Clinical Radiology 74 (2019) 816.e19–816.e28

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Localised grey matter atrophy in multiple sclerosis is network-based: a coordinate-based meta-analysis

F.L. Chiang [a,b,*], Q. Wang [c], F.F. Yu [d], R.S. Romero [e], S.Y. Huang [f,g,h,i], P.M. Fox [b], B. Tantiwongkosi [a], P.T. Fox [a,b,e,j,**]

[a] *Department of Radiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[b] *Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[c] *Department of Neurology, Beijing Tian Tan Hospital, Capital Medical University, Beijing, China*
[d] *Division of Neuroradiology, Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA*
[e] *Department of Neurology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[f] *Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA, USA*
[g] *Division of Neuroradiology, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA*
[h] *Harvard Medical School, Boston, MA, USA*
[i] *Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA*
[j] *South Texas Veterans Health Care System, San Antonio, TX, USA*

ARTICLE INFORMATION

Article history:
Received 10 May 2019
Accepted 10 July 2019

AIM: To test the network degeneration hypothesis in multiple sclerosis (MS) with a two-stage coordinate-based meta-analysis by: (1) characterising regional selectivity of grey matter (GM) atrophy and (2) testing for functional connectivity involving these regions.

MATERIALS AND METHODS: Meta-analytic sources included 33 journal articles (1,666 MS patients and 1,269 healthy controls) with coordinate-based results from voxel-based morphometry analysis demonstrating GM atrophy. Mass univariate and multivariate coordinate-based meta-analyses were performed to identify a convergent pattern of GM atrophy and determine inter-regional co-activation (as a surrogate of functional connectivity), with anatomical likelihood estimation and functional meta-analytic connectivity modelling, respectively.

RESULTS: Localised GM atrophy was demonstrated in the thalamus, putamen, caudate, sensorimotor cortex, insula, superior temporal gyrus, and cingulate gyrus. This convergent pattern of atrophy displayed significant inter-regional functional co-activations.

CONCLUSION: In MS, GM atrophy was regionally selective, and these regions were functionally connected. The meta-analytic model-based results of this study are intended to guide future development of quantitative neuroimaging markers for diagnosis, evaluating disease progression, and monitoring treatment response.

* Guarantor and correspondent: F. L. Chiang, Department of Radiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive–MC7800, San Antonio, TX, 78229, USA. Tel.: +1 (210) 567 6482; fax: +1 (210) 567 5541.
** Guarantor and correspondent: P.T. Fox, Research Imaging Institute, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive–MC 6240, San Antonio, TX 78229, USA. Tel: +1 (210) 567 8100; fax: +1 (210) 567 8152.
E-mail addresses: florence.l.chiang@gmail.com (F.L. Chiang), fox@uthscsa.edu (P.T. Fox).

https://doi.org/10.1016/j.crad.2019.07.005
0009-9260/Published by Elsevier Ltd on behalf of The Royal College of Radiologists.

Introduction

Multiple sclerosis (MS) is classically described as an inflammatory and demyelinating condition involving the white matter (WM) of the central nervous system.[1] Current clinical magnetic resonance imaging (MRI) methods focus primarily on the enhancement patterns of demyelinating lesions for diagnosis, which show limited correlation with disease progression.[2] Additionally, treatment with immunomodulatory therapy has been found to be partly effective in early MS but inadequate in managing the spectrum of disease subtypes.[1] These limitations in patient management have prompted further research to elucidate the pathophysiology of MS. More recently, MS effects have been shown to involve the grey matter (GM) and appear to be more widespread than previously thought.[3,4] Although inflammation and atrophy have both been found in GM to some degree, neurodegeneration has been described as the primary process that is present throughout the disease course.[3,5] Although the pathological substrate of GM atrophy is as yet unknown, it is evident that GM atrophy is nevertheless a substantial component of MS pathology.

The distribution of GM atrophy in MS has been reported to be focal, involving selective regions, rather than diffuse.[6,7] There is growing evidence that localised atrophy of subcortical structures demonstrates a strong association with cognitive impairment, more so than the WM lesion load.[8,9] Additionally, GM atrophy involving the sensorimotor cortex has been shown to correlate strongly with clinical disability.[6,7,10] Given the difficulty of visualising subtle GM changes, quantitative neuroimaging methods such as voxel-based morphometry (VBM) can be used to characterise GM atrophy on T1-weighted MRI; this analysis, however, is limited to group-wise testing.[11] On the other hand, functional imaging enables analysis at the per-subject level.[12] Furthermore, detection of functional abnormalities may be more sensitive than structural abnormalities.[13,14]

Functional network abnormalities have been described in several neurodegenerative disorders.[15–17] Additionally, brain regions that are selectively vulnerable to GM atrophy have been shown to act as "nodes" in functional networks; this forms the basis for the network degeneration hypothesis (NDH).[17,18] One could then consider the regions affected by GM atrophy as a network and assess the functional relationship between these regions (i.e., functional connectivity). In MS, functional network abnormalities have been demonstrated, but the heterogeneity of study designs and findings necessarily limit their generalisability.[19] Therefore, to test the NDH in MS, there is a need to determine convergent structural and functional changes by: (1) defining localised regions of GM atrophy and (2) creating a functional connectivity model based on these GM regions. To this end, the BrainMap neuroimaging database was used to perform structure-based functional connectivity modelling meta-analytically.[20]

Coordinate-based meta-analysis (CBMA) using BrainMap is a powerful method used to quantify consistent structural brain alterations and determine associated functional network involvement without laboratory bias.[21] The BrainMap environment includes published coordinate-based results data standardised using an x–y–z mapping system of the brain.[20] There are two domains in the database: functional (3,261 publications, 16,158 experiments, 125,588 coordinates, 72,299 patients) and structural (994 publications, 3,151 experiments, 125,588 coordinates, 72,299 patients).[22] This large-scale, data-driven approach mitigates against the limitations faced by individual primary studies with relatively restricted sample sizes. Additionally, CBMA uses data-reduction to circumvent the issue of heterogeneity in the literature. This is accomplished by applying the anatomical likelihood estimation (ALE) algorithm to BrainMap data, which provides statistical rigor in computing significant convergence of neuroimaging results.[14,16,23] ALE first estimates the spatial uncertainty (probability distribution) of each point in coordinate-based data by accounting for inter-subject and inter-laboratory variability typically observed in individual experiments.[23] Then, the algorithm computes the union of spatial probabilities for each voxel and calculates the above-chance clustering of results between experiments (i.e., random-effects analysis). Subsequently, the structural results from ALE can be used in functional meta-analytic connectivity modelling (fMACM) to determine inter-regional co-activation, which is a surrogate for functional connectivity.[24,25] fMACM results are comparable to functional connectivity analyses in healthy controls and have been validated using resting-state functional MRI (fMRI).[24–26] Thus, the disease-specific functional network model derived from this study can be applied directly in primary resting-state fMRI data to characterise functional connectivity abnormalities in MS patients.

