Ultrahigh field in vivo characterization of microstructural abnormalities in the orbitofrontal cortex and amygdala in autism

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Abstract
There are currently no biomarkers for autism spectrum disorder (ASD). This neurodevelopmental condition has previously been associated with histopathological findings, including increased neuronal packing density in the amygdala, abnormal laminar cytoarchitecture and increased average neuronal density in the prefrontal cortex. The present study examined whether new brain imaging technologies could reveal in vivo, in adults with ASD, the manifestation of previously described histopathological changes. Using quantitative mapping at ultrahigh field (7 Tesla), we show that we can observe microstructural alterations in the right lateral orbitofrontal cortex and the bilateral amygdala in adult individuals with ASD in vivo. These imaging alterations point to an abnormal laminar cytoarchitecture and to an increased neuronal density, similar to what has been previously described in post-mortem data in ASD. Our data demonstrate that it is possible to visualize, in vivo and at the individ-

Abbreviations: Amyg, amygdala; ASD, autism spectrum disorder; CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; DSM, Diagnostic and Statistical Manual of Mental Disorders; FDR, false discovery rate; GM, grey matter; MRI, magnetic resonance imaging; MP2RAGE, Magnetization-Prepared two inversion-contrast Rapid Gradient Echoes sequence; OFC, orbitofrontal cortex; ROI, region of interest; T1-rt, T1 relaxation time; T1w, T1-weighted; TI, inversion time; TIV, total intracranial volume; TR, repetition time; WIP, work-in-progress; WM, white matter.

Cristina Granziera and Nouchine Hadjikhani have equal contribution.
At the subcortical level, alterations of cortical and subcortical microstructure in ASD. Future studies will be needed to extend these findings to a larger group of individuals and evaluate their association with symptomatology as well as their specificity among the different neurodevelopmental disorders.

**KEYWORDS**

amygdala, autism, biomarkers, prefrontal cortex, quantitative MRI

## 1 | INTRODUCTION

Autism spectrum disorder (ASD) is a common, heterogeneous neurodevelopmental condition affecting more than 1% of children, according to the Centers for Disease Control and Prevention (CDC) (Baio et al., 2018). Currently, there are no biomarkers for ASD, which relies principally on behavioural observation for its diagnosis. ASD is under substantial genetic influence, with a concordance rate in monozygotic twins of up to 90% (Rosenberg et al., 2009); however, identified genetic causes only explain up to 17% of cases (Sanders et al., 2015). ASD already begins in utero, affecting neurons during essential development processes such as proliferation, neuronal growth and differentiation, migration, synapse formation and network construction (e.g., Bauman & Kemper, 1985; Casanova et al., 2002).

Disruption of post-natal neuron migration and/or differentiation may contribute the observed cortical anatomical disorganization reported in ASD individuals (Stoner et al., 2014) and also to reported alteration in basic functional cortical units (i.e., cortical minicolumns, Mountcastle, 1997), which have been described in ASD (Buxhoeveden et al., 2006; Casanova et al., 2002; Opris & Casanova, 2014).

At the subcortical level, post-mortem histological studies have revealed increased neuronal packing density in the amygdala (Bauman & Kemper, 1985). Histological studies of the cortex in ASD have concentrated in the prefrontal cortex and reported laminar disorganization with the presence of focal cortical dysplasia (i.e., disorganization of the normal cortical cytoarchitecture and myeloarchitecture) (Stoner et al., 2014), as well as heterotopia (i.e., when neurons that are supposed to form part of the cerebral cortex do not reach their correct location within the cortical ribbon and are misplaced and clustered in other regions) (Wegiel et al., 2010; for review, see, e.g., Amaral et al., 2008; Palmen et al., 2004).

