

# **Profiles in Genetic Frontotemporal Dementia: A Meta-Analysis and Systematic Review**

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## SUPPLEMENTARY DATA

### Appendix A. Search terms used for this meta-analysis.

| Database searched                              | Platform         | Years of coverage | Records | Records after duplicates removed |
|------------------------------------------------|------------------|-------------------|---------|----------------------------------|
| Embase                                         | Embase.com       | 1971 - Present    | 2179    | 2159                             |
| Medline ALL                                    | Ovid             | 1946 - Present    | 1286    | 243                              |
| Web of Science Core Collection*                | Web of Knowledge | 1975 - Present    | 2053    | 833                              |
| PsycINFO                                       | Ovid             | 1806 - Present    | 906     | 195                              |
| Cochrane Central Register of Controlled Trials | Wiley            | 1992 - Present    | 18      | 4                                |
| Additional Search Engines: Google Scholar      |                  |                   | 200     | 100                              |
| Total                                          |                  |                   | 6642    | 3534                             |

\*Science Citation Index Expanded (1975-present); Social Sciences Citation Index (1975-present); Arts & Humanities Citation Index (1975-present); Conference Proceedings Citation Index- Science (1990-present); Conference Proceedings Citation Index - Social Science & Humanities (1990-present); Emerging Sources Citation Index (2005-present).

Embase.com

('frontotemporal dementia'/exp OR 'Pick presenile dementia'/de OR 'tauopathy'/de OR (((frontotemporal\* OR fronto-temporal\*) NEAR/3 (dementia\* OR degenerat\*)) OR tauopath\* OR FTD OR FTLD OR (pick\* NEAR/3 disease\*) OR progressive-aphasia\*):ab,ti,kw) AND ('genetics'/exp OR 'heredity'/exp OR 'progranulin'/exp OR 'valosin containing protein'/de OR (heredit\* OR famil\* OR genet\* OR MAPT OR microtubule-associated-protein-tau\* OR GRN OR progranulin\* OR granulin\* OR C9ORF72 OR Chromosome-9-open-reading-frame\* OR TBK1 OR tank-binding-kinase-1\* OR FUS OR fused-in-sarcoma\* OR VCP OR valosin-containing-protein\* OR CHMP2B OR charged-multivesicular-body-protein-2B):ab,ti,kw) AND ('cognition'/de OR 'attention'/de OR 'executive function'/de OR 'memory'/exp OR 'memory disorder'/de OR 'social cognition'/de OR 'neuropsychological test'/de OR 'language'/de OR (cognit\* OR attention\* OR ((executive\*) NEAR/3 (function\* OR control\*)) OR memor\* OR neuropsychological\* OR language\*):ab,ti,kw) NOT ((animal/exp OR animal\*:de OR nonhuman/de) NOT ('human'/exp)) NOT [review]/lim NOT [conference abstract]/lim

Medline

(exp Frontotemporal Dementia/ OR Tauopathies/ OR (((frontotemporal\* OR fronto-temporal\*) ADJ3 (dementia\* OR degenerat\*)) OR tauopath\* OR FTD OR FTLD OR (pick\* ADJ3 disease\*) OR progressive-aphasia\*):ab,ti,kf.) AND (exp Genetics/ OR Heredity/ OR exp Progranulins/ OR Valosin Containing Protein/ OR (heredit\* OR famil\* OR genet\* OR MAPT OR microtubule-associated-protein-tau\* OR GRN OR progranulin\* OR granulin\* OR C9ORF72 OR Chromosome-9-open-reading-frame\* OR TBK1 OR tank-binding-kinase-1\* OR FUS OR fused-in-sarcoma\* OR VCP OR valosin-containing-protein\* OR CHMP2B OR charged-multivesicular-body-protein-2B):ab,ti,kf.) AND (Cognition/ OR Attention/ OR Executive Function/ OR exp Memory/ OR Memory Disorders/ OR Neuropsychological Tests/ OR Language/ OR (cognit\* OR attention\* OR ((executive\*) ADJ3 (function\* OR control\*)) OR memor\* OR neuropsychological\* OR language\*):ab,ti,kf.) NOT (exp animals/ NOT humans/) NOT (news OR comment\* OR editorial\* OR congres\* OR abstract\* OR book\* OR chapter\* OR dissertation abstract\* OR review\*).pt.