The goal of this study was to test the NDH in localised GM atrophy using coordinate-based meta-connectomic modelling techniques.[27] It was hypothesised that in MS (1) GM atrophy would be regionally selective and (2) these affected regions would be connected functionally. This model-based strategy may serve to guide future development of quantitative neuroimaging markers for diagnosis, evaluating disease progression, and monitoring treatment response.

Materials and methods

The study protocol adhered to standard quality criteria of BrainMap CBMA, which is based on the BrainMap metadata coding scheme.[21] This study was also compliant with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[28]

Data sources and searches

VBM publications considered for meta-analysis were identified in BrainMap using Sleuth (Version 2.4, http://www.brainmap.org/sleuth/). The search logic included: (Diagnosis matches "Any"—either MS or clinically isolated syndrome [CIS]) AND (Contrast is GM). To identify

publications not yet in BrainMap, a comprehensive search was performed in PubMed, Science Direct, Web of Knowledge, and Scopus from inception to 19 October 2017 for peer-reviewed English-language journal articles. Keywords for the search included: [("multiple sclerosis" OR "MS"), ("clinically isolated syndrome" OR "CIS")] AND [("voxel-based morphometry" OR "VBM" OR "voxelwise")]. Referenced publications were also searched for additional sources of data. Papers that included x–y–z coordinate-based data in Montreal Neurological Institute (MNI) or Talairach space were coded and submitted to BrainMap using Scribe (Version 3.0, http://www.brainmap.org/scribe/). Submitted papers were published in the database after thorough review and quality control by dedicated support staff.[21]

Study selection

VBM publications identified in BrainMap were reviewed systematically (Fig 1). The data were screened for duplication at the paper and experiment level. An experiment is defined as a group contrast resulting in a statistical parametric map. Particular attention was paid to publications by the same authors to avoid redundancy of datasets. Eligibility criteria were applied for study inclusion: whole-brain VBM analysis, results demonstrating GM atrophy, and group contrast of MS or CIS with healthy controls.

Data extraction from BrainMap

Coordinate-based data were exported from BrainMap in MNI standard space using Sleuth (Version 2.4, http://www.brainmap.org/sleuth/) for ALE analysis. Coordinates originally in Talairach standard space were transformed with *icbm2tal*, which minimises spatial disparity between Talairach and MNI coordinates, thus facilitating accuracy of CBMA.[29]

Data synthesis and analysis

ALE

ALE analysis was performed to determine a consistent pattern of GM atrophy in MS (GingerALE 2.3.6, http://www.brainmap.org/ale/). The defined regions of atrophy (i.e.

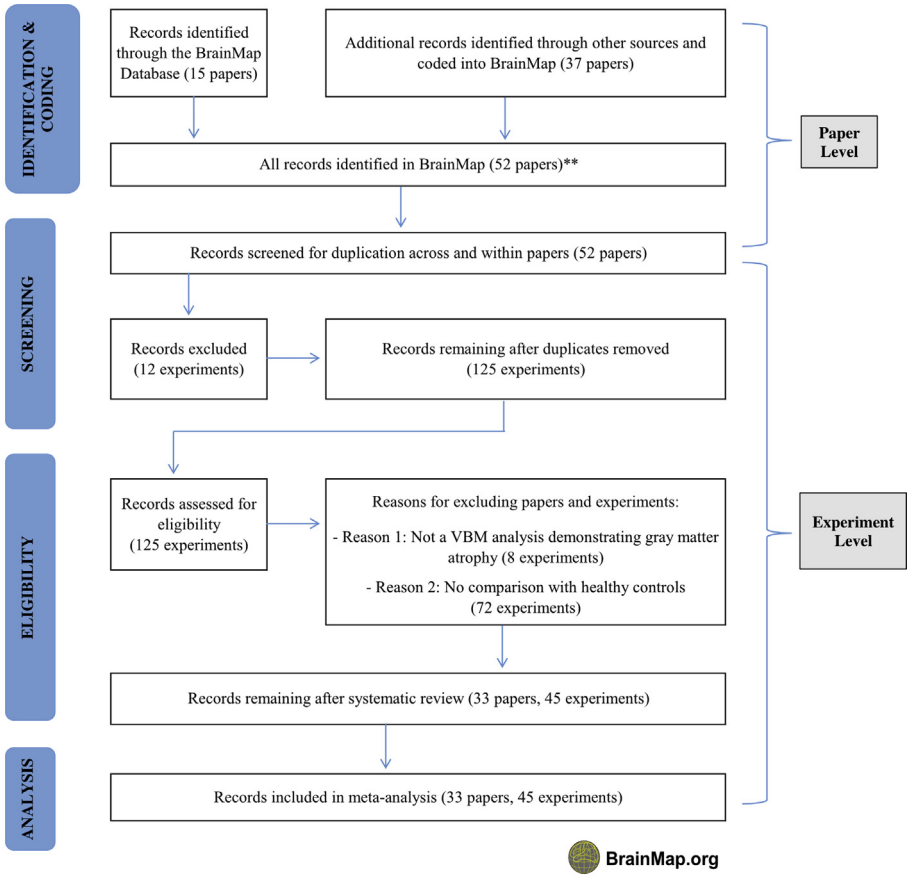

Figure 1 Systematic review and study selection in coordinate-based meta-analysis. Published voxel-based morphometry studies in MS and clinically isolated syndrome were systematically reviewed for inclusion in the meta-analysis. Study selection adhered to standard quality criteria of BrainMap coordinate-based meta-analysis in addition to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. **Data included in this step has already been screened for region-of-interest data—only whole-brain coordinate results are coded into the BrainMap database.

