RESEARCH PAPER

The grey matter correlates of impaired decision-making in multiple sclerosis

Nils Muhlert,1,2 Varun Sethi,1 Lisa Cipolotti,3 Hamied Haroon,4 Geoff J M Parker,4 Tarek Yousry,5 Claudia Wheeler-Kingshott,1 David Miller,1 Maria Ron,1 Declan Chard1,6

ABSTRACT

Objective People with multiple sclerosis (MS) have difficulties with decision-making but it is unclear if this is due to changes in impulsivity, risk taking, deliberation or risk adjustment, and how this relates to brain pathology.

Methods We assessed these aspects of decision-making in 105 people with MS and 43 healthy controls. We used a novel diffusion MRI method, diffusion orientational complexity (DOC), as an index of grey matter pathology in regions associated with decision-making and also measured grey matter tissue volumes and white matter lesion volumes.

Results People with MS showed less adjustment to risk and slower decision-making than controls. Moreover, impaired decision-making correlated with reduced executive function, memory and processing speed. Decision-making impairments were most prevalent in people with secondary progressive MS. They were seen in patients with cognitive impairment and those without cognitive impairment. On diffusion MRI, people with MS showed DOC changes in all regions except the occipital cortex, relative to controls. Risk adjustment correlated with DOC in the hippocampi and deliberation time with DOC in the medial prefrontal, middle frontal gyrus, anterior cingulate and caudate parcellations and with white matter lesion volumes.

Conclusions These data clarify the features of decision-making deficits in MS, and provide the first evidence that they relate to grey and white matter abnormalities seen using MRI.

INTRODUCTION

Impaired decision-making is seen in people with relapsing–remitting (RR)1,2 and progressive forms of multiple sclerosis (MS).3 It may be detected in the early stages of the disease,2 and is known to deteriorate over time.4 Impaired decision-making is of clinical relevance as it impacts on treatment compliance,5 employment6 and function in everyday life.7 However, it is unclear exactly which components of decision-making are most affected, and whether or not these differ between MS subtypes.

Effective decision-making requires processing information, forming preferences, selecting and executing actions and assessing outcomes. Impaired decision-making can therefore reflect a variety of problems, including difficulties in assessing outcomes, increased impulsivity and poor adjustment to risk. MS studies have used the Iowa Gambling Task,8 a test providing a general measure of decision-making, but not of its separate components. Abnormal performance in different neurological populations has been variously linked to impairments in working memory,8 risk taking9 or emotional response to feedback.10 MS studies using the Iowa Gambling Task have not found correlations with performance on tests of executive function, working memory or processing speed,11,12 and it has been suggested that impaired decision-making may reflect poor learning of outcomes or mood-disturbance.6 It remains to be determined whether impulsivity and poor adjustment to risk also play a role in MS. No associations have been reported between impaired decision-making and MRI abnormalities in MS, and the contributions of grey matter (GM) and white matter (WM) pathology remain to be determined. In this study, we used the Cambridge Gambling Task (CGT,13,14) to assess decision-making. As opposed to the Iowa Gambling Task, which relies on implicit learning of outcomes, the CGT gives participants explicit information about outcome probabilities (Figure 1). In doing so, it can independently measure impulsivity, risk taking, deliberation and risk adjustment.

Functional MRI studies in healthy adults demonstrate that networks involved in decision-making are widespread, including dorsolateral and medial prefrontal cortices,15 the hippocampus14 and striatum.15 Neuropsychological studies also highlight the role of prefrontal cortices and the striatum in decision-making, with impairments observed following lesions to the ventromedial prefrontal cortex16,17 and in those with conditions affecting frontostriatal circuits, such as Parkinson’s disease18 and Huntington’s disease.19 However, to the best of our knowledge, the structural substrates of decision-making deficits in MS have not been investigated.

