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Brain monoamine oxidase B and A in human parkinsonian dopamine deficiency disorders

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The enzyme monoamine oxidases (B and A subtypes, encoded by *MAOB* and *MAOA*, respectively) are drug targets in the treatment of Parkinson's disease. Inhibitors of MAOB are used clinically in Parkinson's disease for symptomatic purposes whereas the potential disease-modifying effect of monoamine oxidase inhibitors is debated. As astroglial cells express high levels of MAOB, the enzyme has been proposed as a brain imaging marker of astrogliosis, a cellular process possibly involved in Parkinson's disease pathogenesis as elevation of MAOB in astrocytes might be harmful. Since brain monoamine oxidase status in Parkinson's disease is uncertain, our objective was to measure, by quantitative immunoblotting in autopsied brain homogenates, protein levels of both monoamine oxidases in three different degenerative parkinsonian disorders: Parkinson's disease ($n = 11$), multiple system atrophy ($n = 11$), and progressive supranuclear palsy ($n = 16$) and in matched controls ($n = 16$). We hypothesized that if MAOB is 'substantially' localized to astroglial cells, MAOB levels should be generally associated with standard astroglial protein measures (e.g. glial fibrillary acidic protein). MAOB levels were increased in degenerating putamen (+83%) and substantia nigra (+10%, non-significant) in multiple system atrophy; in caudate (+26%), putamen (+27%), frontal cortex (+31%) and substantia nigra (+23%) of progressive supranuclear palsy; and in frontal cortex (+33%), but not in substantia nigra of Parkinson's disease, a region we previously reported no increase in astrocyte protein markers. Although the magnitude of MAOB increase was less than those of standard astrocytic markers, significant positive correlations were observed amongst the astrocyte proteins and MAOB. Despite suggestions that MAOA (versus MAOB) is primarily responsible for metabolism of dopamine in dopamine neurons, there was no loss of the enzyme in the parkinsonian substantia nigra; instead, increased nigral levels of a MAOA fragment and 'turnover' of the enzyme were observed in the conditions. Our findings provide support that MAOB might serve as a biochemical imaging marker, albeit not entirely specific, for astrocyte activation in human brain. The observation that MAOB protein concentration is generally increased in degenerating brain areas in multiple system atrophy (especially putamen) and in progressive supranuclear palsy, but not in the nigra in Parkinson's disease, also distinguishes astrocyte behaviour in Parkinson's disease from that in the two 'Parkinson-plus' conditions. The question remains whether suppression of either MAOB in astrocytes or MAOA in dopamine neurons might influence progression of the parkinsonian disorders.

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Abbreviations: fMAOA25 = a 25 kDa fragment of MAOA; HMW = high molecular weight; Hsp27 = heat shock protein-27; LMW = low molecular weight; MAOA/B = monoamine oxidase A/B; MSA = multiple system atrophy; PSP = progressive supranuclear palsy

Introduction

For over half a century levodopa dopamine substitution therapy has remained the mainstay, most efficacious, pharmacological treatment for Parkinson's disease (Birkmayer and Hornykiewicz, 1961). However, interest has also focused on the enzyme monoamine oxidase B (MAOB) as a secondary drug target in Parkinson's disease (Birkmayer *et al.*, 1975; Youdim *et al.*, 2006; Finberg, 2014; Li *et al.*, 2014; Miklya, 2016) and also as a brain glial biomarker (Rodriguez-Vieitez *et al.*, 2016). MAOB is one of the two subtypes (MAOA and MAOB) of the major monoamine metabolizing enzyme that oxidizes the neurotransmitter dopamine and breaks down other amines (Shih *et al.*, 1999; Youdim *et al.*, 2006; Finberg and Rabey, 2016). MAOB is considered to be localized primarily (but not exclusively, e.g. serotonin neuron cell bodies) to astrocytes whereas MAOA is located largely to neurons in the brain (Levitt *et al.*, 1982; Westlund *et al.*, 1985, 1993; Shih *et al.*, 1999; Sader-Mazbar *et al.*, 2013, Finberg and Rabey, 2016; but see Youdim and Bakhle, 2006; Harris *et al.*, 2015). Inhibitors of MAOB (e.g. selegiline, rasagiline) are used clinically to provide symptomatic benefit in Parkinson's disease because of the elevation of brain dopamine by inhibiting its breakdown (Riederer and Youdim, 1986; Youdim and Bakhle, 2006; Youdim *et al.*, 2006). More speculatively, MAOB inhibitors have been used as potential neuroprotective agents (Olanow *et al.*, 2009; Rascol *et al.*, 2011), with the hope that MAOB inhibition might prevent formation of damaging dopamine-derived oxidation products (Jenner, 2004; Rascol *et al.*, 2011; Finberg, 2014; Finberg and Rabey, 2016) or possible conversion of an endogenous/environmental MPTP-like compound to a neurotoxic substance (Heikkila *et al.*, 1984; Youdim *et al.*, 2006). Although inhibitors of MAOA are used clinically mainly for the treatment of mood disorders, MAOA suppression might also be neuroprotective (Naoi *et al.*, 2011; Goldstein, 2013; Fitzgerald *et al.*, 2014; Goldstein *et al.*, 2016). Indeed, in studies of induced pluripotent stem-cells (iPSCs)-derived dopamine neurons from patients with triplicated α-synuclein (*SNCA*) gene (Byers *et al.*, 2011), with parkin (*PRKN*) (Jiang *et al.*, 2012; but see Imaizumi *et al.*, 2012) or *LRRK2* (Nguyen *et al.*, 2011) mutations, enhanced expression/activities of MAOA and/or MAOB were observed in differentiated dopamine neurons leading to oxidative stress.

More recent attention has focused on the involvement of MAOB in astroglial cells. Astrocytes, in particular reactive astrocytes (Ekblom *et al.*, 1993) such as those in brains of patients with Alzheimer's disease (Nakamura *et al.*, 1990; Saura *et al.*, 1994; Gulyas *et al.*, 2011), express high levels of MAOB but not MAOA (Levitt *et al.*, 1982; Westlund *et al.*, 1985, 1993; Sader-Mazbar *et al.*, 2013); thus, the enzyme has been proposed as a brain PET biomarker of astrogliosis, a typical consequence of toxic brain damage, and PET with the MAOB ligand ^{11}C-L-deprenyl-D_2 (see 'Discussion' section) has been examined in several neurological conditions with astrocytosis including epilepsy (Kumlien *et al.*, 1995, 2001; Bergstrom *et al.*, 1998), traumatic brain injury (Fowler *et al.*, 1999), Creutzfeldt–Jakob disease (Engler *et al.*, 2003), and amyotrophic lateral sclerosis (Johansson *et al.*, 2007), with particular recent emphasis on using this imaging modality for the early detection of astroglial activation in prodromal Alzheimer's disease (Carter *et al.*, 2012; Choo *et al.*, 2014; Rodriguez-Vieitez *et al.*, 2015, 2016; Scholl *et al.*, 2015). Although the function of astrocytes activated during neurodegeneration continues to be debated [i.e. beneficial versus detrimental; A2 versus A1 phenotypes (Verkhratsky *et al.*, 2013; Liddelow *et al.*, 2017)], some experimental findings show that elevated MAOB in astrocytes can induce Parkinson's-like pathologies (Mallajosyula *et al.*, 2008), suggesting that astrocytic MAOB might exacerbate the parkinsonian degenerative process and that MAOB inhibitors might help suppress presumably harmful astroglial activation and neuroinflammation accompanying neurodegeneration.

