**Supplementary material**

**Supplementary Table 1. ADNI extracted variables.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Demographical** | **Neuropsychological** | **Biomarker** | **Neuroimaging** |
| Sex | Clinical Dementia Rating Scale | CSF Aβ42 | FDG-PET |
| Age | Mini-Mental State Examination | CSF total tau | AV-45-PET |
| Ethnicity | Montreal Cognitive Assessment | CSF phosphorylated tau | MRI volumetric measures |
| Marital status | Patient’s self-reported ECog |  | T-1 weighted sequence |
| Years of education | Patient’s ECog assessment by partner |  | rs-fMRI BOLD sequence |
| APOEε4 status | Alzheimer’s Disease Assessment Scale |  | Fluid attenuated inverse recovery sequence |
|  | Functional Activities Questionnaire |  |  |
|  | Rey Auditory Verbal Learning Test trial scores |  |  |
|  | Immediate recall total score |  |  |
|  | Delayed recall total score |  |  |
|  | ADNI memory composite score |  |  |
|  | ADNI executive functioning composite score |  |  |
|  | GDS |  |  |
|  | NPI |  |  |

ADNI: Alzheimer’s Disease Neuroimaging Initiative. CSF: cerebrospinal fluid. Aβ1-42: amyloid β peptide 42. FDG: 18F-fluorodeoxyglucose. PET: positron emission tomography. AV-45: Florbetapir. MRI: magnetic resonance imaging. ECog: Everyday Cognition scale. APOEε4: Apolipoprotein E ε4 genotyping. GDS: Geriatric Depression Scale. NPI: Neuropsychiatric Inventory.

**Supplementary Table 2a. Local correlation differences at baseline**

|  |
| --- |
| **Local correlation at baseline** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Network\* | Region (Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) | Network\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) |
| Sensorimotor | * Right postcentral gyrus

(+16 -33 +67)* Right superior parietal lobule

(+45 -36 +41)* Right precentral gyrus

(+30 -28 +71)* Left postcentral gyrus

(-24 -40 +54) | * 1551
 | T= 5.16 (≤0.001) | Visual  | * Right lateral occipital cortex

(+54 -70 +09)* Right occipital pole

(+10 -86 -18)* Right lingual gyrus

(+15 -85 -11) | * 3187
 | T= -6.87 (≤0.001) |
| Salience | * Left frontal pole

(-08 +56 +18)* Left anterior cingulare cortex

(-03 +30 +17)* Left paracingulate cortex

(-12 +33 +20) | * 479
 | T= 4.95 (≤0.001) | Salience | * Right middle frontal gyrus

(+41 +16 +39)* Right frontal pole

(+32 +49 +22)* Right superior frontal pole

(+24 +26 +42) | * 1265
 | T= -5.58 (≤0.001) |
| Default mode | * Right frontal pole

(+19 +50 -16)* Right frontal orbital cortex

(+26 +40 -16)* Right paracingulate gyrus

(+08 +50 -05) | * 520
 | T= 4.35 (≤0.001) | Default tmode | * Left temporal fusiform cortex

(-40 -20 -28)* Left temporal pole

(-49 +07 -42)* Left middle temporal gyrus

(-55 +03 -28) | * 866
 | T= -5.45 (≤0.001) |
| * Left hippocampus

(-33 -37 -06) | * 28
 | T= 3.75 (≤0.001) | Language | * Left supramarginal gyrus

(-54 -44 +50)* Left angular gyrus

(-50 -50 +34)* Left postcentral gyrus

(-41 -37 +61) | * 1014
 | T= -4.86 (≤0.001) |

**\*** **Characterization of each network is derived from the spatial overlap between the CONN network template and the local correlation between-group differences.** **\*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between groups for a specific region or cluster).**

**Supplementary Table 2b. Between-network FC differences at baseline**

|  |
| --- |
| **Between-network functional connectivity at baseline** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Networks\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) | Networks\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) |
| Salience and frontoparietal  | * Anterior right supramarginal gyrus