In this study we addressed four questions: First, which aspects of decision-making are impaired in MS? Second, does the pattern or impairment differ between MS subtypes? Third, is impaired decision-making related to disease duration? Fourth, is decision-making impairment related to GM and WM abnormalities? Changes in GM structures associated with decision-making can be assessed using measures of volume loss (ie, atrophy) and diffusion MRI changes. To assess diffusion changes in GM we used a recently developed measure, diffusion orientational complexity (DOC). DOC uses a bootstrap approach to analyse diffusion data and...
We obtained written informed consent. Scores were determined for patients. Demographics of the participants. Values are mean (SDs) unless otherwise stated and Reingold criteria. The proportion of each varies between trials. The participant is hidden in 1 of 10 boxes. The boxes are either red or blue, and the amount bet automatically increases or decreases with time until a decision is made. Patients were classified as cognitively impaired if they scored 1.96 SDs below the mean of the controls (ie, at the p<0.05 level) on two or more cognitive tests (Hayling overall, Stroop B time, Story memory immediate recall, Story memory delayed recall, Figure recall immediate, Figure recall delayed, symbol digit modalities test). Working memory, as measured using the Wechsler Adult Intelligence Scale-III (WAIS-III) digit span test, was also assessed and compared between the cognitively impaired people with MS, those who were cognitively unimpaired and healthy controls. EDSS scores were determined for patients.

**MATERIALS AND METHODS**

**Participants**

We recruited 105 participants with MS (61 RR, 26 secondary progressive (SP) and 18 primary progressive (PP)) who had not experienced a relapse or received corticosteroids within the preceding 4 weeks (Table 1). Their median Expanded Disability Status Scale (EDSS) score was 5 (range 0–8.5) and their mean disease duration was 14.9 years (range 1–45 years). We also examined 43 healthy volunteers with no known neurological or psychiatric disorders. MS subtypes were classified as per Lublin and Reingold criteria. We obtained written informed consent.

**Clinical assessment**

Cognitive assessment was conducted by an experienced neuropsychologist usually on the same day as scanning. Full details of the cognitive battery and CGT are presented in the online supplementary material. Brieﬂy, in the CGT a token is randomly hidden in 1 of 10 boxes. The boxes are either red or blue, and the proportion of each varies between trials. The participant is asked to predict which colour box contains the token, and gamble points on this. For each trial the amount bet automatically increases or decreases with time until a decision is made. The results of the CGT are broken down into: (1) rational-choices, the proportion of trials in which the participant chooses the likely outcome; (2) deliberation time; (3) amount bet; (4) impulsivity index, the difference in percentage bet in ascending and descending conditions (consistent early bets produce a high impulsivity index); and (5) risk-adjustment index, the adjustment of bets to match the odds.

Patients were classified as cognitively impaired if they scored 1.96 SDs below the mean of the controls (ie, at the p<0.05 level) on two or more cognitive tests (Hayling overall, Stroop B time, Story memory immediate recall, Story memory delayed recall, Figure recall immediate, Figure recall delayed, symbol digit modalities test). Working memory, as measured using the Wechsler Adult Intelligence Scale-III (WAIS-III) digit span test, was also assessed and compared between the cognitively impaired people with MS, those who were cognitively unimpaired and healthy controls.

**MRI sequences**

MRI data were acquired to look for associations between structural brain abnormalities and decision-making deﬁcits. Based on previous work, DOC derived from diffusion imaging was used to look for microstructural GM tissue changes and volumetric imaging to look for tissue atrophy, both of which may be associated with cognitive deﬁcits.

High angular resolution diffusion imaging (HARDI) scans were obtained using a cardiac-gated spin-echo echo-planar sequence acquired axial-oblique and aligned with the anterior commissure (AC)-posterior commissure (PC) line (2 mm×2 mm×2 mm, 61 isotropically distributed diffusion-weighted directions with b=1200 s/mm², 7 non-diffusion-weighted (b=0) volumes, TE=68 ms, TR ∼24 s (depending on cardiac rate), SENSE factor=3.1). Dual-echo proton density/T2-weighted axial-oblique scans aligned with the AC-PC line (1 mm×1 mm×3 mm, TR=3500 ms, TE=19/85 ms) and 3D sagittal T1-weighted fast field echo (FFE) scans (1 mm×1 mm×1 mm, TR=6.9 ms, TE=3.1 ms) were also acquired.

