Association of 10 VEGF Family Genes with Alzheimer's Disease Pathology at Single Cell Resolution

Yiyang Wu[1], Julia B Libby[1], Logan Dumitrescu[1,2], Philip L. De Jager[3,4], Vilas Menon[3], Julie A. Schneider[5], David A. Bennett[5], Timothy J Hohman[1,2]

[1]*Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN*

[2]*Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN*

[3]*Center for Translational & Computational Neuroimmunology, Department of Neurology, Columbia University Irving Medical Center, New York, NY*

[4]*Taub Institute for Research on Alzheimer's Disease and Aging Brain, Columbia University Irving Medical Center, New York, NY*

[5]*Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL*

21 **Abstract**

22 **Background**

23 The role of the vascular endothelial growth factors (VEGFs) in the pathogenesis of Alzheimer's
24 disease (AD) has been recently described, including notable changes along the VEGFB/FLT1
25 signaling pathway. However, cell-type specific alterations are yet to be characterized in depth.
26 In this study, we utilized a large single-nucleus RNA sequencing dataset (N = 424) to investigate
27 the effect of 10 VEGF genes' expression (*VEGFA*, *VEGFB*, *VEGFC*, *VEGFD*, *PGF*, *FLT1*, *FLT4*, *KDR*,
28 *NRP1*, and *NRP2*) on cognitive performance and AD pathology, as well as on the associated
29 VEGF signaling pathways in 8 cell types from postmortem human brains.

30 **Methods**

31 The single-nucleus transcriptomes, derived from Dorsolateral Prefrontal Cortex (DLFPC) tissues
32 of 424 unique donors from the Religious Orders Study and Memory and Aging Project
33 (ROS/MAP; AD Knowledge Portal syn2580853), were collected by the Rush Alzheimer's Disease
34 Center and processed at Columbia University Medical Center. Mean age of death of the cohort
35 was 89 years, among which 68% were females, and 52% were clinical AD cases. Negative
36 binomial mixed models implemented in Nebula R package were used for differential expression
37 analysis between autopsy confirmed AD dementia and normal cognition groups, and for
38 association analysis with amyloid burden, tangle burden, and both cross-sectional and
39 longitudinal global cognitive function. Intercellular VEGF-associated communication pattern
40 among cell types was also profiled using CellChat.

41 **Results**

Higher microglia expressed *FLT1*, endothelial *FLT4*, astrocyte *VEGFD*, and oligodendrocyte precursor cell (opc) *NRP1* expression associated with greater β-amyloid burden. Higher oligodendrocyte *VEGFB* expression associated with greater β-amyloid burden and worse cognitive trajectories, whereas higher *VEGFB* expression in inhibitory neurons was associated with lower β-amyloid burden. Higher astrocyte *NRP1* was associated with lower tangle burden. Higher expression of microglia and endothelial *FLT1* associated with worse cognitive trajectories and lower cognition scores at the last clinic visit before death. As for association with diagnosis, prefrontal cortical *FLT1* expression was upregulated in clinical AD patients compared to cognitively normal controls in both endothelial and microglial cells. For VEGF-associated intercellular communication, VEGFA-mediated signals contributed the most to the communication in both AD and normal cognition groups. Interestingly, although FLT1 expression was significantly elevated in AD endothelial cells, these cells still showed comparable VEGFA-FLT1 communication strength to the cognitively normal controls.

Conclusions

Consistent with our previously reported results from bulk omics data, prefrontal cortical expression of *FLT1* and *FLT4* were associated with cross-sectional global cognitive function, longitudinal cognitive trajectories, and AD neuropathology, and our study showed these associations appear to be driven by endothelial and microglial cells. In contrast, *VEGFB* expression seems to have opposing effects on amyloid burden depending on the cell types, suggesting its more dynamic role in AD pathology.

Key Words: VEGF, vascular endothelial growth factor, Alzheimer's disease, Dementia, snRNAseq, Single cell transcriptome, association analysis, signaling pathway.

64 **Background**

65 Neurovascular unit dysfunction is a hallmark of progression of AD. The vascular
66 endothelial growth factor (VEGF) family of signaling proteins are responsible for the growth and
67 maintenance of cells involved in vascularization and neuralization [1]. The members of the
68 VEGF family include five ligand genes (*VEGFA*, *VEGFB*, *VEGFC*, *VEGFD*, and *PGF*), three receptor
69 genes (*FLT1*, *KDR*, and *FLT4*), and two co-receptor genes (*NRP1* and *NRP2*; Figure 1a). These
70 genes play a role in brain injury [2], stroke [3, 4], and the progression of neurodegenerative
71 disease [5], particularly Alzheimer's disease (AD). Within AD, disruptions in vascularization and
72 circulation of the brain have been shown to contribute to neurodegeneration and the
73 development of neuropathology [6–13]. As a result, VEGFs have become exciting targets for
74 research to better understand vascular contributions to AD.

75 The role of VEGFs in AD appears to vary depending on the gene family member. Some
76 family members have protective effects [9, 14, 15], while others contribute to the progression
77 of neurodegeneration [16–18]. Earlier work from our group observed that cerebrospinal fluid
78 levels of VEGFA displayed a protective effect [15]. When we expanded our analyses to brain
79 tissues we observed that *VEGFB*, *FLT1*, *PGF*, and *FLT4* all appear to contribute to the
80 progression of AD pathology and cognitive decline [16]. Within the prefrontal cortex, higher
81 expression of these four genes (*VEGFB*, *FLT1*, *PGF*, and *FLT4*) was associated with more rapid
82 cognitive decline and higher pathology burden [16]. Similar associations are observed when
83 measuring the protein abundance of these VEGF family members in brain tissue and extend to
84 other brain regions including the posterior cingulate gyrus [18].

85 To better understand VEGF associations in the human brain within their cellular context,
86 we previously investigated single nucleus expression from 48 post-mortem DLPFC samples,
87 evaluating their expression in astrocytes, microglia, oligodendrocytes, oligodendrocyte
88 progenitor cells (OPCs), pericytes, endothelial cells, excitatory and inhibitory neurons [18].
89 Fascinatingly, we found that the robust *FLT1* and *VEGFB* signals that we had observed in bulk
90 tissue were driven by expression in microglia for both genes, along with endothelial cells,
91 oligodendrocytes, and OPCs for *VEGFB.* While results were encouraging, the small sample size
92 and few endothelial and microglial cells in this initial dataset made interpretation challenging.
93 The goal of this study is to further disentangle the cell-type specific VEGF expression
94 changes in relation to AD endophenotypes by analyzing a much larger AD snRNA cohort
95 (N=424). Specifically, we investigated 10 VEGF (*VEGFA*, *VEGFB*, *VEGFC*, *VEGFD*, *PGF*, *FLT1*, *FLT4*,
96 *KDR*, *NRP1*, and *NRP2*) family members' expression within eight brain cell types to test for
97 differential expression between cognitively normal participants and those with AD, along with
98 expression associations with global cognition (cross-sectional and longitudinal trajectories) and
99 AD pathology (β-amyloid and tau neurofibrillary tangle burden; Figure 1b). In addition, we
100 evaluated cell-type specific changes in the VEGF-associated signaling pathway during AD by
101 conducting an intercellular communication analysis for these 10 VEGF family members.