(+47 -29 +39)* Right postcentral gyrus

(+48 -28 +40)* Posterior right supramarginal gyrus

(+50 -37 +48)  | * 396
* 324
* 122
 | T= 3.29 (0.006) | Salience and cerebellar  | * Precentral gyrus

(+52 -05 +36) | * 48
 | T= -3.64 (0.002) |
| * Left planum polare

(-48 +08 -11)* Left anterior superior temporal gyrus

(-50 00 -08) | * 45
* 31
 | T= -2.13 (0.048) |
| Default mode and cerebellar  | * Right hippocampus

(+30 -20 -20)* Right posterior middle temporal gyrus

(+52 -18 -14)* Right posterior parahippocampal gyrus

(+25 -23 -17)* Right cerebellum IV

(+14 -32 -20)* Right anterior middle temporal gyrus

(+52 -08 -24) | * 124
* 111
* 45
* 39
* 33
 | T= 2.97 (0.016) | Salience and default mode  | * Right paracingulate gyrus

(+10 +29 +27) | * 29
 | T= -2.65 (0.039) |
| * Posterior right supramarginal gyrus

(+50 -37 +48) | * 122
 | T= -2.32 (0.046) |
| Default mode and salience  | * Right temporal pole

(+48 +16 -21) * Right inferior frontal gyrus

(+53 +28 -01)* Right temporal fusiform cortex

(+26 -23 -26) * Right amygdala

(+23 -03 -19)* Right planum polare

(+47 00 -14) | * 196
* 144
* 127
* 78
* 74
 | T= 2.74 (0.008) | Default mode and cerebellar | * Right planum polare

(+47 00 -14)* Right frontal orbital cortex

(+18 +10 -17)* Right cerebellum III

(+20 -36 -38)  | * 74
* 29
* 22
 | T= -2.22 (0.048) |

**\* Characterization of each network is derived from the spatial overlap between the CONN network template and** **the independent component between-group differences. \*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between a specific region and** **an independent component).** **Some T-values relate to multiple regions (i.e., clusters) inside an independent component, hence one T-value for multiple regions.**

**Supplementary Table 3a. Local correlation differences at baseline +12 months**

|  |
| --- |
| **Local correlation at 12 months** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Network\* |  Region (Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) | Network\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) |
| Cerebellar | * Right cerebellum

(+36 -68 -30) | * 1098
 | T= 4.44 (≤0.001) | Visual  | * Right cuneal cortex

(+07 -83 +15)* Right intracalcarine cortex

(+18 -80 +30)* Right lingual cortex

(+15 -72 -03) | * 1199
 | T= -4.30 (≤0.001) |
| * Left cerebellum

(-34 -52 -30) | * 462
 | T= 4.13 (≤0.001) |
| Deafult mode | * Right temporal pole

(+55 +06 -16)* Right amygdala

(+28 +00 -18) | * 802
 | T= 6.44 (≤0.001) | * Left frontal pole

(-50 +42 -10) | * 117
 | T= -5.22 (≤0.001) |
| Sensorimotor | * Left postcentral gyrus

(-37 -46 +57)* Left superior pareital lobule

(-68 -18 +32)* Left supramarginal gyrus

(-59 -26 +20) | * 1282
 | T= -5.34 (≤0.001) |
| Salience | * Left insular cortex

(-30 +12 -20)* Left frontoorbital cortex

(-12 +09 -15) | * 777
 | T= 5.92 (≤0.001) | * Right thalamus

(+20 -02 +08)* Right putamen

(+23 + 04 +05) | * 586
 | T= -6.08 (≤0.001) |
| Salience | * Right anterior cingulate cortex

(+16 +10 +50) | * 371
 | T= -4.18 (≤0.001) |

**\* Characterization of each network is derived from the spatial overlap between the CONN network template and the local correlation between-group differences. \*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between groups for a specific region or cluster).** **Multiple T-values correspond to more than one independent cluster within the same network with a high local correlation difference between the compared groups.**