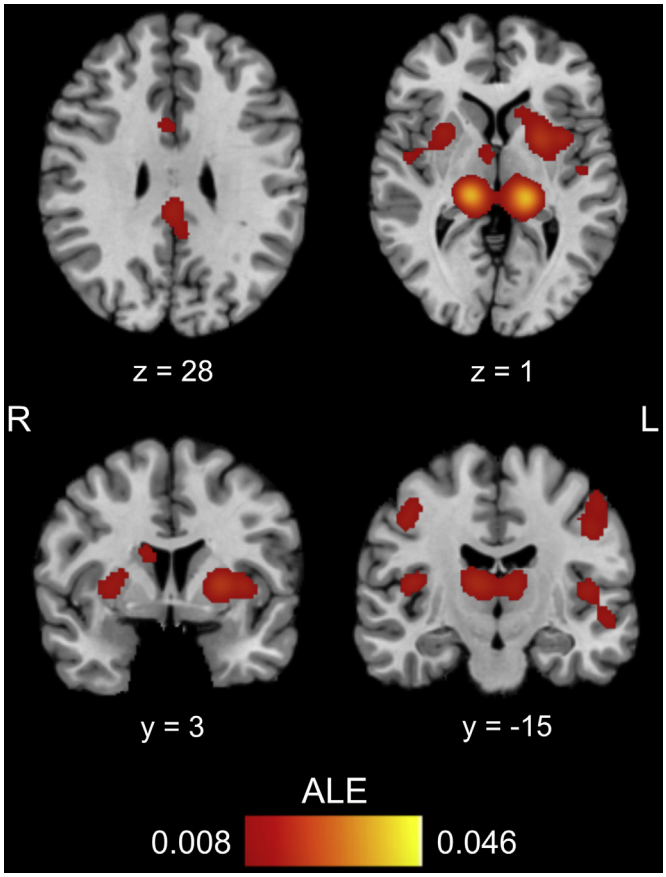

Figure 2 Anatomical likelihood estimation (ALE) atrophy map. A convergent pattern of GM atrophy was identified in MS. Regionally selective neurodegeneration affected both cortical and subcortical structures: bilateral thalamic pulvinar, right thalamic medial dorsal nucleus, right caudate body, left caudate head, right anterior cingulate cortex, left posterior cingulate cortex, left claustrum, bilateral insula, bilateral putamen, bilateral precentral gyrus, bilateral postcentral gyrus, and left superior temporal gyrus. ALE results were family-wise error corrected with a cluster-forming threshold of $p<0.001$ and cluster-level inference of 0.05. Results were overlaid on the Colin27 brain template in Montreal Neurological Institute coordinate space.

atrophy seeds/nodes) then served as regions-of-interest (ROIs) in the subsequent fMACM analysis. The ALE algorithm treats each coordinate as a Gaussian probability distribution to account for spatial uncertainty.[23] A whole-brain statistical parametric map was created by calculating the spatial convergence (i.e. above-chance clustering) of coordinates within and across experiments.[30] Each voxel was assigned an ALE value to reflect the union of these probabilities after mass univariate testing.[23] The statistical significance threshold was determined with a Monte Carlo-based approach to permutation testing.[23,30] To minimise within-experiment and within-group effects, the optimised ALE algorithm was used, which allows the ALE values to more accurately reflect the degree of foci convergence across studies.[31]

The ALE maxima of the cluster results were modelled as three-dimensional (3D) Gaussian point-spread functions to account for error in spatial localisation, and the full-width half-maximum of the Gaussians were calculated with the random-effects approach, which scales spatial uncertainty with sample size.[30] Thus, ALE results would be weighted more reasonably toward experiments with larger sample sizes.[30] To avoid overcorrection resulting in an inappropriately small full-width half-maximum, 4 mm was applied to the ALE settings for the VBM dataset.

Each publication utilised voxel-wise group-level comparisons, the methods of which are well-described.[11] The most common source of bias within individual studies was small sample size, which is corrected for in the ALE algorithm.[31] Failure to report negative findings (file-drawer effect) is a form of publication bias that is problematic for meta-analytic computations of effect size but inconsequential for CBMA, which compute cross-study convergence.[32] False-positive effects, on the other hand, are a serious problem for functional neuroimaging, for which CBMA offers a robust solution.[33,34]

fMACM

fMACM was utilised to assess for functional connectivity involving regions of GM atrophy in a multivariate manner.[24] Seed-to-whole-brain and region-to-region analyses were performed for ROIs defined at atrophy seeds/nodes, which were centred at local ALE maxima from the VBM ALE analysis. For seed-to-whole brain fMACM, whole-brain co-activation was tested for each atrophy seed; the co-activation images were then binarised and added spatially using the Multi-image Analysis GUI software (Mango; http://ric.uthscsa.edu/mango/). Additionally, region-to-region fMACM was performed for each atrophy seed to identify the most significant functional co-activations. An ROI diameter of 10 mm was used for all fMACM analyses, which follows updated guidelines for performing a valid ALE analysis with cluster-level thresholding.[35] The fMACM model was constructed using task-evoked fMRI and positron-emission tomography (PET) activations-only data from healthy controls within BrainMap (2,395 publications, 9,007 experiments, 76,252 coordinates, 39,268 patients, 8,724 conditions).

Data availability

The year of publication, first author, journal, and unique BrainMap identification number of all publications in this meta-analysis are provided in Electronic Supplementary Material Table S1 to allow replication of findings.

Results

Study inclusion and characteristics

Thirty-three publications with 45 experiments were included in the VBM ALE analysis (Electronic Supplementary Material Table S1), which included 562 coordinates and 2,935 patients (1,666 MS patients and 1,269 healthy controls). The dataset fulfils the ALE-specific criteria for determining sufficient power to detect moderate effects, which requires at least 20 experiments within each dataset.[35] Initially, 15 publications were identified in BrainMap;

Table 1
Anatomical likelihood estimation (ALE) clusters.

Cluster no.	Volume (mm^3)	Seed/node no.	Anatomical regions	Maximum ALE value ($\times 10^{-3}$)	MNI coordinates of local maxima		
					x	y	z
1	29,824	1	Right thalamus, pulvinar	45.8	14	−26	6
		2	Left thalamus, pulvinar	38.0	−14	−28	4
		3	Right thalamus, mediodorsal nucleus	15.9	2	−8	10
		4	Right caudate, body	12.9	14	10	18
		5	Right anterior cingulate cortex, BA 24	9.5	4	8	28
2	7,768	6	Left lentiform nucleus, putamen	18.0	−24	4	2
		7	Left claustrum	14.0	−34	4	2
		8	Left caudate, head	11.6	−12	18	−4
3	4,960	9	Right insula, BA 13	13.5	42	−16	10
		10	Right lentiform nucleus, putamen	12.1	30	6	0
4	4,792	11	Right precentral gyrus, BA 4	13.9	46	−12	40
		12	Right postcentral gyrus, BA 3	13.4	42	−22	50
5	4,208	13	Left precentral gyrus, BA 4	12.1	−46	−14	38
		14	Left postcentral gyrus, BA 2	11.4	−54	−26	44
6	2,112	15	Left insula, BA 13	12.5	−44	−14	6
		16	Left superior temporal gyrus, BA 22	10.8	−54	−14	−8
7	2,040	17	Left posterior cingulate cortex, BA 23	12.8	0	−34	26
8	1,128	-	Right middle frontal gyrus, BA 9	12.5	48	18	30

Convergent findings of localised grey matter atrophy in multiple sclerosis were demonstrated as clusters. Each cluster contained one or more local ALE maxima in distinct anatomical regions, which were used to define regions-of-interest in functional meta-analytic connectivity modelling. The right middle frontal gyrus demonstrated focal atrophy but did not reach the specified level of significance with cluster-level thresholding.
BA, Brodmann area, MNI, Montreal Neurological Institute.

however, after an exhaustive search of online databases, an additional 37 publications were coded into BrainMap. A search of referenced publications did not yield additional sources of data. Twelve experiments were removed with screening procedures for duplication. Application of eligibility criteria excluded 80 experiments in total. All included studies were prospective, and MRI acquisition was evenly distributed on 1.5 and 3 T MRI machines. There were on

