Cholinergic and perfusion brain networks in Parkinson’s disease dementia

Sean J. Colloby Ph.D¹, Ian G. McKeith MD¹, David J. Burn MD¹, David J. Wyper Ph.D², John T. O’Brien DM³* and John-Paul Taylor Ph.D¹*

¹Institute of Neuroscience, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne. NE4 5PL. UK.

²SINAPSE, University of Glasgow, Institute of Neuroscience and Psychology, Glasgow G12 8QB. UK.

³Department of Psychiatry, University of Cambridge, Level E4, Box 189, Cambridge. CB2 0QC. UK.

*joint senior authors

Key Words: Parkinson’s disease dementia, Muscarinic receptors, SPECT, Molecular Imaging, rCBF, spatial covariance, cholinergic networks, perfusion networks.

Correspondence:

Sean J. Colloby Ph.D
Institute of Neuroscience
Newcastle University
Campus for Ageing and Vitality
Newcastle upon Tyne
NE4 5PL.
UK
Tel: +44 191 208 1321
Fax: +44 191 208 1301
E-mail: sean.colloby@ncl.ac.uk

ian.mckeith@newcastle.ac.uk
david.burn@newcastle.ac.uk
dave.wyper@glasgow.ac.uk
john.obrien@medschl.cam.ac.uk
john-paul.taylor@newcastle.ac.uk
Disclosures

Dr Colloby reports no disclosures.

Professor McKeith has been a consultant for GE Healthcare, Bayer Healthcare and Nutricia.

Professor Burn has received an honorarium from Acadia.

Professor Wyper reports no disclosures.

Professor O’Brien has been a consultant for GE Healthcare, Lilly, Bayer Healthcare, TauRx and Nutricia and has received honoraria for talks from GE Healthcare, Lilly and Novartis.

Dr Taylor has been a consultant of Lundbeck and received honoraria for talks from GE Healthcare and Flynn pharmaceuticals.

Author contributions

Dr Colloby: Co-designed the study, conducted all image and data analyses and wrote the manuscript.

Professor McKeith: Reviewed the manuscript and secured project funding.

Professor Burn: Reviewed the manuscript and secured project funding.

Professor Wyper: Reviewed the manuscript and secured project funding.

Professor O’Brien: Reviewed the manuscript and secured project funding.

Dr Taylor: Co-designed the study and co-wrote the manuscript.
Abstract

Objective: To investigate muscarinic M1/M4 cholinergic networks in Parkinson’s disease dementia (PDD) and their association with changes in MMSE after 12 weeks of treatment with donepezil.

Methods: Forty-nine participants (25 PDD and 24 elderly controls) underwent $^{123}$I-QNB and $^{99m}$Tc-exametazime SPECT scanning. We implemented voxel principal components (PC) analysis, producing a series of PC images of patterns of interrelated voxels across individuals. Linear regression analyses derived specific M1/M4 and perfusion spatial covariance patterns ( SCPs).

Results: We found that in ChEI naive PDD patients, a M1/M4 SCP of relative decreased binding in basal forebrain, temporal, striatum, insula and anterior cingulate ($F_{1,47} = 31.9$, $p<0.001$), implicating limbic-paralimbic and salience cholinergic networks. The corresponding rCBF SCP showed relative decreased uptake in temporo-parietal and prefrontal areas ($F_{1,47} = 177.5$, $p<0.001$), nodes of the fronto-parietal (F-P) and default mode networks (DMN). The M1/M4 pattern that correlated with an improvement in MMSE ($r = 0.58$, $p = 0.005$), revealed relatively preserved/increased pre/medial/orbito frontal, parietal and posterior cingulate, areas coinciding with the DMN and F-P networks.

