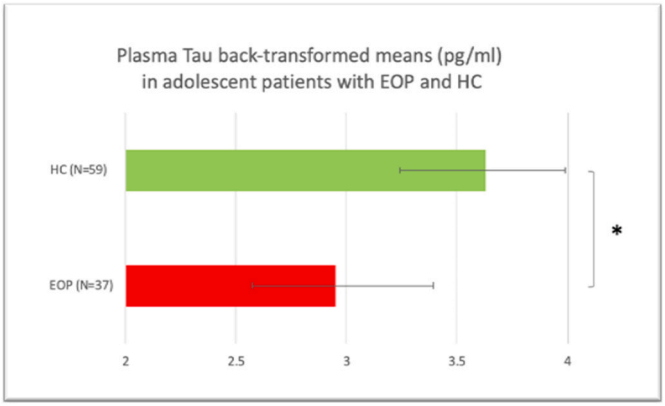


**Fig. 1.** Back-transformed sex- and age-adjusted tau means from the multivariate model (ANCOVA) in adolescent patients with early-onset psychosis (EOP) and healthy controls (HC)
*$p < 0.05$.

### 3.4. Extended MRI analysis

We extended the analysis to include all 68 (34 left and 34 right) regional SAs based on the Desikan-Killiany FreeSurfer Atlas (Desikan et al., 2006). Among patients, there were nominally significant positive correlations between logtau and left ($r = 0.391$, $p = 0.048$) and right ($r = 0.389$, $p = 0.049$) lateral orbitofrontal SAs, left ($r = 0.458$, $p = 0.019$) and right ($r = 0.397$, $p = 0.044$) lingual SAs, left medial orbitofrontal SA ($r = 0.421$, $p = 0.032$) and right pars orbitalis SA ($r = 0.461$, $p = 0.018$) whilst controlling for sex, age and scanner (Fig. 2 and Suppl. Table 1). Among HC, there were no nominally significant correlations between logtau and SAs, whilst controlling for sex, age and scanner. No correlations from the extended analysis survived the FDR correction.

## 4. Discussion

The main finding of the present study was the *lower* circulating tau concentrations in adolescent patients with psychosis compared to HC (Fig. 1). In line with this result, Demirel et al. reported significantly lower circulating total tau levels in adult patients with schizophrenia ($n = 42$) compared to HC ($n = 42$) (Demirel et al., 2017). There are two previous CSF tau studies in schizophrenia (Frisoni et al., 2011; Schonknecht et al., 2003). In the earliest CSF study by Schonknecht et al., total tau levels did not differentiate older (age >50 years) or younger (age <50 years) adult patients with schizophrenia from HC, although a non-significant total tau decrease was present in older patients relative to older HC (Schonknecht et al., 2003). In the later CSF study, Frisoni et al. reported non-significantly lower CSF total tau levels (−33%) in elderly adult patients with schizophrenia relative to HC and significantly lower levels (−78%) relative to patients with Alzheimer's disease (Frisoni et al., 2011). In studies investigating circulating and CSF tau in patients with Alzheimer's disease and HC, there were no correlation between the two measures (Fossati et al., 2019; Mattsson et al., 2016; Zetterberg et al., 2013), which may explain the discrepancy between CSF and circulating tau studies in the psychosis literature.