Given the above considerations, we felt that it might be helpful to know whether MAOB levels are abnormal in brain of patients with Parkinson's disease, and for comparison, in the different 'Parkinson-plus' disorders of multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), which have more widespread pathological changes but have not been examined for MAOs. Early reports of MAO status in Parkinson's disease were non-specific for subtypes (Lloyd *et al.*, 1975; Schneider *et al.*, 1981) whereas results of measurements of MAOB activity were problematic and variable (normal in substantia nigra and putamen: Yong and Perry, 1986; Gargalidis-Moudanos *et al.*, 1997; moderate increase in substantia nigra and putamen: Riederer and Jellinger, 1983; increase only in putamen: Jellinger and Riederer, 1984; moderate increase in substantia nigra: Riederer *et al.*, 1989) (*cf.* Strolin

Benedetti and Dostert, 1989; Oreland, 1991). A neuropathological investigation (Damier *et al.*, 1996) reported above-normal number of MAOB immunoreactive 'glial cells' in Parkinson's disease substantia nigra; however, measurement of total MAOB in the nigra was not determined. With regard to MAOA in Parkinson's disease, anecdotal reports of MAOA activities from the same laboratory were inconsistent, ranging from no change to +90% in substantia nigra (Riederer and Jellinger, 1983; Jellinger and Riederer, 1984; Riederer *et al.*, 1989). Methodologically, enzyme activity and immunohistochemical assays of MAOs were not absolutely specific for the two isozymes, which may have contributed to literature inconsistency; in contrast, by using highly specific and potent antibodies, we recently established quantitative immunoblotting assays that distinguish MAOB and MAOA proteins unequivocally (Tong *et al.*, 2013). The present study was therefore undertaken to measure protein levels of MAOB and MAOA in autopsied brain of patients with Parkinson's disease, PSP and MSA. Because of the evolving interest (Rodriguez-Vieitez *et al.*, 2016) in use of MAOB as a brain imaging marker of astrogliosis in humans, and the paucity of supportive quantitative investigations in different brain disorders in which astroglial activation is expected, we compared MAOB levels to those of other astroglial markers including glial fibrillary acidic protein (GFAP), vimentin and heat shock protein-27 (Hsp27) (Tong *et al.*, 2015). We hypothesized that the degree and regional specificity of any MAOB increase would generally be associated with those of other astroglial markers reported previously in the parkinsonian conditions. Given the presumed localization of MAOA to dopamine neurons, we also hypothesized that levels of MAOA in substantia nigra would be decreased in the dopamine deficiency disorders.

Materials and methods

Subjects

Autopsied brains were obtained from patients with Parkinson's disease ($n = 11$), MSA ($n = 11$), and PSP ($n = 16$) and matched controls ($n = 16$). No significant difference was found in post-mortem interval (h) (control: 12 ± 1; Parkinson's disease: 14 ± 2; MSA: 13 ± 2; PSP: 11 ± 1; mean $\pm$ SEM) or age (years) (control: 71 ± 2; Parkinson's disease: 77 ± 3; MSA: 65 ± 3; PSP: 73 ± 3) among the four groups. One half-brain was used for neuropathological examination, whereas the other half was frozen for neurochemical analyses. The characteristics of the patients were previously reported (Tong *et al.*, 2010, 2015, see Supplementary Table 1). All levodopa treated patients with Parkinson's disease had good response to the therapy whereas levodopa treatment in MSA and PSP produced only varying, at most moderate response. No detailed information on the neuropsychological or mental function of the patients was available. The causes of death for the controls were cardiovascular illnesses ($n = 10$), bronchopneumonia ($n = 2$), pulmonary oedema ($n = 2$), breast cancer ($n = 1$), and natural death ($n = 1$).

Neuropathological assessment

Neuropathological findings (qualitative only) of neuronal loss by routine haematoxylin and eosin stain and assessments of the pathological hallmarks including Lewy bodies, glial cytoplasmic inclusions and neurofibrillary tangles in brains of patients with Parkinson's disease, MSA and PSP were previously reported (Tong *et al.*, 2010, 2015; see Supplementary Table 1 for a summary). Lewy bodies (haematoxylin and eosin stain) were confirmed in all Parkinson's disease patients (idiopathic), with significant Lewy body pathology restricted to substantia nigra, locus coeruleus and other brainstem areas and with the anterior cingulate, hippocampus including transentorhinal cortex, and frontal and temporal neocortices showing no obvious Lewy body pathology. Biochemical analyses confirmed accumulation of high molecular weight (HMW) α-synuclein species in substantia nigra in all Parkinson's disease cases, in putamen in four cases but in caudate and frontal cortex of only one case, confirming that the Parkinson's disease cases had brainstem-predominant α-synuclein accumulation. Lewy bodies were absent in all MSA cases. The presence of glial cytoplasmic inclusions (by Bielschowsky silver impregnation and α-synuclein immunohistochemistry) was confirmed in five MSA patients whereas the analysis of the remaining MSA patients was conducted prior to the consensus statement on the diagnosis of MSA (Gilman *et al.*, 1999), which incorporated assessment of the neuropathology of glial cytoplasmic inclusions. However, all MSA cases showed characteristic regional pattern of degenerative changes in the striato-nigral and pontocerebellar brain regions with marked cell loss with gliosis in substantia nigra, putamen, globus pallidus, locus ceruleus, the olives, pontine nuclei, cerebellum and autonomic nuclei. Further, characteristic heterogeneous accumulation of HMW α-synuclein species in the widespread brain regions and white matters of all MSA cases was confirmed (Supplementary Table 1). For all PSP cases, pathological examination confirmed absence of Lewy bodies and the presence of neuronal loss in substantia nigra, globus pallidus, subthalamic nucleus, brainstem, and cerebellar dentate nucleus together with tau-positive neurofibrillary tangles (by Bielschowsky silver impregnation and tau immunohistochemistry). No systematic or quantitative assessment of gliosis (microglia and astrocytes) was performed during the neuropathological examination.

SDS-PAGE and western blotting

Brain dissection followed published procedures (Kish *et al.*, 1988) using the atlas of Riley (Riley, 1943). Brain regions examined in this study included substantia nigra pars compacta (referred to as 'substantia nigra' for simplicity only), putamen, caudate, and frontal cortex (Brodmann area 9). Substantia nigra samples (20–30 mg wet weight) were taken from slices at the level of red nucleus, corresponding roughly to plates T4-1308 and T4-1443 of Riley (1943), (*cf.* slices #10–12 of Kish *et al.*, 1988), with pars reticulata excluded as much as possible from the excised pigmented pars compacta area; caudate and putamen samples were taken from the representative intermediate (along a dorsoventral gradient)

subdivision of the middle (along a rostrocaudal gradient) portion of both nuclei, i.e. slices #5 or #6 for caudate and slices #7 or #8 for putamen as described in Kish *et al.* (1988). Dissected tissue was homogenized (10×, vol/vol) by sonication in ice-cold 50 mM Tris-HCl, 2 mM EGTA, pH 7.4, containing 1% (vol/vol) protease inhibitors (cat# P8340, Sigma-Aldrich). Aliquoted homogenates were used for the quantitative immunoblotting assays of MAOA and MAOB with a five-point tissue standards composed of a pooled human striatal sample (see Tong *et al.*, 2013 for details and antibodies used). Briefly, after probing for MAOA, the PVDF membranes were stripped and reprobed for MAOB. The antibodies used were rabbit polyclonal antibodies from Santa Cruz Biotechnology (sc-20156, H-70, against C-terminal amino acids 458–527 of human MAOA) and Abcam (ab67297, against amino acids 448–466 of human MAOB), respectively. [It should be noted that the H-70 MAOA antibody reacts non-specifically with a soluble plasma protein in both human and rat that is slightly larger in molecular weight (~70 kDa) than that of MAOA (65 kDa)]. Levels of MAOs (in ng/μg protein) in the tissue standard were calibrated by using recombinant human MAOA (M7316) and MAOB (M7441) from Sigma-Aldrich (Tong *et al.*, 2013). Levels of GFAP, vimentin, and Hsp27, including the low molecular weight (LMW) and HMW species, were previously reported (Tong *et al.*, 2015). Concentrations of the 'control' proteins neuron specific enolase (NSE) and α-tubulin were determined by the same immunoblotting technique in the SDS-PAGE samples. For simplicity only, 'immunoreactivity' of the proteins examined will be referred to as 'levels'.