Web of Science

TS=(((frontotemporal\* OR fronto-temporal\*) NEAR/2 (dementia\* OR degenerat\*)) OR tauopath\* OR FTD OR FTLD OR (pick\* NEAR/2 disease\*) OR progressive-aphasia\*)) AND ((heredit\* OR famil\* OR genet\* OR MAPT OR microtubule-associated-protein-tau\* OR GRN OR progranulin\* OR granulin\* OR C9ORF72 OR

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Chromosome-9-open-reading-frame\* OR TBK1 OR tank-binding-kinase-1\* OR FUS OR fused-in-sarcoma\* OR VCP OR valosin-containing-protein\* OR CHMP2B OR charged-multivesicular-body-protein-2B)) AND ((cognit\* OR attention\* OR ((executive\*) NEAR/2 (function\* OR control\*)) OR memor\* OR neuropsychological\* OR language\*)) NOT ((animal\* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent\* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar\* OR chick\* OR zebrafish\* OR baboon\* OR nonhuman\* OR primate\* OR cattle\* OR goose OR geese OR duck OR macaque\* OR avian\* OR bird\* OR fish\*) NOT (human\* OR patient\* OR women OR woman OR men OR man))) AND DT=(Article OR Review OR Letter OR Early Access)

Cochrane

(((((frontotemporal\* OR fronto NEXT temporal\*) NEAR/3 (dementia\* OR degenerat\*)) OR tauopath\* OR FTD OR FTLD OR (pick\* NEAR/3 disease\*) OR progressive NEXT aphasia\*):ab,ti,kw) AND ((heredit\* OR famil\* OR genet\* OR MAPT OR microtubule NEXT associated NEXT protein NEXT tau\* OR GRN OR progranulin\* OR granulin\* OR C9ORF72 OR "Chromosome 9 open reading frame" OR TBK1 OR tank NEXT binding NEXT kinase NEXT 1\* OR FUS OR fused NEXT in NEXT sarcoma\* OR VCP OR valosin NEXT containing NEXT protein\* OR CHMP2B OR charged NEXT multivesicular NEXT body NEXT protein NEXT 2B):ab,ti,kw) AND ((cognit\* OR attention\* OR ((executive\*) NEAR/3 (function\* OR control\*)) OR memor\* OR neuropsychological\* OR language\*):ab,ti,kw) NOT "conference abstract":pt

PsycINFO

(Semantic Dementia/ OR Picks Disease/ OR (((frontotemporal\* OR fronto-temporal\*) ADJ3 (dementia\* OR degenerat\*)) OR tauopath\* OR FTD OR FTLD OR (pick\* ADJ3 disease\*) OR progressive-aphasia\*).ab,ti.) AND (exp Genetics/ OR (heredit\* OR famil\* OR genet\* OR MAPT OR microtubule-associated-protein-tau\* OR GRN OR progranulin\* OR granulin\* OR C9ORF72 OR Chromosome-9-open-reading-frame\* OR TBK1 OR tank-binding-kinase-1\* OR FUS OR fused-in-sarcoma\* OR VCP OR valosin-containing-protein\* OR CHMP2B OR charged-multivesicular-body-protein-2B).ab,ti.) AND (Cognition/ OR Attention/ OR Executive Function/ OR exp Memory/ OR Memory Disorders/ OR Social Cognition/ OR Neuropsychological Assessment/ OR Language/ OR (cognit\* OR attention\* OR ((executive\*) ADJ3 (function\* OR control\*)) OR memor\* OR neuropsychological\* OR language\*).ab,ti.) NOT ((animal.po. OR exp animals/) NOT human.po.) NOT (news OR comment\* OR editorial\* OR congres\* OR abstract\* OR book\* OR chapter\* OR dissertation abstract\* OR review\*).pt.

Google Scholar

'frontotemporal|fronto-temporal dementia|degeneration'|tauopathy|tauopathies|FTD|FTLD|'pick|picks disease' hereditary|familial|genetic|genetics cognition|attention|'executive function|control'|memory|neuropsychological|language

### Appendix B. Overview of cognitive domains and processes, and tests assigned in meta-analysis.

| Cognitive domain                    | Cognitive process      | Tests                                                                      |
|-------------------------------------|------------------------|----------------------------------------------------------------------------|
| Language                            | Naming                 | (abbreviated) BNT, MINT, graded naming test                                |
|                                     | Fluency                | Semantic and letter fluency tests                                          |
|                                     | Semantic processing    | Modified Camel & Cactus Test, SAT verbal, Pyramids & Palm trees            |
| Attention & mental processing speed | Attention              | TMT A, Digit Span forwards, Stroop CWT card 1 and 2, Spatial Span forwards |
|                                     | Information processing | LDST, Digit Symbol test                                                    |
| Executive function                  | Working memory         | Digit Span backwards, Spatial Span backwards, Letter Number Sequencing     |
|                                     | Inhibitory control     | Stroop CWT card 3, Hayling test                                            |