The heterotopias and laminar disorganization described by Stoner et al. were associated with the presence of abnormal laminar cytoarchitecture in Layers 4 and 5 (therefore affecting both neurons and their axonal projections and incoming axonal fibres from the thalamus), measuring up to 11.0 mm (Stoner et al., 2014), supporting the notion of faulty axon pathfinding and circuit development in ASD.

Anatomical studies of the orbitofrontal cortex (OFC) in ASD (reviewed in Liu et al., 2020) have revealed abnormalities in the size and the structure of the OFC, together with differences in the subcortical white matter (WM) in this region, and more recently, Liu et al. (2020) have reported post-mortem histological abnormalities in the right OFC of adult ASD individuals, with laminar-specific abnormalities of the density and the diameter of myelinated axons in that specific area.

Interestingly, areas described in the histological studies mentioned above were characterized by a significant increase in the average neuronal density as compared with control samples. However, there are no reports in vivo showing the presence and nature of such abnormalities in ASD individuals, and conventional structural magnetic resonance imaging (MRI) so far has not been able to provide imaging correlates of all the neuropathological and morphological findings in autism.

There have been many reports of abnormal anatomical findings using MRI in ASD, but most of them were macroscopic, non-specific findings, including early brain overgrowth (e.g., Chawarska et al., 2011; Courchesne et al., 2003, 2007, 2011; Hazlett et al., 2011; Sparks et al., 2002).

MRI can provide in vivo information not only about tissue types (grey matter [GM], WM and cerebrospinal fluid [CSF]) but also tissue architecture and intratissue properties. For example, the tissue architecture of cortical GM is made by a characteristic organization of neurons, glia cells and more or less myelinated axons, which can be imaged with T1 relaxometry. Quantitative T1 mapping is a predictor not only of myelin presence in GM (Eickhoff et al., 2005) but also of cellular density as recently shown in a combined MRI and histology study (Goubran et al., 2015). Moreover, recent advances in MRI hardware and software have also permitted to achieve a submillimetric spatial resolution in clinically compatible scan times, allowing to quantify T1 relaxation times in different cortical layers (Setsompop et al., 2016). Previous...
work from our group has shown that it is possible to disentangle different tissue properties in the deep GM nuclei, with results that are compatible with histological findings in the same region (Bonnier et al., 2016). We have also acquired preliminary data showing that T1 relaxometry acquired at submillimeter resolution in healthy controls show patterns of GM architecture, which can be related to cortical histological properties (Bonnier et al., 2017). Using 7-T MRI, it is possible to achieve submillimeter spatial resolution in clinically compatible scan times with minimal penalties in signal-to-noise ratio. Thanks to this, 7-T MRI allows to study the microstructural characteristics and the presence of subtle alterations in the cortical ribbon in vivo in individual subjects.

Here, we used cutting-edge technology (ultrahigh field MRI, 7-T quantitative MRI) to examine in a proof-of-concept study whether we could observe in vivo the alterations previously described in histological studies in ASD. Considering histological post-mortem data, we decided to focus on the prefrontal cortex, on the lateral OFC in particular and on the amygdala.

2 MATERIALS AND METHODS

All procedures were approved by the local Institutional Review Board and all participants provided written consent. Images of brain T1 relaxometry were acquired with a 7-T Siemens whole-body scanner (Siemens Healthcare, Erlangen, Germany) using magnetization-prepared two inversion-contrast rapid gradient echoes (MP2RAGE) sequence providing both a uniform T1 weighted contrast and a T1 map (T1 relaxation time, T1-rt) corrected for the proton density, T2* contrast, and B1 inhomogeneities (O’Brien et al., 2014; Marques et al., 2010). The MP2RAGE data acquisition and online image reconstruction were performed with a vendor-supplied MP2RAGE package (WIP #944), with 0.75-mm isotropic voxel size and the following protocol parameters: T11/T12/ λ = 800/2,700/6,000 ms.