Conclusions: Dysfunctional limbic-paralimbic and salience cholinergic networks were associated with PDD. Established cholinergic maintenance of the DMN and F-P networks may be pre-requisite for cognitive remediation following cholinergic treatment in this condition.
Introduction

In Parkinson’s disease (PD), development of dementia (PDD) occurs in up to 80% of people 15-20 years after PD diagnosis,\(^1\) with 50% developing cognitive impairment within 6 years.\(^2\) In PDD, cholinergic dysfunction is strongly implicated in cognitive deficits, fluctuating cognition and visual hallucinations.\(^3\) Reductions in choline acetyltransferase are marked in PDD compared to Alzheimer's disease and PD,\(^4\) while clinically, cholinesterase inhibitors (ChEIs) can ameliorate cognition and visual hallucinations. However, response is variable with some efficacy.\(^5\)

Since the brain is a networked entity, pathologic change in one area may influence other topographically distant regions. Indeed, distributed network dysfunction is now considered a key contributor to symptoms that manifest in neurodegenerative dementias.\(^6\) In PDD, theoretical models of dysfunctional neural networks have been proposed. In particular, several cholinergic networks arising from the nuclear basalis of Meynert (NBM) projecting to specific brain regions are thought to effect major cognitive domains e.g. attention (NBM → neocortex), visuoperceptual (NBM → parieto-occipital, parahippocampal-fusiform) and memory (NBM → medial temporal).\(^7\) One way to examine functional brain connectivity is by spatial covariance analysis.

We applied spatial covariance to (R, R)\(^{123}\) I-QNB SPECT data,\(^8\) acquired in ChEI naïve PDD patients, to investigate disease associated M1/M4 cholinergic networks. Also, as cholinergic network dysfunction is implicated in cognitive impairment and amelioration of cholinergic function is an important aspect of treatment, we derived a M1/M4
covariance pattern that correlated with a change in MMSE score, after 12 weeks of treatment with the ChEI (donepezil), to probe the clinical significance of these networks.

**Methods**

**Standard protocol approvals, registrations, and patient consents**

Study approval was from the UK department of health’s administration of radioactive substances advisory committee (ARSAC) and Newcastle, North Tyneside and Northumberland research ethics committee. All participants and/or nearest relative gave written informed consent for the study including treatment.

**Participants**

Study comprised of 49 individuals (25 PDD and 24 similarly aged controls). Patients were recruited from outpatient movement disorder clinics in Newcastle-upon-Tyne and Gateshead, while healthy controls were from patient spouses and friends in this and other studies. Participants had physical, neurological and neuropsychiatric assessments, including mental state, history, physical examination and, for patients, blood screen with B12 and folate levels. The study battery administered included the Mini-Mental State Examination (MMSE)\(^9\), Neuropsychiatric Inventory (NPI)\(^10\), Cambridge Cognitive Examination (CAMCOG)\(^11\) with memory and executive function subscales (CAMCOG\(_{\text{memory}}\), CAMCOG\(_{\text{exec}}\)).

Diagnosis was carried out consensually between two clinicians using the diagnostic criteria for PDD.\(^12\) Patients with PDD were on levodopa and carbidopa or benserazide
combination therapy and, were naïve to ChEI treatment at the time of QNB imaging. Participants on any of the following medications were excluded from the study: antipsychotics, cholinergic, anticholinergics, and antidepressant medications. Clinicopathological diagnosis was established for 11 cases (2 controls, 9 PDD).

**Radiochemistry**

Using the technique of Lee *et al.*, (R, R) $^{123}$I-QNB radiosynthesis was conducted, the specifics of which are described elsewhere.

**Acquisition**

Participants were scanned with a triple-head gamma camera (Picker 3000XP), 5 hours post injection of (R, R) $^{123}$I-QNB using a previously reported imaging protocol. Within 4 weeks of the (R, R) $^{123}$I-QNB scan, individuals underwent $^{99m}$Tc-exametazime regional cerebral blood flow (rCBF) SPECT imaging in accordance with a past scanning procedure.