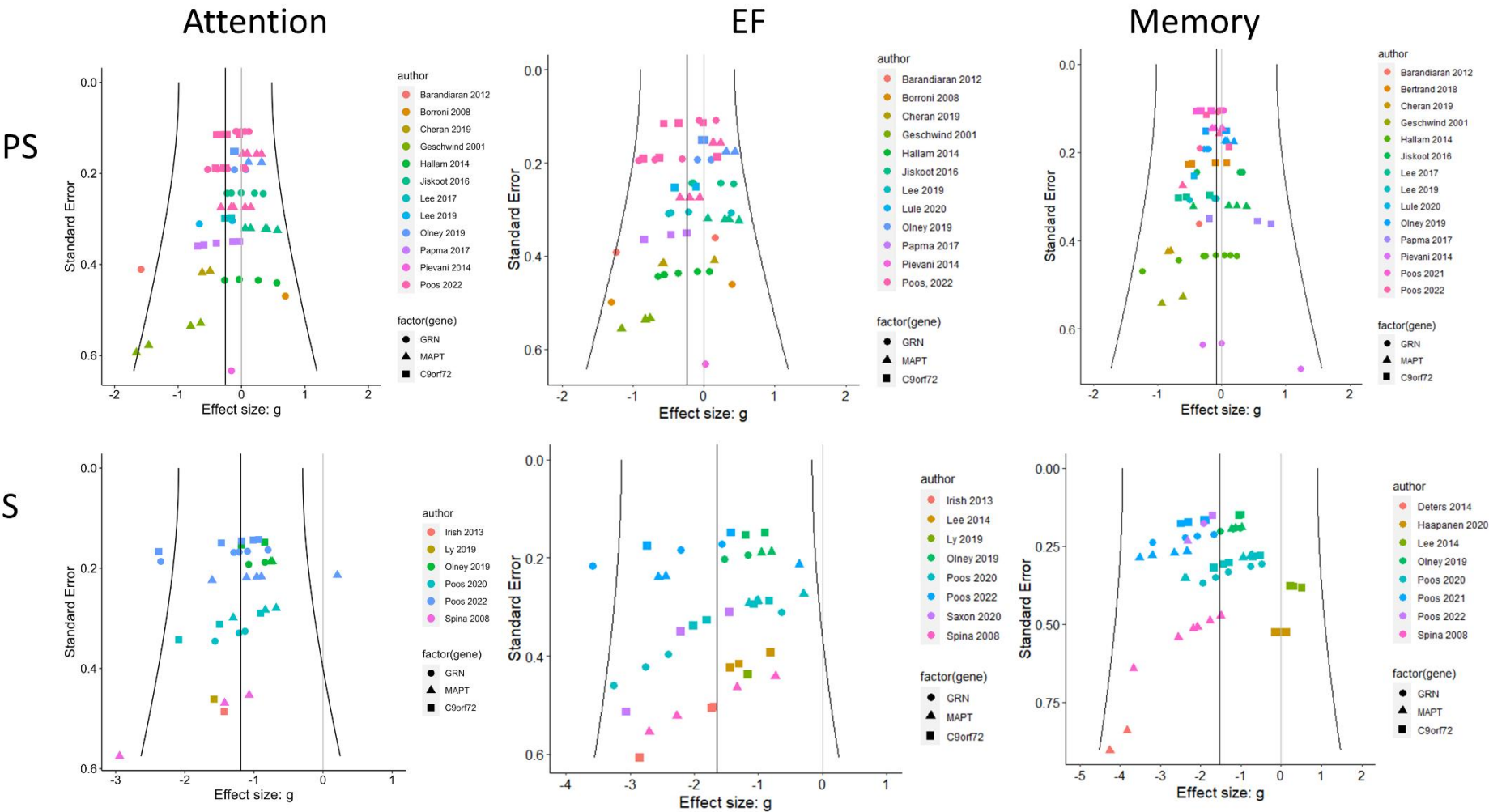
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|                        |                                      |                                                                                                                                                                                                                                                                                      |
|------------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        | Cognitive flexibility                | TMT B, (m)WCST, design fluency, Brixton test, D-KEFS sorting test                                                                                                                                                                                                                    |
| Memory                 | Immediate recall                     | RAVLT immediate recall, RBMT immediate recall, CERAD word list immediate recall, logical memory immediate recall, Craft immediate recall, FCSRT immediate recall, CVLT immediate recall, SRT immediate recall                                                                        |
|                        | Delayed free recall                  | Benson Figure recall, RAVLT delayed recall, RBMT delayed recall, CERAD word list delayed recall, RCF delayed recall, logical memory delayed recall, Craft delayed recall, FCSRT delayed recall, CVLT free recall, short story recall, SRT delayed recall, Visual Reproduction recall |
|                        | Cued free recall                     | Benson Figure recognition, RAVLT recognition, VAT, CVLT cued recall, CERAD word list recognition, Doors B                                                                                                                                                                            |
| Social cognition       | Perception and automatic attribution | ERT, facial emotion recognition, Ekman 60 faces, mini-SEA emotion recognition                                                                                                                                                                                                        |
|                        | Understanding and Interpretation     | Faux-pas, Happé cartoons, mini-SEA faux-pas                                                                                                                                                                                                                                          |
|                        | Reasoning and Regulation             | SNQ                                                                                                                                                                                                                                                                                  |
| Visuospatial abilities | Visuoconstruction                    | Block design, Benson Figure copy, clock drawing, RCF copy, CERAD constructional praxis, Visual Reproduction                                                                                                                                                                          |