Data were acquired in 16 ASD participants (three females) and 12 controls (two females), matched for age (ASD = 26.5 ± 2.5; CON 26.8 ± 2.3; p = .9). None of the participants in either group had intellectual disability. All ASD patients had previously received a formal autism diagnosis by a psychiatrist or a licensed psychologist according to the DSM IV TR or the DSM 5. After preprocessing and quality evaluation of acquired MR images, two ASD subjects were excluded due to motion, distortion and other artefacts in the MP2RAGE.

Total intracranial volume (TIV) extraction, tissue segmentation and definition of cortical and subcortical regions of interest (ROI) were performed over the MP2RAGE uniform image using the fully automatized FreeSurfer software (Fischl et al., 2002). In light of the published histopathological data, two ROIs in each hemisphere were specifically selected: the lateral OFC and the amygdala.

Tissue concentration maps were computed over the same image by estimating the concentration of GM, WM and CSF in each voxel with an in-house software based on Bonnier et al. (2019). This was done by assigning to each imaging voxel a value computed as a mixture of tissues instead of assigning them a single tissue type as in Bonnier et al. (2019). Mean values for GM and WM were initialized at 1,000 and 2,000 ms, resp. according to Marques et al. (2010). The algorithm was applied on each ROI separately to account for the variability of T1 signal over the brain.

The mean T1-weighted (T1w) uniform intensity, mean T1-rt and GM concentration values as well as the ROI size (in number of voxels) were computed. In order to detect subtle alterations in tissue concentration in the cortical regions under study (effects that may be hidden by the macroscopic effect due to the averaging of the individual voxel values), we selected the number of voxels per ROI having a GM concentration higher that 95% and 90%, respectively.

Differences in T1w intensities, qT1, tissue concentrations and number of voxels containing GM concentrations higher from the selected threshold were evaluated between ASD and healthy controls using a non-parametric Wilcoxon test. For each variable, extreme values (values beyond the 95th percentile of the dataset) were identified based on the chi-squared score, defined as $\chi^2 = N \times (x - \text{mean}(x))^2 / \text{var}(x)$. From these extreme values, and after visual quality check of the Freesurfer’s ROI segmentation, the outlier values that corresponded to segmentation failures were removed from the dataset. The resulting p values were corrected for multiple comparisons using false discovery rate (FDR). Statistical analyses were run in RStudio (running R version 3.4.1.).

Focal abnormalities in the layer architecture along the OFC—that were considered as anatomical surrogate of cortical lamina—of GM were visually evaluated and counted by two experts (CG and NH) independently and then agreed by consensus.

3 RESULTS

The qualitative evaluation of areas with abnormalities in the layer architecture in the OCF showed a higher number of discrete abnormalities in ASD patients compared with healthy controls (ASD n = 69 and HC
n = 4, illustrated in Figure 1). Their size and location are comparable with those reported by Stoner et al. (2014).

The quantitative analysis of GM concentration and of the number of voxels with high GM concentration in OFC and amygdala in controls and ASD patients is reported in Figures 2 and 3. Although no significant differences were present in the left OFC, the right OFC showed significant increase in mean GM concentration (p = .042), as well as in the number of voxels with a GM concentration superior to 0.95 (p = .024) and in the number of voxels with a GM concentration superior to 0.90 (p = .042), in line with the changes reported by Liu et al. in the right OFC (Figure 2).

In the amygdala (Figure 3), the mean GM concentration did not differ between groups. The number of voxels with a GM concentration superior to 0.95 was significantly higher in ASD bilaterally (left amygdala: p = .036; right amygdala: p = .036). This was also the case for the number of voxels with a GM concentration higher than 0.90 (left amygdala: p = .018; right amygdala: p = .015). There was also a significant positive correlation between the GM concentration between the right amygdala and the right OFC (Spearman $r = .371$, p = .045) across groups; however, we did not have the power to show any such correlation when groups were treated separately. No significant differences were found for T1 relaxation times after FDR correction.