102 **Methods**

103 **Participants**

104 The participants included in this study were from two longitudinal clinical-pathological
105 cohort studies including the Religious Orders Study and the Memory and Aging Project
106 (ROS/MAP). Each study was approved by the Institutional Review Board (IRB) of Rush University
107 Medical Center. At enrollment, all participants were free of dementia and agreed to annual
108 clinical evaluation and the donation of their brain at the time of their death [19–21]. Secondary
109 analyses of this extant data were approved by the Vanderbilt University Medical Center IRB.
110 ROS/MAP data can be accessed online at the Rush Alzheimer's Disease Center Resource Sharing
111 Hub (https://www.radc.rush.edu/), as well as on the Accelerating Medicines Partnership-
112 Alzheimer's Disease (AMP-AD) Knowledge Portal (syn3219045).

113 **Single nucleus RNA sequencing**

114 Specimens were collected on availability of frozen pathologic materials from the dorsal
115 lateral prefrontal cortex (DLPFC). The tissue specimens were received from the Rush
116 Alzheimer's Disease center. Participants with a post-mortem interval < 41 hours and whole
117 genome sequence data were selected to go through a series of rigorous quality control steps
118 [22–24], which resulting in 424 participants. The participants had a median of 3,824 sequenced
119 nuclei. In the final data, there were 8 major cell types, including astrocytes, endothelial cells,
120 inhibitory neurons, microglia, oligodendrocytes, oligodendrocyte precursor cells (OPCs), and
121 CUX2- and CUX2+ excitatory neurons. snRNAseq data can be downloaded from AD Knowledge
122 Portal (Accession Number: syn31512863). Additional filters applied before analyses included

123 removing genes with expression in less than 10% of all cells, removing cells with less than 200
124 or more than 20,000 total RNA UMIs or had more than 5% mitochondrial mapped reads.

125 **Measurements of Cognitive Function**

126 The measurement of global cognition was derived from 17 different neuropsychological
127 tests across five domains of cognition (semantic, episodic, and working memory, perceptual
128 speed, and perceptual orientation). The z-scores of all the available tests were averaged to
129 create a global cognition composite. Further details on the development of this composite have
130 been previously described [25]. For cross-sectional cognition function related analysis, global
131 cognitive score at last visit before death was used from 369 participants. Longitudinal cognitive
132 trajectory was derived from a linear mixed effects model with global cognition as the outcome
133 and the intercept and interval (years from last visit) entered as fixed and random effects. The
134 derived "cognition slope" was calculated as the sum of the random and fixed effects for each
135 participant. 423 participants are included in this analysis.

136 **Measurements of AD pathology**

137 Measures of pathology were previously characterized in ROS/MAP [19, 20]. Measured
138 by immunohistochemistry at autopsy, β-amyloid and tau tangle burden were quantified as the
139 average percent area occupied by β-amyloid (using antibodies specific to $A\beta_{42}$) or tau (using
140 antibodies specific to AT8 epitope of abnormally phosphorylated tau) across 8 brain regions at
141 autopsy: hippocampus, angular gyrus, and entorhinal, midfrontal, inferior temporal, calcarine,
142 anterior cingulate, and superior frontal cortices. Then, values were transformed to approximate
143 a normal distribution. 421 participants are included in amyloid and tau burden analysis.

144 **Statistical Analysis**

145 Statistical analyses were completed using RStudio (R version 4.3.1) and code is available
146 upon request from the corresponding author. Significance was set to a priori to a=0.05.
147 Additionally, p-values were corrected for all *VEGF* predictors across AD-associated outcomes
148 (290 models) using the false discovery rate (FDR) procedure.
149 Negative binomial mixed models implemented by the Nebula R package[26]; v1.4.2)
150 were used to analyze the association between each *VEGF* gene within each of the eight cell
151 types and AD diagnosis, global cognition longitudinally and at last visit before death, and β-
152 amyloid and tau burden at death. For analysis of diagnosis, 299 individuals were included: 142
153 normal cognition controls (cogdx = 1) and 157 AD dementia patients (cogdx = 4 or 5). All models
154 covaried for age at death, sex, post-mortem interval (PMI), and the interval between last
155 cognitive visit and death in years (for cognition). One participant didn't have PMI data, hence,
156 was removed from association analysis. The gene count matrix input of the models was the
157 UMI count data from the RNA assay normalized and scaled by the "sctransform" R package
158 (https://github.com/satijalab/sctransform).
159 **VEGF-mediated Intercellular Communication Profiling**
160 Intercellular communication pattern involving these 10 VEGF genes among cell types
161 was analyzed using the 'CellChat' R package [27](v2.0). Due to lack of some of the evident
162 ligand-receptor pairs involving these 10 VEGF genes from the default CellChat database
163 (CellChatDB), we manually updated CellChatDB by incorporating those curated additionally
164 from the CellTalk DB (v1.0, https://github.com/ZJUFanLab/CellTalkDB/tree/master/database).
165 Otherwise, we performed the analysis according to the default setting, skipping projecting gene
166 expression data onto human protein-protein interaction network.

167 **Results**

168 **Participant Characteristics**

169 The snRNAseq data used for our analysis consisted of 424 non-Hispanic White
170 participants (**Table 1**) with an average PMI of 7.7 hours (SD = 5.1 hours), 68% of whom are
171 females, 52% are clinical AD dementia patients (cogdx = 4 or 5), and 27% carried at least one
172 APOE4 allele. The cohort has a mean age at death at 89 years old with an average of 13 years of
173 education.