**Spatial pre-processing**

All SPECT scans were registered to match, where applicable, a $^{123}$I-QNB or $^{99m}$Tc-exametazime SPECT template in standard stereotactic MNI space using linear image registration software. Generation of specific template images have been described. The spatially transformed images were then smoothed with a 16mm FWHM 3D Gaussian filter.
Multivariate spatial covariance analysis

Principal component (PC) analysis was applied on a voxel basis to all processed $^{123}$I-QNB SPECT images using covariance analysis software (http://www.nitrc.org/projects/gcva_pca), producing a series of PC images. For each PC image, voxels had either positive or negative weights that represent the sign and strength of covariance between voxels. In this study, voxels with positive and negative weights were viewed as concurrently preserved/increased and decreased M1/M4 binding, respectively. The extent to which an individual expressed the PC image was by way of a subject scaling factor (SSF) for that PC, calculated by superimposing the PC image onto an individual’s processed QNB scan by computation of a ‘dot product’, which involves image multiplication on a voxel basis followed by summation of the products generating a score. Higher SSF scores for an individual for that PC image represents greater increased binding in voxels with positive weights and greater concurrent decreased binding in voxels with negative weights. To identify the QNB spatial covariance pattern (SCP) that distinguished PDD from controls; each individual SSF was entered into a linear regression model as explanatory variables with group as the dependent parameter. Akaike’s information criteria determined how many PCs should be included to reach optimal bias-variance trade-off. The set of PCs yielding the lowest Akaike’s information criterion (AIC) value were used to derive the SCP$_{QNB}$. The degree to which each subject expressed the SCP$_{QNB}$ was by the SSF$_{QNB}$.

The same approach was applied to the $^{99m}$Tc-exametazime SPECT images. Therefore, positive and negative weights were interpreted as concurrent increased and decreased
The analysis produced the SCP_{rCBF} that best separated PDD from controls, while each subject expressed the SCP_{rCBF} by their SSF_{rCBF}.

Following their $^{123}$I-QNB scan, the majority of patients (n=18) were then treated with the ChEI donepezil titrated up to the standard daily clinical dose of 10mg. After a period of 12 weeks, patients underwent repeated MMSE assessments. We derived a ChEI naïve M1/M4 SCP that correlated with $\Delta$MMSE_{rel,b}, which described the percentage change in MMSE relative to baseline. This involved conducting a separate analysis, generating a series of PCs expressed by each subject by the SSFs, which in turn were introduced into a regression model as predictor variables with $\Delta$MMSE_{rel,b} as the response parameter. The resulting linear combination with the smallest AIC value generated the SCP_{$\Delta$mmse} ($R^2 = 0.34$, $p = 0.005$), where each individual expressed the pattern by the SSF_{$\Delta$mmse}.

Stability and reliability of the SCPs were assessed by bootstrap resampling (1000 iterations), to identify areas that contributed to the patterns with high confidence. This transforms the voxel weights of each SCP into Z maps, computed as the ratio of voxel weight and bootstrap standard deviation. The Z-statistic follows roughly a standard normal distribution where a one-tailed $p \leq 0.05$ infers a threshold of $|Z| \geq 1.64$.18

**Statistical analyses**

Continuous variables were tested for normality using visual inspection of histograms and Shapiro-Wilk test. Demographic, clinical and imaging measures were assessed, where applicable, using parametric (ANOVA) and non-parametric $\chi^2$ tests. Correlations were
performed using Pearson’s r coefficients. Statistical tests were interpreted as significant if p ≤ 0.05. Data analysis used the Statistical Package for Social Sciences software (SPSS ver. 22.0, http://www-01.ibm.com/software/analytics/spss/products/statistics/).

Results

Demographics and clinical characteristics
Table 1 shows demographic and clinical characteristics of the study sample. Groups were similar in age and gender, while as expected, all other variables differed (p<0.001).

Spatial covariance analysis
The SCP_QNB that distinguished PDD from controls is shown in figures 1A and 1B. SSF_QNB scores were higher in PDD than controls (mean ± SD; controls = 1.5 ± 2.5, PDD = 6.2 ± 3.3, F_{1,47} = 31.9, p<0.001, figure 1C). The pattern was mainly characterised by concomitant decreases in M1/M4 binding (blue regions) in basal forebrain, temporal, striatal, insula and anterior cingulate together with concomitant preserved or increases (red regions) in frontal and parieto-occipital areas. Table e1 presents detailed description of specific regions contributing to the M1/M4 disease related pattern.

The associated SCP_{rCBF} that differentiated PDD from controls is illustrated in figures 2A and 2B, where SSF_{rCBF} scores differed between groups (controls = 0.4 ± 0.9, PDD = 6.2 ± 1.9, F_{1,47} = 177.5, p<0.001, figure 2C). The pattern mainly comprised of relative decreased rCBF (blue) in temporo-parietal and prefrontal areas with relative increases
(red) in cerebellum, brain stem, striato-thalamic and motor regions. Detailed description of specific regions participating in the rCBF disease related pattern is provided (table e2).