Some antipsychotic drugs can reduce tau levels (McCormick et al.,

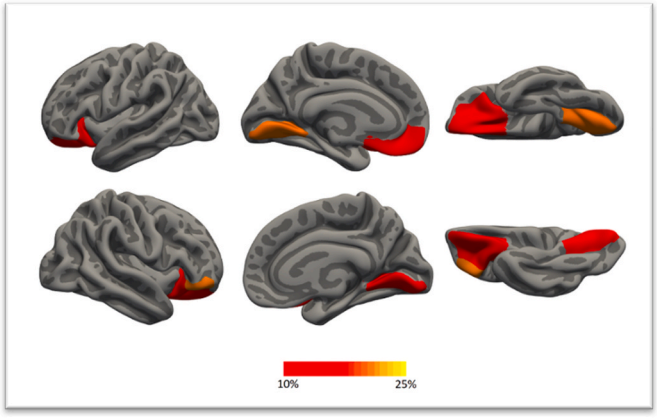


**Fig. 2.** The extended MRI analysis showed nominally significant positive partial correlations ($p < 0.05$) between logtau and the left lateral orbitofrontal, left lingual, left medial orbitofrontal, right lateral orbitofrontal, right lingual and right pars orbitalis surface areas (SAs) among adolescent patients with early-onset psychosis ($n = 29$), whilst controlling for sex, age and scanner. These six SAs are illustrated on the left and right hemisphere (lateral, medial and inferior surfaces are shown). Color bar represents the variation in SAs explained by logtau (R-squared). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2013) and tau phosphorylation (Koppel et al., 2016). Among EOP patients, we did not find any significant correlations between antipsychotic use, CPZ or CPZ years and tau levels. This observation is particularly important for the interpretation of the present results as it lessens the likelihood that the lower tau levels in EOP patients are a result of antipsychotic medication use. Of note, we have analyzed adolescent patients early after the onset of psychosis (median DOI one year) which further supports the notion that the lower tau levels might be due to an underlying disorder-related mechanism.

In the context of the neurodevelopmental paradigm of schizophrenia, the results from *ex-vivo*, MRI, genetic and animal model studies are suggestive of abnormal neuronal migration (Brent et al., 2013; Muraki and Tanigaki, 2015). For instance, neuregulin 1 has been implicated in schizophrenia (Mostaid et al., 2016) and plays a crucial role in radial migration (Anton et al., 1997; Rio et al., 1997). Radial migration is the travel of the glutamatergic neurons from the ventricular zone where they are born to their final destination at the cortical surface (Rakic, 1995) and is achieved with the involvement of the radial glial cell fibers (Lee, 2019). The microtubule network is essential for the radial neuronal migration (Lasser et al., 2018; Lee, 2019). In particular, during this vital early neurodevelopmental process, the neuronal microtubular cytoskeleton enables morphological changes and movement of neurons to their final cortical destination (Lee, 2019). Low tau levels disturb the morphology of the neuronal leading edge and inhibit thereby neuronal migration (Sapir et al., 2012). The lower circulating tau concentrations may be indicative of such early migration disturbances.

Brain differentiation and maturation aberrations have been found in schizophrenia including smaller neuronal cells and prefrontal cortex and hippocampal maturation aberrations (Brent et al., 2013; Glausier and Lewis, 2013; Hagihara et al., 2013, 2014; Torkamani et al., 2010). The microtubule network is crucial for the differentiation of the nerve cells during which axon specification and elongation, dendrite and synapse formation occur (Lasser et al., 2018). Further, excessive dendritic pruning during adolescence has been suggested to be implicated in psychosis (Brent et al., 2013). Tau inhibition induces microtubule decomposition which is an early step of dendritic pruning (Herzmann et al., 2017). The present results showing lower circulating tau levels in adolescent patients with EOP relative to HC may reflect such neurodevelopmental disturbances.

In our hypothesis-driven MRI analysis we found that among patients only, tau concentrations were significantly positively correlated with the cortical orbitofrontal SA. The effect size was large with logtau explaining 24% of the variation in the orbitofrontal SA. Of note, patients had smaller orbitofrontal SA than HC which is in line with the report by Jalbrzikowski et al. (2019). The orbitofrontal cortex, which is a part of the prefrontal cortex, is implicated in the understanding of causal associations and reward processing (Noonan et al., 2017). Orbitofrontal cortex abnormalities have been linked to schizophrenia (Isomura et al., 2017; Kanahara et al., 2013; Nakamura et al., 2008), while reward processing abnormalities are present in the disorder and could partially explain some of the key deficits (Gold et al., 2008). Interestingly, a temporal pattern of gray matter loss has been suggested in schizophrenia starting from posterior regions in childhood and continuing with anterior regions including the prefrontal cortex in adolescence (Brent et al., 2013). Even though this is the first study investigating putative associations between circulating tau and MRI measures in psychosis, there are previous reports searching for such associations in patients with neurodegenerative disorders. In an integrated positron emission tomography (PET)/MRI study of patients with neurodegenerative disorders, there were significant positive correlations between circulating total tau levels and cortical tau tracer uptake, with the strongest correlation for frontal regions (Li et al., 2021). Further, in a mixed sample of HC, patients with mild cognitive impairment and patients with Alzheimer's disease, among amyloid-positive participants only, higher circulating total tau was associated with lower gray matter density in several brain regions including the frontal lobes (Deters et al., 2017).