174 ***VEGFs* Associations with Cognition**

175 Higher expression of *FLT1* in endothelial cells and microglia was associated with worse
176 cognitive performance at last visit before death (endothelial cells (logFC= -0.09, FDR= 0.009)
177 and microglia (logFC= -0.18, FDR= 0.009)) and cognitive trajectories (endothelial-*FLT1* (logFC= -
178 0.77, FDR= 0.04) and microglia-*FLT1* (logFC= -1.96, p= 0.009)). Additionally, higher expression of
179 *VEGFB* in oligodendrocytes (logFC= -0.56, FDR= 0.02) was also associated with a worse cognitive
180 trajectory. **Table 2** listed all statistically significant associations between 10 VEGF gene
181 expression and various AD outcomes tested (the complete result can be found in **Supplemental**
182 **Table 1**).

183 ***VEGFs* Associations with AD Pathology**

184 Multiple cell types and *VEGF* genes were associated with β-amyloid burden (**Table 2**).
185 Higher microglia-*FLT1* (logFC= 0.05, FDR= 0.0008), oligodendrocyte-*VEGFB* (logFC= 0.01, FDR=
186 0.009), endothelial-*FLT4* (logFC= 0.03, FDR= 0.01), astrocyte-*VEGFD* (logFC= 0.02, FDR= 0.03),
187 and oligodendrocyte precursor cell-*NRP1* (logFC= 0.02, FDR= 0.05) were all associated with

188 higher β-amyloid burden. On the contrary, within inhibitory neurons, higher expression of
189 *VEGFB* was associated with lower β-amyloid burden (logFC= -0.01, FDR= 0.02).

190 **Differential Expression of *VEGFs in AD***

191 We also tested for differences in *VEGF* expression between neuropathologically
192 confirmed AD dementia cases and cognitively normal controls. We observed that AD patients
193 had higher expression levels of *FLT1* within microglia (logFC= -0.45, FDR= 0.009) and endothelial
194 cells (**Table 2**, logFC= -0.20, FDR= 0.01).

195 **VEGF-associated Intercellular Communication Profile**

196 Both incoming and outgoing interaction strength (calculated by in-degree and out-
197 degree network centrality scores respectively) associated with these 10 VEGFs among cell types
198 was reduced in AD comparing to cognitive normal controls, especially signals from astrocytes to
199 neurons and endothelial cells, but the differences are not statistically significant (**Figure 2c**).
200 VEGFA was the most abundantly expressed VEGF ligand investigated, primarily in astrocytes,
201 and for that reason the cell-cell communication profile of these cells was predominantly VEGFA
202 driven; sending from astrocytes to themselves and to other cell types, among which excitatory
203 neurons were the top receiver of the signal for the cognitively normal group, and endothelial
204 cells were the primary receiver for AD group (**Figure 2a-b**). Top Ligand-Receptor pair
205 contributors to VEGFA-induced signaling in this DLPFC dataset are "VEGFA-GRIN2B" (39.5%),
206 "VEGFA-SIRPA" (10.7%), "VEGFA-EGFR" (9.5%), and "VEGFA-FLT1" (9.5%) among cognitively
207 normal participants, while "VEGFA-GRIN2B" (37.8%), "VEGFA-FLT1" (13.8%), "VEGFA-EGFR"
208 (10.2%), and "VEGFA-SIRPA" (10.2%) contributed among the AD participants. Although the
209 VEGFA-FLT1 signal, from astrocytes to endothelial cells exclusively, showed a comparable

210 communication probability between cells in AD and cognitive normally participants (0.073 vs
211 0.076) (**Supplemental Table 2**), the relative contribution to their overall VEGFA-induced
212 signaling did increase in AD group comparing to normal (13.8% vs 9.5%).

213 **Discussion**

214 In this study we have provided the most comprehensive exploration into cell-specific
215 effects of the VEGF family in the context of AD. Our results build on previous evidence from
216 bulk tissue at the protein and transcriptomic level that *VEGFB, FLT1, FLT4,* and *NRP1* relate to
217 the clinical progression and neuropathology of AD [16, 18]. The single cell resolution here builds
218 on our early single nucleus data (18) to provide the clearest picture of the important and
219 distinct roles the VEGF family members play in various brain cell types. Our results particularly
220 highlight the diverse associations for VEGF family members across endothelial cells, microglial
221 cells, astrocytes, oligodendrocytes, and neurons. While *FLT1* showed strong upregulation in the
222 AD brain in endothelial cells as might be expected, we also observed strong upregulation of
223 *FLT1* in microglial cells. Yet, regardless of the upregulation of *FLT1*, our intercellular
224 communication analyses suggest that FLT1-associated canonical VEGF signaling pathways
225 themselves are in fact comparable in the AD brain to normal brain. In contrast to the consistent
226 effects observed for *FLT1*, we observed opposing direction of effect on β-amyloid burden for
227 *VEGFB* expression in oligodendrocytes vs inhibitory neurons, whereby higher levels of
228 oligodendrocyte *VEGFB* related to higher pathology, while higher levels of neuronal *VEGFB*
229 related to lower pathology. Together, these results suggest that in addition to the classic
230 vascular signaling pathway underlying the associations between VEGF family members and AD,

231 there may also be immune (e.g., microglial *FLT1*) and neuronal (e.g., neuronal *VEGFB*) signaling
232 cascades that contribute to AD pathogenesis.
233 The central role of VEGF signaling is angiogenesis under both health and disease
234 conditions [28, 29]. Pathological angiogenesis is a hallmark of AD, which is believed to both
235 drive and respond to multiple AD pathologies driving hypoxia, oxidative stress, inflammation,
236 and Aβ accumulation [30]. Indeed, previous work has identified a marked upregulation of
237 angiogenic factors and mediators in the AD brain [31, 32]. In the present results, the
238 upregulation of *FLT1* in endothelial cells among AD patients could reflect a repair response. The
239 increase in vascularization and blood flow could be a response to AD neuropathology similar to
240 the response that has been indicated in other neurodegenerative and neuropsychiatric diseases
241 such as ALS [33] and schizophrenia [34]. On the other hand, the elevated endothelial *FLT1* could
242 drive AD neuropathology. For example, it has been shown that VEGF-induced pathological
243 angiogenesis can facilitate Aβ generation [35]. VEGF-induced pathological angiogenesis can also
244 worsen AD pathology by disrupting permeability of the blood-brain barrier (BBB) [36, 37]. BBB
245 is formed by physical interaction of multiple brain cell types, with a common structure
246 consisting of blood capillaries formed by endothelial cells (ECs), pericytes, and the astrocytic
247 end feet [38]. As a natural protective barrier of the central nervous system (CNS), BBB
248 homeostasis is strictly regulated, disruption of which can lead to many neurological conditions
249 including AD [39, 40]. Our intercellular communication profile showed that signals
250 communicated among these 10 VEGF genes were predominantly from astrocytes to ECs, hinting
251 at the canonical angiogenesis pathway at the blood brain barrier as a primary driver here. In
252 fact, evidence is already emerging that demonstrates CNS angiogenesis can be regulated

253 through VEGF-dependent signaling at the BBB [41]. Characterizing the interplay between VEGF
254 family genes and BBB integrity in the context of AD may provide more insight into the
255 mechanistic pathways underlying the associations observed here.

