Microstructural plasticity in nociceptive pathways after spinal cord injury

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ABSTRACT
Objective To track the interplay between (micro-) structural changes along the trajectories of nociceptive pathways and its relation to the presence and intensity of neuropathic pain (NP) after spinal cord injury (SCI).

Methods A quantitative neuroimaging approach employing a multiparametric mapping protocol was used, providing indirect measures of myelination (via contrasts such as magnetisation transfer (MT) saturation, longitudinal relaxation (R1)) and iron content (via effective transverse relaxation rate (R2*)) was used to track macrostructural changes within nociceptive pathways. In order to characterise concurrent changes along the entire neuroaxis, a combined brain and spinal cord template embedded in the statistical parametric mapping framework was used. Multivariate source-based morphometry was performed to identify naturally grouped patterns of structural variation between individuals with and without NP after SCI.

Results In individuals with NP, lower R1 and MT values are evident in the primary motor cortex and dorsolateral prefrontal cortex, while increases in R2* are evident in the cervical cord, periaqueductual grey (PAG), thalamus and anterior cingulate cortex when compared with pain-free individuals. Lower R1 values in the PAG and greater R2* values in the cervical cord are associated with NP intensity.

Conclusions The degree of microstructural changes across ascending and descending nociceptive pathways is critically implicated in the maintenance of NP. Tracking maladaptive plasticity unravels the intimate relationships between neurodegenerative and compensatory processes in NP states and may facilitate patient monitoring during therapeutic trials related to pain and neuroregeneration.

INTRODUCTION
The underlying pathophysiology of neuropathic pain (NP) after spinal cord injury (SCI) is complex and involves alterations within ‘bottom-up’ nociceptive processing (ie, afferent integrity) and ‘top-down’ endogenous pain modulation.1 Functional changes within descending modulatory pathways have been related to the presence of NP after spinal cord injury (SCI).2 The descending pain modulatory network encompasses a cortical–subcortical–brainstem network involved in the modulation of afferent nociceptive information.3 Key constituents involved in nociceptive information processing are the posterior insula, thalamus, periaqueductal grey (PAG), the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) (for review, see Wiech4). Within ascending nociceptive pathways, inhibition and facilitation of afferent input already occurs at the level of the dorsal horn where primary afferent fibres synapse onto projection neurons.5 Modulatory changes within these regions can precipitate a pro-nociceptive state and potentially contribute to the emergence and chronification of NP.6 Traumatic SCI triggers a cascade of trauma-induced secondary neurodegenerative processes, involving demyelination and iron accumulation in the spinal cord and brain,7 which can be tracked using quantitative MRI (qMRI).8 To date, increases and decreases in brain and cord macrostructural (ie, volumetric) changes have been associated with the occurrence of NP.9 Moreover, macrostructural tissue sparing (ie, ventral tissue bridges) could be related to the emergence and maintenance of NP after SCI.10 However, microstructural correlates of these NP associated processes within areas undergoing atrophy and beyond are understudied. Based on recent studies illustrating that activity-dependent plasticity can translate into changes in myelin architecture, we hypothesised that such pathophysiological processes will be reflected in microstructural changes to myelin and iron content along nociceptive pathways.

We used a multi-parametric mapping (MPM) protocol8 that provides contrasts that are sensitive to myelination (via magnetisation transfer (MT) saturation, longitudinal relaxation (R1)) and iron content in tissue as well as in blood (using the effective transverse relaxation rate (R2*)) to track the complex relationship between structural and metabolic changes along the trajectories of nociceptive pathways and its relation to the presence and intensity of NP. To characterise simultaneously NP related changes across the neuroaxis, we used a combined brain and spinal cord template14 embedded in the statistical parametric mapping (SPM) framework. Finally, we applied multivariate source-based morphometry (SBM), which estimates interrelationships among voxels across the neuroaxis to identify naturally grouped patterns of structural variation between groups.15 The multivariate (SBM) tests for group effects are, in principle, much more sensitive than the equivalent mass univariate (voxel-based morphometry (VBM)) tests one would obtain from analysing the volumetric and microstructural images directly.
To assess group differences for the demographics (ie, lesion level, level of injury (%)) and other causes like musculoskeletal pain had to be required its presence in an area of sensory deficit (at or below the history of head and brain lesions, no pre-SCI and healthy controls were older than 18 years, and had no indications to MRI.