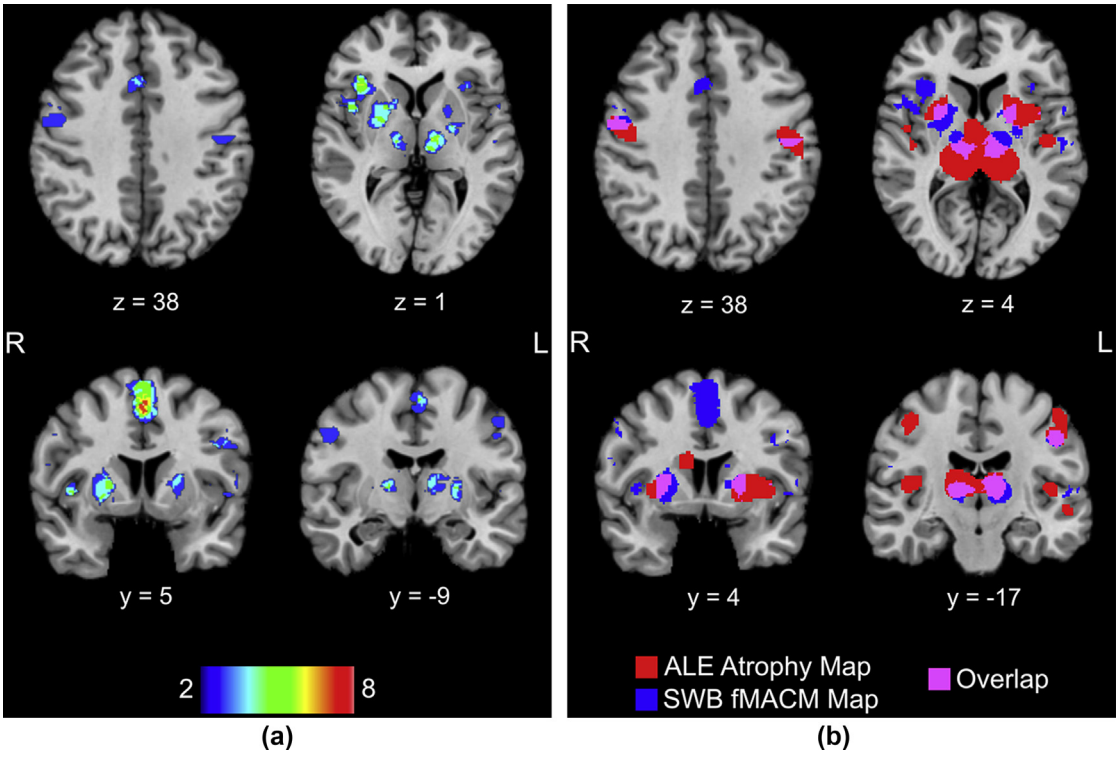

Figure 3 Seed-to-whole-brain (SWB) functional meta-analytic connectivity modelling (fMACM) map. (a) Composite SWB co-activation. The SWB fMACM map was created by binarising and spatially adding SWB results of all atrophy seeds. The number of connections to each seed region ranged from 2 to 8. (b) Restriction of SWB co-activation. Whole-brain co-activations were localised to regions of GM atrophy in MS. Results were overlaid on the Colin27 brain template in Montreal Neurological Institute coordinate space.

average 33 patients per group (range=6–249) with a female predominance and an average age range of 23–54 years. The included papers were published between the years of 2006 and 2017 (mean=2011).

ALE results

A localised GM atrophy pattern was found to involve both subcortical and cortical structures in MS (Fig 2; Table 1). These regional effects were demonstrated by seven ALE clusters, with each containing at least one ALE maximum. ALE maxima (in x–y–z coordinates) were found in the bilateral thalamic pulvinar, right thalamic medial dorsal nucleus, right caudate body, left caudate head, right anterior cingulate cortex, left posterior cingulate cortex, left claustrum, bilateral insula, bilateral putamen, bilateral precentral gyrus, bilateral postcentral gyrus, and left superior temporal gyrus. These ALE maxima demonstrated peak convergence of coordinate-based data and were utilised to define the atrophy seeds. Additionally, a cluster was found in the right middle frontal gyrus, which fell just short of the significance threshold. Results were family-wise error corrected for multiple comparisons with a cluster-level inference of 0.05 (cluster-forming threshold, $p<0.001$; number of permutations=1,000), which are the recommended ALE settings.[34,35]

fMACM results

Significant cortico-cortical and subcortico-cortical co-activation patterns involving atrophy seeds were identified. Seed-to-whole-brain fMACM results demonstrated co-activations in regions that were consistently atrophied (cluster-forming threshold=0.05, $p<0.001$; number of permutations=1,000); at least two co-activations involve each region of GM atrophy (Fig 3a). Conversely, GM regions without atrophy did not demonstrate significant co-activation with the atrophy seeds (Fig 3b). Region-to-region fMACM testing quantified the co-activations as a connectivity matrix ($-2.07<z<8.21$; Fig 4a). The inter-regional co-activation results were Bonferroni-corrected ($p<0.001$, $z>2.97$) for 34 co-activations (Table 2).[36] The most significant co-activations ($z>5.00$) were identified as follows: left precentral gyrus and right precentral gyrus, right putamen and left putamen, left precentral gyrus and left putamen, left claustrum and left putamen, as well as right putamen and left claustrum. Significant co-activations with $4.00<z<5.00$ were demonstrated between homotopic anatomical structures in the insula and thalamic pulvinar. Additionally, several co-activations were noted with $3.00<z<4.00$: right medial dorsal nucleus and left putamen,

Table 2
Region-to-region functional meta-analytic connectivity modelling (fMACM) co-activations.

Seed	Meta-analytic co-activation (*z*)	Node
L Pre	8.43	R Pre
R Put	7.13	L Put
L Pre	6.57	L Put
L Claus	6.01	L Put
R Put	5.17	L Claus
R Ins	4.44	L Ins
R Pulv	4.19	L Pulv
R MDN	3.80	L Put
L Pre	3.67	R Put
R Pre	3.59	L Put
L Post	3.22	L Pulv
R MDN	3.20	R Pulv
L Post	3.18	R Post
R Post	2.97	R Pre

Significant co-activations involved localised regions of grey matter atrophy in multiple sclerosis ($p<0.001$, $z>2.97$, corrected for multiple comparisons). Network seed and node abbreviations: right, R; left; L; precentral gyrus, Pre; postcentral gyrus, Post; insula, Ins; claustrum, Claus; thalamic pulvinar, Pulv: thalamic medial dorsal nucleus, MDN; putamen, Put.

