Prefrontal involvement related to cognitive impairment in progressive muscular atrophy


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ABSTRACT

Objective: To examine brain activation patterns during verbal fluency performance in patients with progressive muscular atrophy (PMA) and amyotrophic lateral sclerosis (ALS).

Methods: fMRI was used to examine the blood oxygen level–dependent response during letter and category fluency performance in 18 patients with PMA, 21 patients with ALS, and 17 healthy control subjects, matched for age and education. fMRI results are reported at \( p < 0.05 \), family-wise error (FWE)-corrected for multiple comparisons. We analyzed effects of performance, age-related white matter changes (ARWMC), and regional brain volumes; all participants underwent neuropsychological investigation.

Results: Disease duration of patients with PMA (mean 26.0 months, SD 13.6) and ALS (22.2 months, SD 11.4) was comparable. Patients with PMA and ALS had mild to moderate disease severity and showed impaired letter fluency compared with controls. Between-group analysis showed a main effect of group in the left inferior frontal gyrus (IFG, Brodmann area 45) during letter fluency, which was unaffected by performance, ARWMC, and IFG volume: patients with PMA showed lower activation than controls but higher than that of patients with ALS (ALS, PMA, healthy controls; \( p_{FWE} = 0.035; z \) score 4.11; cluster size = 11). A more caudal region in the IFG showed lower activation in patients with PMA than controls during letter fluency performance (post hoc test; \( p_{FWE} = 0.026 \)). No activation differences were observed during the category fluency task.

Conclusion: Prefrontal activation abnormalities are related to an important clinical measure of executive dysfunction in patients with motor neuron disease with and without upper motor neuron signs. Neurology® 2014;83:818–825

GLOSSARY

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; ARWMC = age-related white matter changes; BA = Brodmann area; BOLD = blood oxygen level–dependent; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; FWE = family-wise error; HC = healthy control; IFG = inferior frontal gyrus; MND = motor neuron disease; PFC = prefrontal cortex; PMA = progressive muscular atrophy; UMN = upper motor neuron.

Motor neuron disease (MND) encompasses amyotrophic lateral sclerosis (ALS) and progressive muscular atrophy (PMA; only lower motor neuron clinical features). Approximately 30% to 50% of patients with ALS have cognitive impairments, which are correlated to impaired decision-making (e.g., feeding tube insertion and noninvasive ventilation) and decreased survival.1–3 One of the most consistently reported cognitive abnormalities is letter fluency impairment, which is used as a clinical screening measure and has been related to reduced activation in prefrontal and temporal brain regions on fMRI and PET.4–7 These functional imaging findings have been corroborated by studies relating abnormal regional brain metabolites and gray matter densities to fluency impairment in ALS.8,9
In PMA, nonmotor cerebral involvement is disputed: no abnormalities have been shown on cognitive testing, regional cerebral blood flow imaging, or magnetic resonance spectroscopy of the prefrontal cortex (PFC) in patients with PMA. However, we previously found fluency deficits in patients with PMA and reduced fractional anisotropy in the white matter of the PFC in another cohort of patients with PMA, suggesting nonmotor cerebral involvement, although neuropsychological assessment was not performed in the latter study.

The presence of nonmotor cerebral involvement in PMA would add to clinical, genetic, and pathologic findings, which support the view that a proportion of patients with PMA should be regarded as having ALS. The latter is important for future revisions of diagnostic criteria of MND (should PMA with cognitive impairments be regarded as ALS?) and eligibility for therapeutic trials.

The aim of this study was to examine whether nonmotor cerebral involvement in PMA could be established using fMRI. We hypothesized that patients with PMA show nonmotor cerebral involvement in frontal and temporal brain regions previously associated with fluency performance in ALS.

