Response to the commentary of Yates RL and DeLuca GC on the study: HLA-DRB1*1501 associations with magnetic resonance imaging measures of grey matter pathology in multiple sclerosis

Özgür Yaldizli (**1,2**)*, Varun Sethi (**1**), Matteo Pardini (**1,3**), Carmen Tur (**1,4**), Kin Y Mok (**5,6**), Nils Muhlert (**1,7,8**), Zheng Liu (**1,9**), Rebecca S. Samson (**1**), Claudia AM Wheeler-Kingshott (**1**), Tarek A Yousry (**1,10,11,12**), Henry Houlden (**5**), John Hardy (**5**), David H Miller (**1,10**), Declan T Chard (**1,10**)

1 Queen Square MS Centre NMR Research Unit, Department of Neuroinflammation, UCL Institute of Neurology, London, UK
2 Department of Neurology, University Hospital Basel, Basel, Switzerland
3 Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy
4 MS Centre of Catalonia (Cemcat), Neurology-Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, Spain
5 Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK
6 Division of Life Science, Hong Kong SAR, China
7 School of Psychology and Cardiff University Brain Research Imaging Centre, Cardiff University, Cardiff, UK
8 School of Psychological Sciences, University of Manchester, Manchester, UK
9 Department of Neurology, Xuanwu Hospital of Capitl Medical University, Beijing, China
10 National Institute for Health Research NIHR, UCLH Biomedical Research Centre, UK
11 Brain Repair and Rehabilitation, UCL Institute of Neurology, London, UK
12 Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, London, UK

*corresponding author

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Yates and De Luca's commentary on our recent article highlights an interesting point that we did not address in our work: That age may diminish the effects genetic factors have on pathology in multiple sclerosis (MS). It also reveals a citation error in our article, where we reference the group's earlier work on the spinal cord[1] in place of their more recent findings in the motor cortex.[2]

Given the relatively low number of people included in our magnetic resonance imaging (MRI) study (n=85; 30 RRMS, 30 SPMS, 25 PPMS), we were wary of undertaking subgroup analysis. However, as in the study by Yates and colleagues[2], we have now split the cohort around their median age (in our study 50 years; range 21-65). In neither the younger (n=38; Table 1) or older group (n=47; Table 2) - or the whole group[3] - were MRI measures of cortical pathology (lesion and grey matter volumes, and magnetization transfer ratios) significantly more abnormal in HLA-DRB*1501 positive than negative MS groups. We note that Yates et al. (2015), similarly did not find a difference in the extent of cortical demyelination in the whole cohort, but did find one in the younger group.[2]

Both studies are likely to be underpowered, and with regard to the age related findings both are reliant on small subgroup analyses (n=38 in our study, of whom 17 were HLA-DRB*1501 positive, and n=23 in the Yates et al. study, of whom 8 were positive). We are also cautious when trying to compare these studies directly due to clear - and potentially relevant - differences in the cohorts. The subgroup assessed by Yates et al. includes more than double the proportion of people with progressive MS (87% compared with 39% in our subgroup analysis) (Table 3). As such the cohort included in our study is more representative of people living with relapsing-remitting MS, and that included in the Yates et al. study weighted towards people with progressive MS who have died relatively young. A unifying explanation could be that some people who are HLA-DRB*1501 positive run a more aggressive early course, and so are less likely to be part of an MRI cohort but more likely to be included in a *post mortem* study. Further work, in independent cohorts, is required to clarify this. Ideally this would include people who have recently had a clinically isolated syndrome suggestive of MS or who have clinically early MS.

We fully agree with Yates and De Luca that there is great potential for histopathology and MRI studies to provide complementary data, each playing to their strengths. For example, as they note, histopathological studies are much better able to detect cortical lesions than is currently possible with MRI[4], and so it should be possible to detect associations - where

present - between cortical lesions and genetics factors in smaller cohorts. However, histopathology studies have to make use of the material available to them, and so are usually relatively skewed towards older people with progressive MS. Here MRI studies may bridge the gap, albeit requiring more people to detect equivalent associations when compared with histopathological studies, and also allow links between pathology and clinical features to be looked for.

References:

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Table 1: Patient characteristics and MRI measures in 38 patients younger than the median age of the whole MS population (50 years).

Measure	HLA-DRB*1501		P - value	
	Pos	Neg	Unadjusted	Adjusted
N	17/38	21/38	NA	NA
Disease duration (years)	13.4±7.9	8.7±4.9	**0.03**	NA
Age (years)	38.4±6.8	40.5±7.6	0.36	NA
Female	9(53%)	10(48%)	0.74§	NA
BPF (%)	80.9±2.3	79.8±2.6	0.2	0.24
GMF (%)	47.8±1.2	47.6±1.3	0.58	0.88
Intracortical lesion volume (ml)	0.49±0.24	0.54±0.52	0.73	0.4
Leukocortical lesion volume (ml)	0.55±0.63	0.70±1.19	0.61	0.23
MTR intracortical lesions	31.2±1.8	30.9±2.2	0.64	0.64
MTR leukocortical lesions	29.9±2.9	28.5±3.5	0.26	0.28
MTR normal-appearing cortical grey matter	31.9±1.1	31.0±1.5	0.08	0.16

P values are given unadjusted and adjusted for gender, age, disease duration, current and previous disease modifying treatment and smoking status (GLM, confirmed by bootstrap analysis, case resampling n=1000). §Chi Square Test

Table 2: Patient characteristics and MRI measures in 47 patients with the age of 50 or higher.

Measure	HLA-DRB*1501		P - value	
	Pos	Neg	Unadjusted	Adjusted
N	25/47	22/47	NA	NA
Disease duration (years)	22.5±11.5	19.2±9.7	0.3	NA
Age (years)	57.9±4.4	56.9±4.8	0.48	NA
Female	18 (82%)	15 (60%)	0.78§	NA
BPF (%)	79.8±1.2	79.2±1.8	0.16	0.16
GMF (%)	46.5±0.8	46.5±1.7	0.42	0.75
Intracortical lesion volume (ml)	0.42±0.29	0.39±0.53	0.78	0.48
Leukocortical lesion volume (ml)	0.41±0.37	0.61±0.76	0.25	0.82
MTR intracortical lesions	30.5±2.0	29.8±3.2	0.27	0.13
MTR leukocortical lesions	28.7±3.2	28.1±2.9	0.48	0.51
MTR normal-appearing cortical grey matter	31.0±1.3	30.8±0.9	0.63	0.44

P values are given unadjusted and adjusted for gender, age, disease duration, current and previous disease modifying treatment and smoking status (GLM, confirmed by bootstrap analysis, case resampling n=1000). §Chi Square Test

Table 3: Demographics of the young* patients in both publications[2,3]

Parameter	**Yaldizli et al. 2016**	**Yates et al. 2015**
N	38	23
Mean Age in years (range)	39.6 (range: 21-49)	52 (range: 40-60)
Mean Disease duration in years (range)	10.8 (range: 1.6-31)	25 (range: 16-38)
Female	50%	74%
HLA-DRB*1501 positive	17/38	8/23
Progressive MS	39%	87%

Note: *young was defined as age lower than the median of the whole study population