Abbreviations: BNT, Boston Naming Test; MINT, Multilingual Naming Test; SAT, Semantic Association Test; TMT, Trail Making Test; CWT, colour word test; LDST, Letter Digit Substitution Test; (m)WCST, (modified) Wisconsin Card Sorting Test; D-KEFS, Delis-Kaplan Executive Function System; RAVLT, Rey Auditory Verbal Learning Test; RBMT; Rivermead Behavioural Memory Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; FCSRT, Free and Cued Selective Reminding Test; CVLT, California Verbal Learning Test; SRT, Selective Reminding Test; RCF, Rey-Osterrieth Complex Figure; ERT, Emotion Recognition Test; mini-SEA, mini Social Cognition & Emotional Assessment; SNQ, Social Norms Questionnaire.

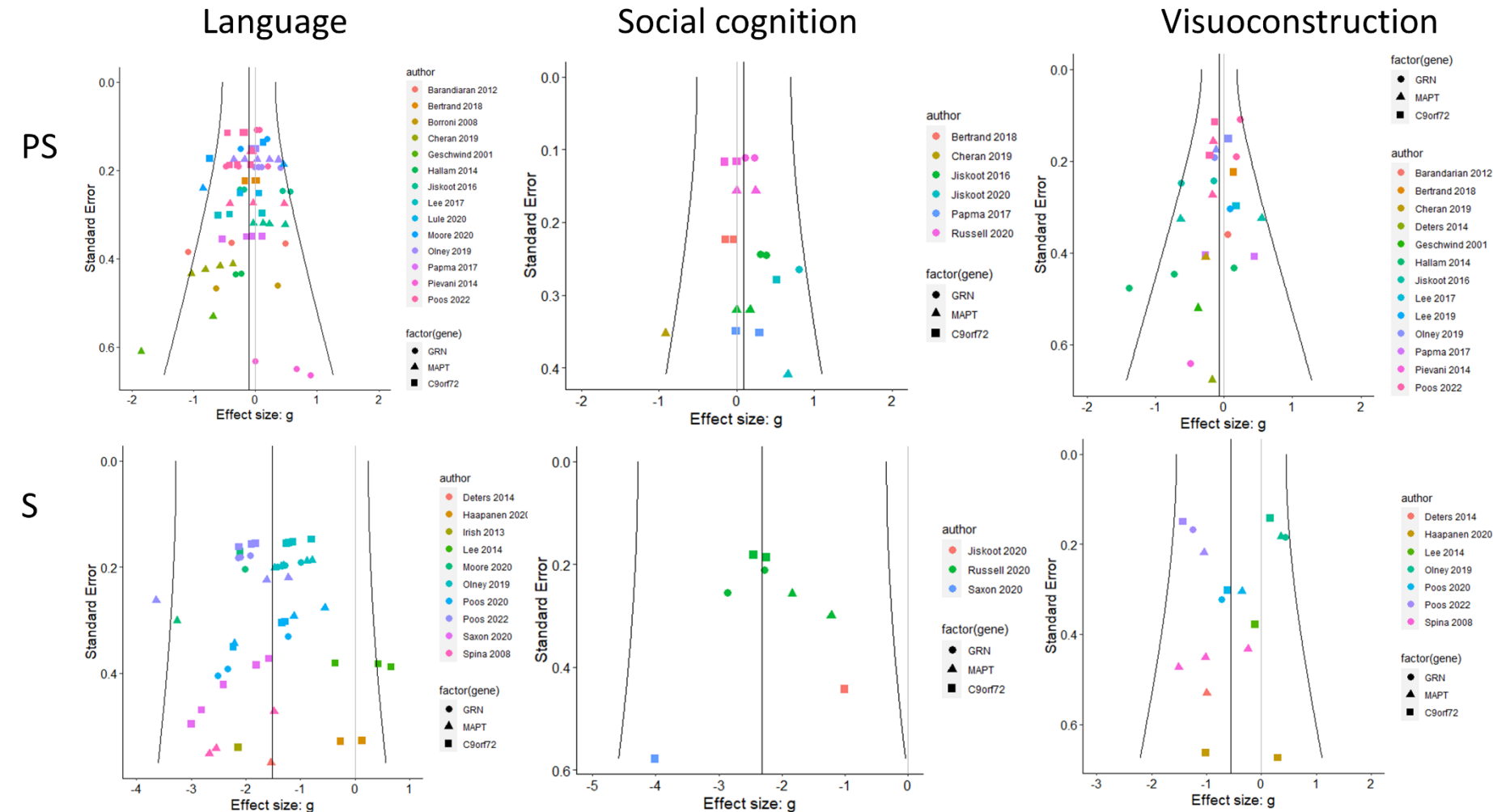
Appendix C. Figures

Fig C.1 Funnel plot for attention, executive function, and memory in presymptomatic and symptomatic mutation carriers.



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Figure C.2. Funnel plot for language, social cognition, and visuoconstruction in presymptomatic and symptomatic mutation carriers.