256 Our results also suggest roles of some of the VEGF family genes in regulating the
257 immune response, including the upregulation of microglial *FLT1* in AD group. Increased
258 microglia function in AD has been observed by many [42–46] in the presence of β-amyloid
259 peptides and facilitates an inflammatory response [47]. FLT1 was believed to be one of the 20
260 or so proteins that has been found to be enriched in Aβ plaques [48], and has recently been
261 showed to interact with VCAM1 and plays a role in VCAM1-dependent chemotaxis of microglia,
262 which enhances microglia clearance of Aβ [49]. Studies have also shown the critical role that
263 FLT1 plays in microglial proliferation and monocyte-macrophage migration [50, 51]. With all
264 these under consideration, elevation of microglial *FLT1* in AD should not be a surprise. The
265 primary ligand for *FLT1* is *VEGFB*, so it is possible that the *VEGFB* association in
266 oligodendrocytes may reflect upregulation of this same pathway. It is well known that
267 oligodendrocytes and microglia work together during regulation of myelination, and this is
268 particularly noticeable during neurodegenerative conditions [52]. Future work confirming these
269 cell-specific transcriptomic effects at the protein level is necessary.

270 One fascinating discovery in the present results is that higher expression of *VEGFB*
271 within inhibitory neurons was associated with lower amyloid burden, which was the only
272 protective effect of any VEGF we tested in this dataset. This result is consistent with the
273 previously reported evidence of the benefits of *VEGFB* expression on neuronal survival and
274 nerve regeneration [53–56]. Perhaps in the early stage of AD when β-amyloid burden is low,

275 inhibitory neurons manage to inhibit apoptosis and promote neurogenesis through
276 upregulating VEGFB. Upregulation of VEGFB could be one of the molecular mechanisms that
277 enables inhibitory neurons to be more resistant to AD neuropathology comparing to excitatory
278 neurons [57]. Interestingly, a study of APP/PS1 amyloidopathy mice did show an increase of
279 inhibitory synapses in hippocampus before pathology develops and then decreased at 12
280 months of age when robust AD pathology was present [58]. Hence, the protective effect of
281 VEGFB from inhibitory neurons to the development of AD pathology could function in a time-
282 sensitive matter. One also cannot rule out the possibility that increased *VEGFB* expression
283 within inhibitory neurons could help with the clearance of β-amyloid.

284 We also observed higher expression of *FLT4* within endothelial cells related to higher
285 amyloid burden. The primary ligand for *FLT4* is *VEGFD* and we also observed an association
286 between elevated *VEGFD* in oligodendrocytes and amyloid burden. In contrast to the other
287 VEGF receptors, the FLT4/VEGFD signaling axis is primarily involved in lymphangiogenesis.
288 Certainly meningeal lymphatics has been implicated in amyloid clearance through a complex
289 interplay with the immune system [59], so it is quite possible that lymphatics underly the
290 observed *VEGFD* and *FLT4* associations with β-amyloid. In previous work, we identified an
291 associated between higher expression of *FLT4* in the dorsal lateral prefrontal cortex and worse
292 neuropathology[16], but also identified higher expression of *FLT4* in the caudate nucleus
293 associated with lower amyloid levels and tau levels [18]. Others have also observed these flips
294 in direction with associations depending on the brain region [60]. Combined, these results
295 suggest that tissue and cell-type are important considerations when looking at the role of *FLT4*
296 in the brain within the context of AD.

297 Finally, we observed a cell-type specific effect of NRP1. Higher expression of *NRP1* in
298 astrocytes was associated with lower levels of neurofibrillary tangles, but higher expression of
299 *NRP1* within oligodendrocyte precursor cells was associated with higher amyloid burden. Other
300 work from our group has also observed differing roles of *NRP1* when pertaining to AD
301 neuropathology [18]. However, this is the first time we have observed statistically significant
302 associations within specific cell-types. All above results further highlight the complexity of the
303 *VEGF* family and their role within neurodegeneration. To fully understand the clinical potential
304 of *VEGF* as a biomarker and therapeutic target, in-depth understanding of each of the tissue
305 and cell-type is necessary.

306 This study has many strengths. ROS/MAP is a well-characterized cohort with longitudinal
307 cognitive data, comprehensive neuropathology data with multiple cell-type measures of *VEGF*
308 expression. Additionally, this study reports novel discoveries and replication of the effects of
309 *VEGF* family members on AD phenotypes including pathology and cognition at the
310 transcriptomic level within a large sample size. Because of the larges sample size and cell-type
311 specific expression measurements, we were able to provide more comprehensive data and
312 hypotheses about cellular context.

313 Despite these strengths, this study also has limitations. ROS/MAP is enriched for non-
314 Hispanic white, highly educated individuals which limits the generalizability to more
315 representative populations. Further, while being able to examine cell-type specific effects in a
316 large sample size, we are limited to the dorsolateral prefrontal cortex tissue.

317 To conclude, this study provides an extensive characterization within a large sample size
318 of the *VEGF* signaling family members in the context of cognitive aging and AD. Our results

319 provide evidence that further supports the role of *VEGFB*, *VEGFD*, *FLT1*, *FLT4* and *NRP1* play
320 inside and outside of classic VEGF signaling axis in AD, with support for both an endothelial and
321 microglial signaling cascade that could underly these well-established associations. For the first
322 time, we provide evidence that *VEGFB* expression in inhibitory neurons may relate to a
323 protective effect against AD neuropathology as has been hypothesized previously and observed
324 in models of Parkinson's disease. These results provide compelling evidence that VEGFB and
325 FLT1 may have potential as therapeutic targets in AD, but there remains a need to confirm
326 these single nucleus transcriptomic results at the protein level, and establish causality through
327 experimental approaches.
328