Statistical analyses

Statistical analyses on differences in MAO levels among controls and parkinsonian conditions were performed using one-way ANOVA followed by *post hoc* Newman-Keuls multiple comparison tests. Correlations were examined by Pearson product-moment or Spearman rank order correlation analyses as indicated in the text. The criterion of statistical significance was $P < 0.05$.

Results

Characteristics of MAOB and MAOA in autopsied human brain and detection of protein fragments

As expected (Tong *et al.*, 2013), the MAOB antibody detected the major intact MAOB protein at the expected molecular weight position (64 kDa). In addition, the antibody detected in many, but not all, samples a slightly smaller, faint protein band of ~62 kDa (Fig. 1), especially in aged brain. This truncated form of MAOB was also detected in purified recombinant MAOB (Tong *et al.*, 2013) and in rat brain (data not shown). Similar to intact MAOB (Tong *et al.*, 2013), truncated MAOB was membrane-bound and there was a significant age-related increase in truncated MAOB levels in the frontal cortex of autopsied human brain (Supplementary Fig. 1); truncated MAOB was detected in frontal cortex of only 1 of 34 subjects under 18 years old, 4 of 15 aged 18–50, but 16 of 21 above 50 years of age. Overall, truncated MAOB levels were positively correlated with those of intact MAOB. However, levels of truncated MAOB were generally low and comprised <5% of the intact protein with the exception of putamen of MSA, frontal cortex of 1 of 16 patients with PSP and across examined brain regions of 1 of 11 patients with Parkinson's disease (Table 1 and Fig. 2).

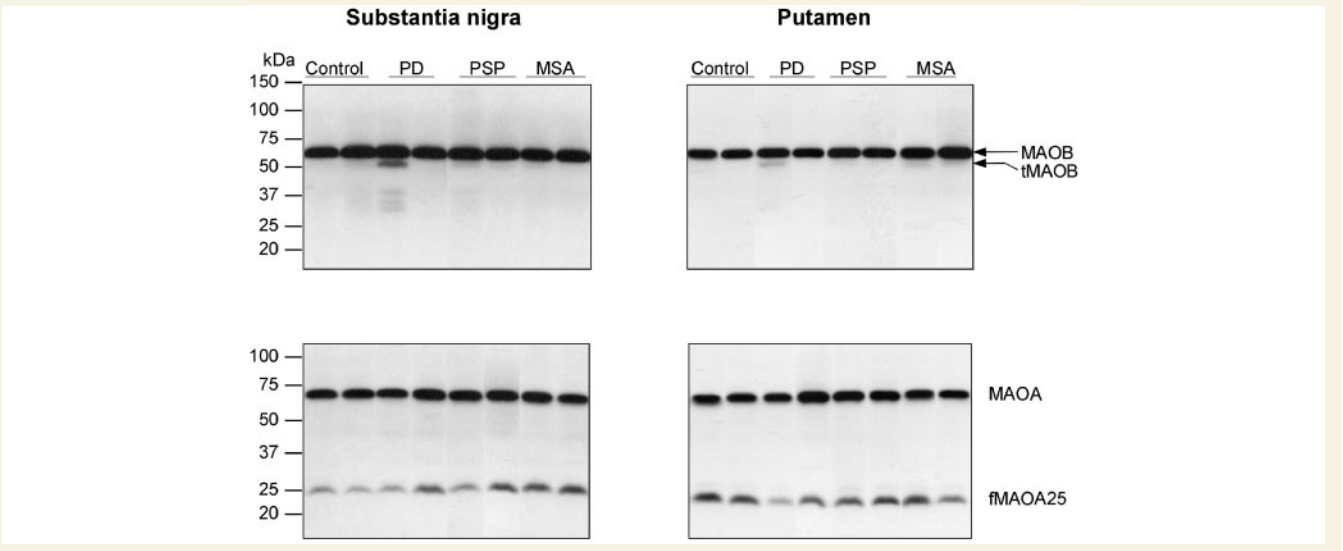

Figure 1 Substantia nigra and putamen. Representative immunoblots of monoamine oxidase (MAOB and MAOA) in controls and in patients with Parkinson's disease (PD), PSP and MSA. Protein bands for the intact proteins (MAOB, 64 kDa and MAOA, 65 kDa) and the partially proteolysed species, i.e. truncated MAOB (tMAO-B, 62 kDa) and a 25 kDa fragment of MAOA (fMAOA25) are identified.

Table 1 Levels of MAOB and MAOA in brain of patients with Parkinson's disease, PSP, and MSA

	Control (n = 10–16)	PD (n = 10–11)	PSP (n = 10–16)	MSA (n = 9–10)	P
Substantia nigra pars compacta					
MAOB	4.46 ± 0.20	4.67 ± 0.28	5.50 ± 0.14** (+23%)	4.91 ± 0.24	0.011
tMAOB	0.067 ± 0.009	0.105 ± 0.041	0.072 ± 0.008	0.073 ± 0.010	0.61
tMAOB/MAOB	1.5 ± 0.2%	2.1 ± 0.8%	1.3 ± 0.1%	1.5 ± 0.2%	0.60
MAOA	0.64 ± 0.03	0.67 ± 0.03	0.63 ± 0.04	0.61 ± 0.03	0.61
fMAOA25	0.095 ± 0.005	0.127 ± 0.009* (+33%)	0.126 ± 0.009** (+32%)	0.133 ± 0.009** (+40%)	0.008
fMAOA25/MAOA	15.4 ± 1.2%	19.2 ± 1.7%	20.5 ± 1.6%	22.1 ± 1.7%* (+44%)	0.028
Putamen					
MAOB	2.64 ± 0.19	3.41 ± 0.20	3.37 ± 0.22* (+27%)	4.82 ± 0.38*** (+83%)	<0.0001
tMAOB	0.089 ± 0.006	0.104 ± 0.024	0.095 ± 0.008	0.220 ± 0.019*** (+147%)	<0.0001
tMAOB/MAOB	3.5 ± 0.2%	3.1 ± 0.6%	2.8 ± 0.2%	4.6 ± 0.2%* (+32%)	0.0047
MAOA	0.41 ± 0.03	0.53 ± 0.04* (+29%)	0.45 ± 0.02	0.31 ± 0.04* (-23%)	0.002
fMAOA25	0.144 ± 0.012	0.103 ± 0.016	0.153 ± 0.013	0.106 ± 0.017	0.031
fMAOA25/MAOA	39.6 ± 6.6%	19.9 ± 2.9%	34.6 ± 2.5%	37.8 ± 7.2%	0.057
Caudate					
MAOB	3.14 ± 0.13	3.51 ± 0.15	3.95 ± 0.12** (+26%)	3.48 ± 0.18	0.0005
tMAOB	0.077 ± 0.006	0.092 ± 0.021	0.091 ± 0.006	0.072 ± 0.010	0.50
tMAOB/MAOB	2.5 ± 0.2%	2.5 ± 0.4%	2.3 ± 0.1%	2.1 ± 0.3%	0.78
MAOA	0.39 ± 0.02	0.41 ± 0.02	0.47 ± 0.02* (+19%)	0.36 ± 0.02	0.0013
fMAOA25	0.065 ± 0.008	0.075 ± 0.010	0.081 ± 0.012	0.077 ± 0.013	0.71
fMAOA25/MAOA	17.2 ± 2.4%	18.2 ± 2.3%	18.6 ± 3.2%	23.2 ± 4.9%	0.62
Frontal cortex					
MAOB	1.18 ± 0.08	1.56 ± 0.10* (+33%)	1.55 ± 0.09* (+31%)	1.36 ± 0.11	0.010
tMAOB	0.041 ± 0.003	0.047 ± 0.011	0.043 ± 0.007	0.033 ± 0.004	0.65
tMAOB/MAOB	3.5 ± 0.3%	3.0 ± 0.5%	2.8 ± 0.5%	2.5 ± 0.2%	0.35
MAOA	0.49 ± 0.03	0.56 ± 0.02	0.48 ± 0.02	0.58 ± 0.05	0.075
fMAOA25	0.061 ± 0.014	0.071 ± 0.016	0.047 ± 0.007	0.059 ± 0.012	0.60
fMAOA25/MAOA	13.2 ± 3.2%	13.0 ± 3.1%	10.6 ± 2.2%	11.3 ± 3.0%	0.89