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Appendix D. Overview of the sample sizes included in the meta-analysis for each cognitive domain and sub-process.

| Domain   | Subprocess   | <i>n</i> mutation carriers    |      | <i>n</i> controls |
|----------|--------------|-------------------------------|------|-------------------|
| Language | Total domain | Total sample                  | 3613 | 2001              |
|          |              | Total <i>GRN</i>              | 1114 |                   |
|          |              | Total <i>MAPT</i>             | 850  |                   |
|          |              | Total <i>C9orf72</i>          | 1619 |                   |
|          |              | Total presymptomatic          | 2132 |                   |
|          |              | Presymptomatic <i>GRN</i>     | 817  |                   |
|          |              | Presymptomatic <i>MAPT</i>    | 589  |                   |
|          |              | Presymptomatic <i>C9orf72</i> | 841  |                   |
|          |              | Total symptomatic             | 1336 |                   |
|          |              | Symptomatic <i>GRN</i>        | 297  |                   |
|          |              | Symptomatic <i>MAPT</i>       | 261  |                   |
|          |              | Symptomatic <i>C9orf72</i>    | 778  |                   |
|          | Naming       | Total sample                  | 1253 | 597               |
|          |              | Total <i>GRN</i>              | 379  |                   |
|          |              | Total <i>MAPT</i>             | 252  |                   |
|          |              | Total <i>C9orf72</i>          | 622  |                   |
|          |              | Total presymptomatic          | 706  |                   |
|          |              | Presymptomatic <i>GRN</i>     | 270  |                   |
|          |              | Presymptomatic <i>MAPT</i>    | 145  |                   |
|          |              | Presymptomatic <i>C9orf72</i> | 291  |                   |
|          |              | Total symptomatic             | 547  |                   |
|          |              | Symptomatic <i>GRN</i>        | 109  |                   |
|          |              | Symptomatic <i>MAPT</i>       | 107  |                   |
|          |              | Symptomatic <i>C9orf72</i>    | 331  |                   |
|          | Fluency      | Total sample                  | 1445 |                   |
|          |              | Total <i>GRN</i>              | 524  |                   |
|          |              | Total <i>MAPT</i>             | 260  |                   |
|          |              | Total <i>C9orf72</i>          | 661  |                   |

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|                                     |                     |                               |      |      |
|-------------------------------------|---------------------|-------------------------------|------|------|
|                                     |                     | Total presymptomatic          | 728  | 785  |
|                                     |                     | Presymptomatic <i>GRN</i>     | 415  |      |
|                                     |                     | Presymptomatic <i>MAPT</i>    | 145  |      |
|                                     |                     | Presymptomatic <i>C9orf72</i> | 313  |      |
|                                     |                     | Total symptomatic             | 572  |      |
|                                     |                     | Symptomatic <i>GRN</i>        | 109  |      |
|                                     |                     | Symptomatic <i>MAPT</i>       | 115  |      |
|                                     |                     | Symptomatic <i>C9orf72</i>    | 348  |      |
|                                     | Semantic processing | Total sample                  | 915  | 619  |
|                                     |                     | Total <i>GRN</i>              | 211  |      |
|                                     |                     | Total <i>MAPT</i>             | 338  |      |
|                                     |                     | Total <i>C9orf72</i>          | 336  |      |
|                                     |                     | Total presymptomatic          | 698  |      |
|                                     |                     | Presymptomatic <i>GRN</i>     | 132  |      |
|                                     |                     | Presymptomatic <i>MAPT</i>    | 299  |      |
|                                     |                     | Presymptomatic <i>C9orf72</i> | 237  |      |
|                                     |                     | Total symptomatic             | 217  |      |
|                                     |                     | Symptomatic <i>GRN</i>        | 79   |      |
|                                     |                     | Symptomatic <i>MAPT</i>       | 39   |      |
|                                     |                     | Symptomatic <i>C9orf72</i>    | 99   |      |
| Attention & mental processing speed | Total domain        | Total sample                  | 3684 | 1437 |
|                                     |                     | Total <i>GRN</i>              | 1287 |      |
|                                     |                     | Total <i>MAPT</i>             | 676  |      |
|                                     |                     | Total <i>C9orf72</i>          | 1721 |      |
|                                     |                     | Total presymptomatic          | 2282 |      |
|                                     |                     | Presymptomatic <i>GRN</i>     | 1049 |      |
|                                     |                     | Presymptomatic <i>MAPT</i>    | 400  |      |
|                                     |                     | Presymptomatic <i>C9orf72</i> | 833  |      |
|                                     |                     | Total symptomatic             | 1494 |      |
|                                     |                     | Symptomatic <i>GRN</i>        | 330  |      |