Relationship between SCP expressions and age, MMSE, CAMCOG, CAMCOG\textsubscript{memory}, CAMCOG\textsubscript{exec}, total NPI, NPI\textsubscript{hall} and UPDRS III were investigated in PDD. No correlations were found between SSF\textsubscript{QNB} and these measures (|r| ≤ 0.23, p ≥ 0.14). For the rCBF pattern expression, total NPI correlated with SSF\textsubscript{rCBF} (ρ = 0.62, p = 0.006), which was not observed for the other variables (|r| ≤ 0.28, p ≥ 0.09). An exploratory examination of NPI subscores did not yield any specific relationships with SCP expressions.

Summary data for the donepezil treated group are shown (table 2). During the observation period, differences in MMSE were identified between baseline and 12 week scores (p < 0.001). The resultant SCP\textsubscript{\Delta mmse} is presented in figures 3A and 3B, while figure 3C depicts SSF\textsubscript{\Delta mmse} plotted as a function of ΔMMSE\textsubscript{rel,b}. The pattern consists of concurrent decreases in M1/M4 binding (blue) in fusiform, anterior cingulate, lingual gyrus and precentral areas with concurrent preserved or increases (red) in pre/medial/orbito frontal, parietal and posterior cingulate regions. Details of specific regions participating in the pattern are supplied (table e3).

**Discussion**

We undertook a multivariate network perspective of (R, R)\textsuperscript{123}I-QNB SPECT, a M1/M4 receptor ligand in ChEI naïve PDD patients. We derived a disease related M1/M4 pattern
of spatial covariance that appears largely distinct from rCBF, which implies the presence of several dysfunctional cholinergic networks in PDD. We also identified a clear M1/M4 covariance pattern that was associated with an improvement in MMSE; this network had distinctive spatial elements suggesting certain cortical regions and their associated cholinergic innervation may have a more pre-eminent role in cognitive amelioration by cholinergic treatments. Relevant to the present study, this spatial covariance technique has extensively and successfully been utilized to perfusion SPECT and glucose metabolism PET data for the investigation of disease progression and symptomatology in PD.19-22

We derived a voxel cholinergic SCP from $^{123}$I-QNB images that differentiated PDD from controls. The disease related pattern comprised of decreased and preserved/increased M1/M4 uptake in a number of concomitant brain regions or networks. The covariant negative weighted pattern mainly converged on limbic/paralimbic regions. Notably this cholinergic receptor network mapped onto previously described resting state networks, including anterior insula and the anterior cingulate, key nodes of the ‘salience network’ (SN), which is important for initiation of cognitive control and switching between networks to aid access to working memory and attention resources.23, 24 Networks involving the insula have also been shown to play an role in episodic memory,25 while hippocampus, parahippocampus and amygdala are known to be involved in memory storage and retrieval.26 As such, this pattern would align with a cognitive network deficit implicating the basal forebrain and these structures, i.e., a cholinergic limbic-paralimbic/salience network dysfunction. The disease-related pattern also encompassed
regions implicated in dorsal (occipital → parietal) and ventral (occipital → temporal → limbic) visual streams,\textsuperscript{27} providing indirect evidence for the role of distinct cholinergic networks in visual function in PDD which would be in keeping with known visuo-perceptual deficits and predisposition to visual hallucinations; symptoms which both show good response to cholinesterase inhibitors.\textsuperscript{28, 29}