**METHODS**

Patients. Patients were recruited from tertiary referral centers for MND in Amsterdam (Academic Medical Center) and Utrecht (University Medical Center). Spouses and friends participated as healthy controls (HCs), matched for education and age. The patients with ALS could be classified as probable or definite ALS (revised El Escorial criteria). Patients with PMA fulfilled the criteria as earlier described: (1) diagnosed within 5 years, (2) clinical and electrophysiologic evidence of lower motor neuron involvement in 2 or more regions (bulbar, cervical, thoracic, and lumbosacral), (3) no conduction blocks on extensive nerve conduction studies, and (4) no clinical upper motor neuron (UMN) signs and symptoms. We excluded patients and controls if they had preexistent frontotemporal dementia or another dementia according to consensus criteria (DSM-IV and Lund–Manchester criteria), a history of another neurologic disorder associated with cognitive impairment, a vital capacity lower than 70% of the predicted value, and severe dysarthria. Patients had to be able to push a button with the index finger of the right hand without difficulty, had to be free of psychoactive medication, and had to speak Dutch fluently.

Before this study, one comparable fMRI study in ALS had been performed precluding a valid power analysis. Moreover, for fMRI, generally accepted methods for power calculation are not yet available. Methodologic studies with simulated and real data have shown that group sizes of 12 to 20 participants are sufficient for detecting small to medium effects.

**Standard protocol approvals and patient consents.** This study was approved by the medical ethical committees of the hospitals. Written informed consent was obtained from all participants.

**Clinical assessment.** We used the revised ALS Functional Rating Scale (ALSFRS-R) to assess the functional status of the patients. Further assessments included site of onset (bulbar or limb); bulbar involvement (score <4 on one or more of the bulbar items of the ALSFRS-R); UMN score (sum score of myostatic and pathologic UMN reflexes and pseudobulbar affect; range 0–48; based on Ellis et al. and described earlier); disease duration (months between first sign of muscle weakness and the MRI scan); and the number of years of formal education.

**Neuropsychological assessment.** Patients and controls underwent a comprehensive neuropsychological examination in an outpatient clinic near the patient’s home, including rest periods if needed. The tests were administered in a fixed order and covered premorbid intellectual ability, global cognitive impairment, executive functions, memory, language, attention and working memory, psychomotor speed, and visuospatial functions as described earlier (tests and adjustments for motor and speech impairment are described in appendix e-1 on the Neurology® Web site at Neurology.org). We used 2 fluency tests: letter fluency (Controlled Oral Word Association Test, using the letters K, O, and M) and category fluency (animals and supermarket items). We rated anxiety and depression using the Hospital Anxiety and Depression Scale.

**Statistical analysis of neuropsychological test results.** Group differences of neuropsychological measures (PMA vs ALS and controls) were analyzed using analysis of variance, χ²/Fisher exact test, or Student t test, where appropriate. Two-sided p values <0.05 were considered significant. Data were analyzed with SPSS version 21 (IBM Corp., Armonk, NY).

**MRI.** Patients and controls underwent an MRI scan within 4 weeks of the neuropsychological examination, i.e., not on the same day to prevent fatigue effects. Images were acquired on a Philips Intera 3T MRI scanner (Philips Medical Systems, Best, the Netherlands) with a SENSE-6 channel head coil for radiofrequency transmission and reception.

**fMRI task.** The letter and category fluency tasks used here have shown robust left prefrontal activation in HCs with a mean age of 60 years (SD 8.2) in a previous study. Three letter fluency blocks and 3 category fluency blocks, of 30 seconds each, alternated with 7 blocks of a baseline task (counting backward) of 15 seconds each. During the fluency blocks, participants had to press a button for every covertly generated word (without pronouncing the word, to reduce movement artifacts and not to burden patients with bulbar involvement) either starting with the letter or belonging to the category. Participants were informed about the task before entering the scanner and examples of each of both tasks, not used in the scanner or in the neuropsychological investigation, were given. Patients were instructed not to produce names and consecutive words starting with the same prefix and to keep their eyes open during the experimental and baseline conditions. During the baseline task, participants pressed a button for every covertly counted backward. Performance was measured as the total number of button presses registered through 2 magnet-compatible button boxes. To reduce possible retest effects, we used parallel versions of the fluency tests with the letters D, A, and T and categories “vegetables/fruit,” “tools,” and “occupations.”