Data, expressed in mean ± SEM (% change versus control in cases with significant changes), are in ng/μg protein. tMAOB = a truncated form of MAOB; PD = Parkinson's disease. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, Parkinsons' disease, PSP, or MSA versus controls (one-way ANOVA followed by *post hoc* Newman-Keuls multiple comparison tests).

The MAOA H-70 antibody, as reported previously (Tong *et al.*, 2013), detected a major 65 kDa band as well as a small fragment of ~25 kDa (fMAOA25) across the examined brain regions (Fig. 1) and in recombinant MAOA. Similar to intact MAOA, this fragment was membrane-bound and was also detected in rat brain by H-70 (data not shown). Unlike MAOA, which is highly expressed in brain of infants to teenagers (Tong *et al.*, 2013), fMAOA25 was detected in frontal cortex of only 5 of 34 subjects under 18 years old but in variable levels in all adults. Therefore, although a significant positive correlation with age was observed when including all age groups, fMAOA25 levels were not changed during adulthood (Supplementary Fig. 1), a finding similar to that of the intact protein. Levels of fMAOA25 were highly variable and were not correlated with that of intact MAOA. The putamen had higher levels of the MAOA fragment and larger ratios of fMAOA25 versus MAOA than other brain regions examined (Table 1 and Fig. 3; see also Fig. 1).

MAOB and MAOA in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy

As shown in Table 1, levels of (intact) MAOB were significantly increased in putamen of MSA (+83%), in substantia

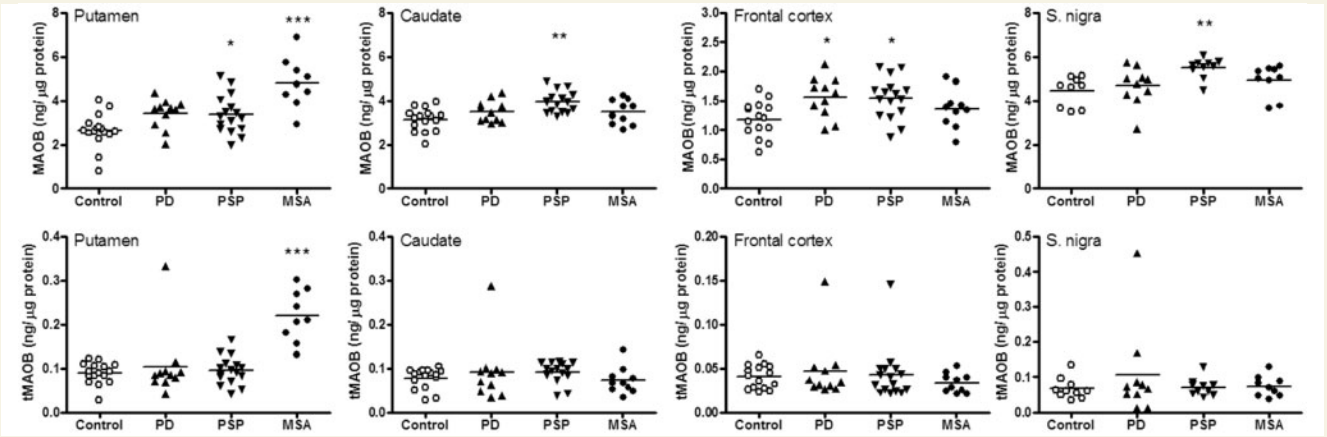

Figure 2 MAOB. Scatter plots of levels of MAOB and the truncated form (tMAOB) in brain regions of patients with Parkinson's disease (PD), PSP and MSA. ***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$, PD, PSP, or MSA versus controls (one-way ANOVA followed by *post hoc* Newman-Keuls multiple comparison tests).

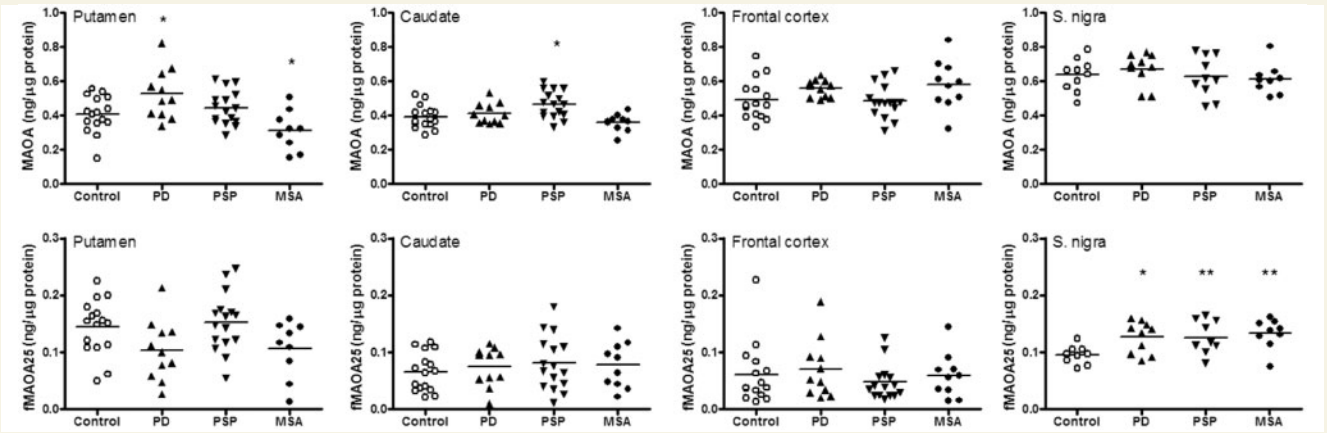

Figure 3 MAOA. Scatter plots of levels of MAOA and the 25 kDa fragment (fMAOA25) in brain regions of patients with Parkinson's disease (PD), PSP and MSA. **$P < 0.01$, and *$P < 0.05$, PD, PSP, or MSA versus controls (one-way ANOVA followed by *post hoc* Newman-Keuls multiple comparison tests).

nigra (+23%), caudate (+26%), putamen (+27%) and frontal cortex (+31%) of PSP, and in frontal cortex (+33%) of Parkinson's disease. Analysis of the individual data (Fig. 2) disclosed that the MSA putamen values had the least overlap between control and neurological subject ranges. Significant differences in levels of the truncated form of MAOB were limited to a marked increase (+147%) in the MSA putamen, with no overlap between control and MSA patient values. A single patient 'outlier' with Parkinson's disease showed high levels of truncated MAOB across brain regions examined (Fig. 1) and one PSP patient had a high level of truncated MAOB in frontal cortex although levels of intact MAOB in these patients were not outstanding.