The associated rCBF pattern largely comprised of relative decreases in temporo-parietal and prefrontal areas along with relative increases in cerebellum, brain stem, striato-thalamic and motor regions that implicate a number of functional networks in PDD. Regions that were concomitantly reduced appear to involve hubs of the fronto-parietal (F-P) attention (inferior parietal, dorsolateral prefrontal cortex)\textsuperscript{30} and default mode networks (DMN) (medial prefrontal, posterior cingulate, ventral precuneus, inferior parietal),\textsuperscript{31, 32} which is of interest since, respectively, attention deficits are one of the most disabling cognitive symptoms in PDD,\textsuperscript{33} whilst network theories have strongly implicated the DMN in contributing to cognitive decline.\textsuperscript{34} Our previous studies revealed modulation of the F-P network in PDD that was similar to patients with dementia with Lewy bodies (DLB),\textsuperscript{35} while also demonstrating, albeit in DLB, its relationship with severity and frequency of cognitive fluctuations.\textsuperscript{36} Other investigations have reported decreases in DMN connectivity in PDD\textsuperscript{37} and its association with cognitive dysfunction in PD.\textsuperscript{38} These and our rCBF findings appear to provide further evidence that implicates the DMN and F-P networks in the pathogenesis of symptoms in PDD, in particular cognitive. Moreover, if perhaps not unexpected, the rCBF pattern seemed to represent an extended topography of the PD related motor and cognitive patterns (PDRP, PDCP) which have
been previously reported from $^{18}$F-FDG PET studies using similar network approaches, thus indirectly validating the analytic methodology used in the present study.

We failed to detect any correlations between the M1/M4 pattern expressions and neuropsychological and neuropsychiatric measures in PDD. For rCBF pattern expression, only total NPI score was found to correlate. Thus, patients with more global severe neuropsychiatric symptoms, a marker of greater disease severity, were more likely to express the perfusion SCP characteristic of PDD. The lack of correlations may be explained by either the notion that each spatial covariance pattern is likely to characterise a number of overlapping and convergent brain networks and thus fails to project on specific cognitive and clinical parameters or that patterns derived from combined (control-dementia) cohorts are less sensitive. Isolating key networks from these patterns could increase sensitivity, but this is methodologically challenging.

We found a clear M1/M4 covariance pattern that correlated with a change in MMSE that could indicate a positive treatment response. This pattern showed relative decreases in fusiform, striatum, anterior cingulate, lingual gyrus and precentral areas with relative preservation or increase in pre/medial/orbito frontal, parietal and posterior cingulate regions. From a network perspective, there was covariant preservation/upregulation in regions overlapping key nodes of the DMN and F-P networks that could imply that a relative cholinergic maintenance of these networks is pre-requisite for ChEI treatment response in PDD, and more generally may point toward the potential relevance of these networks and their cholinergic innervation and its associated cognitive symptoms.
Notably, a recent study showed that cholinergic and serotoninergic antagonists can impair DMN-like network in mice similarly, suggesting that both neurotransmitter systems are involved in maintaining the integrity of the DMN-like networks.\textsuperscript{40} Hence, this pattern appears to provide some evidence which supports the cholinergic DMN maintenance hypothesis, and its potential significance as a predictor of positive treatment response in PDD and perhaps in other neurodegenerative disorders.

Modest sample sizes and uncertainty regarding which receptor subtype is affected (that is, M1 vs. M4) are limitations of the study. Another limitation was the use of MMSE rather than MoCA to assess cognitive function in these patients reflecting the fact that our data were collected before the widespread use of the latter scale. Replication of this study with neuropsychological assessments which align more with the cognitive deficit profile of PDD may provide a more nuanced cholinergic response network pattern. Strengths were scanning and clinically assessing PDD patients, free from cholinergic medications with perfusion and muscarinic SPECT images available for all participants. We also had, in a sizeable minority, autopsy confirmation of diagnoses.

Our findings imply several dysfunctional cholinergic and perfusion networks in PDD. The relevance of these networks may be important in terms of their contribution to cognitive and, in particular, attentional deficits of this condition. The use of ChEIs could improve such deficits; but there is marked heterogeneity in response to these agents and it is not possible to reliably predict on clinical grounds who might respond to these drugs. Although tentative, we observed a SCP that suggests those with cholinergic maintenance
of DMN and F-P networks could experience cognitive improvement with ChEI treatment. These findings provide further neurobiological insights into therapies targeted at improving cholinergic neurotransmission and treatment outcomes in PDD.