The HARDI scans were processed in native participant space. For each participant the T1-weighted FFE scan was registered to the HARDI data set (see online supplementary material). All registrations (except eddy-current correction) were carried out using NiftyReg (http://sourceforge.net/projects/niftyreg/). An experienced rater (VS) determined whole brain WM lesion volumes on the PD/T2-weighted scans using a semiautomated tool in JIM V6.0 (Xinapse Systems, Leicester, UK).

Generation of DOC, FA and MD, as well as GM parcellations and registrations were carried out as described earlier.

### Table 1  Demographics of the participants. Values are mean (SDs) unless otherwise stated

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>All MS</th>
<th>RR</th>
<th>SP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>43</td>
<td>105</td>
<td>61</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td><strong>Age</strong> (mean (SD))</td>
<td>41.9 (13.1)</td>
<td>45.9 (10.4)</td>
<td>42.0 (9.6)</td>
<td>52.3 (8.0)**</td>
<td>50.2 (10.4)*</td>
</tr>
<tr>
<td><strong>Duration of MS from first clinical event (mean)</strong></td>
<td>–</td>
<td>14.9 (9.6)</td>
<td>12.1 (8.2)</td>
<td>23.7 (9.0)</td>
<td>11.7 (7.0)</td>
</tr>
<tr>
<td><strong>EDSS</strong> (median [range])**</td>
<td>5 (0–8.5)</td>
<td>2 (0–7.5)</td>
<td>6.5 (4.5–8.5)</td>
<td>6 (1.5–6.5)</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001 (comparisons are for the whole MS group against healthy controls or MS clinical subgroups against healthy controls). EDSS, expanded disease severity scale; MS, multiple sclerosis; PP, primary progressive; RR, relapsing-remitting.

---

**Figure 1** A screenshot from the Cambridge Gambling Task (CGT). In the CGT a token is randomly placed in 1 of 10 coloured boxes. The boxes are either red or blue, and the proportion of each varies between trials. The participant is asked to predict which colour box contains the token, and gamble points on this. For each trial, the amount bet automatically increases or decreases with time until a decision is made.
On the basis of previous decision-making studies, a set of a priori parcellations (medial prefrontal cortex, middle frontal gyrus, dorsolateral prefrontal cortex, anterior cingulate, hippocampus and caudate) from the Harvard-Oxford atlas were transformed into native diffusion space and masked with GM tissue masks. These parcellations were chosen a priori given their well-known involvement in decision-making and to average MRI values across anatomical features, in line with previous studies. Regional specificity was assessed by examining changes in the occipital pole, a region where pathology would be unlikely to contribute to decision-making. Mean diffusion-based measurements were extracted from left-sided and right-sided parcellations and mean scores across both were used, as previous studies in people with traumatic brain injury report impaired CGT performance related to bilateral diffusion abnormalities.

GM volume within each parcellation (in native T1 space) was measured using SPM8 tissue maps binarised with an in-house maximum likelihood algorithm. Total intracranial volume was quantified by summing the GM, WM and CSF volumes from the binarised whole brain tissue maps. The study did not aim to investigate regional cortical atrophy, but at detecting the subtle regional GM abnormalities using DOC. However, the measure of GM volume in the same parcellation allowed us to control for the possible effects of brain atrophy.

In additional work, using the diffusion mean FA and MD values within each GM parcellation were also measured using previously described measures (see online supplementary material). Statistical analysis

Group differences in demographics, clinical scores and decision-making measures were tested between controls and people with MS using unpaired t tests and χ2 tests, as appropriate. All data were checked for normality on skewness and kurtosis measures. Non-normally distributed data was analysed using Spearman correlations or Mann-Whitney tests, as appropriate. An executive function z-score was produced by averaging z-scores on the Hayling, p=0.005; Stroop, p<0.001. On tests of memory, the MS group showed worse immediate (p<0.001) and delayed (p<0.001) story recall, and worse immediate (p<0.001) and delayed (p<0.001) figure recall, relative to controls. Patients had significantly lower scores than controls on the executive function z-score (p<0.001) and memory function z-score (p<0.001). On the Hospital Anxiety and Depression Scale (HADS), the MS group showed significantly higher scores than controls for depression (p<0.001), but not anxiety (p=0.37). Thirty patients were classified as cognitively impaired and 75 as unimpaired. In the control group only 3 of 40 participants were classified as cognitively impaired. Cognitively impaired patients showed significantly worse working memory on the digit-span test than healthy controls (p<0.01), but there were no significant differences between those who were cognitively unimpaired and healthy controls (p=0.23).