The neurological examination was performed according to CLINICAL ASSESSMENT in a longitudinal study.17–19 Eligible individuals with a traumatic (online supplemental S1). These participants were also enrolled NP (table 1).

Thirty chronic traumatic SCI patients (13 with and 17 without healthy controls. A T1-weighted (T1w) structural scan was acquired using a 3D MPRAGE (magnetisation-prepared rapid acquisition gradient echo) sequence with the following: field of view (FoV) of 224×256×176 mm³, matrix size 224×256×176, isotropic resolution of 1 mm³, repetition time (TR)=2420 ms, echo times (TE)=4.18 ms, flip angle (α)=9°, inversion time=960 ms, and readout bandwith of 150 Hz per pixel.

A whole-brain multi-parameter mapping (MPM) qMRI protocol,22 using a multi-echo 3D FLASH (fast low-angle shot) sequence, was performed. The following parameters were used: FoV of 240×256×176 mm³, matrix size=240×256×176, isotropic resolution of 1 mm³, GRAPPA parallel imaging in phase-encoding direction (anterior–posterior) with speed-up factor of 2, partial Fourier acquisition with 6/8 sampling factor in the partition direction (left–right) and a readout bandwidth of 480 Hz per pixel. Differently weighted MRI images were achieved by choices of TR and flip angle (α): (1) T1 weighted (T1w): 25 ms/23°, (2) PD weighted (PDw): 25 ms/4° and (3) MT weighted (MTw): 37 ms/9° with off-resonance MT saturation RF pulse prior to excitation. This MT pulse consists of a Gaussian shaped off resonance pulse at 1.2 kHz with length 10 ms, pulse angle 500° and MT pulse bandwidth of 192 Hz. Echoes were acquired at seven equidistant TE, from 2.46 ms to 17.22 ms for all volumes and an additional echo at 19.68 ms for PDw and T1w.

DATA ANALYSIS
We used SPM12 spatial routines on the T1w images and MPM maps. As a novelty, we used a brain plus spinal cord (BSC) template23 covering the brain and the upper cervical spinal cord in the unified segmentation approach,24 which allowed us to assess brain and cervical cord changes within the same statistical framework. This BSC template was specified as a tissue probability map (ie, spatial prior) in the unified segmentation step. This procedure assumes every voxel to be drawn from an unknown mixture of 12 Gaussians, which were grouped into seven distinct tissue classes: grey matter (GM, using one Gaussian), white matter (WM, using one Gaussian) and cerebrospinal fluid (using one Gaussian), bone and air (using three Gaussians), soft tissue (using three Gaussians), non-neural tissues (using three Gaussians) and air/background (using three Gaussians).24 For volumetric analysis, we applied SPM12’s unified segmentation, including the BSC template, to each subject’s MPRAGE image (ie, T1w). T1w images were non-linearly transformed into standard MNI (Montreal Neurological Institute) space using diffeomorphic group-wise registration (Dartel) implemented in SPM12.25 This defined the space for subsequent modelling steps. Finally, GM and WM probability maps were smoothed with an isotropic Gaussian kernel of 5 mm full width at half maximum.

For microstructural analysis, the acquired T1w, PDw and MTw FLASH echoes from the MPM protocol, were first American Spinal Cord Injury Association (ASIA) Injury Severity at baseline (AIS grade).

DATA ACQUISITION
Structural whole-brain data, including the cervical cord down to vertebra C5, were acquired on a 3T Magnetom-Verio MRI scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 16-channel radiofrequency (RF) receive head and neck coil and RF body transmit coil. The scanner was upgraded during the study period (from Verio to Skyra) which resulted in 15 controls and 20 patients being scanned on the Verio and 8 controls and 10 patients being scanned on the Skyra system.

This is because multivariate analyses do not try to assign a significance to each voxel or region—they test for distributed effects that covary among individuals.16 Due to SBMs sensitivity to minute changes, this approach was chosen to detect microstructural changes. To dissociate NP-associations of changes from trauma-induced changes we first compared MRI indices between SCI patients with and without NP and then between SCI patients and healthy controls.

