Supplementary Methods 1 - Definitions and methods used for the scoring of clinical features

For the scoring of clinical features, only the clinical records concerning the first three years from disease onset were taken into account. To be scored as "present", the symptoms must not have been the result of substance abuse, administered drugs or another medical condition.

1. **Depression (0-1)** [1]

   The feature "depression" was given a score of "1" if a clinical episode of depression was explicitly mentioned in the clinical records and\or if the overall description of an episode lasting at least 2 weeks included at least two items from the following list:

   - Depressed mood most of the time
   - Markedly diminished interest or pleasure in activities most of the time
   - Significant weight loss or weight gain (not better explained by another medical condition), or decrease/increase in appetite
   - Constant fatigue or loss of energy most of the time
   - Feelings of worthlessness and/or guilt most of the time
   - Thoughts of death, suicidal ideation or a suicide attempt

2. **Mania (0-1)** [1]

   The feature "mania" was given a score of "1" if a clinical episode of mania\hypomania and\or a diagnosis of "bipolar disorder" was explicitly mentioned in the clinical records.

3. **Hallucinations (0-1)** [1,2]

   The feature "hallucinations" was given a score of "1" if a clinical episode of hallucinations was explicitly mentioned in the clinical records and\or an episode was mentioned consisting of a false perception, namely a perception in the absence of an external stimulus that is experienced as real. Hallucinations in all sensory modalities were taken into account, as well as both elementary and complex hallucinations.

4. **Delusions (0-1)** [1,2]

   The feature "delusions" was given a score of "1" if a clinical episode of delusions was explicitly mentioned in the clinical records and\or an episode was mentioned consisting of false beliefs, namely beliefs based on wrong assumptions about external reality that persist despite contrary evidence.

5. **Disinhibition (0-3)** [3]

   The following "disinhibition" subcategories were given a score "1" if mentioned, "0" if not mentioned. The single scores were summed and the total score was used.

- Socially inappropriate behavior
- Loss of manners or decorum
- Impulsive, rash or careless actions

6. **Apathy\inertia (0-2)** [3]

   The following "apathy/inertia" subcategories were given a score "1" if mentioned, "0" if not mentioned. The single scores were summed and the total score was used.

   - Apathy
   - Inertia

7. **Perseverative\compulsive behavior (0-3)** [3]

   The following "perseverative\compulsive behaviour" subcategories were given a score "1" if mentioned, "0" if not mentioned. The single scores were summed and the total score was used.