**Supplementary Table 3b. Between-network FC differences at baseline +12 months**

|  |
| --- |
| **Between-network functional connectivity at 12 months** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Networks\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\*(p-FDR) | Networks\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\*(p-FDR) |
| Default mode and dorsal attention  | * Left angular gyrus

(-56 -60 +12) | 26 | T= 4.05 (0.032) | Default mode and cerebellar | * Right cerebellum

(+14 -52 -44) | 42 | T= -4.24 (0.016) |
| Dorsal attention and cerebellar | * Left cerebellum

(-20 -62 -40) | 32 | T= 3.69 (0.04) | * Right cerebellum

(+30 -64 -36) | 34 | T= -3.93 (0.049) |
| Default mode and visual | * Left lateral occipital cortex

(-52 -66 +36) | 56 | T= 3.6 (0.025) | Default mode and salience | * Posterior cingulate cortex

(+00 -32 +36) | 119 | T= -3.98 (0.041) |
| Default mode and sensorimotor | * Left thalamus

(-06 -14 -06) | 100 | T= -3.39 (0.037) |
| Visual and sensorimotor | * Right precentral gyrus

(+36 -14 +52) | 25 | T= -4.09 (0.014) |
| Visual and salience | * Left paracingulate cortex

(-16 +44 +14) | 56 | T= -4.01 (0.037) |

**\* Characterization of each network is derived from the spatial overlap between the CONN network template and the independent component between-group differences. \*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between a specific region and an independent component). Some T-values relate to multiple regions (i.e., clusters) inside an independent component, hence one T-value for multiple regions.**

**Supplementary Table 4a. Local correlation differences at baseline +24 months**

|  |
| --- |
| **Local correlation at 24 months** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Network\* | Region (Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) | Network\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) |
| Cerebellar | * Right cerebellum

(+24 -64 -36)* Left cerebellum

(-26 -63 -53) | * 2864
 | T= 5.22 (≤0.001) | Default mode | * Left temporal pole

(-18 -06 -24) | * 1940
 | T= -6.03 (≤0.001) |
| * Left inferior temporal gyrus

(-58 -56 -12) | * 676
 | T= -5.11 (≤0.001) |
| Senorimotor | * Right precentral gyrus

(+38 -14 +44)* Right postcentral gyrus

(+40 -26 +59)* Left precentral gyrus

(-24 -34 6+8) | * 2408
 | T= 4.99 (≤0.001) | * Right angular gyrus

(+34 -64 +24) | * 540
 | T= -4.88 (≤0.001) |
| * Right frontal pole

(+32 +48 +02) | * 629
 | T= -4.21 (≤0.001) |
| Sensorimotor | * Left supramarginal gyrus

(-58 -40 +16) | * 859
 | T= -4.97 (≤0.001) |
| * Left frontal pole

(-30 +44 +30) | * 1237
 | T= -5.68 (≤0.001) |
| Salience | * Right anterior cingulate coretx

(+12 +34 +34) | * 459
 | T= -4.46 (≤0.001) |

**\* Characterization of each network is derived from the spatial overlap between the CONN network template and the local correlation between-group differences. \*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between groups for a specific region or cluster). Multiple T-values correspond to more than one independent cluster within the same network with a high local correlation difference between the compared groups.**

**Supplementary Table 4b. Between-network FC differences at baseline +24 months**

|  |
| --- |
| **Between-network functional connectivity at 24 months** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Networks\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) | Networks\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) |
| Default mode and salience  | * Right inferior frontal gyrus

(+43 +24 -09)* Right middle frontal gyrus

(+50 +08 +18)* Right frontal orbital cortex

(+46 +22 -06)* Right insular cortex

(+38 +05 +05)* Right frontal operculum cortex

(+50 +17 0)* Right central opercular cortex

(+49 +16 -03) | * 296
* 139
* 125
* 71
* 66
* 40
 | T= 3.24 (0.009) | Default mode and salience | * Precuneus