MATERIALS AND METHODS
Participants
Thirty chronic traumatic SCI patients (13 with and 17 without NP (table 1)) and 23 healthy controls participated in the study (online supplemental S1). These participants were also enrolled in a longitudinal study.17–19 Eligible individuals with a traumatic SCI and healthy controls were older than 18 years, and had no history of head and brain lesions, no pre-existing neurological, mental or medical disorders affecting outcome, and no contra-indications to MRI.

CLINICAL ASSESSMENT
The neurological examination was performed according to the International Standards for Neurological Classification of Spinal Cord Injury.20 The pain intensity was quantified using an 11-point numeric rating scale with ‘0’ indicating no pain and ‘10’ indicating the worst imaginable pain. NP was defined according to the standard taxonomy related to SCI,21 which required its presence in an area of sensory deficit (at or below the lesion level) and other causes like musculoskeletal pain had to be ruled out during the clinical assessment. We used ANOVA tests to assess group differences for the demographics (ie, lesion level, AIS grade (%)) and ‘10’ indicating the worst imaginable pain. NP was defined according to the standard taxonomy related to SCI,21 which required its presence in an area of sensory deficit (at or below the lesion level) and other causes like musculoskeletal pain had to be ruled out during the clinical assessment. We used ANOVA tests to assess group differences for the demographics (ie, lesion level,
averaged to increase signal to noise ratio. Unified segmen-
tation based correction of R1 brain maps for RF transmit field
inhomogeneities (UNICORT) was then used for correcting RF
transmit field inhomogeneity and to calculate quantitative maps
of MT saturation, R1 and R2*. MT maps were segmented
using the unified segmentation approach that included the BSC
template.14 Segmented MT maps were then transformed non-
linearly to standard MNI space using DARTEL, but without scaling
by the Jacobian determinants (ie, no ‘modulation’ of parameter
values). Additionally, all MPM maps (MT, R1 and R2*) were
warped to the MNI space by using the participant specific flow
fields from the MT maps and finally smoothed using a previ-
ously established tissue-weighted-smoothing procedure with a
kernel of 5 mm, in order to preserve quantitative values within
the GM and WM tissue classes of each MPM map.

Subsequent modelling and analysis were performed for
smoothed, normalised morphometric and microstructural
parameter images (for WM and GM) across the brain and cervical
cord, simultaneously. Each of the morphometric and microstruc-
tural parameter images were then individually analysed using
SBM.16 SBM is a multivariate analysis approach, implemented
in the SBM toolbox within Group ICA Toolbox (GIFT) (http://
mlab.mrn.org) that estimates covarying networks. SBM can be
considered as a multivariate extension of VBM which accounts
for spatial dependencies among different regions and increases
sensitivity to effects distributed across the neuraxis. SBM applies
spatial independent component analysis30 (organised as subjects-
by-voxels) to produce maximally independent components
(components-by-voxels) and their associated mixing-matrices
(subjects-by-components). The number of components (k) for
subsequent ICA were estimated using a principled information
theoretic approach (rather than arbitrarily selecting the number
of components36). ICA was then applied to the T1w WM images
of 23 HC, 12 NP and 17 without NP, which were arranged into
one 53-row (subject-by-T1w-WMvoxels) data matrix. This data
matrix was then decomposed into a mixing matrix (subjects by
components) and a component matrix (components by voxels).
The mixing matrix expresses the relationship between 53 subjects
and k components. The rows of the mixing matrix indicate the
contribution of each k component to a given subject, whereas
the columns indicate how each component contributes to the 53
subjects. The component matrix on the other hand expresses the
relationship between the k components and brain/cord voxels.
The rows of the component matrix indicate how one compo-
nent contributes to different voxels, whereas the columns of the
component matrix indicate how one voxel contributes to each
of the components.

The mixing matrix was used for subsequent statistical analysis,
where every column of the mixing matrix quantifies the contribu-
tion of each component to the 53 subjects. An ANOVA was
applied to each column to assess which components showed a
significant group difference, adjusted for covariates of no interest
(ie, age, gender, total intracranial volume (TIV) and scanner).
A false discovery rate controlling procedure with \( q^* = 0.05 \)
was used to assess which components were statistically signifi-
cant. The significant component that survived FDR correction
was thresholded at a value of \(|Z| > 3 \) as described in Xu et al36
and was scaled to unit SD (SBM Z map). A significant compo-
nent comprises clusters of voxels—with positive and negative
values—reflecting group effects in different regions of brain and
spinal cord that are interrelated to each other.