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|                    |                        |                               |      |      |
|--------------------|------------------------|-------------------------------|------|------|
|                    |                        | Symptomatic <i>MAPT</i>       | 276  |      |
|                    |                        | Symptomatic <i>C9orf72</i>    | 888  |      |
|                    | Attention              | Total sample                  | 3043 | 1041 |
|                    |                        | Total <i>GRN</i>              | 1043 |      |
|                    |                        | Total <i>MAPT</i>             | 579  |      |
|                    |                        | Total <i>C9orf72</i>          | 1421 |      |
|                    |                        | Total presymptomatic          | 1760 |      |
|                    |                        | Presymptomatic <i>GRN</i>     | 759  |      |
|                    |                        | Presymptomatic <i>MAPT</i>    | 327  |      |
|                    |                        | Presymptomatic <i>C9orf72</i> | 674  |      |
|                    |                        | Total symptomatic             | 1283 |      |
|                    |                        | Symptomatic <i>GRN</i>        | 284  |      |
|                    |                        | Symptomatic <i>MAPT</i>       | 252  |      |
|                    |                        | Symptomatic <i>C9orf72</i>    | 747  |      |
|                    | Information processing | Total sample                  | 641  | 396  |
|                    |                        | Total <i>GRN</i>              | 244  |      |
|                    |                        | Total <i>MAPT</i>             | 97   |      |
|                    |                        | Total <i>C9orf72</i>          | 300  |      |
|                    |                        | Total presymptomatic          | 522  |      |
|                    |                        | Presymptomatic <i>GRN</i>     | 290  |      |
|                    |                        | Presymptomatic <i>MAPT</i>    | 73   |      |
|                    |                        | Presymptomatic <i>C9orf72</i> | 159  |      |
|                    |                        | Total symptomatic             | 211  |      |
|                    |                        | Symptomatic <i>GRN</i>        | 46   |      |
|                    |                        | Symptomatic <i>MAPT</i>       | 24   |      |
|                    |                        | Symptomatic <i>C9orf72</i>    | 141  |      |
| Executive function | Total domain           | Total sample                  | 3568 |      |
|                    |                        | Total <i>GRN</i>              | 1123 |      |
|                    |                        | Total <i>MAPT</i>             | 724  |      |
|                    |                        | Total <i>C9orf72</i>          | 1721 |      |

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|  |                    |                               |      |      |
|--|--------------------|-------------------------------|------|------|
|  |                    | Total presymptomatic          | 2000 | 1945 |
|  |                    | Presymptomatic <i>GRN</i>     | 819  |      |
|  |                    | Presymptomatic <i>MAPT</i>    | 410  |      |
|  |                    | Presymptomatic <i>C9orf72</i> | 771  |      |
|  |                    | Total symptomatic             | 1568 |      |
|  |                    | Symptomatic <i>GRN</i>        | 304  |      |
|  |                    | Symptomatic <i>MAPT</i>       | 314  |      |
|  |                    | Symptomatic <i>C9orf72</i>    | 950  |      |
|  | Working memory     | Total sample                  | 1178 | 630  |
|  |                    | Total <i>GRN</i>              | 376  |      |
|  |                    | Total <i>MAPT</i>             | 252  |      |
|  |                    | Total <i>C9orf72</i>          | 550  |      |
|  |                    | Total presymptomatic          | 662  |      |
|  |                    | Presymptomatic <i>GRN</i>     | 267  |      |
|  |                    | Presymptomatic <i>MAPT</i>    | 145  |      |
|  |                    | Presymptomatic <i>C9orf72</i> | 250  |      |
|  |                    | Total symptomatic             | 516  |      |
|  |                    | Symptomatic <i>GRN</i>        | 109  |      |
|  |                    | Symptomatic <i>MAPT</i>       | 107  |      |
|  |                    | Symptomatic <i>C9orf72</i>    | 300  |      |
|  | Inhibitory control | Total sample                  | 861  | 501  |
|  |                    | Total <i>GRN</i>              | 281  |      |
|  |                    | Total <i>MAPT</i>             | 147  |      |
|  |                    | Total <i>C9orf72</i>          | 433  |      |
|  |                    | Total presymptomatic          | 512  |      |
|  |                    | Presymptomatic <i>GRN</i>     | 215  |      |
|  |                    | Presymptomatic <i>MAPT</i>    | 85   |      |
|  |                    | Presymptomatic <i>C9orf72</i> | 212  |      |
|  |                    | Total symptomatic             | 349  |      |
|  |                    | Symptomatic <i>GRN</i>        | 66   |      |