The tau protein is encoded by the *MAPT* gene located on chromosome 17. *MAPT* gene mutations have been associated with orbitofrontal gray matter atrophy not only in patients with frontotemporal dementia but also in presymptomatic *MAPT* carriers which further supports the notion of a tau implication in this cortical region (Greaves and Rohrer, 2019). *MAPT* mutations can result in a structurally impaired less soluble tau protein with subsequent neurofilament formation and deposits in neurons and glia (Ghetti et al., 2015) which could constitute a neuropathological substrate for the gray matter atrophy found in frontotemporal dementias (Ghetti et al., 2015; Greaves and Rohrer, 2019; Spina et al., 2017). Interestingly, *MAPT* gene variation, in particular carrying at least one H2 allele of the extended *MAPT* haplotype, has been linked to increased risk of psychotic symptoms, mainly hallucinations but also delusions, among patients with Alzheimer's disease (Creese et al., 2014).

In our extended MRI analysis, we showed that tau levels were positively correlated with frontal (left and right lateral orbitofrontal, left medial orbitofrontal and right pars orbitalis) and occipital (left and right lingual) regional SAs (Fig. 2) among patients whereas there were no such correlations in HC. The results of the extended MRI analysis did not survive correction for multiple testing and are therefore not further discussed. However, the presence of six nominally significant correlations in patients vs. none in HC may further support the notion of a tau implication in brain structural changes in EOP.

The present study has certain limitations. First, the sample size was relatively small and we therefore analyzed adolescent patients with non-affective and affective psychosis as one group. Further, due to the relatively small sample size our extended MRI analysis on all SAs was explorative. However, the results of the hypothesis-driven analysis are supported by the *MAPT* gene literature (Ghetti et al., 2015; Greaves and Rohrer, 2019) diminishing the risk that the tau-orbitofrontal SA link among adolescent patients is due to chance. Finally, we have assumed that circulating tau levels reflect early or late neurodevelopmental processes in the central nervous system, but we cannot exclude that circulating tau levels reflect other unknown processes. Similarly, the interpretation of the associations of circulating tau levels with MRI measures as indication of an underlying neurodevelopmental process is necessarily speculative. However, we believe that our two findings combined, showing both lower tau levels in patients and positive correlations between tau and MRI measures in patients only, support the implication of tau in adolescent psychosis through a neurodevelopmental route.

Summarizing, we found significantly lower circulating tau concentrations in EOP suggesting an involvement of this microtubule-associated protein in the pathophysiology of the disorder. In addition, tau levels were positively correlated with the orbitofrontal SA among patients but not HC. The results are suggestive of an abnormal neurodevelopment in EOP where the tau protein and the microtubule network are implicated.

## Contributors

DA drafted the manuscript, performed the statistical analysis and interpreted the data. DA and IA conceptualized and designed the work. IA initiated and supervised the study. KNJ and SN contributed to the processing and extraction of MRI data. RES, KWR and CHJ had substantial contributions to the acquisition of data. KB and HZ were responsible for the plasma tau measurements. All co-authors had substantial contributions to the interpretation of data, critically revised the manuscript for important intellectual content and approved the final version to be published.

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## Declaration of competing interest

OAA received speaker's honorarium from Lundbeck. HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). All other authors reported no potential conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.10.031.

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