**Structural MRI acquisition and analysis.** For each subject, a 3-dimensional, gradient-echo, T1-weighted image and a T2-weighted structural image were acquired (appendix e-2). We...
ARWMC scores and mean volumes of the structures containing matter changes and regional volume, in addition, we added the variance related to these factors. To investigate an effect of white matter changes, scale (maximum score 48; normal score is 16). We constructed a composite mask with the aid of the Anatomical Automatic Labeling implemented in the WFU PickAtlas using the following labels: Frontal_Inf_Tri_L, Frontal_Inf_Oper_L, Frontal_Mid_L, Temporal_Mid_L, Cingulum_Ant_L, and Cingulum_Ant_R. Main effects of group (F test) and post hoc t tests are reported at $p < 0.05$, FWE-corrected for the extent of this composite mask. A similar approach for category fluency analyses is described in appendix e-2.

**RESULTS** MRI scans of 18 patients with PMA, 21 patients with ALS, and 17 HCs were analyzed. Thirty-six participants (64.2%) underwent the neuropsychological investigation first; the other 20 participants underwent MRI scanning first. The order of the investigations (neuropsychological investigation and MRI) did not differ among PMA, ALS, and HC groups ($p = 0.35$). Three left-handed participants were included. UMN score, site of onset, and bulbar involvement differed between ALS and PMA patients; none of the demographic and other clinical characteristics differed significantly between the groups (table 1).

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**Table 1** Demographic and clinical characteristics of patients with PMA and ALS and control subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PMA (n = 18)</th>
<th>ALS (n = 21)</th>
<th>HC (n = 17)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>13/5</td>
<td>15/6</td>
<td>10/7</td>
<td>0.481</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.4 (9.7)</td>
<td>60.3 (10.2)</td>
<td>59.0 (10.8)</td>
<td>0.904</td>
</tr>
<tr>
<td>Handedness, R/L</td>
<td>16/2</td>
<td>21/0</td>
<td>16/1</td>
<td>0.301</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>100.8 (16.9)</td>
<td>104.4 (16.4)</td>
<td>106.2 (16.8)</td>
<td>0.656</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.4 (3.1)</td>
<td>14.1 (2.6)</td>
<td>13.9 (2.1)</td>
<td>0.843</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>4.3 (2.5), 0%</td>
<td>3.9 (3.0), 0%</td>
<td>4.7 (3.2), 5.9%</td>
<td>0.671</td>
</tr>
<tr>
<td>HADS depression</td>
<td>3.9 (2.6), 0%</td>
<td>4.1 (3.6), 9.5%</td>
<td>3.5 (4.1), 11.8%</td>
<td>0.840</td>
</tr>
<tr>
<td>HADS total</td>
<td>8.2 (4.8)</td>
<td>8.2 (6.8)</td>
<td>8.0 (6.2)</td>
<td>0.994</td>
</tr>
<tr>
<td>Disease duration, mo</td>
<td>26.0 (13.8)</td>
<td>22.2 (11.4)</td>
<td>—</td>
<td>0.353</td>
</tr>
<tr>
<td>Bulbar onset, n (%)</td>
<td>0 (0)</td>
<td>5 (23.8)</td>
<td>—</td>
<td>0.050</td>
</tr>
<tr>
<td>Bulbar region affected</td>
<td>4 (22.2)</td>
<td>12 (57.1)</td>
<td>—</td>
<td>0.037</td>
</tr>
<tr>
<td>Familial/sporadic, n (%)</td>
<td>1/17</td>
<td>4/17</td>
<td>—</td>
<td>0.355</td>
</tr>
<tr>
<td>ALSFRS-R$^d$</td>
<td>41.5 (3.7)</td>
<td>40.0 (4.9)</td>
<td>—</td>
<td>0.298</td>
</tr>
<tr>
<td>Upper motor neuron score$^c$</td>
<td>16.0 (6.8)</td>
<td>33.3 (7.1)</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White matter changes score$^f$</td>
<td>1.5 (1.4)</td>
<td>2.3 (2.3)</td>
<td>1.2 (1.3)</td>
<td>0.137</td>
</tr>
</tbody>
</table>

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised; HADS = Hospital Anxiety and Depression Scale; HC = healthy control; PMA = progressive muscular atrophy. Values are mean (SD), unless stated otherwise.