**Funding**

Medical Research Council UK [grant number G9817682], and by the National Institute for Health Research (NIHR) Research for Public Benefit, Wellcome Trust (WT088441MA Fellowship funding J-P.T). NIHR Dementia Biomedical Research Unit at Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The NIHR Newcastle Biomedical Research Centre in Ageing and Chronic Disease and Biomedical Research Unit in Lewy Body Dementia based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University.
References


Table 1. Participant characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PDD</th>
<th>Statistic, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Sex (m: f)</td>
<td>15: 9</td>
<td>17: 8</td>
<td>$\chi^2 = 0.2, 0.7$</td>
</tr>
<tr>
<td>Age</td>
<td>74.1 ± 5.1</td>
<td>72.0 ± 5.0</td>
<td>$F_{1,47} = 2.0, 0.2$</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.3 ± 1.5</td>
<td>18.8 ± 4.9</td>
<td>$F_{1,47} = 82.3, &lt; 0.001$</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>95.0 ± 3.9</td>
<td>63.0 ± 14.2</td>
<td>$F_{1,47} = 113.8, &lt; 0.001$</td>
</tr>
<tr>
<td>CAMCOG&lt;sub&gt;memory&lt;/sub&gt;</td>
<td>22.1 ± 1.9</td>
<td>16.1 ± 4.7</td>
<td>$F_{1,47} = 32.6, &lt; 0.001$</td>
</tr>
<tr>
<td>CAMCOG&lt;sub&gt;exec&lt;/sub&gt;</td>
<td>20.8 ± 4.2</td>
<td>8.5 ± 3.1</td>
<td>$F_{1,47} = 135.2, &lt; 0.001$</td>
</tr>
<tr>
<td>NPI</td>
<td>1.3 ± 2.3</td>
<td>19.7 ± 17.8</td>
<td>U = 73.0, 0.002</td>
</tr>
<tr>
<td>NPI&lt;sub&gt;hall&lt;/sub&gt;</td>
<td>Na</td>
<td>3.5 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>UPDRS III</td>
<td>0.9 ± 1.5</td>
<td>38.5 ± 11.6</td>
<td>U = 600.0, &lt; 0.001</td>
</tr>
</tbody>
</table>

Values denote mean ± 1 SD.

NPI<sub>hall</sub>=Neuropsychiatric Inventory hallucinations subscale; UPDRS=Unified Parkinson’s disease rating scale; Na=Not applicable.
Table 2. Summary data of PDD patients treated with donepezil.

<table>
<thead>
<tr>
<th></th>
<th>PDD\textsubscript{donepezil}</th>
<th>Statistic, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Sex (m: f)</td>
<td>11:7</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>71.6 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>(\text{MMSE}_b)</td>
<td>18.1 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>(\text{MMSE}_{12w})</td>
<td>22.4 ± 4.7</td>
<td></td>
</tr>
<tr>
<td>(</td>
<td>\text{MMSE}_{12w} - \text{MMSE}_b</td>
<td>)</td>
</tr>
<tr>
<td>(\Delta \text{MMSE}_{\text{rel}, b} (%))</td>
<td>26.8 ± 24.6</td>
<td></td>
</tr>
</tbody>
</table>

Values denote mean ± 1 SD.

\(b = \) at Baseline, \(12w = \) at 12 weeks.

\(\Delta \text{MMSE}_{\text{rel}, b} (%) = \{(\text{MMSE}_{12w} - \text{MMSE}_b) / \text{MMSE}_b\} \times 100\%\)
**Short title:** Muscarinic M1/M4 spatial covariance pattern in PDD.

**Figure 1.** Disease related M1/M4 spatial covariance pattern in PDD projected onto orthogonal (A) and rendered (B) displays of the QNB template. Distribution of subject scaling factor (SSFQNB) scores across groups (C). L = left, R = right, Ant = anterior, Pos = posterior, Sup = superior.

**Short title:** rCBF spatial covariance pattern in PDD.

**Figure 2.** Disease related rCBF spatial covariance pattern in PDD projected onto orthogonal (A) and rendered (B) displays of the rCBF template. Distribution of subject scaling factor (SSFrCBF) scores across groups (C).

**Short title:** M1/M4 SCPΔMMSE in PDD (n=18).

**Figure 3.** M1/M4 spatial covariance pattern in PDD (n=18) that correlated with ΔMMSErel,b.