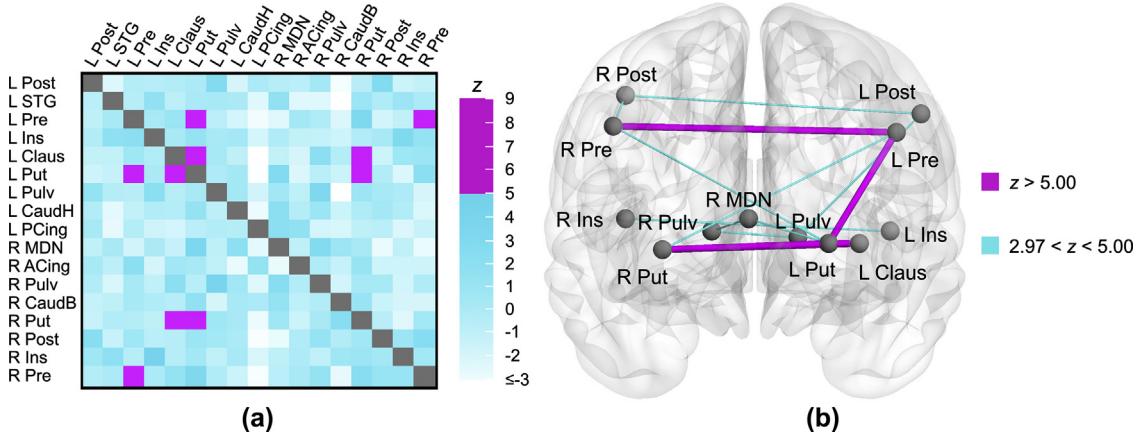

Figure 4 Region-to-region fMACM co-activations. (a) fMACM connectivity matrix. Inter-regional co-activations were present in GM affected by atrophy in MS. The most significant co-activations are highlighted ($z>5.00$). (b) fMACM node-and-edge model. Functional connectivity between regions of atrophy were demonstrated ($p<0.001$, $z>2.97$, corrected for multiple comparisons). The most significant results indicate involvement of the corticostriatal network ($z>5.00$). These paths can be tested as predictors of disease-related changes in resting-state fMRI, which are intended to guide future diagnostic algorithm development. Network seed and node abbreviations: right, R; left; L; precentral gyrus, Pre; postcentral gyrus, Post; insula, Ins; claustrum, Claus; thalamic pulvinar, Pulv; thalamic medial dorsal nucleus, MDN; putamen, Put; superior temporal gyrus, STG; head of caudate, CaudH; body of caudate, CaudB; posterior cingulate cortex, PCing; anterior cingulate cortex, ACing.

left precentral gyrus and right putamen, right precentral gyrus and left putamen, left postcentral gyrus and left pulvinar, right medial dorsal nucleus and right pulvinar, as well as left postcentral gyrus and right postcentral gyrus. Co-activation remained significant but relatively weaker between the right postcentral gyrus and right precentral gyrus. Region-to-region fMACM results were visualised as a node-and-edge model in BrainNet Viewer (Fig 4b).[36]

Discussion

In this two-stage meta-analysis in MS, both hypotheses were confirmed. First, this study demonstrated that GM atrophy was regionally selective; and second, that these brain regions were connected functionally. The present findings suggest that neurodegeneration in MS does not occur randomly. Moreover, the functional organisation of these regions may provide an explanation for localised GM atrophy in MS. By using CBMA, a data-driven functional network model was created. This laboratory non-specific analytic prior is intended to guide future targeted quantitative analysis of primary datasets in MS.

Convergent pattern of regionally selective GM atrophy

A pattern of localised GM atrophy was identified cortically and subcortically, predominantly involving the thalamus, basal ganglia, sensorimotor cortex, and cingulate gyrus. This ALE pattern of atrophy is highly similar to that reported in other recent studies; that is, the effects converge with prior studies describing regional selectivity of GM atrophy.[6,7] Although the pathophysiology of localised GM atrophy in MS is unclear, several causes have been suggested, including: cerebrospinal fluid (CSF)-mediated inflammation of GM; axonal transection leading to trans-synaptic degeneration; cytotoxic tissue damage secondary to lymphoid tissue formation; neuronal mitochondrial dysfunction; and antigenic variability in neuronal sub-populations.[4,5,37–39] Although these theories are plausible, they do not fully account for the specific pattern of localised GM atrophy. Therefore, this study focused on testing the NDH, which addresses regional GM atrophy at the whole-brain level.

Functional connectivity involving regions of GM atrophy

Using disease-specific nodes (from the ALE analysis), functionally covariant GM regions were observed in healthy controls using fMACM. This suggests that these regions are members of a functional network that is selectively attacked by MS. Although the fMACM model does not indicate functional abnormality in MS, the results do describe the healthy functional organisation of these nodes.[26,40] This model-based hypothesis could be tested with the expectation that the model fit would be degraded in MS.[24,25]

To validate the fMACM model, a seed-to-whole-brain analysis was performed, followed by a region-to-region analysis. The seed-to-whole-brain approach ensured that the fMACM results were not biased by restriction to predefined nodes. The region-to-region analysis quantified connectivity strength per path. The present findings indicate a pattern of co-activation involving GM regions that were consistently affected by atrophy. Further, GM not affected by atrophy did not display significant co-activation with the atrophy seeds; that is, co-activations were restricted to regions of atrophy. Thus, the fMACM model supports the notion that localised GM atrophy in MS is network-based.

The NDH emerged from observations in neurodegenerative disorders causing cognitive and motor performance degradation. Distinct, non-random, disease-specific atrophy patterns were observed in Alzheimer's disease, frontotemporal dementia, and Parkinson's disease; in each instance, the affected brain regions appeared to be functionally connected, i.e., form functional networks.[17,41] These observations have been interpreted to mean that GM atrophy in degenerative disorders is network-based. In MS, the concept of "hubs" (i.e. nodes that are more connected to other nodes) has been suggested as an explanation of the non-random atrophy pattern, a possible extension of the NDH.[18] The implication is that GM atrophy initially affects hub regions and subsequently involves functionally connected non-hub brain regions; however, validation of this temporal sequence would necessitate longitudinal evaluations. Additionally, it has been suggested that WM pathology may drive the initial atrophy at the local level in hub regions, which then has "second-order effects" resulting in atrophy of functionally connected brain areas.[6] The present results are in line with this concept, wherein the second-order effects are facilitated by network connectivity between regions of localised GM atrophy; however, the initial involvement of WM pathology is unlikely to fully capture the pathophysiology of MS given the limited correlation of WM lesions with clinical progression.[5–10] All in all, the NDH seems to be a reasonable consideration for explaining the pathophysiology of non-random GM atrophy in MS.