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|        |                       |                               |      |      |
|--------|-----------------------|-------------------------------|------|------|
|        |                       | Symptomatic <i>MAPT</i>       | 62   |      |
|        |                       | Symptomatic <i>C9orf72</i>    | 221  |      |
|        | Cognitive flexibility | Total sample                  | 1529 | 814  |
|        |                       | Total <i>GRN</i>              | 466  |      |
|        |                       | Total <i>MAPT</i>             | 325  |      |
|        |                       | Total <i>C9orf72</i>          | 738  |      |
|        |                       | Total presymptomatic          | 826  |      |
|        |                       | Presymptomatic <i>GRN</i>     | 337  |      |
|        |                       | Presymptomatic <i>MAPT</i>    | 180  |      |
|        |                       | Presymptomatic <i>C9orf72</i> | 309  |      |
|        |                       | Total symptomatic             | 703  |      |
|        |                       | Symptomatic <i>GRN</i>        | 129  |      |
|        |                       | Symptomatic <i>MAPT</i>       | 145  |      |
|        |                       | Symptomatic <i>C9orf72</i>    | 429  |      |
| Memory | Total domain          | Total sample                  | 6820 | 2064 |
|        |                       | Total <i>GRN</i>              | 2049 |      |
|        |                       | Total <i>MAPT</i>             | 1487 |      |
|        |                       | Total <i>C9orf72</i>          | 3284 |      |
|        |                       | Total presymptomatic          | 3853 |      |
|        |                       | Presymptomatic <i>GRN</i>     | 1398 |      |
|        |                       | Presymptomatic <i>MAPT</i>    | 846  |      |
|        |                       | Presymptomatic <i>C9orf72</i> | 1609 |      |
|        |                       | Total symptomatic             | 2967 |      |
|        |                       | Symptomatic <i>GRN</i>        | 651  |      |
|        |                       | Symptomatic <i>MAPT</i>       | 641  |      |
|        |                       | Symptomatic <i>C9orf72</i>    | 1675 |      |
|        | Immediate recall      | Total sample                  | 1658 |      |
|        |                       | Total <i>GRN</i>              | 487  |      |
|        |                       | Total <i>MAPT</i>             | 379  |      |
|        |                       | Total <i>C9orf72</i>          | 792  |      |

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|  |                     |                               |      |     |
|--|---------------------|-------------------------------|------|-----|
|  |                     | Total presymptomatic          | 863  | 694 |
|  |                     | Presymptomatic <i>GRN</i>     | 315  |     |
|  |                     | Presymptomatic <i>MAPT</i>    | 181  |     |
|  |                     | Presymptomatic <i>C9orf72</i> | 367  |     |
|  |                     | Total symptomatic             | 795  |     |
|  |                     | Symptomatic <i>GRN</i>        | 172  |     |
|  |                     | Symptomatic <i>MAPT</i>       | 198  |     |
|  |                     | Symptomatic <i>C9orf72</i>    | 425  |     |
|  | Delayed free recall | Total sample                  | 2692 | 694 |
|  |                     | Total <i>GRN</i>              | 781  |     |
|  |                     | Total <i>MAPT</i>             | 592  |     |
|  |                     | Total <i>C9orf72</i>          | 1319 |     |
|  |                     | Total presymptomatic          | 1509 |     |
|  |                     | Presymptomatic <i>GRN</i>     | 520  |     |
|  |                     | Presymptomatic <i>MAPT</i>    | 349  |     |
|  |                     | Presymptomatic <i>C9orf72</i> | 640  |     |
|  |                     | Total symptomatic             | 1183 |     |
|  |                     | Symptomatic <i>GRN</i>        | 261  |     |
|  |                     | Symptomatic <i>MAPT</i>       | 243  |     |
|  |                     | Symptomatic <i>C9orf72</i>    | 679  |     |
|  | Cued free recall    | Total sample                  | 2470 | 676 |
|  |                     | Total <i>GRN</i>              | 781  |     |
|  |                     | Total <i>MAPT</i>             | 516  |     |
|  |                     | Total <i>C9orf72</i>          | 1173 |     |
|  |                     | Total presymptomatic          | 1481 |     |
|  |                     | Presymptomatic <i>GRN</i>     | 563  |     |
|  |                     | Presymptomatic <i>MAPT</i>    | 316  |     |
|  |                     | Presymptomatic <i>C9orf72</i> | 602  |     |
|  |                     | Total symptomatic             | 989  |     |
|  |                     | Symptomatic <i>GRN</i>        | 218  |     |