SBM was repeated for each of the volumetric and microstruc-
tural parameter maps. The number of components estimated
were 8, 8, 7, 7, 6, 3, 5, 5 for GM and WM maps from the
MRPAGE, R1, R2* and MT maps, respectively. Components
with loading scores that differed significantly between either
controls and patients or NP patients versus pain-free patients
were identified. No significant components were found for MT
maps. The significant components were rendered on the MNI-
normalised BSC template for appropriate contrasts (controls>pa-
tients, patients>controls, NP patients>pain free, pain free>NP
patients) (figures 1 and 2). For illustrative purposes, the GM and
WM are represented in the same colour for each modality (eg,
volume, R1, R2*) of the significant components.

Finally, in order to explore the association between brain
and spinal cord changes and pain intensity in patients with NP,
we used SPM’s multiple linear regression models adjusting for
potentially confounding effects of age, gender, time since injury,
TIV and scanner upgrade. The explanatory variables in these
analyses were pain intensities (range from 0 to 10), while the
response variables were the volumetric and microstructural
parameter maps above.

RESULTS

Patients’ characteristics and clinical outcomes

The demographics of the patients is shown in table 1. Out of
30 chronic traumatic SCI patients (3.6±6.8 years after the
injury), 13 reported NP (mean age: 42.9 years, SD=18.2,
range=21–73) and 17 were pain-free (mean age: 46.1 years;
SD=14.8, range=19–72). All patients underwent state of the art
neurorehabilitation in a specialised SCI centre immediately after
their injury. The healthy controls had a mean age of 36.9 years
(SD=11.8, range=24.0–66.0). All three groups were compar-
able with respect to age (ANOVA, \( p=0.1516 \)) and patient
groups did not differ with regard to lesion level (\( p=0.28 \) or
AIS grade (\( p=0.18 \)). The mean below level NP intensity was 6.1
(SD=1.9).

Pain-associated changes in SCI patients with NP compared
with pain-free SCI patients

In NP patients, atrophic changes associated with NP were
observed in the cerebellum, middle temporal gyrus and occip-
tital gyrus, while volume increases were observed in the poste-
rior insula, superior temporal, occipital and middle frontal gyrus
when compared with pain-free patients (figure 1A and online
supplemental S2). Analysis of the R1 component showed signal
decreases in primary motor cortex and DLPFC in NP patients
when compared with pain-free patients (figure 2A and online
supplemental S3). In NP patients, the R2* component showed
increased signal in the cervical cord, thalamus, ACC, PAG and
para-hippocampal gyrus, while signal was decreased in the lenti-
form nucleus and substantia nigra when compared with pain-
free patients (figure 2A and online supplemental S4). Note, that
trauma-related differences were predominantly visible in the
medial thalamus whereas pain-related changes were located in
the lateral thalamus.

Magnitude of structural changes is associated with pain
intensity

In NP patients, pain intensity was negatively associated with R1
in the PAG (Z-score=4.59, cluster extent voxels=72, \( p=0.004 \),
FWE corrected) and positively correlated with R2* in the cervical
cord (Z-score=4.04, cluster extent voxels=123, \( p=0.025 \), FWE
corrected) (figure 3).

Trauma-associated changes in SCI patients compared with
healthy controls

We first confirmed previous reports showing trauma-induced
macrostructural and microstructural changes across the motor,
sensory and limbic system. Specifically, macroscopic changes (decreased volume) were observed in the cervical cord, cerebellum, thalamus, posterior cingulate, lingual gyrus, precuneus, superior and medial temporal gyrus and para-hippocampal gyrus (figures 1B and 2) when all patients (NP+pain free) were compared with controls. In these atrophied areas and beyond,
R1 component was decreased in the sensorimotor cortices, middle frontal gyrus, precuneus and inferior parietal lobule when compared with healthy controls. The R2* component showed an increase in the cervical cord, lentiform nucleus, cerebellum, posterior cingulate, middle temporal gyrus, right cerebellum and fusiform gyrus (figure 2B and online supplemental S3 and S4).