As shown in Table 1 and Fig. 3, increased levels of MAOA were only observed in caudate of PSP (+19%) and putamen of Parkinson's disease (+29%). Mean levels of MAOA were below normal in putamen of MSA (−23%). Levels of fMAOA25 in the parkinsonian conditions were generally not significantly different from those of the controls, with the exception of the substantia nigra, in which levels of the MAOA fragment were significantly higher in MSA (+40%), PSP (+32%) and Parkinson's disease (+33%), and with the ratios of fMAOA25 versus MAOA significantly above normal in MSA (+44%) (see also Fig. 1).

NSE and α-tubulin in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy

As expected, MSA patients had marked losses of NSE and α-tubulin in the putamen (−54% and −54%, respectively) and in substantia nigra (−33% and −27%, respectively).

PSP patients had significant losses of NSE and α-tubulin in the substantia nigra (−47% and −27%, respectively). Levels of NSE and α-tubulin were otherwise normal in other brain regions examined in MSA and PSP and in all brain regions examined in Parkinson's disease.

MAOB versus conventional astroglial markers in progressive supranuclear palsy nigra and multiple system atrophy putamen

As shown in Fig. 4, in MSA putamen and PSP substantia nigra, the two brain areas with the most marked increase in astroglial marker proteins (Tong *et al.*, 2015), the magnitude of MAOB increase was less than that of the other astroglial markers examined, with concentrations (% increase) of vimentin >> Hsp27 > GFAP > MAOB. However, as shown in Table 2 (see also Fig. 5), significant positive correlations were observed between levels of MAOB and those of Hsp27 (total and tHsp27), vimentin (total and LMW) and GFAP (HMW) in MSA putamen (r = 0.71–0.91, $P < 0.05$); those of Hsp27 (total and tHsp27), vimentin (LMW) and GFAP (HMW) in PSP putamen (r = 0.63–0.82, $P < 0.05$); and those of Hsp27 (total) and GFAP (HMW) in PSP substantia nigra (r = 0.67 and 0.73, respectively, $P < 0.05$). No consistent correlations were observed between levels of MAOA and those of the astroglial markers with the exception of the MSA putamen where levels of fMAOA25 were negatively correlated with those of MAOB (r = −0.68, $P = 0.042$), Hsp27 (total: r = −0.71, $P = 0.034$; tHsp27: r = −0.70, $P = 0.036$), vimentin (total: r = −0.88, $P = 0.002$; LMW: r = −0.90, $P = 0.001$) and GFAP (HMW: r = −0.63, $P = 0.069$).

MAOB versus astroglial markers in the entire group of controls and parkinsonian patients

We also examined whether MAOB levels were correlated with those of the three astroglial markers within the entire group of controls and parkinsonian patients. Significant positive correlations were observed between levels of the astroglial markers (total, LMW, and/or HMW species of

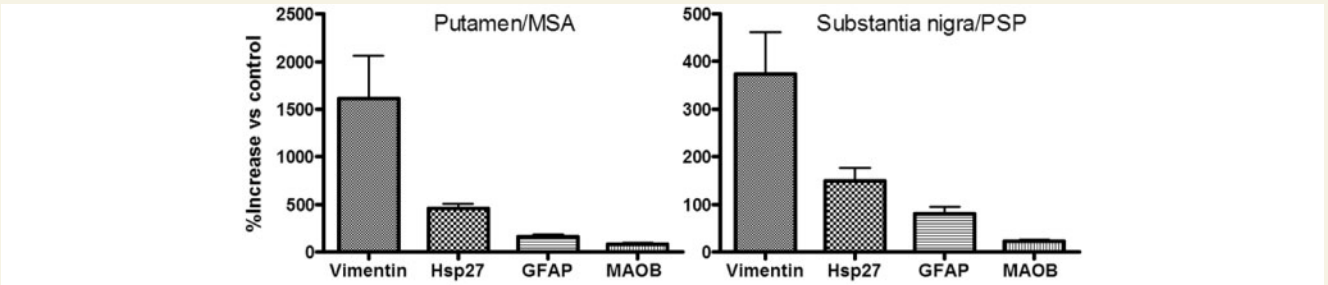

Figure 4 MAOB versus other astrocyte markers. Comparison of changes (% above control) in levels of the astroglial marker proteins in putamen of patients with MSA and in substantia nigra of patients with PSP. Data for Hsp27, vimentin and GFAP were previously published (Tong *et al.*, 2015).

Table 2 Correlations between levels of MAOB and MAOA and levels (total, LMW, and HMW) of the astroglial markers (GFAP, vimentin, and Hsp27) in individual brain regions of patients with PSP and MSA

	GFAP			Vimentin		Hsp27	
	Total	LMW	HMW	Total	LMW	Total	tHsp27
MSA: putamen (*n* = 9)							
MAOB	0.39	0.34	**0.73 (0.026)**	**0.73 (0.024)**	**0.71 (0.033)**	**0.91 (0.001)**	**0.89 (0.001)**
MAOA	−0.44	−0.46	−0.30	−0.28	−0.10	0.02	−0.15
PSP: putamen (*n* = 10)							
MAOB	0.21	0.15	**0.63 (0.05)**	0.43	**0.75 (0.013)**	**0.70 (0.024)**	**0.82 (0.003)**
MAOA	0.40	0.37	0.59 (0.07)	0.24	0.50	0.62 (0.06)	**0.79 (0.01)**
PSP: substantia nigra (*n* = 10)							
MAOB	0.17	-0.34	**0.73 (0.016)**	0.34	0.18	**0.67 (0.03)**	0.58 (0.08)
MAOA	0.27	0.14	0.09	−0.23	−0.21	0.08	−0.15
MSA: substantia nigra (*n* = 8–9)							
MAOB	0.32	0.29	0.30	0.06	0.39	−0.33	−0.28
MAOA	**0.79 (0.011)**	**0.75 (0.02)**	0.15	0.40	0.26	0.42	0.24

Shown are Pearson product-moment correlation coefficients r and the *P*-values in parentheses where there is a significant correlation (in bold) or only a trend. tHsp27 = truncated Hsp27. Note mostly positive correlations between levels the astroglial markers and those of MAOB but not of MAOA. Data for Hsp27, vimentin and GFAP were previously published (Tong *et al.*, 2015).

GFAP, vimentin and Hsp27) and those of MAOB (intact or truncated form) in the putamen (MAOB: r = 0.58–0.75, n = 38–39, $P < 0.0001$; Fig. 5A; truncated MAOB: r = 0.56–0.71, n = 38–39, $P < 0.0002$) and substantia nigra (MAOB: r = 0.44–0.52, n = 37–38, $P < 0.007$; Fig. 5B). In caudate and frontal cortex, in which astroglial changes were more limited in the parkinsonian conditions, the correlations between levels of MAOB and the astrocyte markers were much milder or absent (Supplementary Fig. 2).

MAOB and MAOA versus α-synuclein, and serotonin and dopamine 'metabolism'

Similar to results of our previous report of positive correlations between levels of astroglial markers and α-synuclein accumulation in brain of MSA patients (Tong *et al.*, 2015), nigral MAOB levels of these patients were also correlated positively with that of membrane bound α-synuclein (17 kDa intact: r = 0.73, n = 9, P = 0.027; HMW species: r = 0.70, n = 9, P = 0.037).