$^a$For HADS subscales, the proportions of subjects with scores above the cutoff (≥10) for moderate or severe disturbances are given ($p = 0.320$ for anxiety and 0.388 for depression).

$^b$p Values <0.05.

$^c$Bulbar region affected = score below 4 on one of the bulbar items of the ALSFRS-R.

$^d$Maximum score = 48; indicates no handicap.

$^e$Maximum score = 48; normal score is 16.

$^f$Age-related white matter changes scale (maximum score = 30; indicates severe white matter changes).

used T1-weighted scans for a preprocessing step of the fMRI analysis and to calculate mean volumes of structures containing significant activation effects—scaled for total gray matter volume. T2-weighted images were used to rate white matter lesions according to the age-related white matter changes (ARWMC) scale.

**fMRI acquisition and analysis.** For each subject, 250 echo planar imaging volumes sensitive to the blood oxygen level-dependent (BOLD) effect were obtained, entailing a T2-weighted, gradient-echo sequence (repetition time 2,300 milliseconds, echo time 30.0 milliseconds, flip angle 80°) using axial whole-brain acquisition, with an interleaved slice acquisition order. The echo planar imaging volumes were acquired at 40 slices (3-mm thickness, no gap); matrix size 96 × 96 voxels; in-plane resolution 2.29 × 2.29 mm.

fMRI data were preprocessed and analyzed (appendix e-2) using Statistical Parametric Mapping software (SPM8) implemented in MATLAB version 7.8.0 (The MathWorks Inc., Natick, MA).

Following the summary statistics approach, contrast images were calculated per subject on a voxel-by-voxel basis and entered into second-level analyses for between-group (PMA, ALS, HC) comparisons (analysis of covariance) with performance as covariate (set to interact with factor “group” to allow further investigation of performance effects within groups). The main effect of the fMRI task is reported at a threshold of $p < 0.05$ whole brain corrected for family-wise error (FWE).

Age and education were added to the model to account for variance related to these factors. To investigate an effect of white matter changes and regional volume, in addition, we added the ARWMC scores and mean volumes of the structures containing significant activation effects as covariates.
Neuropsychological test performance. The PMA, ALS, and HC groups showed significant differences on 2 tests: letter fluency (table 2) and digit backward raw score, which is a measure of attention and working memory (see appendix e-1 for neuropsychological test results).

Performance in the scanner: Letter and category fluency. The mean number of words generated on the letter fluency task in the scanner differed among the PMA, ALS, and HC groups ($F = 3.7; p < 0.05$); patients with PMA generated on average 38.2 (SD 12.5) words, patients with ALS generated 31.1 (10.8) words, and HCs generated 40.6 (11.3) words ($p < 0.05$ for ALS vs HCs). Performance during the control condition (counting backward) did not differ significantly between groups.

The mean number of words generated on the category fluency task in the scanner was higher than that of the letter fluency task: patients with PMA generated 44.2 (14.1) words, patients with ALS generated 38.8 (10.2) words, and HCs generated 44.3 (11.0) words. This result indicates that the participants complied with the task instructions, because similar differences between letter and category fluency performance were found during neuropsychological testing outside the scanner, and have been reported in the literature. Note that the neuropsychological examination and fMRI tasks differed in time durations regarding fluency, hampering a direct comparison.

Cerebral activation related to letter fluency performance: BOLD activation. Whole-brain analysis of functional activation data across all participants showed letter fluency–related activation of left-sided brain regions, including inferior frontal, dorsal lateral prefrontal, anterior cingulate, and posterior temporal and bilateral occipital cortices (figure 1). The category fluency fMRI task showed robust left frontal and left (para) hippocampal activation ($p < 0.05$ whole brain corrected for family-wise error), also as described before.