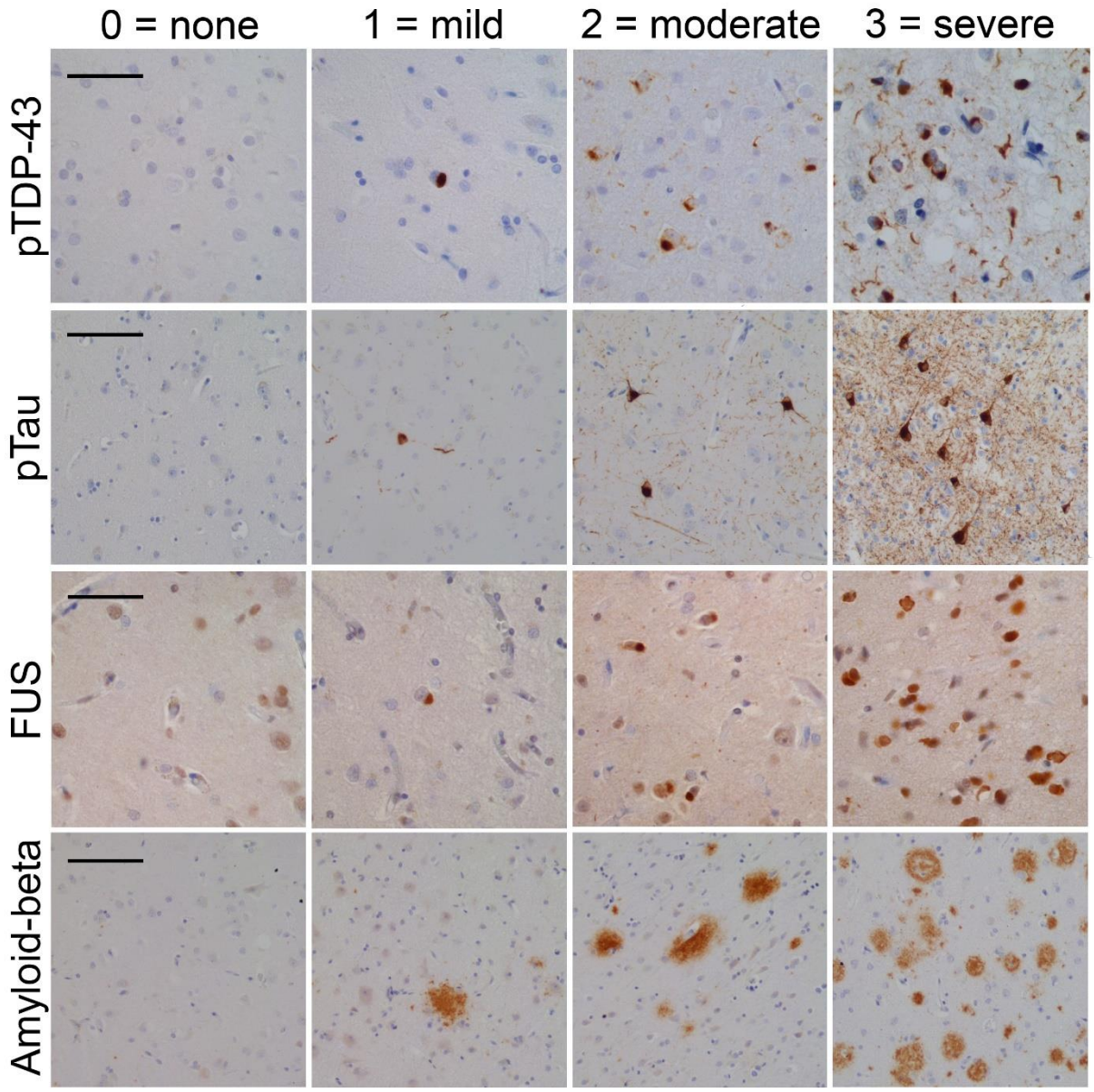
   - Simple repetitive movements
   - Complex, compulsive or ritualistic behaviors
   - Stereotypy of speech

8. **Hyperorality (0-3)** [3]

   The following "hyperorality" subcategories were given a score "1" if mentioned, "0" if not mentioned. The single scores were summed and the total score was used.

   - Altered food preferences
   - Binge eating, increased consumption of alcohol or cigarettes
   - Oral exploration or consumption of inedible objects

Supplementary Fig. 1 – Pathology scores



pTDP-43. The presence of pTDP-43 immunoreactive structures, namely neuronal cytoplasmic inclusions (NCI) and threads, was scored as follows at magnification x200: 0, absent; 1, mild (0-5 NCI or long threads, 0-10 small threads); 2, moderate (6-15 NCI or long threads, 11-25 small threads); 3, severe (>15 NCI or long threads, >25 small threads).[4] Scale bar = 50 µm.

pTau. The presence of pTau immunoreactive structures, at magnifications x100 and x200, was scored as follows: 0, absent; 1, mild (immunoreactivity barely noted at low magnification); 2, moderate (immunoreactivity easily seen at both magnifications); 3, severe (immunoreactivity seen even without the microscope).[5] Scale bar = 100 µm.

FUS. The presence of FUS immunoreactive structures, namely NCI or vermiform neuronal intranuclear inclusions (VNII), was scored as follows at magnification x200: 0, absent; 1, mild (<5 NCI or VNII); 2, moderate (6-15 NCI or VNII); 3, severe (>15 NCI or VNII). Scale bar = 50 μm.