In the striatum (putamen and caudate) of the parkinsonian patients, the ratio of 5-hydroxyindoleacetic acid (5-HIAA) versus serotonin, an index of serotonin metabolism, correlated significantly and positively with levels of total MAOA (MAOA plus fMAOA25: r = 0.49, n = 83, $P < 0.0001$) but not with that of MAOB (MAOB plus truncated MAOB: r = −0.09, n = 83, P = 0.40) (Supplementary Fig. 3). Dopamine metabolism in the striatum as indexed by the ratio of homovanillic acid (HVA) versus dopamine was not correlated with levels of either MAOB or MAOA.

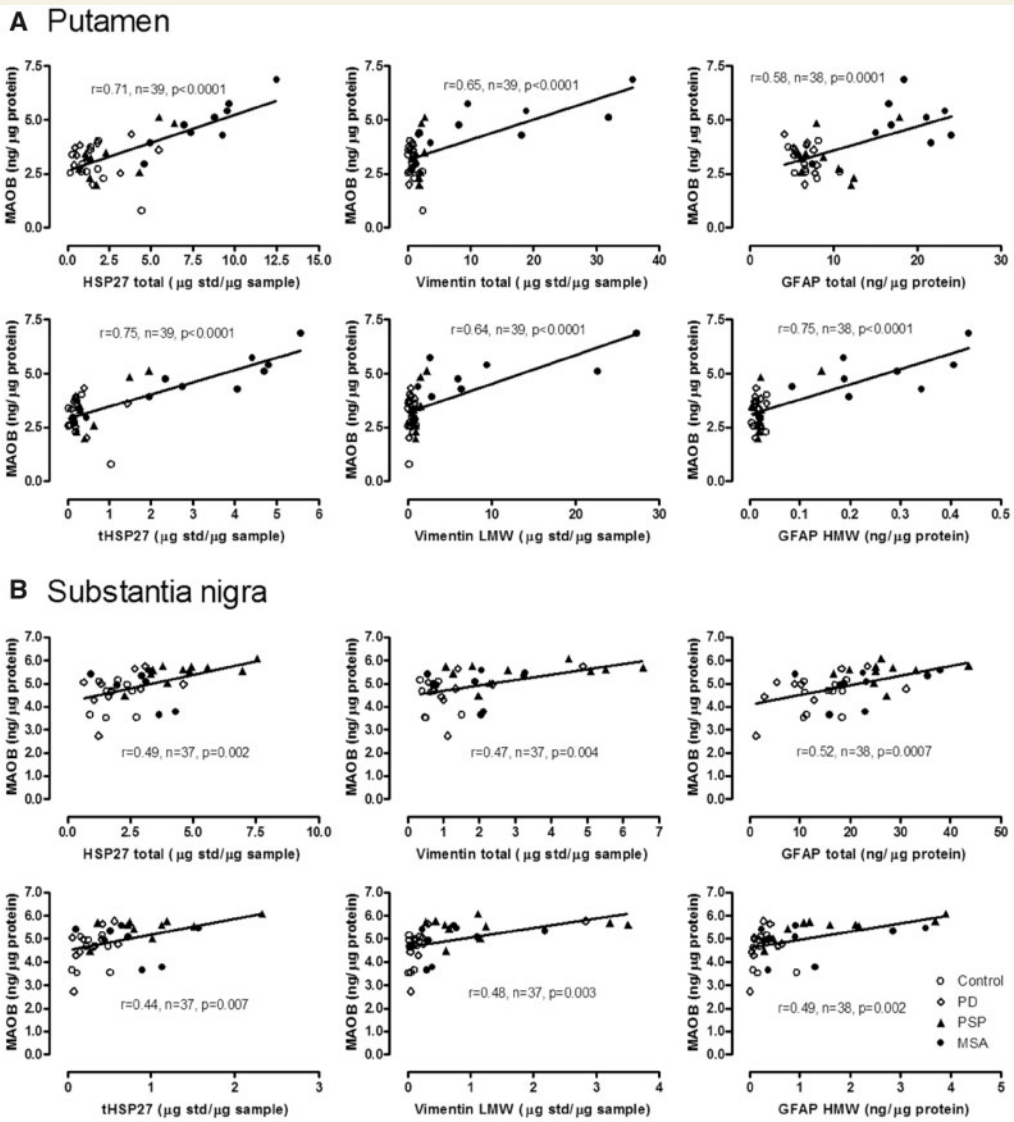

Figure 5 Correlations in putamen and substantia nigra. Correlations (Pearson) between levels of MAOB and those of the astroglial marker proteins in putamen (**A**) and substantia nigra (**B**) of patients with Parkinson's disease (PD), PSP and MSA and control subjects. tHsp27 = truncated Hsp27. Data for Hsp27, vimentin and GFAP were previously published (Tong *et al.*, 2015).

Discussion

The major finding of our study is that brain protein levels of MAOB are normal or elevated in the three parkinsonian conditions—with MAOB increase generally associated with elevations in levels of astrocyte markers. Brain MAOA concentrations were, somewhat surprisingly, not decreased in Parkinson's disease, PSP, or MSA, with the exception of the atrophic putamen in MSA, despite loss of dopamine neurons that presumably contain this enzyme (see below). Our data, unequivocally distinguishing by immunoblotting the two MAO subtypes—and for the first time across different parkinsonian disorders—provide some support to the use of MAOB as an astrocyte activation marker and might also be relevant for speculations in the literature that brain MAOB (e.g. that localized to astrocytes) and MAOA (e.g. that expressed by dopamine neurons) might be harmful.

MAOB and MAOA in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy versus present findings

To our knowledge, brain MAOB and MAOA have not yet been measured in either PSP or MSA. In Parkinson's disease, the only previous investigation of either MAOB or MAOA protein appears to be that of Damier *et al.* (1996) who reported in substantia nigra a marked (+200%) increase in number of MAOB-positive 'glia' which was accompanied by a loss (by 54%) of MAOB-positive neurons; however, as the investigators noted, no assessment of total nigral MAOB protein was made. As mentioned in the 'Introduction' section, the results of brain MAOB and MAOA activity measurements in Parkinson's disease were conflicting, sparse, or problematic. An *in vivo* PET imaging study with the first generation irreversible MAOB ligand ^{11}C-deprenyl found normal brain (substantia nigra not examined) MAOB availability in Parkinson's disease (Fowler *et al.*, 1993, 1994) although interpretation of the findings is uncertain as only a small number (four to six) of Parkinson's disease subjects were assessed and the time-activity curves of ^{11}C-deprenyl binding, as well as that of the later deuterated ^{11}C-L-deprenyl-D_2 (see below), in brain also include a contribution from the radiolabelled metabolite, *N*-^{11}C-methamphetamine which is present in brain tissue as well as plasma (Fowler *et al.*, 1988; Cumming *et al.*, 1999). The limited MAOB and MAOA literature in parkinsonian conditions makes comparison with our new data difficult.