**DISCUSSION**

This study shows both decreased and increased myelin-sensitive and iron-sensitive content differences associated specifically with NP along the trajectory of ascending and descending nociceptive pathways after SCI. Most group effects are located within key structures involved in endogenous pain modulation. As SCI provides an ideal model to differentially study trauma-related and pain-related effects—following a defined lesion to the nervous system—these findings speak to specific pathophysiological mechanisms related to the development and maintenance of chronic NP after SCI.

We first dissociated trauma-induced changes from NP associated (micro-)structural changes. In agreement with previous reports, trauma-induced atrophic changes, as well as myelin and iron changes, were evident across the sensorimotor and limbic system (for review, see Freund et al7). Accompanying trauma-induced changes, volumetric increases and decreases in the cervical cord, thalamus, primary somatosensory cortex, ACC and DLPFC have been also associated with NP following SCI.9 The neuronal substrates underlying injury-induced volumetric alterations remain incompletely understood. Pathophysiologically, chronic ectopic electrical activity in residual spinothalamic tract axons,29 upregulation of sodium channels in nociceptive neurons,30 and increases in pro-inflammatory cytokines37 are potential mechanisms involved. As volumetric changes
can represent a myriad of physiologically and pathophysiologi-
cal changes, we sought to reveal the underlying microstruc-
tural substrates of such pain-associated volumetric changes by
revealing changes in myelin and iron content along the trajecto-
ries of ascending and descending nociceptive pathways. Specif-
ically, $R_2^*$ increases were detectable in the spinal cord, PAG,
thalamus, ACC and para-hippocampal gyrus, suggesting iron
accumulation due to neurodegenerative processes in regions
that have previously been implicated in NP after SCI. It
remains speculative which pathophysiological processes drive
changes in $R_2^*$ contrasts as a range of physiological and patho-
physiological processes can contribute to the gradient echo signal
decay (and thus $R_2^*$). Remyelination, during recovery and reor-
ganisation processes may impact myelin architecture and thereby
$R_2^*$. Inflammatory processes leading to microglial activation
and neurodegenerative processes may result in changes in $R_2^*$,
but also to changes in metabolic demand affecting the concentra-
tion of deoxyhaemoglobin in certain brain areas also influences
$R_2^*$. However, although there is a complex interplay between
myelin, iron accumulation and $R_2^*$ values in brain pathology,
remote spinal cord and brain changes following SCI are likely
related to anterograde and retrograde degeneration and subse-
quent changes in diaschitic regions.
Communication between the prefrontal cortical areas and the PAG has been recently shown in functional MRI studies.\textsuperscript{34} Here, we provide evidence for further downstream effects. Notably, microstructural alterations were detected within the spinal cord and also the PAG. These effects were related to pain intensity; furnishing an important predictive validity to this imaging phenotype. The PAG is known to serve as a link between the forebrain and the lower brainstem and is pivotal for the descending modulation of pain. It receives input from between the forebrain and the lower brainstem and is pivotal for NP following SCI. In conjunction with microstructural alteration in the injured spinal cord, these findings are compatible with the notion of a dysfunctional spinal–bulbo–spinal loop, a key circuit of the descending pain modulatory system.\textsuperscript{3}

Additional evidence for an impaired descending pain modulation system can be inferred from microstructural changes in other key constituents of this network, namely the ACC (ie, increased iron accumulation) and DLPFC circuitry\textsuperscript{4} (ie, reduced myelin content). Previous studies had found structural and functional NP associations in the DLPFC\textsuperscript{17} in those with NP. For example, reduced GM volume and hypometabolism in the left DLPFC were observed in SCI patients suffering from NP when compared with healthy controls.\textsuperscript{38} Here, we not only show that this reduction in volume is linked to a decrease in myelin-sensitive R1, but also that it is pain specific—as this reduction was not observed in pain-free patients. As the DLPFC is both involved in top-down inhibition and facilitation of pain, the decreases in myelin content reported herein align well with the concept of pathological nociceptive gain control in NP after SCI.\textsuperscript{2}

The thalamus is considered to play an important role in the pathophysiology of central NP after SCI.\textsuperscript{32} After a spinal lesion ascending somatosensory pathways are damaged, which may result in deafferentation of rostral relay structures such as the thalamus. Intriguingly, our finding of R2* signal changes which may reflect iron accumulation in the thalamus in SCI patients with NP was confined to lateral thalamic nuclei, while volumetric changes in the medial thalamus were trauma-related (ie, found in SCI with and without NP). These findings offer an essential line of evidence that structural plasticity within the thalamus is specifically linked to the pathophysiology of NP after SCI.