Amyloid-beta. The presence of amyloid-beta (Aβ) plaques, at magnification x100, was scored as follows: 0, absent; 1, mild (1-5 plaques); 2, moderate (6-20 plaques); 3, severe (>20 plaques).[6] Scale bar = 100 μm.

Supplementary References

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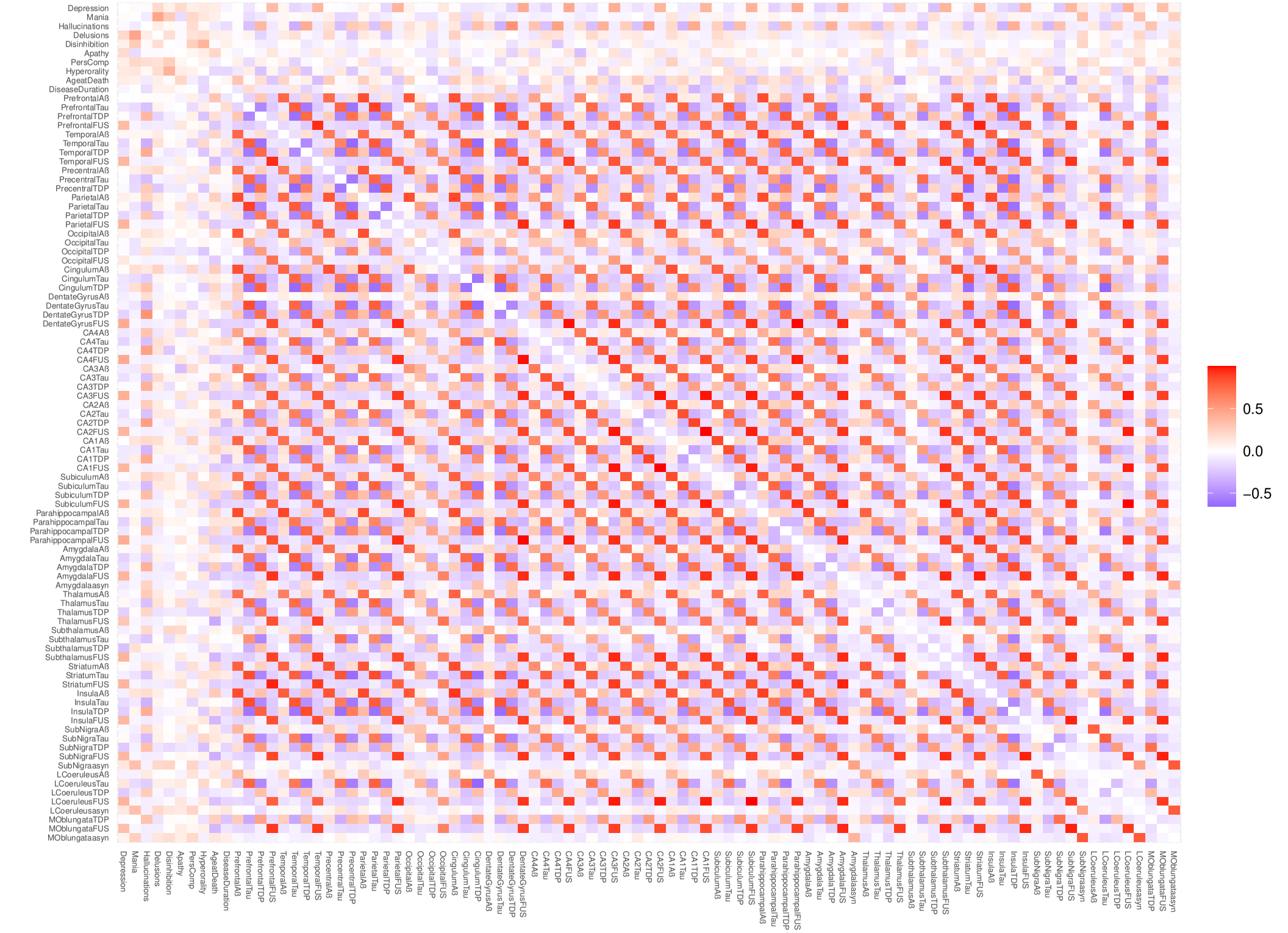
Supplementary Fig. 2 – Unthresholded partial correlations matrix