Decision-making in people with MS and controls

The MS group had longer deliberation times (p=0.002) and worse risk adjustment (p=0.003) than controls, but there were no significant group differences on amount bet, impulsivity or rational-choice components. Similar findings were observed when comparing cognitively impaired patients to controls and those who were cognitively unimpaired to controls, with slower deliberation (p<0.001 and 0.040, respectively) and worse risk adjustment (p<0.001 and 0.020, respectively). In addition, those with MS who were cognitively impaired performed worse on the rational-choice component than controls (p=0.037). Impairment on one or more CGT components was seen in 30% (31/105) of patients and 12% (5/43) of controls. Impairment on one or more CGT components was more common in SPMS (46%, 12/26) than controls (χ2 test, p=0.001), but did not significantly differ between controls and RR (23%, 14/61) or PP 28% (5/18) patients (p=0.14 and p=0.12, respectively), or between the MS subtypes. Age was not significantly correlated with any decision-making component in people with MS or controls. The group differences in decision-making remained significant after controlling for age and gender.

In the MS group, the executive function z-score correlated with rational-choices (r=0.28, p=0.005), deliberation time (r=...
and showed a non-significant trend for an association with risk-adjustment scores ($r=0.23$, $p=0.02$). Similarly, memory $z$-scores correlated with deliberation time ($r=-0.31$, $p=0.003$), amount bet ($r=-0.26$, $p=0.01$) and risk-adjustment scores ($r=0.40$, $p<0.001$), and showed a non-significant trend for an association with rational-choices ($r=0.21$, $p=0.04$). Information processing speed on the SDMT correlated with deliberation time ($r=-0.37$, $p<0.001$), and showed non-significant trends for associations with amount bet ($r=-0.20$, $p=0.04$) and risk-adjustment ($r=0.23$, $p=0.02$). Higher anxiety scores correlated with lower rational-choices scores ($r=-0.20$, $p=0.04$; ie, participants choosing the majority colour less often) but there were no other significant correlations between mood and decision-making. In those with MS, repeating the decision-making-cognition correlations after controlling for levels of anxiety (ie, partial correlations) did not affect the associations with risk adjustment or deliberation but the correlations between amount bet and memory and executive function were, however, no longer significant. In controls, risk adjustment correlated with memory $z$-scores ($r=0.53$, $p<0.001$), executive function $z$-scores ($r=0.42$, $p=0.005$) and processing speed on the SDMT ($r=0.46$, $p=0.002$). There were no other significant correlations between decision-making components and cognitive measures in controls.

### Decision-making in different MS subtypes

The MANOVA revealed significant group differences in deliberation ($p=0.001$) and risk adjustment ($p=0.008$) but not in rational-choices, amount bet or impulsivity scores (table 3). Post hoc Tukey’s tests showed significantly slower deliberation times in SPMS than controls (corrected $p<0.001$) and patients with RRMS (corrected $p=0.042$). Risk adjustment was significantly worse in SPMS than controls (corrected $p=0.007$) and a similar trend was present in patients with RRMS (corrected $p=0.06$). In the whole MS group, only deliberation time correlated with duration of disease ($r=0.38$, $p<0.001$) and disability (EDSS, $r_s=0.23$, $p=0.025$). Differences between SPMS and controls remained significant after controlling for age (analysis of covariance; deliberation times, $p=0.003$; risk-adjustment, $p=0.007$).

### MRI measures

The MS group had significantly smaller normalised GM volumes (ie, atrophy) than controls in the anterior cingulate ($p<0.001$), caudate ($p<0.001$) and occipital pole ($p=0.001$) parcellations (table 4).