Structurally-based functional network involvement

Current literature indicates impaired signal transmission in cortico-subcortical functional networks in MS, which has been linked to physical disability and cognitive dysfunction.[10,42] Specifically, it has been reported that the cortico-striatal network may be affected, which is compatible with the motor, cognitive, and affective symptom profile in MS.[1,43–47] The present fMACM results support these previous observations given the highly significant functional connectivity of the putamen with the primary motor cortex and thalamus. Neuro-anatomically, the cortico-striatal-thalamo-cortical circuitry involves projections from multiple cortical regions to the basal ganglia; the striatum—composed of the caudate, putamen, and nucleus accumbens—serves as the primary input structure.[47] Efferent signals are then relayed to specific cortical regions.[46] A commonly accepted functional model of the basal ganglia involves topographically organised and functionally segregated circuitry, with the final segment terminating in

motor, cognitive, and limbic cortical regions.[25,46–48] Additionally, functional parcellation of the striatum has demonstrated distinct functional connectivity profiles for each striatal sub-region.[43] Further, CBMA and neurophysiological studies have characterised the striatal functional distribution as exhibiting a ventro-dorsal gradient with cognitive–motor topology[25,49]; however, it has been suggested that there is complex integration of information across functional subdivisions of the basal ganglia prior to information output back to the frontal cortex.[46,49,50] Therefore, although the fMACM results suggest that the motor component of the corticostriatal network is involved in MS, cognitive and limbic processes may also play a role in refining motor function prior to the execution of goal-directed behaviors.[46,47]

The motor component of the corticostriatal network has been reported to receive projections from several cortical areas including the primary motor, supplementary motor, premotor, and somatosensory cortices.[46,49] In resting-state fMRI of MS, increased functional connectivity of the premotor area and dorsal caudal putamen appears to be associated with motor decline as demonstrated by positive correlation with the Expanded Disability Status Scale.[43] Additionally, there is evidence to suggest that the corticostriatal network is affected in postural adaptation as well as acquisition and retention of motor skills in MS.[51] These prior findings are supported neuro-anatomically in that brain regions receiving subcortical output includes the supplementary motor area, which is important in programming and control of movement.[48] Taken together with these observations, the present results suggest that motor integration may be affected in MS due to involvement of the corticostriatal network.

Clinical implications

Although conventional MRI methods provide valuable clinical information *in vivo*, more advanced techniques are necessary to improve standard-of-care imaging in MS and solidify our understanding of the neurodegenerative pathophysiology. Currently, clinical imaging relies on lesion detection using T1-and T2-weighted techniques; however, due to the recent reports of GM atrophy in MS, it is evident that there is a need for more sensitive imaging methods to characterise neurodegenerative changes.[52] Given that GM atrophy is not readily apparent on visual assessment, quantitative neuroimaging analysis offers improved evaluation of GM pathology. For analysis of T1-weighted MRI, VBM can identify subtle focal GM atrophy, but this technique is limited in that only group-level comparisons are achievable.[11] On the other hand, analysis of fMRI has the potential to enrich the imaging-based armamentarium in the clinical setting via individualised evaluation. To this end, functional connectivity measures can be examined using fMRI time series data to provide per-subject level information.[12] Additionally, it has been shown that fMRI is a more sensitive method in detecting abnormalities when compared with structural imaging, which may help diagnose MS earlier in the course of disease or pre-clinically.[13,14,41] Nevertheless, to avoid laboratory-specific bias, the development of a functional imaging tool would benefit from a meta-analytic model-based approach prior to analysis of primary functional imaging data.

In this study, ALE and fMACM were used sequentially to characterise consistent findings from existing primary studies, the results of which can be applied step-wise in primary fMRI data.[20] This modelled approach provides a selection of quantitative imaging measures that could be incorporated into diagnostic algorithms to enhance clinical evaluation of MS patients. Specifically, the most significant functional co-activations from fMACM can be tested as predictors of disease-related change in resting-state fMRI. fMACM has been validated in resting-state fMRI data and can be applied directly in imaging results of MS patients and healthy controls.[24–26] Using this technique, a functional connectivity model with improved generalisability was constructed, which capitalises on an extensive compilation of published neuroimaging literature and addresses the limited sample sizes of individual primary studies.[21] In contrast to task-based fMRI, utilisation of resting-state fMRI is well-suited for the clinical setting and has the benefit of evaluating network-based changes without the complexity of task-performance testing or the confounding effects of task-performance variation.[53] Further, it has been shown that brain activity during activation and rest are correspondent, as demonstrated by a study comparing results of independent component analysis using BrainMap task-based fMRI data and primary resting-state fMRI data.[40] Therefore, the co-activation pattern determined by fMACM can guide subsequent analysis of resting-state fMRI data to characterise functional connectivity changes in MS.

Limitations

Several limitations were associated with included publications of the meta-analysis. First, there is currently no consensus on the best approach for connectivity analysis (e.g., seed-based versus independent components analysis), and some have proposed a hybrid approach in defining seeds.[54] Similarly, ALE, a non-model restricted approach, was used to identify the seeds used in the subsequent fMACM analysis, which may improve robustness of the seed-based connectivity analysis. Second, network laterality may be dependent on characteristics of the meta-data, which is more robust than a single study but may not detect all brain networks. Although it is uncertain whether hemispheric activation bias exists in resting-state data, independent component analysis of the BrainMap literature does not demonstrate such asymmetry.[40] Third, nodal proximity may also affect connectivity analysis. The co-activations of closely located ROIs could be a result of synchronous signal fluctuation or artefact of the ALE smoothing algorithm that considers the two ROIs as similar in anatomical location.[30] Fourth, there was variation in the analytic methods employed in the meta-data. Although GM volumes may vary between different analytic methods, group-level comparisons between MS and healthy controls have demonstrated comparable results.[55] Fifth, data acquisition was not

harmonised given the meta-analytic nature of the study, the differences of which may affect the results of brain tissue classification; however, results from multicentre studies have shown negligible differences relative to neurodegenerative disease when there is on-site imaging acquisition of both experimental and control groups.[56,57] Lastly, CBMA is an effect location meta-analysis, which is more robust to inter-laboratory methodological variation than effect size meta-analyses or pooling of primary data.

Future directions

The results of this study encourage future work in networked-based imaging biomarker development. It has been suggested that structural and functional covariance patterns may be closely related.[15] The correspondence between structure and function has been described by network-based trophic influences that may shape structural modification of the brain.[17,58] More recently, a longitudinal study in MS reported that structurally and functionally related brain regions may demonstrate accelerated tissue loss in patients who progress in clinical disability.[8] Furthermore, it has been shown that structural covariance of localised regions of the brain could be detected prior to overt atrophy.[59] Given the limitations in identifying GM atrophy patterns at a per-subject level, particularly in early disease, structural covariance may serve as an alternative imaging-based measure of regionally selective neurodegeneration in MS.[13,60] Other considerations may be to refine the meta-analytic models by applying connectivity-based parcellation and behavioural filtering to BrainMap data; this would improve targeted functional connectivity testing in primary data via identification of pertinent clinical features.[25,61] Altogether, further work using network-based approaches may offer additional insights into the pathophysiology of localised GM atrophy in MS and improve clinical management.

In conclusion, GM atrophy in MS affected localised brain regions that were functionally connected. This study identified consistent, regionally selective neurodegenerative changes and characterised the inter-regional co-activations meta-analytically. The functional network model serves as a framework for future quantitative analysis of per-subject resting-state fMRI data. Such individualised imaging metrics should inform future diagnostic and prognostic imaging marker development strategies.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by grant funding from the National Institutes of Health (R01MH074457, R25EB016631, and K23NS096056) and Radiological Society of North America (RR1826). The authors thank Crystal Franklin, Eithan Kotkowski, Thomas J. Vanasse, Jodie Grey, and Wei Zhang for advice and feedback on project design. The authors also thank Michaela Robertson, Angela M. Uecker, and Janaye Dews for BrainMap support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2019.07.005.