(-08 -63 +51)* Right precentral gyrus

(+29 -14 +60)* Posterior cingulate cortex

(+01 -46 +44)* Left precentral gyrus

(-04 -32 +61)* Left postcentral gyrus

(-08 -58 +55)* Right postcentral gyrus

(+09 -20 +55) | * 425
* 246
* 218
* 163
* 99
* 47
 | T= -2.01 (0.049) |
| Default mode and cerebellar | * Right cerebellum Crus 2

(+41 -69 -54)* Right cerebellum Crus 1

(+46 -70 -40)* Right cerebellum VI

(+36 -67 -33)* Right cerebellum VIII

(+11 -84 -43)* Right angular gyrus

(+52 -55 +20)* Right middle temporal gyrus

(+57 -34 00)* Right lateral occipital cortex

(+16 -70 -20) | * 219
* 182
* 182
* 164
* 263
* 218
* 210
 | T= 2.99 (0.006) | Language and cerebellar | * Left cerebellum VI

(-22 -72 -29)* Brain stem (Left pons)

(-14 -38 -34)* Left cerebellum IX

(-03 -49 -45)* Left cerebellum IV-V

(-18 -70 -19)* Left lingual gyrus

(-18 -67 -13) | * 129
* 117
* 48
* 39
* 26
 | T= -2.71 (0.037) |

**\* Characterization of each network is derived from the spatial overlap between the CONN network template and the independent component between-group differences. \*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between a specific region and an independent component).**

**Supplementary Table 5a. Local correlation differences at baseline +≥48 months**

|  |
| --- |
| **Local correlation at ≥48 months** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Network\* | Region (Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) | Network\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) |
| Sensorimotor | * Left middle frontal gyrus

(-48 +09 +22)* Left superior frontal gyrus

(-43 +09 +53)* Right superior frontal gyrus

(+26 +02 +68) | * 2747
 | T= 10.32 (≤0.001) | Cerebellar | * Right cerebelum

(+40 -76 -40)* Left cerebellum

(-10 -84 -22) | * 3373
 | T= -6.15 (≤0.001) |
| * Vermix

(+06 -44 -04) | * 537
 | T= -4.70 (≤0.001) |
| * Left lateral occipital cortex

(-49 -67 +42)* Left supramarginal gyrus

(-56 -40 +54) | * 940
 | T= 4.68 (≤0.001) | Sensorimotor | * Right putamen

(+09 +10 +05)* Right thalamus

(+12 -18 -08)* Right caudate

(+10 +06 +10) | * 797
 | T= -5.99 (≤0.001) |
| * Left superior frontal gyrus

(-06 +36 +44)* Right paracingulate gyrus

(+09 +24 +36) | * 478
 | T= 4.16 (≤0.001) |
| * Precuneus

(+14 -60 +50) | * 218
 | T= -4.35 (≤0.001) |

**\* Characterization of each network is derived from the spatial overlap between the CONN network template and the local correlation between-group differences. \*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between groups for a specific region or cluster). Multiple T-values correspond to more than one independent cluster within the same network with a high local correlation difference between the compared groups.**

**Supplementary Table 5b. Between-network FC differences at baseline +≥48 months**

|  |
| --- |
| **Between-network functional connectivity at ≥48 months** |
| **sMCI>pMCI** | **pMCI>sMCI** |
| Network\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) | Networks\* | Region(Peak activation coordinate) | Cluster size (voxels) | Size of effect\*\* (p-FDR) |
| Sensorimotor and cerebellar  | * Right lateral occipital cortex

(+47 -81 -04)* Right occipital pole

(+44 -78 -02)* Right lingual gyrus

(+07 -78 -10)* Left cerebellum IX

(-05 -55 -44)* Left cerebellum VIII

(-28 -71 -39)* Left cerebellum vermis VII

(-01 -67 -34)* Left lingual gyrus

(-11 -46 -02)* Brainstem

(+04 -42 -55) | * 290
* 267
* 126
* 34
* 31
* 33
* 87
* 41
 | T= 3.08 (0.018) | Frontoparietal and salience  | * Right inferior frontal gyrus