Supplementary Fig.3 – Partial correlations matrix with lFDR threshold = 0.01


Depression
Mania
Hallucinations
Delusions
Disinhibition
Apathy
PersComp
Hyperorality
AgeatDeath
DiseaseDuration
PrefrontalAß
PrefrontalTau
PrefrontalTDP
PrefrontalFUS
TemporalAß
TemporalTau
TemporalTDP
TemporalFUS
PrecentralAß
PrecentralTau
PrecentralTDP
ParietalAß
ParietalTau
ParietalTDP
ParietalFUS
OccipitalAß
OccipitalTau
OccipitalTDP
OccipitalFUS
CingulumAß
CingulumTau
CingulumTDP
DentateGyrusAß
DentateGyrusTau
DentateGyrusTDP
DentateGyrusFUS
CA4Aß
CA4Tau
CA4TDP
CA4FUS
CA3Aß
CA3Tau
CA3TDP
CA3FUS
CA2Aß
CA2Tau
CA2TDP
CA2FUS
CA1Aß
CA1Tau
CA1TDP
CA1FUS
SubiculumAß
SubiculumTau
SubiculumTDP
SubiculumFUS
ParahippocampalAß
ParahippocampalTau
ParahippocampalTDP
ParahippocampalFUS
AmygdalaAß
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AmygdalaFUS
Amygdalaasyn
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ThalamusTau
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SubthalamusTDP
SubthalamusFUS
StriatumAß
StriatumTau
StriatumFUS
InsulaAß
InsulaTau
InsulaTDP
InsulaFUS
SubNigraAß
SubNigraTau
SubNigraTDP
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SubNigraasyn
LCoeruleusAß
LCoeruleusTau
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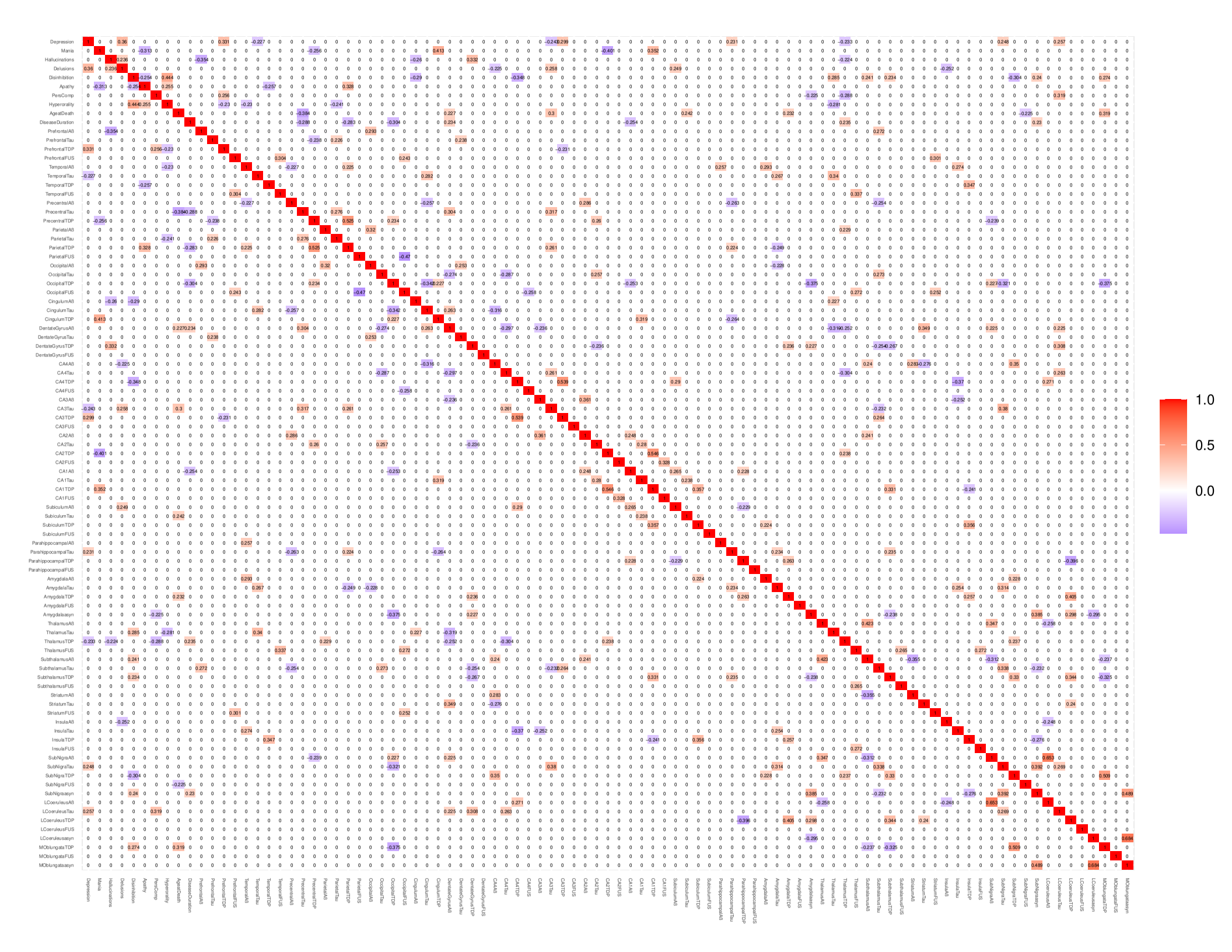
Depression
Mania
Hallucinations