329 **References**

330 1. de Almodovar CR, Lambrechts D, Mazzone M, Carmeliet P. Role and therapeutic potential of
331 VEGF in the nervous system. Physiol Rev. 2009;89:607–648.
332 2. Linton AE. Pathologic sequelae of vascular cognitive impairment and dementia sheds light on
333 potential targets for intervention. Cereb Circ-Cogn Behav. 2021;2:100030.
334 3. Greenberg DA. Vascular Endothelial Growth Factors (VEGFs) and Stroke. Cell Mol Life Sci.
335 2013;70:1753–1761.
336 4. Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RC-M. Decreased Serum Brain-Derived Neurotrophic
337 Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and
338 Meta-Analysis. Int J Mol Sci. 2019;20:257.
339 5. Melincovici CS. Vascular endothelial growth factor (VEGF) – key factor in normal and
340 pathological angiogenesis. Rom J Morphol Embryol. 2018;59:455–467.
341 6. Silva T. Circulating levels of vascular endothelial growth factor in patients with Alzheimer's
342 disease: A case-control study. Behav Brain Res. 2023;437.
343 7. Ali M. VEGF Paradoxically Reduces Cerebral Blood Flow in Alzheimer's Disease Mice.
344 Neurosci Insights. 2022;17.
345 8. Guo L-H, Alexopoulos P, Perneczky R. Heart-type fatty acid binding protein and vascular
346 endothelial growth factor: cerebrospinal fluid biomarker candidates for Alzheimer's
347 disease. Eur Arch Psychiatry Clin Neurosci. 2013;263:553–560.
348 9. Huang L, Jia J, Liu R. Decreased serum levels of the angiogenic factors VEGF and TGF-β1 in
349 Alzheimer's disease and amnestic mild cognitive impairment. Neurosci Lett. 2013;550:60–
350 63.
351 10. Harris R, Miners JS, Allen S, Love S. VEGFR1 and VEGFR2 in Alzheimer's Disease. J
352 Alzheimers Dis. 2018:1–12.
353 11. Provias J, Jeynes B. Reduction in Vascular Endothelial Growth Factor Expression in the
354 Superior Temporal, Hippocampal, and Brainstem Regions in Alzheimer's Disease. Curr
355 Neurovasc Res. 2014:1–14.
356 12. Tang H, Mao X, Xie L, Greenberg DA, Jin K. Expression level of vascular endothelial growth
357 factor in hippocampus is associated with cognitive impairment in patients with
358 Alzheimer's disease. Neurobiol Aging. 2013;34:1412–1415.
359 13. Thomas T, Miners S, Love S. Post-mortem assessment of hypoperfusion of cerebral cortex
360 in Alzheimer's disease and vascular dementia. Brain. 2015;138:1059–1069.
361 14. Garcia KO, Ornellas FLM, Martin PKM, Patti CL, Mello LE, Frussa-Filho R, et al. Therapeutic
362 effects of the transplantation of VEGF overexpressing bone marrow mesenchymal stem
363 cells in the hippocampus of murine model of Alzheimer's disease. Front Aging Neurosci.
364 2014;6:6–30.
365 15. Hohman TJ, Bell SP, Jefferson AL. The Role of Vascular Endothelial Growth Factor in
366 Neurodegeneration and Cognitive Decline: Exploring Interactions With Biomarkers of
367 Alzheimer Disease. JAMA Neurol. 2015;72:520–529.
368 16. Mahoney ER, Dumitrescu L, Moore AM, Cambronero FE, De Jager PL, Koran MEI, et al.
369 Brain expression of the vascular endothelial growth factor gene family in cognitive aging
370 and Alzheimer's disease. Mol Psychiatry. 2019. 22 July 2019.
371 https://doi.org/10.1038/s41380-019-0458-5.

17. Libby JB, Seto M, Khan OA, Liu D, Petyuk VA, Oliver N, et al. Whole blood transcript and protein abundance of the vascular endothelial growth factor family relate to cognitive performance. Neurobiol Aging. 2023;124:11–17.
18. Seto M, Dumitrescu L, Mahoney ER, Sclafani AM, De Jager PL, Menon V, et al. Multi-omic characterization of brain changes in the vascular endothelial growth factor family during aging and Alzheimer's disease. Neurobiol Aging. 2023;126:25–33.
19. Bennett DA, Schneider JA, Arvanitakis Z, Wilson RS. Overview and findings from the religious orders study. Curr Alzheimer Res. 2012;9:628.
20. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the Rush Memory and Aging Project. Curr Alzheimer Res. 2012;9:646.
21. Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious Orders Study and Rush Memory and Aging Project. J Alzheimers Dis. 2018;64:S161–S189.
22. Fujita M, Gao Z, Zeng L, McCabe C, White CC, Ng B, et al. Cell-subtype specific effects of genetic variation in the aging and Alzheimer cortex. 2022.
23. Cain A, Taga M, McCabe C, Green GS, Hekselman I, White CC. Multicellular communities are perturbed in the aging human brain and Alzheimer's disease. Nat Neurosci. 2023;26:1267–1280.
24. Habib N, Avraham-Davidi I, Basu A, Burks T, Shekhar K, Hofree M, et al. Massively parallel single-nucleus RNA-seq with DroNc-seq. Nat Methods. 2017;14:955–958.
25. Wilson RS, Boyle PA, Yu L, Barnes LL, Sytsma J, Buchman AS, et al. Temporal course and pathologic basis of unawareness of memory loss in dementia. Neurology. 2015;85:984–991.
26. He L, Davila-Velderrain J, Sumida TS, Hafler DA, Kellis M, Kulminski AM. NEBULA is a fast negative binomial mixed model for differential or co-expression analysis of large-scale multi-subject single-cell data. Commun Biol. 2021;4:629.
27. Jin S, Guerrero-Juarez CF, Zhang L, Chang I, Ramos R, Kuan C-H, et al. Inference and analysis of cell-cell communication using CellChat. Nat Commun. 2021;12:1088.
28. Hicklin DJ, Ellis LM. Role of the Vascular Endothelial Growth Factor Pathway in Tumor Growth and Angiogenesis. J Clin Oncol. 2005;23:1011–1027.
29. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis. Genes Cancer. 2011;2:1097–1105.
30. Jefferies WA, Price KA, Biron KE, Fenninger F, Pfeifer CG, Dickstein DL. Adjusting the compass: new insights into the role of angiogenesis in Alzheimer's disease. Alzheimers Res Ther. 2013;5:64.
31. Lau S-F, Cao H, Fu AKY, Ip NY. Single-nucleus transcriptome analysis reveals dysregulation of angiogenic endothelial cells and neuroprotective glia in Alzheimer's disease. Proc Natl Acad Sci. 2020;117:25800.
32. Tsartsalis S, Sleven H, Fancy N, Wessely F, Smith AM, Willumsen N, et al. A single nuclear transcriptomic characterisation of mechanisms responsible for impaired angiogenesis and blood-brain barrier function in Alzheimer's disease. Nat Commun. 2024;15:2243.
33. Hunter M, Spiller KJ, Dominique MA, Xu H, Hunter FW, Fang TC, et al. Microglial transcriptome analysis in the rNLS8 mouse model of TDP-43 proteinopathy reveals discrete expression profiles associated with neurodegenerative progression and recovery. Acta Neuropathol Commun. 2021;9:140.