Between-group comparison of letter fluency–related cerebral activation. Between-group comparison of activation changes with performance as a covariate showed a significant difference of letter fluency BOLD activation among PMA, ALS, and HC groups in the left IFG (Brodmann area [BA] 45) (figure 2 and table 3). The BOLD activation in BA 45 of patients with PMA was lower compared to that of controls and higher compared to that of patients with ALS ($p = 0.035; z$ score 4.11; cluster size = 11). Another cluster in the IFG (BA 9) showed a trend ($z$ score 3.92; $p = 0.069$; cluster size = 8) with lower activation in both PMA and ALS patients compared with HCs (table 3). Repeated analysis without performance as a covariate revealed similar results for the cluster in the left IFG (BA 45; $z$ score 4.24; $p = 0.022$; cluster size = 14). Repeated analysis with age and education as covariates (BA 45; $z$ score 4.72; $p = 0.003$; cluster size = 21) and adding the ARWMC and volume of the IFG (BA 45; $z$ score 4.53; $p = 0.008$; cluster size = 15) did not change the results. Excluding 5 familial cases (BA 45; $z$ score 4.12;
DISCUSSION This study revealed cerebral activation abnormalities in MND patients with and without clinical signs of UMN involvement. A letter fluency task showed lower activation in the IFG of patients with PMA and ALS, which was most pronounced in patients with ALS. These results demonstrate that fMRI is a feasible and sensitive measure to detect nonmotor cerebral changes related to cognitive dysfunction in MND.

Our finding of lower regional cerebral activation in PMA complements reduced fractional anisotropy in the prefrontal white matter on diffusion tensor imaging in 10 other patients with PMA in our earlier study. A cerebral blood flow study (PET) during a joystick movement paradigm in patients with PMA did not show changes in the PFC, which may have been related to the task used and a relatively small sample (n = 5). Magnetic resonance spectroscopy showed a correlation between a reduced N-acetyl acetate/creatine-phosphocreatinine ratio in the PFC and letter fluency performance in patients with ALS, but not in patients with PMA. Also in this study, a small sample size (n = 5 patients with PMA) precluded firm conclusions.

The neuropsychological assessment in the present study showed letter fluency impairment in patients with PMA, which is the most consistent cognitive abnormality in ALS and has likewise been described in limb-onset ALS patients and PMA patients. The neuropsychological assessment further showed that the cognitive profile of patients with ALS was largely in agreement with that reported in the literature, including deficits on letter and category fluency, naming, and memory. The present study thus demonstrates that nonmotor cerebral activation abnormalities (impaired recruitment of the left IFG) are linked to impairment on an important clinical measure of executive dysfunction in patients with PMA comparable to findings in patients with ALS.

Cortical atrophy of the PFC, including the IFG, is a consistent imaging finding in ALS, in particular in patients with ALS–frontotemporal dementia. The IFG contains BA 45 and showed lower activation in patients with MND in the present study, which is in agreement with fMRI findings in ALS patients without dementia by others. BA 45 is designated as Broca area together with BA 44, and has been implicated in word retrieval. A postmortem study...
Table 3  Comparison of letter fluency fMRI activation between groups

<table>
<thead>
<tr>
<th>Contrast</th>
<th>k</th>
<th>Side</th>
<th>BA</th>
<th>MNI coordinates</th>
<th>F/t</th>
<th>z</th>
<th>P_{FWE}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of diagnosis</td>
<td>11</td>
<td>L</td>
<td>45</td>
<td>IFG</td>
<td>–48</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>L</td>
<td>9</td>
<td>IFG</td>
<td>–36</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>PMA, ALS, HC</td>
<td>2</td>
<td>L</td>
<td>32</td>
<td>Ant Cing</td>
<td>–6</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>PMA &lt; HC</td>
<td>9</td>
<td>L</td>
<td>9</td>
<td>IFG</td>
<td>–33</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>L</td>
<td>32</td>
<td>Ant Cing</td>
<td>–6</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>PMA &lt; HC</td>
<td>3</td>
<td>L</td>
<td>45</td>
<td>IFG</td>
<td>–51</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>ALS &lt; HC</td>
<td>24</td>
<td>L</td>
<td>45</td>
<td>IFG</td>
<td>–48</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>L</td>
<td>9</td>
<td>IFG</td>
<td>–36</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>L</td>
<td>6</td>
<td>Mid Fr G</td>
<td>–33</td>
<td>6</td>
<td>51</td>
</tr>
</tbody>
</table>

Abbreviations: ALS = amyotrophic lateral sclerosis; Ant Cing = anterior cingulate cortex; BA = Brodmann area; FWE = family-wise error; HC = healthy control; IFG = inferior frontal gyrus; k = number of voxels; Mid Fr G = middle frontal gyrus; MNI = Montreal Neurological Institute; PMA = progressive muscular atrophy.