MAOB versus astroglial markers

We expected that if, as suggested by Nordberg and colleagues and others (Carter *et al.*, 2012; Choo *et al.*, 2014; Rodriguez-Vieitez *et al.*, 2015, 2016; Scholl *et al.*, 2015), MAOB is an astrogliosis 'biomarker', albeit not entirely specific, protein levels of the enzyme should be higher than normal in degenerating areas of human brain in which astrogliosis would be expected to be present. Our post-mortem brain findings in PSP and in MSA generally support this possibility. Thus, in the two brain areas in PSP and MSA, substantia nigra and putamen, respectively, which we previously found to contain the highest concentration of the three examined (standard) astroglial markers (Tong *et al.*, 2015), levels of MAOB (but not those of MAOA) were increased. Amongst the three dopamine deficiency conditions, PSP had the most marked increase of MAOB in substantia nigra and also increased MAOB in every brain region examined, an observation consistent with generally more severe nigral pathology and gliosis in PSP as compared with Parkinson's disease and MSA and widespread pathology, e.g. tau, and astroglial activation, in this condition (Tong *et al.*, 2015). In frontal cortex in Parkinson's disease, the mild increase in MAOB levels is consistent with a trend for increased levels of aggregates (GFAP) and fragments (vimentin and Hsp27) of other astroglial markers. Further, in several brain areas in PSP (substantia nigra, caudate, putamen) and MSA (putamen, substantia nigra), positive correlations were observed between MAOB (but not MAOA) and each of the astroglial markers (vimentin, GFAP, Hsp27), whereas in Parkinson's disease substantia nigra, in which levels of the astroglial markers were normal (GFAP, Hsp27) or only a trend for an increase was observed (vimentin), MAOB protein concentration was normal. Our inability to find increased level of MAOB in substantia nigra [and also in striatum (putamen and caudate] of Parkinson's disease is consistent with findings of others suggesting at most limited astrogliosis in the dopamine depleted striatum and substantia nigra in Parkinson's disease (Banati *et al.*, 1998; Mirza *et al.*, 2000; Song *et al.*, 2009; Saal *et al.*, 2017; but see Liddelow *et al.*, 2017) (for reviews see Halliday and Stevens, 2011; Tong *et al.*, 2015; Bruck *et al.*, 2016).

When including, for the correlations, values from all subject groups, generally significant positive correlations were observed between MAOB versus the astroglial markers in substantia nigra, putamen, and caudate, but not in the cerebral cortical area examined. These associations between MAOB and astroglial markers add to the literature evidence supporting the localization of MAOB to astrocytes and the possible use of MAOB as a astroglial biomarker in imaging studies of living brain (Nakamura *et al.*, 1990; Ekblom *et al.*, 1993; Saura *et al.*, 1994; Kumlien *et al.*, 1995; Gulyas *et al.*, 2011; Carter *et al.*, 2012; Choo *et al.*, 2014; Rodriguez-Vieitez *et al.*, 2015, 2016; Scholl *et al.*, 2015). Our findings also add to the evolving literature distinguishing the astroglial response in PSP and MSA from that of Parkinson's disease (Song *et al.*, 2009; Halliday and Stevens, 2011; Tong *et al.*, 2015; Bruck *et al.*, 2016). Although the absolute extent of localization of MAOB to astroglial versus neurons in human brain is not yet established, MAOB is likely expressed to some degree by different types of neurons (e.g. histamine, acetylcholine) (Lin *et al.*, 1993; Vitalis *et al.*, 2002), and in

particular, by serotonin neurons in the brainstem (Levitt *et al.*, 1982; Westlund *et al.*, 1985, 1988). This means, for example, that in brain neurodegenerative conditions having loss of monoaminergic neurons, any MAOB increase resulting from astroglial changes could be 'confounded' to some extent by loss of MAOB containing neurons in the same brain areas. Thus, in the present study, increased levels of MAOB in MSA were only observed in putamen but not in other brain regions where significant elevation of other astroglial markers was observed (Tong *et al.*, 2015). This might be explained by loss, in MSA, of serotonin neurons enriched in MAOB (Adams *et al.*, 1964; Sawada *et al.*, 1985; but see Benarroch *et al.*, 2007).

A recent finding in developing MAOB PET imaging as a biomarker of brain astrocytosis has been the observation of increased ^{11}C-L-deprenyl-D_2 MAOB binding in prodromal but not in early symptomatic Alzheimer's patients, indicating that astroglial activation might be an early feature of the dementia. However, the negative finding in symptomatic Alzheimer's patients is somewhat surprising, given pathological evidence of marked astrogliosis and increased MAOB levels in post-mortem brain of Alzheimer patients (Nakamura *et al.*, 1990; Jossan *et al.*, 1991; Saura *et al.*, 1994; Gulyas *et al.*, 2011), with the explanation for the 'discrepancy' uncertain. One possibility could be inadequate sensitivity of ^{11}C-L-deprenyl-D_2 binding relative to the magnitude of disease effect. In principle, a phenotype switch from MAOB-rich to MAOB-poor astrocytes (Ekblom *et al.*, 1993; John Lin *et al.*, 2017) during chronic neurodegeneration could be an explanation for negative findings in early symptomatic Alzheimer's disease (Carter *et al.*, 2012; Choo *et al.*, 2014; Rodriguez-Vieitez *et al.*, 2015, 2016) and in Parkinson's disease (this study). To improve sensitivity for detecting astrogliosis, one approach to avoid pitfalls of early MAOB radiotracer development would be use of a newer MAOB radiotracer e.g. ^{11}C-SL25.1188 with no brain-penetrating metabolites and improved reversibility (Saba *et al.*, 2010; Rusjan *et al.*, 2014). Radiotracers with such characteristics might be better astrogliosis biomarkers for disease monitoring and it will be interesting in future to compare findings in Alzheimer's disease with these second-generation radiotracers. Notwithstanding the above limitations and uncertainties, our post-mortem brain findings do add to the support for the possibility that MAOB PET imaging could be a useful biomarker for brain astrogliosis and possibly disease progression related to gliosis.

MAOA versus degenerative neuronal changes in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy

Although the literature has been aware of the existence of MAOA for 50 years (Johnston, 1968), there still remains, surprisingly, much uncertainty regarding the actual localization (e.g. neurons versus glia; neuronal cell body versus axonal terminals; dopamine versus non-dopamine neurons) of the enzyme in human brain—making interpretation of our present MAOA findings difficult. Based on suggestions, or perhaps assumptions, that MAOA is the MAO subtype primarily responsible for dopamine metabolism inside dopamine neurons (Stenstrom *et al.*, 1985; Fagervall and Ross, 1986; O'Carroll *et al.*, 1987; Butcher *et al.*, 1990; Wachtel and Abercrombie, 1994; Finberg *et al.*, 1995; Di Monte *et al.*, 1996; Fornai *et al.*, 1999) (for reviews see Youdim *et al.*, 2006; Finberg, 2014), loss of dopamine neuron innervation to striatum in the three parkinsonian conditions should have caused a significant loss of MAOA protein in this dopamine-rich brain region (see also below). However, in animal models of parkinsonism with lesions of nigrostriatal dopamine neurons, most studies did not observe a loss of striatal MAOA (Carlsson *et al.*, 1981; Van der Krogt *et al.*, 1983; Francis *et al.*, 1987; Sader-Mazbar *et al.*, 2013; but see Agid *et al.*, 1973; Demarest *et al.*, 1980; Stenstrom *et al.*, 1985), suggesting that MAOA might not be highly localized in dopamine neurons in striatum; these ('negative') experimental data are consistent with our findings of generally preserved MAOA in putamen and caudate of Parkinson's disease and PSP and in caudate of MSA. Indeed, slightly increased levels of MAOA were observed in Parkinson's disease putamen (+29%) and PSP caudate (+19%) and the magnitude of MAOA loss in MSA putamen, the brain structure with severe atrophy and gliosis in this condition, was also less than expected from NSE loss (−23% versus −56%). Possibly, loss of dopamine innervation, e.g. in the putamen of Parkinson's disease, might have induced sprouting of serotonin terminals that are suggested to contain MAOA (Sader-Mazbar *et al.*, 2013), which could offset to some extent any enzyme reduction caused by loss of dopamine neurons.