Delusions
Disinhibition
Apathy
PersComp
Hyperorality
AgeatDeath
DiseaseDuration
PrefrontalA8
PrefrontalTau
PrefrontalTDP
PrefrontalFUS
TemporalA8
TemporalTau
TemporalTDP
TemporalFUS
PrecentralA8
PrecentralTau
PrecentralTDP
ParietalA8
ParietalTau
ParietalTDP
ParietalFUS
OccipitalA8
OccipitalTau
OccipitalTDP
OccipitalFUS
CingulumA8
CingulumTau
CingulumTDP
DentateGyrusA8
DentateGyrusTau
DentateGyrusTDP
DentateGyrusFUS
CA4A8
CA4Tau
CA4TDP
CA4FUS
CA3A8
CA3Tau
CA3TDP
CA3FUS
CA2A8
CA2Tau
CA2TDP
CA2FUS
CA1A8
CA1Tau
CA1TDP
CA1FUS
SubiculumA8
SubiculumTau
SubiculumTDP
SubiculumFUS
ParahippocampalA8
ParahippocampalTau
ParahippocampalTDP
ParahippocampalFUS
AmygdalaA8
AmygdalaTau
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AmygdalaFUS
Amygdalaasyn
ThalamusA8
ThalamusTau
ThalamusTDP
ThalamusFUS
SubthalamusA8
SubthalamusTau
SubthalamusTDP
SubthalamusFUS
StriatumA8
StriatumTau
StriatumFUS
InsulaA8
InsulaTau
InsulaTDP
InsulaFUS
SubNigraA8
SubNigraTau
SubNigraTDP
SubNigraFUS
SubNigraasyn
LCoeruleusA8
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LCoeruleusFUS
LCoeruleusasyn
MOblongataTDP
MOblongataFUS
MOblongataasyn
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0.5
0.0

Supplementary Table 1A - Correlations between regional cumulative pathology burden and psychiatric symptoms in FTLD donors (*n* = 87)