Main effects of group and post hoc t tests are reported at p < 0.05, FWE-corrected for the extent of the composite mask with performance as covariate.

* Statistically significant values.

has shown pronounced pathologic changes in BAs 45 and 44 in patients with MND who have aphasia or dementia.37 Together with evidence of language and semantic memory impairment in patients with MND who do not have dementia, this supports the notion that the left IFG is vulnerable to the pathologic process underlying the MND–frontotemporal dementia spectrum.6,7,35,38

Together with clinical, pathologic, and imaging evidence of corticospinal tract changes in PMA, the impaired prefrontal activation as shown in the present study argues against the view of PMA and ALS being separate diseases.11,14,16 Therefore, the current diagnostic criteria for MND, which are based on the presence of UMN signs and actually exclude PMA, may need to be reconsidered.17

Several methodologic issues of the present study warrant consideration. First, dysarthria may result in overestimation of fluency impairment. Three features argue against such a bias: (1) none of our patients with PMA had bulbar onset, (2) 4 patients with PMA had only slight bulbar involvement, which did not affect fluency testing (an exploratory analysis showed that their demographically corrected fluency scores were normal; percentile range: 21–70); and (3) we used a covert fluency fMRI task, minimizing orofacial movements in the scanner.

Second, because of careful matching of PMA patients with ALS patients and HC subjects, and the results of the analyses of covariance, we think it is unlikely that the impaired prefrontal activation is related to depression, anxiety, age, education, or white matter changes.

Furthermore, impaired IFG activation in the present study is unlikely to result from noncompliance because (1) the use of fluency performance as a covariate did not substantially alter the results, (2) performance of the control condition (counting backward) in the scanner did not differ between groups, and (3) differences between performance on letter and category fluency tasks (higher scores for category) in the scanner are compatible with that in the neuropsychological investigation outside the scanner in our study, and similar differences have been reported in our earlier work and the literature.26

Some potential limitations of this study should be noted. First, patient samples are relatively small and we obtained some trend-significant results on neuropsychological and fMRI analyses, suggesting that more power is needed to establish the nonmotor cerebrovascular involvement of PMA in more detail. Second, although disease duration of patients with PMA was limited to 5 years, the remaining heterogeneity within the PMA cohort may have obscured fMRI changes.

Our results indicate impaired prefrontal activation related to fluency deficits in patients with MND regardless of UMN signs. Future studies should examine patients with PMA at an early disease stage to assess whether nonmotor changes have an impact on treatment issues, patient-caregiver interaction, and survival duration, similar to ALS.2,39,40 Also, studies on nonmotor changes in MND should include measures of UMN severity in addition to the ALSFRS-R (which is mostly a lower motor neuron measure) to further confirm the hypothesis that a proportion of patients with PMA may be viewed as having ALS minus detectable UMN signs.

AUTHOR CONTRIBUTIONS

Dr. Raaphorst: drafting the manuscript for content, study design, analysis and interpretation of the data, acquisition of the data, statistical analysis, and study coordination. M.-J. van Tij: revising the manuscript for...
content, study design, analysis and interpretation of the data, acquisition of the data, statistical analysis. P. Groot: analysis and interpretation of the data. E. Altena and Y. van der Werf: revising the manuscript for content, study design. Dr. Majos: revising the manuscript for content, analysis and acquisition of the data, study design. Dr. van der Koos and Dr. van den Berg: revising the manuscript for content, acquisition of the data. B. Schmand: revising the manuscript for content, interpretation of the data, study design. Dr. de Visser and Dr. Veltman: revising the manuscript for content, study design, interpretation of the data, study supervision.

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REFERENCES
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