Compared with controls, the MS group had significantly lower DOC in the medial prefrontal ($p<0.001$), middle frontal gyrus ($p<0.001$), anterior cingulate ($p=0.002$) and caudate parcellations ($p=0.003$). On the other hand, the MS group showed

---

### Table 2  Mean performance of the control and MS groups (and the MS subgroups) on each of the cognitive tests

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>All MS</th>
<th>RR</th>
<th>SP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General cognitive function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid IQ (NART)</td>
<td>109.7 (10.3)</td>
<td>107.2 (11.0)</td>
<td>106.5 (11.3)</td>
<td>108.2 (9.2)</td>
<td>108.1 (12.7)</td>
</tr>
<tr>
<td>Current IQ (WAIS-III)</td>
<td>112.9 (15.0)</td>
<td>100.1 (15.8)***</td>
<td>101.6 (15.2)***</td>
<td>96.7 (17.3)***</td>
<td>99.1 (16.1)**</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>6.0 (4.1)</td>
<td>6.6 (4.0)</td>
<td>6.2 (3.8)</td>
<td>7.4 (4.5)</td>
<td>6.7 (4.3)</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>2.9 (3.0)</td>
<td>6.1 (3.8)***</td>
<td>5.5 (3.7)***</td>
<td>7.1 (3.9)</td>
<td>6.7 (3.7)***</td>
</tr>
<tr>
<td><strong>Executive function tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayling sentence completion</td>
<td>61.1 (1.4)</td>
<td>51.2 (2.0)**</td>
<td>53.2 (2.1)*</td>
<td>51.2 (2.0)*</td>
<td>4.9 (2.1)*</td>
</tr>
<tr>
<td>Stroop time (seconds)</td>
<td>113.3 (22.9)</td>
<td>155.1 (66.9)***</td>
<td>140.9 (55.5)**</td>
<td>175.0 (78.2)**</td>
<td>178.2 (77.5)***</td>
</tr>
<tr>
<td>Information processing speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol digits modalities test (z-score)</td>
<td>0.56 (1.1)</td>
<td>-0.97 (1.4)***</td>
<td>-0.78 (1.4)**</td>
<td>-1.3 (1.1)**</td>
<td>-1.2 (1.5)**</td>
</tr>
<tr>
<td>Memory tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMIBP immediate story recall</td>
<td>37.7 (8.5)</td>
<td>31.4 (10.4)**</td>
<td>32.9 (9.86)*</td>
<td>28.7 (10.5)**</td>
<td>30.1 (11.4)**</td>
</tr>
<tr>
<td>AMIBP delayed story recall</td>
<td>35.7 (8.9)</td>
<td>28.7 (11.0)**</td>
<td>30.5 (19.5)*</td>
<td>25.8 (11.0)**</td>
<td>26.9 (11.7)**</td>
</tr>
<tr>
<td>AMIBP immediate figure recall</td>
<td>67.4 (11.5)</td>
<td>56.7 (14.8)**</td>
<td>60.8 (12.9)**</td>
<td>51.3 (16.3)**</td>
<td>49.1 (15.2)**</td>
</tr>
<tr>
<td>AMIBP delayed figure recall</td>
<td>67.0 (11.7)</td>
<td>55.1 (14.9)**</td>
<td>59.3 (13.3)*</td>
<td>49.1 (14.4)**</td>
<td>47.6 (16.2)**</td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-III digit span (age-scaled score)</td>
<td>10.8 (2.9)</td>
<td>9.8 (2.9)</td>
<td>10.21 (3.1)</td>
<td>9.2 (2.6)</td>
<td>9.5 (3.2)</td>
</tr>
</tbody>
</table>

SDs are expressed in parentheses. *$p<0.05$, **$p<0.01$, ***$p<0.001$ (comparisons are for the whole MS group against healthy controls or MS clinical subgroups against healthy controls). AMIBP, Adult Memory and Information Processing Battery; HADS, Hospital Anxiety and Depression Scale; MS, multiple sclerosis; NART, National Adult Reading Test; PP, primary progressive; RR, relapsing-remitting; WAIS-III, Wechsler Adult Intelligence Scale-III.
Mean (SD) MRI results for MS and control groups and for each clinical subtype