References

1. Noseworthy J, Lucchinetti C, Rodriguez M, *et al*. Multiple sclerosis. *New Engl J Medici* 2000;**343**(13):938–52. https://doi.org/10.1056/NEJM200009283431307.
2. Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited. *Curr Opin Neurol* 2002;**15**(3):239–45.
3. Klaver R, De Vries HE, Schenk GJ, *et al*. Grey matter damage in multiple sclerosis: a pathology perspective. *Prion* 2013;**7**(1):66–75. https://doi.org/10.4161/pri.23499.
4. Wegner C, Esiri MM, Chance SA, *et al*. Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. *Neurology* 2006;**67**(6):960–7. https://doi.org/10.1212/01.wnl.0000237551.26858.39.
5. Calabrese M, Magliozzi R, Ciccarelli O, *et al*. Exploring the origins of grey matter damage in multiple sclerosis. *Nat Publ Gr* 2015;**16**(3):147–58. https://doi.org/10.1038/nrn3900.
6. Steenwijk MD, Geurts JJG, Daams M, *et al*. Cortical atrophy patterns in multiple sclerosis are non-random and clinically relevant. *Brain A J Neurol* 2016;**139**(Pt 1):115–26. https://doi.org/10.1093/brain/awv337.
7. Lansley J, Mataix-Cols D, Grau M, *et al*. Localized grey matter atrophy in multiple sclerosis: a meta-analysis of voxel-based morphometry studies and associations with functional disability. *Neurosci Biobehav Rev* 2013;**37**(5):819–30. https://doi.org/10.1016/j.neubiorev.2013.03.006.
8. Bergsland N, Horakova D, Dwyer MG, *et al*. Grey matter atrophy patterns in multiple sclerosis: a 10-year source-based morphometry study. *NeuroImage Clin* 2018;**17**(November 2017):444–51. https://doi.org/10.1016/j.nicl.2017.11.002.
9. Gouveia A, Dias SP, Santos T, *et al*. Cognitive impairment and magnetic resonance imaging correlates in primary progressive multiple sclerosis. *Acta Neurol Scand* 2017;**136**(2):109–15. https://doi.org/10.1111/ane.12702.
10. Schoonheim MM, Geurts J, Wiebenga OT, *et al*. Changes in functional network centrality underlie cognitive dysfunction and physical disability in multiple sclerosis. *Mult Scler* 2014;**20**(8):1058–65. https://doi.org/10.1177/1352458513516892.
11. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *Neuroimage* 2000;**11**(6 Pt 1):805–21. https://doi.org/10.1006/nimg.2000.0582.
12. Tahedl M, Levine SM, Greenlee MW, *et al*. Functional connectivity in multiple sclerosis: recent findings and future directions. *Front Neurol* 2018;**9**(October):1–18. https://doi.org/10.3389/fneur.2018.00828.
13. Barron DS, Fox PT, Pardoe H, *et al*. Thalamic functional connectivity predicts seizure laterality in individual TLE patients: application of a biomarker development strategy. *NeuroImage Clin* 2015;**7**:273–80. https://doi.org/10.1016/j.nicl.2014.08.002.
14. Barron DS, Fox PM, Laird AR, *et al*. Thalamic medial dorsal nucleus atrophy in medial temporal lobe epilepsy: a VBM meta-analysis. *NeuroImage Clin* 2013;**2**(1):25–32. https://doi.org/10.1016/j.nicl.2012.11.004.
15. Kotkowski E, Price LR, Mickle Fox P, *et al*. The hippocampal network model: a transdiagnostic metaconnectomic approach. *NeuroImage Clin* 2018;**18**(January):115–29. https://doi.org/10.1016/j.nicl.2018.01.002.
16. Yu F, Barron DS, Tantiwongkosi B, *et al*. Patterns of grey matter atrophy in atypical Parkinsonism syndromes: a VBM meta-analysis. *Brain Behav* 2015;**5**(6):1–10. https://doi.org/10.1002/brb3.329.
17. Seeley WW, Crawford RK, Zhou J, *et al*. Neurodegenerative diseases target large-scale human brain networks. *Neuron* 2009;**62**(1):42–52. https://doi.org/10.1016/j.neuron.2009.03.024.
18. Chard DT, Miller DH. What lies beneath grey matter atrophy in multiple sclerosis? *Brain* 2016;**139**(1):7–10. https://doi.org/10.1093/brain/awv354.