Regional cumulative pathology burden[a]	Depression	Mania	Hallucinations	Delusions
Prefrontal	0.104 (0.336)	-0.204 (0.058)	-0.004 (0.969)	-0.144 (0.183)
Temporal	-0.073 (0.503)	0.029 (0.791)	0.073 (0.503)	0.125 (0.247)
Precentral	0.031 (0.773)	-0.164 (0.128)	0.093 (0.392)	-0.033 (0.760)
Parietal	0.021 (0.849)	-0.091 (0.402)	0.133 (0.220)	0.031 (0.774)
Occipital	0.091 (0.403)	-0.067 (0.536)	0.174 (0.106)	0.072 (0.510)
Cingulum	-0.002 (0.983)	0.001 (0.992)	0.047 (0.665)	0.139 (0.200)
Dentate gyrus	0.025 (0.819)	-0.194 (0.072)	0.120 (0.268)	0.058 (0.596)
CA4	-0.109 (0.314)	-0.090 (0.410)	0.098 (0.368)	0.201 (0.062)
CA3	-0.37 (0.737)	-0.087 (0.424)	0.051 (0.639)	0.221 (0.040)
CA2	-0.020 (0.852)	-0.070 (0.522)	0.187 (0.083)	0.154 (0.155)
CA1	0.006 (0.957)	0.082 (0.448)	0.100 (0.359)	0.171 (0.114)
Subiculum	-0.010 (0.928)	0.007 (0.951)	0.051 (0.641)	0.171 (0.112)
Parahippocampal	-0.079 (0.468)	0.091 (0.400)	0.031 (0.776)	0.110 (0.312)
Amygdala	-0.107 (0.323)	-0.026 (0.813)	0.081 (0.454)	0.033 (0.760)
Thalamus	-0.103 (0.343)	-0.032 (0.769)	-0.073 (0.503)	-0.023 (0.834)
Subthalamus	0.032 (0.769)	-0.084 (0.439)	-0.271 (0.011)	-0.010 (0.929)
Striatum	-0.001 (0.992)	-0.076 (0.483)	0.066 (0.541)	0.120 (0.268)
Insula	-0.222 (0.038)	0.027 (0.805)	0.126 (0.245)	0.053 (0.626)
Substantia nigra	-0.002 (0.983)	-0.168 (0.120)	-0.006 (0.953)	0.015 (0.892)
Locus coeruleus	0.147 (0.174)	-0.194 (0.072)	-0.124 (0.251)	0.048 (0.658)
Medulla oblongata	0.147 (0.175)	-0.052 (0.630)	-0.111 (0.307)	0.078 (0.470)

[a]Regional cumulative pathology score is the sum of TDP-43, tau, amyloid-beta and alpha-synuclein regional scores.
Values in the table indicate Spearman's correlation coefficient (uncorrected *P*-value).

Supplementary Table 1B - Correlations between regional cumulative pathology burden and behavioural symptoms in FTLD donors (*n* = 87)