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>All MS</th>
<th>RR</th>
<th>SP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normalised GM volume</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFG</td>
<td>1.30 (0.15)</td>
<td>1.29 (0.14)</td>
<td>1.29 (0.12)</td>
<td>1.31 (0.15)</td>
<td>1.26 (0.13)</td>
</tr>
<tr>
<td>Medial prefrontal</td>
<td>0.37 (0.04)</td>
<td>0.35 (0.04)</td>
<td>0.36 (0.04)</td>
<td>0.35 (0.03)</td>
<td>0.36 (0.04)</td>
</tr>
<tr>
<td>Hippocampi</td>
<td>0.65 (0.04)</td>
<td>0.65 (0.04)</td>
<td>0.65 (0.05)</td>
<td>0.66 (0.04)</td>
<td>0.65 (0.05)</td>
</tr>
<tr>
<td>Anterior</td>
<td>0.89 (0.10)</td>
<td>0.83 (0.11)*</td>
<td>0.84 (0.09)*</td>
<td>0.80 (0.12)**</td>
<td>0.79 (0.14)**</td>
</tr>
<tr>
<td>Cingulate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td>0.44 (0.04)</td>
<td>0.37 (0.08)***</td>
<td>0.39 (0.07)**</td>
<td>0.34 (0.09)***</td>
<td>0.38 (0.09)*</td>
</tr>
<tr>
<td>Occipital pole</td>
<td>1.25 (0.11)</td>
<td>1.16 (0.15)***</td>
<td>1.16 (0.14)**</td>
<td>1.16 (0.17)*</td>
<td>1.19 (0.14)</td>
</tr>
<tr>
<td><strong>Median white matter lesion volume (mL)</strong></td>
<td>9.78 (12.01)</td>
<td>4.30 (12.19)</td>
<td>8.59 (8.15)</td>
<td>6.36 (15.72)</td>
<td></td>
</tr>
<tr>
<td><strong>DOC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFG</td>
<td>3.097 (0.164)</td>
<td>2.963 (0.184)***</td>
<td>2.963 (0.186)***</td>
<td>2.940 (0.156)***</td>
<td>2.995 (0.216)*</td>
</tr>
<tr>
<td>Medial prefrontal</td>
<td>3.277 (0.133)</td>
<td>3.157 (0.188)***</td>
<td>3.162 (0.206)**</td>
<td>3.155 (0.169)**</td>
<td>3.141 (0.154)**</td>
</tr>
<tr>
<td>Hippocampi</td>
<td>2.290 (0.119)</td>
<td>2.352 (0.130)**</td>
<td>2.343 (0.134)*</td>
<td>2.377 (0.124)**</td>
<td>3.141 (0.154)</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>3.011 (0.156)</td>
<td>2.892 (0.231)**</td>
<td>2.956 (0.173)</td>
<td>2.785 (0.260)***</td>
<td>2.829 (0.292)**</td>
</tr>
<tr>
<td>Caudate</td>
<td>2.569 (0.181)</td>
<td>2.463 (0.196)**</td>
<td>2.505 (0.174)</td>
<td>2.383 (0.233)***</td>
<td>2.439 (0.175)*</td>
</tr>
<tr>
<td>Occipital pole</td>
<td>3.153 (0.144)</td>
<td>3.110 (0.179)</td>
<td>3.114 (0.186)</td>
<td>3.093 (0.199)</td>
<td>3.121 (0.124)</td>
</tr>
</tbody>
</table>

*Normalised GM volume is expressed as a percentage of total intracranial volume.

*p<0.05, **p<0.01, ***p<0.001 (comparisons are for the whole MS group against healthy controls or MS clinical subgroups against healthy controls).

DOC, diffusion orientational complexity; GM, grey matter; MFG, middle frontal gyrus; MS, multiple sclerosis; PP, primary progressive; RR, relapsing-remitting; SP, secondary progressive.

significantly higher hippocampal DOC than controls (p=0.008). There was no group difference in occipital pole DOC (p=0.169). All group differences remained significant after covarying for age, gender and GM volume in each parcellation (p=0.046 to <0.001), except for the anterior cingulate (p=0.055).