416 34. Stankovic I, Notaras M, Wolujewicz P, Lu T, Lis R, Ross ME, et al. Schizophrenia endothelial
417 cells exhibit higher permeability and altered angiogenesis patterns in patient-derived
418 organoids. Transl Psychiatry. 2024;14:1–15.
419 35. Desai BS, Schneider JA, Li J-L, Carvey PM, Hendey B. Evidence of angiogenic vessels in
420 Alzheimer's disease. J Neural Transm Vienna Austria 1996. 2009;116:587–597.
421 36. Vogel C, Bauer A, Wiesnet M, Preissner KT, Schaper W, Marti HH, et al. Flt-1, but not Flk-1
422 mediates hyperpermeability through activation of the PI3-K/Akt pathway. J Cell Physiol.
423 2007;212:236–243.
424 37. Gao L, Pan X, Zhang JH, Xia Y. Glial cells: an important switch for the vascular function of
425 the central nervous system. Front Cell Neurosci. 2023;17.
426 38. Sun Q, Xu X, Wang T, Xu Z, Lu X, Li X, et al. Neurovascular Units and Neural-Glia Networks
427 in Intracerebral Hemorrhage: from Mechanisms to Translation. Transl Stroke Res.
428 2021;12:447–460.
429 39. Daneman R, Prat A. The Blood–Brain Barrier. Cold Spring Harb Perspect Biol.
430 2015;7:a020412.
431 40. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood–brain barrier: structure,
432 regulation, and drug delivery. Signal Transduct Target Ther. 2023;8:1–27.
433 41. Zhang S, Kim B, Zhu X, Gui X, Wang Y, Lan Z, et al. Glial type specific regulation of CNS
434 angiogenesis by HIFα-activated different signaling pathways. Nat Commun. 2020;11:2027.
435 42. Egensperger R, Kosel S, von Eitzen U, Graeber MB. Microglial activation in Alzheimer
436 disease: Association with APOE genotype. Brain Pathol. 1998;8:439–447.
437 43. Maezawa I, Zimin PI, Wulff H, Jin LW. Amyloid-beta protein oligomer at low nanomolar
438 concentrations activates microglia and induces microglial neurotoxicity. J Biol
439 Chem;286:3693–3706.
440 44. Malik M, Parikh I, Vasquez JB, Smith C, Tai L, Bu G, et al. Genetics ignite focus on microglial
441 inflammation in Alzheimer's disease. Mol Neurodegener. 2015;10:52.
442 45. Nordengen K, Kirsebom BE, Henjum K, Selnes P, Gisladottir B, Wettergreen M, et al. Glial
443 activation and inflammation along the Alzheimer's disease continuum. J
444 Neuroinflammation. 2019;16:46.
445 46. Rogers J, Strohmeyer R, Kovelowski CJ, Li R. Microglia and inflammatory mechanisms in
446 the clearance of amyloid-beta peptide. Glia. 2002;40:260–269.
447 47. Ryu JK, Cho T, Choi HB, Wang YT, McLarnon JG. Microglial VEGF receptor response is an
448 integral chemotactic component in Alzheimer's disease pathology. J Neurosci. 2009;29:3–
449 13.
450 48. Xiong F, Ge W, Ma C. Quantitative proteomics reveals distinct composition of amyloid
451 plaques in Alzheimer's disease. Alzheimers Dement. 2019;15:429–440.
452 49. Lau S-F, Wu W, Wong HY, Ouyang L, Qiao Y, Xu J, et al. The VCAM1–ApoE pathway directs
453 microglial chemotaxis and alleviates Alzheimer's disease pathology. Nat Aging. 2023:1–18.
454 50. Sawano A, Iwai S, Sakurai Y, Ito M, Shitara K, Nakahata T, et al. Flt-1, vascular endothelial
455 growth factor receptor 1, is a novel cell surface marker for the lineage of monocyte-
456 macrophages in humans. Blood. 2001;97:785–791.
457 51. Hiratsuka S, Minowa O, Kuno J, Noda T, Shibuya M. Flt-1 lacking the tyrosine kinase
458 domain is sufficient for normal development and angiogenesis in mice. Proc Natl Acad Sci.
459 1998;95:9349–9354.

52. Kalafatakis I, Karagogeos D. Oligodendrocytes and Microglia: Key Players in Myelin Development, Damage and Repair. Biomolecules. 2021;11:1058.
53. Li Y, Zhang F, Nagai N, Tang Z, Zhang S, Scotney P, et al. VEGF-B inhibits apoptosis via VEGFR-1–mediated suppression of the expression of BH3-only protein genes in mice and rats. J Clin Invest. 2008;118:913.
54. Falk T, Yue X, Zhang S, McCourt AD, Yee BJ, Gonzalez RT, et al. Vascular endothelial growth factor-B is neuroprotective in an in vivo rat model of Parkinson's disease. Neurosci Lett. 2011;496:43–47.
55. Caballero B, Sherman SJ, Falk T. Insights into the Mechanisms Involved in Protective Effects of VEGF-B in Dopaminergic Neurons. Park Dis. 2017;2017:4263795.
56. Guaiquil VH, Pan Z, Karagianni N, Fukuoka S, Alegre G, Rosenblatt MI. VEGF-B selectively regenerates injured peripheral neurons and restores sensory and trophic functions. Proc Natl Acad Sci U S A. 2014;111:17272–17277.
57. Fu H, Possenti A, Freer R, Nakano Y, Hernandez Villegas NC, Tang M, et al. A tau homeostasis signature is linked with the cellular and regional vulnerability of excitatory neurons to tau pathology. Nat Neurosci. 2019;22:47–56.
58. Kiss E, Gorgas K, Schlicksupp A, Groß D, Kins S, Kirsch J, et al. Biphasic Alteration of the Inhibitory Synapse Scaffold Protein Gephyrin in Early and Late Stages of an Alzheimer Disease Model. Am J Pathol. 2016;186:2279–2291.
59. Da Mesquita S, Papadopoulos Z, Dykstra T, Brase L, Farias FG, Wall M, et al. Meningeal lymphatics affect microglia responses and anti-Aβ immunotherapy. Nature. 2021;593:255–260.
60. Weijts BGMW. Atypical E2fs Control Lymphangiogenesis through Transcriptional Regulation of Ccbe1 and Flt4. PloS One. 2013;8:e73693.