Given the assumption that MAOA is localized at least to some extent in dopamine neurons (e.g. see Fig. 1 in Youdim *et al.*, 2006), we were somewhat surprised to discover that in all three parkinsonian conditions there was no loss of MAOA protein in the substantia nigra (pars compacta), in which dopamine neurons (melanin-containing) account for a vast majority of total number of neurons (Pakkenberg *et al.*, 1991; Gibb, 1992; McRitchie *et al.*, 1996). One possibility is that the enzyme is not highly localized in dopamine neuronal cell bodies in the substantia nigra in the human. In this regard, previous enzyme histochemical (Willoughby *et al.*, 1988; Konradi *et al.*, 1989; Arai *et al.*, 1998; Hida *et al.*, 1999), immunohistochemical (Westlund *et al.*, 1985, 1988, 1993; Konradi *et al.*, 1988) and *in situ* hybridization (Luque *et al.*, 1995; Jahng *et al.*, 1997; Vitalis *et al.*, 2002) studies, as compared to autoradiography and immunoblotting findings (Richards *et al.*, 1992; Saura *et al.*, 1992, 1996; Tong *et al.*, 2013), have shown sometimes inconsistent levels of nigral MAOA. To our knowledge, there has been no examination of MAOA protein in substantia nigra in lesioned animal models of Parkinson's disease. Alternatively, the lack

of any loss of nigral MAOA in the parkinsonian conditions can be explained by upregulation of MAOA expression in remaining dopamine neurons, possible hyperinnervation by other neurotransmitter terminals, e.g. serotonin, as shown in animal models (Zhou *et al.*, 1991; Gaspar *et al.*, 1993) but apparently not in Parkinson's disease (Guttman *et al.*, 2007; Azmitia and Nixon, 2008; Cheshire *et al.*, 2015; Maillet *et al.*, 2016), and/or ectopic expression of MAOA in glial cells. Some contamination of the nigral compacta samples by zona reticulata in our dissection might also have contributed to the lack of MAOA change; however, patients with PSP have been reported to have additional marked loss of reticulata (GABA) neurons (Hardman *et al.*, 1997).

A 'small' fragment of MAOA, fMAOA25, could be detected in human brain samples. We suspect that this fragment likely has no intrinsic function, but possibly could provide an index, for example, of MAOA 'turnover' or metabolism. Interestingly, we observed increased levels of fMAOA25 in substantia nigra in Parkinson's disease, PSP and MSA, supporting the idea that MAOA expression and turnover might be elevated in dopamine neurons of the parkinsonian conditions, explained as a genetic predisposing factor for dopamine neuron vulnerability (Byers *et al.*, 2011; Jiang *et al.*, 2012) or possibly as a response to the compensatory increased dopaminergic activity in surviving dopamine neurons (Sacher *et al.*, 2012). In this regard, levodopa exposure could be a confounding factor, i.e., have contributed to changes or lack of changes in MAOA protein (Sacher *et al.*, 2012), especially in Parkinson's disease; however, the extent of MAOA regulation by dopamine availability in human brain is still uncertain; most of the patients with PSP and MSA did not receive regular levodopa treatment. To our knowledge, only limited information is available regarding brain MAOA expression regulation, e.g. by stress and oxidative stress (Raitsin *et al.*, 2017) and little is known about turnover of the enzyme. An alternative explanation for increased MAOA fragment levels might be generally compromised protein degradation (Pan *et al.*, 2008) and/or stalled axonal mitochondrial protein trafficking (Abeliovich and Gitler, 2016) [e.g. fMAOA25 levels are high in white matter tracts (Tong *et al.*, 2013)] in parkinsonian conditions, resulting in incomplete processing/accumulation of fMAOA25 although brain areas outside of the nigra are also affected by neurodegeneration in MSA and PSP. Unlike truncated MAOB, levels of fMAOA25 are independent of intact protein levels, either during brain development and ageing or among different brain areas. Further studies are required to replicate these preliminary findings and to understand better MAOA expression and metabolism.

MAOB and MAOA as disease-modifying drug targets?

Our post-mortem brain findings may have some clinical relevance, given that both MAO enzymes are drug targets in human brain disorders and that protein levels of the enzymes were generally normal or elevated in the parkinsonian conditions (i.e. the targets are not substantially diminished in concentration despite loss of monoamine neurons). Some experimental data suggest that elevated MAOB expression in astrocytes and ensuing astrocytosis might promote dopamine neurodegeneration by increasing oxidative stress and inhibiting mitochondrial complex-I (Mallajosyula *et al.*, 2008). Assuming that there is some validity to this speculation in the human, our data suggest that, of the three parkinsonian conditions, MAOB inhibition might possibly be more helpful as a neuroprotective agent in PSP, in which an MAOB increase was observed in all examined brain regions, and in MSA, in which a marked (+83%; +147% in truncated MAOB) increase in enzyme concentration was present in the degenerating putamen. In this regard, the MAOB inhibitor deprenyl was found to suppress oxidative stress and glial activation and rescue the MAOB-astrocyte overexpression animal model (Mallajosyula *et al.*, 2008). In Parkinson's disease, clinical evidence supporting a neuroprotective role of MAOB inhibitors is controversial (Ahlskog and Uitti, 2010; Olanow and Rascol, 2010). There is also much uncertainty regarding the status of astrocytes and 'neuroinflammation' in Parkinson's disease (Ghadery *et al.*, 2017; Liddelow *et al.*, 2017; see Tong *et al.*, 2015 for a review). Given the limited availability of drug history information in our post-mortem study, future *in vivo* studies using the new generation of MAOB PET radiotracer, e.g. ^{11}C-SL25.1188 (Rusjan *et al.*, 2014) would help clarify the question of astroglial status, in particular in drug-naïve early stage and progression of Parkinson's disease, and might provide a new imaging approach in differentiating Parkinson's disease from Parkinson-plus movement disorders.

Regarding MAOA as a potential drug target, much evidence from brain imaging and post-mortem brain investigations suggests that globally elevated brain MAOA is associated with mood/sadness in a variety of psychiatric illnesses and prodromal states and therefore represents a potential target for pharmacological intervention to correct the mood disturbance (Meyer *et al.*, 2006, 2009; Sacher *et al.*, 2010; Rekkas *et al.*, 2014; Kolla *et al.*, 2016). A limitation of our study is that subject information on presence of mood problems, which are commonly observed in Parkinson's disease, could not be obtained; however, our data do suggest that a global increase in brain MAOA might not be a characteristic of any of the three parkinsonian conditions. Further investigation, e.g. by ^{11}C-harmine PET, is needed to establish whether brain MAOA might be elevated in subgroups of depressed patients with the movement disorders. On the other hand, given some evidence suggesting that MAOA inhibition can be neuroprotective, our finding of no loss of MAOA and increased MAOA turnover in surviving dopamine neurons might provide a rationale for the clinical use of reversible MAOA inhibitors (without cheese reaction), although there still remains the as yet unanswered question of the net effect of MAOA

inhibition on production of intraneuronal toxic dopamine-derived oxidation products (overall helpful or harmful? Goldstein *et al.*, 2016).

In conclusion, our findings on MAOB in Parkinson's disease, PSP and MSA support the use of MAOB PET binding as a biomarker of astrogliosis in the human brain. Although the preservation or elevation of MAOB and/or MAOA in brain of patients with the parkinsonian conditions may suggest possibility of clinical use of inhibitors of either or both MAO isozymes for symptomatic purposes, it remains to be determined whether such inhibitor drugs possess any disease-modifying (beneficial or detrimental) properties in humans.

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Supplementary material

Supplementary material is available at *Brain* online.

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