**MRI measures in different MS subtypes**

Multivariate ANOVAs revealed significant group differences in DOC in all parcellations except the occipital pole. Post hoc Tukey’s tests showed significantly lower DOC in the medial prefrontal parcellation in RRMS (p=0.006), SPMS (p=0.028) and PPMS (p=0.030), in the middle frontal gyrus parcellation in RRMS (p=0.001) and SPMS groups (p=0.003), in the anterior cingulate in SPMS (p=0.001) and PPMS (p=0.009) groups, and in the caudate in SPMS (p=0.001), compared with controls. SPMS also showed lower DOC in the caudate than patients with RRMS (p=0.031). No other differences reached significance (after correction for multiple comparisons).

**Decision-making and MRI measures in people with MS**

Deliberation time correlated with normalised GM volumes in the caudate (r=−0.40, p<0.001) and with DOC in the medial prefrontal (r=−0.27, p=0.008), and showed non-significant trends for correlations with DOC in the middle frontal gyrus (r=−0.20, p=0.045), anterior cingulate (r=−0.25, p=0.012) and caudate parcellations (r=−0.23, p=0.021). Risk adjustment also showed a non-significant trend for a correlation with hippocampal DOC (r=−0.23, p=0.024). Figure 2 shows parcellations in which DOC correlated with decision-making components. WM lesion volume correlated with deliberation time (r=0.28, p=0.005) but not with risk adjustment.

In regression analyses, deliberation time was significantly related to DOC in the middle frontal gyrus (Exp(β): −0.202, 95% CI −0.403.0 to −0.30.9; p=0.047) and medial prefrontal parcellations (Exp(β): −0.265, 95% CI −0.445.9 to −0.664.8; p=0.009) and to normalised GM volume in the middle frontal gyrus (Exp(β): −0.214, 95% CI −0.577.9.2 to −223.3; p=0.035) but only at trend level with the medial prefrontal parcellation (p=0.06). Risk adjustment was associated with hippocampal DOC (Exp(β): −0.226, 95% CI −2.8 to −0.3; p=0.019), but not with GM volume in any parcellation (all p>0.09). Caudate GM volume was a better predictor of deliberation time (Exp(β): −0.409, 95% CI −10836.5 to −4370.8; p<0.001) than caudate DOC (p=0.60).

**Figure 2** Parcellations in which associations between decision-making components and diffusion orientational complexity (DOC) changes in patients were found. Deliberation time correlated with DOC in the middle frontal parcellation and showed non-significant trends for correlations with DOC (after correcting for multiple comparisons) in the medial prefrontal, caudate and anterior cingulate parcellations (yellow). DOC in the hippocampus (green) showed a non-significant trend for a correlation with risk adjustment.

DISCUSSION

Previous studies have shown impaired decision-making in people with MS but have not clarified which components are most affected. In this work, we found that gauging risk and Go/No-Go tasks. We also showed that WM lesions or metabolic changes in GM, which is in line with previous findings. Increased anxiety levels mediated the relationship between risk adjustment or deliberation time and SDMT performance, suggesting a role for cognitive disturbances in decision-making difficulties in MS, decision-making was impaired in people with and without cognitive impairment. Anxiety also affected decision-making, increasing the number of irrational-choices, which is in line with previous findings. The resulting aberrant connectivity among widely distributed brain regions may impact on networks involved in decision-making and cognitive functions (as suggested by our findings). Future work can help to unravel the impact of pathology on specific networks in MS.

In our study, impaired decision-making was most common in SPMS, and similar in those with RR and PPMS. This is similar to the results for cognitive impairment, which was associated with decision-making deficits, although the PPMS subgroup performed as poorly as the SPMS on many cognitive tests. While both risk adjustment and deliberation time correlated with executive function, information processing speed on the SDMT, and memory, suggesting a role for cognitive disturbances in decision-making impairments may be more common in people with definite MS and some disability, than those with clinically isolated syndromes, or early stable MS with low levels of disability. We also found abnormal diffusion MRI measures to be associated with decision-making which, to the best of our knowledge, is the first time that brain structural abnormalities have been directly linked with decision-making deficits in people with MS.