489 **Table 1. Characteristics of Study Participants**

	Cognitive Normal Controls (N=143)	**Alzheimer's Disease Patients** (N=157)	**Total Cohort** (N=424)	**P value (comparison between Cognitive Normal and AD)**
Age at death (years)	87.20 ± 7.26	91.15 ± 6.56	89.19 ± 6.82	<0.001
Education (years)	16.28 ± 3.45	16.55 ± 3.22	16.31 ± 3.47	0.48
Post-mortem interval (hours)	7.80 ± 4.99	7.25 ± 4.32	7.71 ± 5.11	0.31
Global cognition slope	-0.04 ± 0.04	-0.19 ± 0.09	-0.11 ± 0.09	<0.001
β-amyloid burden	3.12 ± 3.77	5.93 ± 4.46	4.46 ± 4.50	<0.001
Tau burden	2.97 ± 3.36	9.36 ± 9.15	5.98 ± 7.15	<0.001
Male, no. (%)	49 (34)	42 (27)	136 (32)	0.16
APOE4 Carrier, no. (%)	27 (19)	60 (38)	109 (27)	<0.001

490 Values are presented as mean ± standard deviation unless otherwise indicated. P values were

491 derived from Welch Two Sample t-test for continuous variables, and Pearson's Chi-squared test

492 for categorical variables.

493

494

495

496

497

498

499

500

501

502 **Table 2. FDR Significant Cell Type Specific VEGF Associations with Cognition and AD Pathology**

Gene	Outcome	Cell Type	logFC	SE	P Value	P-FDR
FLT1	Last Cognition before Death	Endothelial Cells	-0.089	0.024	1.768E-04	0.009
FLT1	Last Cognition before Death	Microglia	-0.176	0.046	1.492E-04	0.009
FLT1	Cognition Trajectory	Endothelial Cells	-0.771	0.248	0.002	0.041
FLT1	Cognition Trajectory	Microglia	-1.964	0.504	9.716E-05	0.009
VEGFB	Cognition Trajectory	Oligodendrocytes	-0.561	0.166	7.232E-04	0.019
FLT1	Diagnosis	Endothelial Cells	0.195*	0.055	4.232E-04	0.014
FLT1	Diagnosis	Microglia	0.452*	0.113	6.378E-05	0.009
FLT1	β-amyloid Burden	Microglia	0.053	0.011	2.700E-06	7.830E-04
VEGFB	β-amyloid Burden	Oligodendrocytes	0.014	0.004	1.428E-04	0.009
VEGFB	β-amyloid Burden	Inhibitory Neurons	-0.012	0.004	6.529E-04	0.019
FLT4	β-amyloid Burden	Endothelial Cells	0.027	0.008	3.579E-04	0.013
VEGFD	β-amyloid Burden	Astrocytes	0.016	0.005	0.001	0.029
NRP1	β-amyloid Burden	Oligodendrocyte Precursor Cells	0.018	0.006	0.002	0.046
NRP1	Tau Burden	Astrocytes	-0.014	0.004	2.229E-04	0.009

503 *logFC values for diagnosis is gene expression change in AD over normal cognition controls

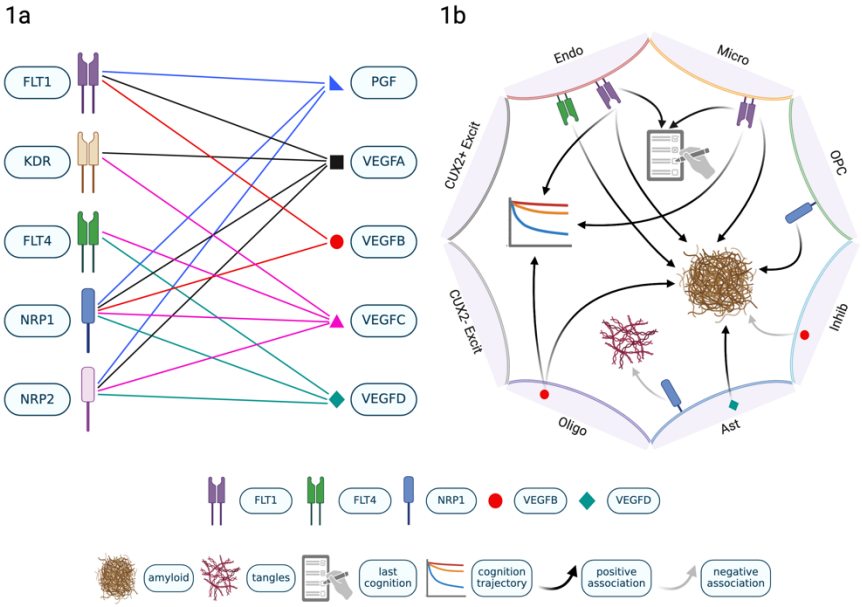

Figure 1. 10 VEGFs and Their Cell-Type Specific Effect On AD Endophenotype
1a. 10 VEGF ligand-receptor system 1b. Association of VEGF and AD endophenotype in DLPFC brain cells. Cell type abbreviations are as follows, Endo, Endothelial Cells; Micro, Microglia; OPC, Oligodendrocyte Precursor Cells; Inhib, Inhibitory Neurons; Ast, Astrocytes; Oligo, Oligodendrocytes; CUX2+ Excit, CUX2+ Excitatory Neurons; CUX2- Excit, all Excitatory Neurons that don't express CUX2-.