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|                  |                                      |                               |      |      |
|------------------|--------------------------------------|-------------------------------|------|------|
|                  |                                      | Symptomatic <i>MAPT</i>       | 200  |      |
|                  |                                      | Symptomatic <i>C9orf72</i>    | 571  |      |
| Social cognition | Total domain                         | Total sample                  | 1416 | 1044 |
|                  |                                      | Total <i>GRN</i>              | 585  |      |
|                  |                                      | Total <i>MAPT</i>             | 258  |      |
|                  |                                      | Total <i>C9orf72</i>          | 573  |      |
|                  |                                      | Total presymptomatic          | 950  |      |
|                  |                                      | Presymptomatic <i>GRN</i>     | 475  |      |
|                  |                                      | Presymptomatic <i>MAPT</i>    | 198  |      |
|                  |                                      | Presymptomatic <i>C9orf72</i> | 277  |      |
|                  |                                      | Total symptomatic             | 466  |      |
|                  |                                      | Symptomatic <i>GRN</i>        | 110  |      |
|                  |                                      | Symptomatic <i>MAPT</i>       | 60   |      |
|                  |                                      | Symptomatic <i>C9orf72</i>    | 296  |      |
|                  | Perception and automatic attribution | Total sample                  | 877  | 673  |
|                  |                                      | Total <i>GRN</i>              | 391  |      |
|                  |                                      | Total <i>MAPT</i>             | 166  |      |
|                  |                                      | Total <i>C9orf72</i>          | 320  |      |
|                  |                                      | Total presymptomatic          | 514  |      |
|                  |                                      | Presymptomatic <i>GRN</i>     | 313  |      |
|                  |                                      | Presymptomatic <i>MAPT</i>    | 124  |      |
|                  |                                      | Presymptomatic <i>C9orf72</i> | 77   |      |
|                  |                                      | Total symptomatic             | 363  |      |
|                  |                                      | Symptomatic <i>GRN</i>        | 78   |      |
|                  |                                      | Symptomatic <i>MAPT</i>       | 42   |      |
|                  |                                      | Symptomatic <i>C9orf72</i>    | 243  |      |
|                  | Understanding and Interpretation     | Total sample                  | 527  |      |
|                  |                                      | Total <i>GRN</i>              | 194  |      |
|                  |                                      | Total <i>MAPT</i>             | 80   |      |
|                  |                                      | Total <i>C9orf72</i>          | 253  |      |

SUPPLEMENTARY DATA

|                        |                          |                               |      |     |
|------------------------|--------------------------|-------------------------------|------|-----|
|                        |                          | Total presymptomatic          | 424  | 339 |
|                        |                          | Presymptomatic <i>GRN</i>     | 162  |     |
|                        |                          | Presymptomatic <i>MAPT</i>    | 62   |     |
|                        |                          | Presymptomatic <i>C9orf72</i> | 200  |     |
|                        |                          | Total symptomatic             | 103  |     |
|                        |                          | Symptomatic <i>GRN</i>        | 32   |     |
|                        |                          | Symptomatic <i>MAPT</i>       | 18   |     |
|                        |                          | Symptomatic <i>C9orf72</i>    | 53   |     |
|                        | Reasoning and Regulation | Total sample                  | 12   | 32  |
|                        |                          | Total <i>GRN</i>              | 0    |     |
|                        |                          | Total <i>MAPT</i>             | 12   |     |
|                        |                          | Total <i>C9orf72</i>          | 0    |     |
|                        |                          | Total presymptomatic          | 12   |     |
|                        |                          | Presymptomatic <i>GRN</i>     | 0    |     |
|                        |                          | Presymptomatic <i>MAPT</i>    | 12   |     |
|                        |                          | Presymptomatic <i>C9orf72</i> | 0    |     |
|                        |                          | Total symptomatic             | 0    |     |
|                        |                          | Symptomatic <i>GRN</i>        | 0    |     |
|                        |                          | Symptomatic <i>MAPT</i>       | 0    |     |
|                        |                          | Symptomatic <i>C9orf72</i>    | 0    |     |
| Visuospatial abilities | Total domain             | Total sample                  | 1299 | 740 |
|                        |                          | Total <i>GRN</i>              | 417  |     |
|                        |                          | Total <i>MAPT</i>             | 280  |     |
|                        |                          | Total <i>C9orf72</i>          | 602  |     |
|                        |                          | Total presymptomatic          | 775  |     |
|                        |                          | Presymptomatic <i>GRN</i>     | 308  |     |
|                        |                          | Presymptomatic <i>MAPT</i>    | 158  |     |
|                        |                          | Presymptomatic <i>C9orf72</i> | 309  |     |
|                        |                          | Total symptomatic             | 524  |     |
|                        |                          | Symptomatic <i>GRN</i>        | 109  |     |

SUPPLEMENTARY DATA

|  |                   |                               |      |     |
|--|-------------------|-------------------------------|------|-----|
|  |                   | Symptomatic <i>MAPT</i>       | 122  |     |
|  |                   | Symptomatic <i>C9orf72</i>    | 293  |     |
|  | Visuoconstruction | Total sample                  | 1299 | 740 |
|  |                   | Total <i>GRN</i>              | 417  |     |
|  |                   | Total <i>MAPT</i>             | 280  |     |
|  |                   | Total <i>C9orf72</i>          | 602  |     |
|  |                   | Total presymptomatic          | 775  |     |
|  |                   | Presymptomatic <i>GRN</i>     | 308  |     |
|  |                   | Presymptomatic <i>MAPT</i>    | 158  |     |
|  |                   | Presymptomatic <i>C9orf72</i> | 309  |     |
|  |                   | Total symptomatic             | 524  |     |
|  |                   | Symptomatic <i>GRN</i>        | 109  |     |
|  |                   | Symptomatic <i>MAPT</i>       | 122  |     |
|  |                   | Symptomatic <i>C9orf72</i>    | 293  |     |

Abbreviations: *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; *C9orf72*, chromosome 9 open reading frame 72.