In this exploratory study we selected regions of interest based on published evidence of impaired decision-making in different neurological and control populations and volumetric and diffusion changes may also have been present in other GM areas. Similarly we did not consider the contribution of normal appearing WM pathology to decision-making and future studies are needed to address these questions. The diffusion MRI measures were obtained at the highest clinically possible resolution (2 mm isotropic), but given the thickness of the cortex (2–5 mm thick) partial volume effects could have affected results. We addressed this by using high-resolution T1-weighted scans to segment brain tissues, a high threshold (50%) for classifying voxels as GM and by building regression models with diffusion and volumetric measures. Moreover, the regional volumetric and diffusion differences make it unlikely that our results are due to partial volume effects alone. Last, our progressive MS subgroups were relatively small (26 SPMS and 18 PPMS). While this represents the largest study of decision-making in people with progressive MS to date, the differences we observed would benefit from replication in larger samples.

In summary, risk adjustment and speed of decision-making were impaired in people with MS, with greater deficits in SPMS than RRMS and less severe impairments in PPMS than SPMS, despite similar levels of physical disability. Decision-making impairment was seen in people with MS who did not show other cognitive deficits and specific testing is required to detect this clinically relevant impairment. In our MS group, abnormalities in GM tissue microstructure (as demonstrated by DOC) were more closely related to impairment in decision-making than measures of GM atrophy.

Author affiliations
1. MMR Research Unit, Department of Neuroinflammation, UCL Institute of Neurology, London, UK
2. London, UK
2 School of Psychology and Cardiff University Brain Research Imaging Centre, Cardiff University, Cardiff, UK
3 Department of Neuropsychology, National Hospital for Neurology and Neurosurgery, London, UK
4 Faculty of Medical & Human Sciences, Centre for Imaging Sciences, Biomedical Imaging Institute, The University of Manchester, Manchester, UK
5 Lysolmeh Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, London, UK
6 National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, London, UK

Acknowledgements NM, DC, LC, GIMP, CW-K, DM and MR designed the study and wrote the paper. VS and HH contributed to the data analysis. TY provided important intellectual input to the paper.

Funding This work was supported by the MS Society of Great Britain and Northern Ireland; UK Department of Health’s NIHR Comprehensive Biomedical Research Centre at UCLH and UCL; Philips Healthcare, Clinical Science Group (Best, NL).

Competing interests DC has received: honoraria (paid to his institution) from Bayer, Teva and the Serono Symposia International Foundation for faculty-led education work, and Teva for advisory board membership; and support for conference attendance from Teva. He holds stock in GlaxoSmithKline. NM is funded by a Wellcome Trust ISSF fellowship. DC has received research support from the MS Society of Great Britain and Northern Ireland, and the UCLH/UCL NIHR Biomedical Research Centre.

Patient consent Obtained.

Ethics approval This study was approved by our local UCL Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, provided it is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES
6 Tanel D, Bechara A, Denburg NL. Asymmetric functional roles of right and left ventromedial prefrontal cortices in social conduct, decision-making, and emotional processing. Cortex 2002;38:589–612.
25 Smith A. Symbol Digit Modalities Test. Western Psychological Services, Los Angeles, 1982.
35 Muhlen N, Atzori M, De Vita E, et al. Memory in multiple sclerosis is linked to glutamate concentration in grey matter regions. J Neurol Neurosurg Psychiatry Published Online First: 15 Jan 2014. doi:10.1136/jnnp-2013-306662
The grey matter correlates of impaired decision-making in multiple sclerosis


*J Neurol Neurosurg Psychiatry* published online July 8, 2014
doi: 10.1136/jnnp-2014-308169

Updated information and services can be found at:
http://jnnp.bmj.com/content/early/2014/07/08/jnnp-2014-308169.full.html

These include:

**Data Supplement**
"Supplementary Data"
http://jnnp.bmj.com/content/suppl/2014/07/08/jnnp-2014-308169.DC1.html

**References**
This article cites 30 articles, 14 of which can be accessed free at:
http://jnnp.bmj.com/content/early/2014/07/08/jnnp-2014-308169.full.html#ref-list-1

**Open Access**
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Published online**
Published online July 8, 2014 in advance of the print journal.

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
Articles on similar topics can be found in the following collections:

- Open access (130 articles)
- Immunology (including allergy) (1662 articles)
- Multiple sclerosis (800 articles)
- Memory disorders (psychiatry) (1196 articles)
- Stroke (1305 articles)

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/