Finally, we observed an unexpected decrease of iron-sensitive R2* in the basal ganglia. The role of the basal ganglia in chronic pain conditions is still poorly understood, but its vast anatomical connections to a multitude of brain areas (including the thalamus) and cerebral cord make it plausible that the basal ganglia could play an important role in aberrant nociceptive bottom-up and top-down signalling (for review, see Borsook et al\textsuperscript{19}). Our findings warrant further studies into the role of basal ganglia pathways in central NP. At present, the implications of these findings remain highly speculative.

From a technical perspective, the multivariate (SBM) tests for group effects described above are, in principle, much more sensitive than the equivalent mass univariate (VBM) tests one would obtain from analysing the volumetric and microstructural images directly. This is because multivariate analyses do not try to assign a significance to each voxel or region—they test for distributed effects that covary among individuals.\textsuperscript{16} Crucially, this multivariate analysis would not have been possible without combining the brain and spinal cord within the same analysis. This speaks to the potential importance of the combined brain and spine template used to spatially normalise our data. This template is available through open access (http://www.fil.ion.ucl.ac.uk/spm/toolbox/TPM/) for related studies that test for distributed effects throughout the neural axis.

**LIMITATIONS**

Our study had some limitations. The cross-sectional nature of the study restricts conclusions to a single time point and thus the temporal evolution of the above-described microstructural changes remains uncertain. Despite the histological evidence that MT, R1 and R2* markers correspond to their biochemical counterparts,\textsuperscript{33} they are indirect contrasts of myelin and iron content and any interpretation should take this into consideration.

It should be noted that concurrently observed changes in R2*, R1 and MT may not be apparent in all microstructural changes. First, the sensitivity or signal-to-noise ratio in these different quantitative measures varies significantly.\textsuperscript{40} Thus, differences in sensitivity may render these measures complementary, that is, certain changes may only be visible in one of the metrics. Second, the different metrics have a distinct specificity and sensitivity to underlying microstructural changes.\textsuperscript{22} For example, R2* is exquisitely sensitive to changes in local susceptibility and concentration of paramagnetic compounds such as iron. Callaghan and colleagues\textsuperscript{41} have demonstrated that R1 can be estimated from R2* and MT measurements by a general linear relaxometry model, which demonstrates that R2* and MT changes may even cancel each other and result in zero change in R1. Thus, partial contributions of unexplored physiological/cellular processes occurring after SCI cannot be excluded. Moreover, current standardised neurological tests cannot account for unobserved latent lifestyle or genetic factors which might be different between SCI patients and controls, a-priori. To mitigate any potential effect of the scanner upgrade on our results, we ensured that the same number of patients and controls were measured before and after upgrade, allowing us to account for the upgrade effect (common to both cohorts) and modelled out any linear effect of these covariates of interest. Moreover, Leutritz et al\textsuperscript{40} demonstrated that the systematic bias in R1, MT and R2* measurements between a Skyra Siemens scanner setup is <4%. Thus, we are confident that the effects seen in this study are related to pathophysiological changes rather than technical sources. Finally, sex was not balanced across groups, with most of the participants being men. However, this is representative of the general population of SCI patients, in which the male to female patients’ ratio is roughly 4:1 and we also adjusted our models for this covariate of no interest.

**CONCLUSION**

This study evinces the microstructural signature of NP, affecting key constituents of the ascending and descending nociceptive pathways—its magnitude being directly linked to NP intensity. The complex interplay between myelin and iron changes in areas related to sensory and affective processing highlights maladaptive plastic processes likely involved in the maintenance of NP. Beyond unravelling the intimate pathophysiology of NP, tracking microstructural plasticity may facilitate patient monitoring during clinical trials for NP.

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Competing interests The Max Planck Institute for Human Cognitive and Brain Sciences and Wellcome Centre for Human Neuroimaging have institutional research agreements with Siemens Healthcare. NW holds a patent on acquisition of MRI data during spoiler gradients (US 10401453 B2). NW was a speaker at an event organised by Siemens Healthcare and was reimbursed for the travel expenses.

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