Regional cumulative pathology burden[a]	Disinhibition	Apathy	Pers/comp	Hyperorality
Prefrontal	-0.082 (0.449)	-0.003 (0.981)	-0.162 (0.135)	0.018 (0.378)
Temporal	-0.083 (0.442)	-0.046 (0.670)	-0.172 (0.111)	-0.145 (0.180)
Precentral	-0.041 (0.705)	0.001 (0.990)	-0.016 (0.886)	-0.059 (0.585)
Parietal	0.014 (0.898)	0.185 (0.087)	-0.015 (0.888)	-0.110 (0.312)
Occipital	-0.033 (0.759).	-0.040 (0.710)	0.020 (0.853)	-0.116 (0.283)
Cingulum	0.025 (0.816)	0.056 (0.605)	0.002 (0.988)	0.018 (0.868)
Dentate gyrus	-0.109 (0.314)	0.047 (0.665)	-0.126 (0.245)	-0.050 (0.644)
CA4	-0.061 (0.573)	0.032 (0.769)	0.047 (0.665)	-0.011 (0.917)
CA3	-0.087 (0.426)	0.049 (0.655)	0.027 (0.802)	-0.099 (0.360)
CA2	0.033 (0.762)	0.076 (0.486)	0.064 (0.559)	-0.033 (0.762)
CA1	0.060 (0.581)	0.004 (0.972)	0.079 (0.465)	-0.020 (0.856)
Subiculum	0.163 (0.131)	0.072 (0.510)	0.015 (0.890)	0.086 (0.426)
Parahippocampal	0.026 (0.808)	0.017 (0.875)	-0.002 (0.987)	-0.211 (0.050)
Amygdala	-0.127 (0.241)	0.075 (0.492)	0.003 (0.981)	-0.117 (0.280)
Thalamus	-0.057 (0.602)	0.043 (0.694)	-0.246 (0.022)	-0.057 (0.599)
Subthalamus	-0.127 (0.240)	0.132 (0.223)	-0.127 (0.240)	0.114 (0.294)
Striatum	0.026 (0.808)	-0.082 (0.452)	0.060 (0.583)	0.032 (0.767)
Insula	-0.083 (0.443)	-0.008 (0.940)	-0.038 (0.725)	-0.108 (0.319)
Substantia nigra	-0.083 (0.444)	-0.018 (0.868)	-0.140 (0.196)	0.114 (0.292)
Locus coeruleus	0.007 (0.947)	0.080 (0.462)	0.023 (0.835)	0.201 (0.061)
Medulla oblongata	-0.017 (0.873)	0.133 (0.220)	-0.035 (0.749)	0.190 (0.079)

[a]Regional cumulative pathology score is the sum of TDP-43, tau, amyloid-beta and alpha-synuclein regional scores.
Values in the table indicate Spearman's correlation coefficient (uncorrected *P*-value).

Supplementary Table 2 - Comparison of regional TDP-43 burden in FTLD-TDP donors between *C9orf72* carriers (*n* = 15) and non-carriers (*n* = 31)

Regional TDP-43 pathology burden	*P*-value[a]
Prefrontal	0.018
Temporal	0.226
Precentral	0.093
Parietal	0.97
Occipital	0.24
Cingulum	0.017
Dentate gyrus	0.324
CA4	0.252
CA3	0.324
CA2	0.446
CA1	0.374
Subiculum	0.568
Parahippocampal	0.141
Amygdala	0.826
Thalamus	0.343
Subthalamus	0.339
Striatum	0.24
Insula	0.255
Substantia nigra	0.506
Locus coeruleus	0.326
Medulla oblongata	0.65

[a]*P*-values in the table refer to Mann-Whitney U tests, uncorrected for multiple comparisons

Supplementary Table 3 – Frequency of psychiatric symptoms in FTLD-TDP brain donors with (*n* = 14) and without (*n* = 32) hippocampal sclerosis

	Hippocampal sclerosis present	Hippocampal sclerosis absent	*P*-value[a]
Depression	1/14 (7.1%)	5/32 (15.6%)	0.65
Mania	1/14 (7.1%)	2/32 (6.3%)	1.0
Hallucinations	3/14 (21.4%)	8/32 (25%)	1.0
Delusions	2/14 (14.3%)	2/32 (6.3%)	0.57

[a]*P*-values refer to Pearson's chi-squared tests, uncorrected for multiple comparisons

Supplementary Table 4 - Comparison of regional TDP-43 burden in FTLD-TDP donors with (*n* = 14) and without (*n* = 32) hippocampal sclerosis

Regional TDP-43 pathology burden	P-value[a]
Prefrontal	0.727
Temporal	0.763
Precentral	0.104
Parietal	0.664
Occipital	0.782
Cingulum	0.592
Dentate gyrus	0.788
CA4	0.219
CA3	0.530
CA2	0.596
CA1	0.816
Subiculum	0.837
Parahippocampal	0.901
Amygdala	0.439
Thalamus	0.916
Subthalamus	0.070
Striatum	0.059
Insula	0.626
Substantia nigra	0.730
Locus coeruleus	0.738
Medulla oblongata	0.901

[a]*P*-values in the table refer to Mann-Whitney U tests, uncorrected for multiple comparisons