(+51 +14 -03)* Right frontal pole

(+54 +26 +16) * Right superior temporal gyrus

(+54 -09 -16) | * 348
* 298
* 41
 | T= -3.9 (0.003) |
| Language and salience | * Right frontal operculum cortex

(+36 +24 +07)* Right temporal fusiform cortex

(+30 -21 -30)* Right middle temporal gyrus

(+56 -10 -14)* Right planum temporale
* (+52 -42 +21)
 | * 78
* 44
* 40
* 34
 | T= -2.64 (0.047) |
| Dorsal attention and salience  | * Right insular cortex

(+37 -12 -17) | * 83
 | T= 2.85 (0.024) | Frontoparietal and cerebellar  | * Right cerebellum VIII

(+06 -59 -47)* Right cerebellum Crus 1

(+11 -78 -27)* Right cerebellum IX

(+15 -64 -47)* Right cerebellum VI

(+10 -78 -26)* Right cerebellum II

(+02 -78 -18)* Right cerebellum vermis VIII

(+05 -67 -46) | * 290
* 265
* 243
* 173
* 87
* 35
 | T= -2.56 (0.028) |

**\* Characterization of each network is derived from the spatial overlap between the CONN network template and the independent component between-group differences. \*\*Size of effect refers to the statistical inference derived from the T-value or the size of the difference relative to the variation of the data (i.e., differences in the mean regional activation between a specific region and an independent component). Some T-values relate to multiple regions (i.e., clusters) inside an independent component, hence one T-value for multiple regions.**

**Supplementary Figure 1. Cognitive function trajectories among aMCI subgroups**

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Parallel plots depicting the individual cognitive trajectories from aMCI patient subgroups over time. aMCI: amnestic mild cognitive impairment. AD: Alzheimer’s disease CDRSB: Clinical dementia rating sum of boxes. MMSE: Mini-mental state examination. MoCA: Montreal cognitive assessment. ADAS: Alzheimer’s disease assessment scale-cognitive subscale. A) Graphical representation of the CDRSB cognitive trajectory. B) Graphical representation of the MMSE cognitive trajectory. C) Graphical representation of the MoCA cognitive trajectory. D) Graphical representation of the ADAS-Cog cognitive trajectory. Each line represents a cognitive profile (i.e., a single patient or a group of patients with the same trajectory). Red lines: aMCI patients who progress to AD (pMCI). Black lines: aMCI patients who remain cognitively stable over time (sMCI).

**Supplementary Figure 2.** **Spatial correlation of independent components to template at baseline**



\* Voxel to voxel one-sample t-tests ICA spatial overlap map with suprathreshold areas (Dice similarity coefficients) with threshold set at Z= 3.5. The larger the box, the stronger the correlation. The best match suggests the network most likely characterized.

**Supplementary Figure 3. Spatial correlation of independent components to template at 12 months**



\* Voxel to voxel one-sample t-tests ICA spatial overlap map with suprathreshold areas (Dice similarity coefficients) with threshold set at Z=3.5. The larger the box, the stronger the correlation. The best match suggests the network most likely characterized.

**Supplementary Figure 4. Spatial correlation of independent components to template at 24 months**



\* Voxel to voxel one-sample t-tests ICA spatial overlap map with suprathreshold areas (Dice similarity coefficients) with threshold set at Z= 3.7. The larger the box, the stronger the correlation. The best match suggests the network most likely characterized.

**Supplementary Figure 5. Spatial correlation of independent components to template at ≥48 months**



\* Voxel to voxel one-sample t-tests ICA spatial overlap map with suprathreshold areas (Dice similarity coefficients) with threshold set at Z= 3.2. The larger the box, the stronger the correlation. The best match suggests the network most likely characterized.