19. Klawiter EC. Current and new directions in MRI in multiple sclerosis. *Contin Lifelong Learn Neurol* 2013;**19**(4):1058–73. https://doi.org/10.1212/01.CON.0000433283.00221.37.
20. Fox PT, Lancaster JL. Mapping context and content: the BrainMap model. *Nat Rev Neurosci* 2002;**3**(4):319–21. https://doi.org/10.1038/nrn789.
21. Fox PT, Laird AR, Fox SP, *et al*. BrainMap taxonomy of experimental design: description and evaluation. *Hum Brain Mapp* 2005;**25**(1):185–98. https://doi.org/10.1002/hbm.20141.
22. Fox PT, Lancaster JL, Laird AR, *et al*. Meta-analysis in human neuroimaging: computational modelling of large-scale databases. *Annu Rev Neurosci* 2014;**37**:409–34. https://doi.org/10.1146/annurev-neuro-062012-170320.
23. Eickhoff SB, Bzdok D, Laird AR, *et al*. Activation likelihood estimation meta-analysis revisited. *Neuroimage* 2012;**59**(3):2349–61. https://doi.org/10.1016/j.neuroimage.2011.09.017.
24. Robinson JL, Laird AR, Glahn DC, *et al*. Metaanalytic connectivity modelling: delineating the functional connectivity of the human amygdala. *Hum Brain Mapp* 2010;**31**(2):173–84. https://doi.org/10.1002/hbm.20854.
25. Robinson JL, Laird AR, Glahn DC, *et al*. The functional connectivity of the human caudate: an application of meta-analytic connectivity modelling with behavioral filtering. *Neuroimage* 2012;**60**(1):117–29. https://doi.org/10.1016/j.neuroimage.2011.12.010.
26. Reid AT, Hoffstaedter F, Gong G, *et al*. A seed-based cross-modal comparison of brain connectivity measures. *Brain Struct Funct* 2017;**222**(3):1131–51. https://doi.org/10.1007/s00429-016-1264-3.
27. Crossley NA, Fox PT, Bullmore ET. Meta-connectomics: human brain network and connectivity meta-analyses. *Psychol Med* 2016;**46**(5):897–907. https://doi.org/10.1017/S0033291715002895.
28. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**, https://doi.org/10.1136/bmj.b2700.
29. Laird AR, Robinson JL, Mcmillan KM, *et al*. Comparison of the disparity between Talairach and MNI coordinates in functional neuroimaging data: validation of the Lancaster transform. *Neuroimage* 2011;**51**(2):677–83. https://doi.org/10.1016/j.neuroimage.2010.02.048.
30. Eickhoff S, Laird A, Grefkes C, *et al*. Coordinate-based ALE meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp* 2009;**30**(9):2907–26. https://doi.org/10.1002/hbm.20718.
31. Turkeltaub PE, Eickhoff SB, Laird AR, *et al*. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Hum Brain Mapp* 2012;**33**(1):1–13. https://doi.org/10.1080/10937404.2015.1051611.
32. Fox PT, Parsons LM, Lancaster JL. Beyond the single study: function/location metanalysis in cognitive neuroimaging. *Curr Opin Neurobiol* 1998;**8**(2):178–87.
33. Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci U S A* 2016;**113**(28):7900–5. https://doi.org/10.1073/pnas.1602413113.
34. Eickhoff SB, Laird AR, Fox PM, *et al*. Implementation errors in the GingerALE software: description and recommendations. *Hum Brain Mapp* 2017;**38**(1):7–11. https://doi.org/10.1002/hbm.23342.
35. Eickhoff SB, Nichols TE, Laird AR, *et al*. Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. *Neuroimage* 2016;**137**:70–85. https://doi.org/10.1016/j.neuroimage.2016.04.072.
36. Xia M, Wang J, He Y, *et al*. BrainNet Viewer: a network visualization tool for human brain connectomics. *PLoS One* 2013;**8**(7):e68910, https://doi.org/10.1371/journal.pone.0068910.
37. Witte ME, Mahad DJ, Lassmann H, *et al*. Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis. *Trends Mol Med* 2014;**20**(3):179–87. https://doi.org/10.1016/j.molmed.2013.11.007.
38. Treaba CA, Granberg TE, Sormani MP. Longitudinal characterization of cortical lesion development and evolution in multiple sclerosis. *Radiology* 2019, https://doi.org/10.1148/radiol.2019181719.
39. Magliozzi R, Howell OW, Reeves C, *et al*. A gradient of neuronal loss and meningeal inflammation in multiple sclerosis. *Ann Neurol* 2010;**68**:477–93. https://doi.org/10.1002/ana.22230.
40. Smith SM, Fox PT, Miller KL, *et al*. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A* 2009;**106**(31):13040–5. https://doi.org/10.1073/pnas.0905267106.
41. Yu F, Barron DS, Tantiwongkosi B, *et al*. Characterisation of meta-analytical functional connectivity in progressive supranuclear palsy. *Clin Radiol* 2018;**73**(4):415.e1–7. https://doi.org/10.1016/j.crad.2017.11.007.
42. Dogonowski A-M, Siebner HR, Sørensen PS, *et al*. Expanded functional coupling of subcortical nuclei with the motor resting-state network in multiple sclerosis. *Mult Scler* 2013;**19**(5):559–66. https://doi.org/10.1177/1352458512460416.
43. Cui F, Zhou L, Wang Z, *et al*. Altered functional connectivity of striatal subregions in patients with multiple sclerosis. *Front Neurol* 2017;**8**:129. https://doi.org/10.3389/fneur.2017.00129.
44. Tortorella C, Romano R, Direnzo V, *et al*. Load-dependent dysfunction of the putamen during attentional processing in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Mult Scler J* 2013;**19**(9):1153–60. https://doi.org/10.1177/1352458512473671.
45. Finke C, Schlichting J, Papazoglou S, *et al*. Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. *Mult Scler* 2015;**21**(7):925–34. https://doi.org/10.1177/1352458514555784.
46. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits — neural substrates of parallel processing. *Trends Neurosci* 1990;**13**(7):266–71.
47. Haber SN. Corticostriatal circuitry. *Dialogues Clin Neurosci* 2016;**18**(1):7–21. https://doi.org/10.1007/978-3-642-40308-8_2.
48. Middleton FA, Strick PL. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. *Brain Cogn* 2000;**42**(2):183–200. https://doi.org/10.1006/brcg.1999.1099.
49. Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 2000;**20**(6):2369–82.
50. Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 1980;**14**(2–3):69–97. https://doi.org/10.1016/0301-0082(80)90018-0.
51. Fling BW, Dutta GG, Horak FB. Functional connectivity underlying postural motor adaptation in people with multiple sclerosis. *NeuroImage Clin* 2015;**8**:281–9. https://doi.org/10.1016/j.nicl.2015.04.023.
52. Thompson AJ, Banwell BL, Barkhof F, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;**17**(2):162–73. https://doi.org/10.1016/s1474-4422(17)30470-2.
53. Damoiseaux JS, Rombouts S a RB, Barkhof F, *et al*. Consistent resting-state networks across healthy patients. *Proc Natl Acad Sci U S A* 2006;**103**(37):13848–53. https://doi.org/10.1073/pnas.0601417103.
54. Kelly RE, Wang Z, Alexopoulos GS, *et al*. Hybrid ICA-seed-based methods for fMRI functional connectivity assessment: a feasibility study. *Int J Biomed Imaging* 2010;**2010**, https://doi.org/10.1155/2010/868976.
55. Popescu V, Schoonheim MM, Versteeg A, *et al*. Grey matter atrophy in multiple sclerosis: clinical interpretation depends on choice of analysis method. *PLoS One* 2016;**11**(1):1–17. https://doi.org/10.1371/journal.pone.0143942.
56. Stonnington CM, Tan G, Klöppel S, *et al*. Interpreting scan data acquired from multiple scanners: a study with Alzheimer's disease. *Neuroimage* 2008;**39**(3):1180–5. https://doi.org/10.1016/j.neuroimage.2007.09.066.
57. Pardoe H, Pell GS, Abbott DF, *et al*. Multi-site voxel-based morphometry: methods and a feasibility demonstration with childhood absence epilepsy. *Neuroimage* 2008;**42**(2):611–6. https://doi.org/10.1016/j.neuroimage.2008.05.007.
58. Zhou J, Kramer JH, Miller BL, *et al*. Predicting regional neurodegeneration from the healthy brain functional connectome. *Neuron* 2012;**73**(6):1216–27. https://doi.org/10.1016/j.neuron.2012.03.004.
59. Coppen EM, van der Grond J, Hafkemeijer A, *et al*. Early grey matter changes in structural covariance networks in Huntington's disease. *NeuroImage Clin* 2016;**12**:806–14. https://doi.org/10.1016/j.nicl.2016.10.009.
60. Vanasse TJ, Fox PM, Barron DS, *et al*. BrainMap VBM: an environment for structural meta-analysis. *Hum Brain Mapp* 2018;**39**(8):3308–25. https://doi.org/10.1002/hbm.24078.
61. Bzdok D, Laird AR, Zilles K, *et al*. An investigation of the structural, connectional, and functional subspecialization in the human amygdala. *Hum Brain Mapp* 2013;**34**(12):3247–66. https://doi.org/10.1002/hbm.22138.