![Magnetization-Prepared two inversion-contrast Rapid Gradient Echoes (MP2RAGE) T1-weighted (T1w) images and grey matter (GM) concentration map of two autism spectrum disorder (ASD) participants and one healthy control, estimated from MP2RAGE images at 7 T at high resolution. Blue corresponds to low GM concentration, whereas red/yellow correspond to high GM concentration. In both examples of ASD participants, one can observe areas of abnormal grey matter concentration in the prefrontal cortex (white arrows), reminiscent of the histological images published by Stoner et al. (2014). Note that these GM concentration differences are not visible on conventional native anatomical images (top row)
DISCUSSION

Our in vivo data support histological observations made in post-mortem brains in autism, namely abnormal laminar cytoarchitecture and abnormalities in GM concentration in the right OFC, as well as increased neuronal density bilaterally in the amygdala.

Disruption of post-natal neuron migration and/or differentiation may contribute to the observed cortical anatomical disorganization reported in ASD individuals (Stoner et al., 2014), and to the reported alteration in basic functional cortical units (i.e., cortical minicolumns), which have been described in ASD (Casanova et al., 2002).

Anatomical studies of OFC in ASD (reviewed in Rolls & Grabenhorst, 2008) have revealed abnormalities its size and structure, and more recently, Liu et al. (Liu et al., 2020) have reported post-mortem histological abnormalities in the right OFC of adult ASD individuals, with laminar-specific abnormalities of inhibitory neurons distribution.

The OFC plays an important role in the limbic system, with its connections with both the amygdala and the anterior cingulate cortex and is involved in social and emotional processing, as well as decision making (Rolls & Grabenhorst, 2008), and in particular decision making in social context. Damage to the OFC has been associated with impairment in emotional behaviour and emotion-related learning. The OFC receives direct projections from the inferior temporal cortex, involved in face processing, has ‘face cells’ as well, and damage to the OFC is associated with impaired emotional face processing (Rolls, 2007).

There are substantial connections between the OFC and the amygdala in primates (Ghashghaei et al., 2007), supporting goal-directed behaviours that are based on emotional information. Alterations in amygdala growth and microstructure, together with atypical amygdala activation have been frequently reported in autism in vivo (Bauman & Kemper, 1985) (for review, see Donovan & Basson, 2017). In addition, the OFC–amygdala coupling has been associated with emotion regulation.
As well as anxiety (Kim et al., 2011) and obsessive compulsive disorder (Paul et al., 2019), two frequent comorbidities in ASD. There are to our knowledge no paediatric study at ultrahigh field in autism, but several groups have recently reported successful data acquisition without sedation in other paediatric conditions such as paediatric-onset multiple sclerosis, Tourette syndrome or attention deficit hyperactivity disorder (Datta et al., 2017; Mahone et al., 2018; Puts et al., 2020) and we hope that future studies will be able to examine younger children with autism using this protocol.

5 | CONCLUSION

Our data show that the OFC and the amygdala display abnormal microstructure that may be associated with the functional abnormalities that have been described in autism, including social emotional processing. Conventional structural MRI so far has not been able to provide imaging correlates of all the neuropathological and morphological findings in autism. Here, we show that with ultrahigh field quantitative MRI, it is possible to see in vivo, at an individual level, alterations of the OFC and amygdala in autism. Given its small size, this constitutes a proof-of-concept study, and future research will need to extend these findings to a larger group of individuals and evaluate their association with symptomatology and their specificity among the different neurodevelopmental disorders.

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CONFLICT OF INTEREST

None.
AUTHOR CONTRIBUTIONS
Conception and design of the study were done by NH and CG. Acquisition and analysis of data were done by EFG, GB, NW, CG and NH. Drafting the text or preparing the figures was done by EFG, GB, CG and NH.

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DATA AVAILABILITY STATEMENT
Data collected for this study are deposited at the National Institute of Mental Health (NIMH) Data archive (NDA).

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