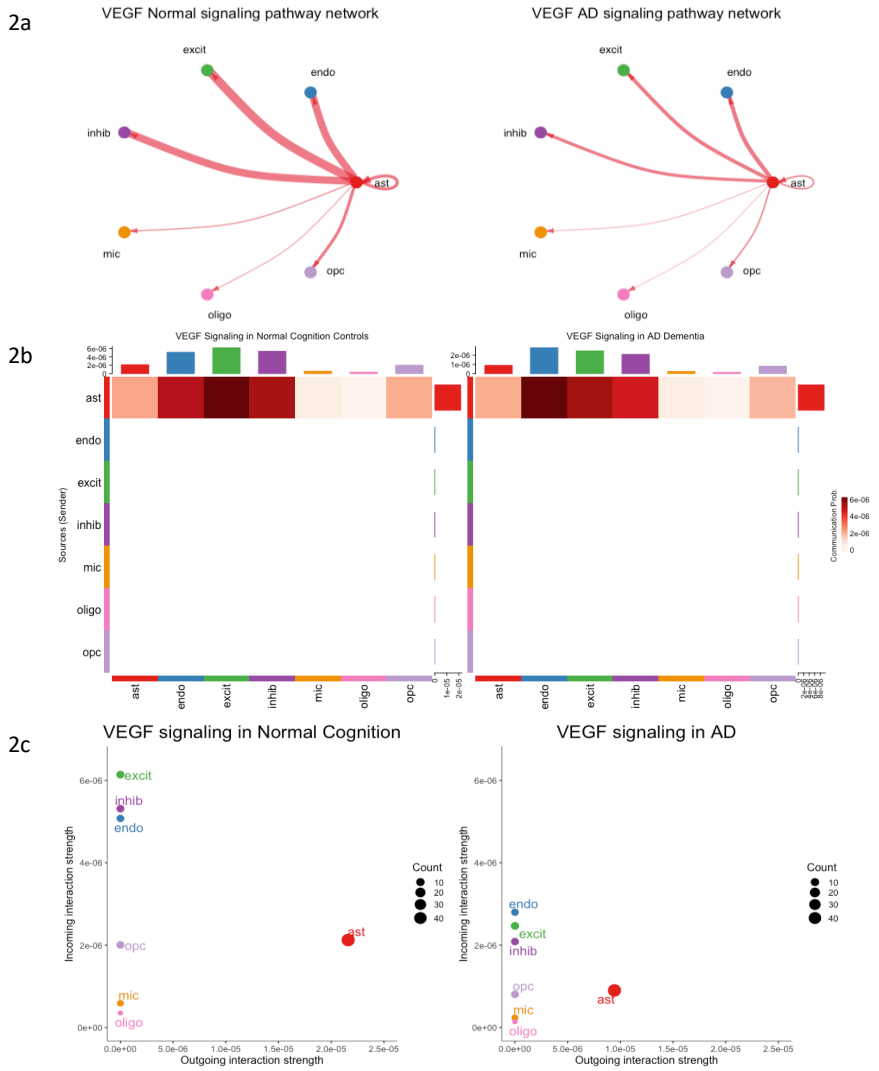

Figure 2. 10 VEGF Genes Associated Signaling Pathway Profile in AD vs Normal Cognition Groups

2a. Circle plot of overall VEGF signaling in each diagnosis group 2b. Heatmap of overall VEGF signaling in each diagnosis group 2c. Overall incoming and outgoing VEGF signaling pattern. Cell type abbreviations are as follows, Endo, Endothelial Cells; Micro, Microglia; OPC, Oligodendrocyte Precursor Cells; Inhib, Inhibitory Neurons; Ast, Astrocytes; Oligo, Oligodendrocytes; CUX2+ Excit, CUX2+ Excitatory Neurons; CUX2- Excit, all Excitatory Neurons that don't express CUX2-.

Supplemental Table 1. Association of 10 VEGF Gene Expression and Various AD Outcomes

Outcome	Gene	Cell Type	logFC*	SE	P	P_FDR
Diagnosis	*FLT1*	Astrocytes	-0.022	0.081	0.783	0.926
Diagnosis	*FLT1*	Endothelial Cells	0.195	0.055	0	0.014
Diagnosis	*FLT1*	CUX2- Excitatory Neurons	0.015	0.083	0.86	0.944
Diagnosis	*FLT1*	CUX2+ Excitatory Neurons	-0.011	0.087	0.896	0.963
Diagnosis	*FLT1*	Inhibitory Neurons	-0.080	0.038	0.035	0.183
Diagnosis	*FLT1*	Microglia	0.452	0.113	0	0.009
Diagnosis	*FLT1*	Oligodendrocytes	-0.054	0.085	0.528	0.773
Diagnosis	*FLT1*	Oligodendrocyte Precursor Cells	0.001	0.119	0.994	0.994
Diagnosis	*FLT4*	Endothelial Cells	0.165	0.088	0.06	0.246
Diagnosis	*KDR*	Endothelial Cells	0.094	0.08	0.24	0.552
Diagnosis	*KDR*	Inhibitory Neurons	0.165	0.072	0.022	0.161
Diagnosis	*KDR*	Oligodendrocytes	-0.009	0.059	0.882	0.958
Diagnosis	*NRP1*	Astrocytes	-0.118	0.064	0.067	0.272
Diagnosis	*NRP1*	Endothelial Cells	0.075	0.065	0.247	0.552
Diagnosis	*NRP1*	CUX2- Excitatory Neurons	-0.071	0.055	0.195	0.523
Diagnosis	*NRP1*	CUX2+ Excitatory Neurons	0.059	0.034	0.084	0.316
Diagnosis	*NRP1*	Inhibitory Neurons	-0.007	0.033	0.833	0.937
Diagnosis	*NRP1*	Microglia	0.084	0.05	0.092	0.329
Diagnosis	*NRP1*	Oligodendrocytes	-0.041	0.063	0.518	0.773
Diagnosis	*NRP1*	Oligodendrocyte Precursor Cells	-0.014	0.066	0.827	0.937
Diagnosis	*NRP2*	Astrocytes	-0.115	0.095	0.228	0.55
Diagnosis	*NRP2*	Endothelial Cells	0.020	0.043	0.634	0.832
Diagnosis	*NRP2*	CUX2- Excitatory Neurons	-0.042	0.034	0.218	0.55
Diagnosis	*NRP2*	CUX2+ Excitatory Neurons	0.025	0.041	0.533	0.773
Diagnosis	*NRP2*	Inhibitory Neurons	-0.069	0.032	0.034	0.181
Diagnosis	*NRP2*	Microglia	-0.101	0.038	0.007	0.086
Diagnosis	*NRP2*	Oligodendrocytes	-0.073	0.056	0.187	0.522
Diagnosis	*NRP2*	Oligodendrocyte Precursor Cells	-0.087	0.075	0.247	0.552
Diagnosis	*PGF*	Astrocytes	-0.090	0.105	0.388	0.647
Diagnosis	*PGF*	Endothelial Cells	0.086	0.079	0.279	0.594
Diagnosis	*VEGFA*	Astrocytes	0.046	0.079	0.561	0.782
Diagnosis	*VEGFA*	Endothelial Cells	0.207	0.096	0.032	0.181
Diagnosis	*VEGFA*	CUX2- Excitatory Neurons	-0.047	0.055	0.391	0.647
Diagnosis	*VEGFA*	CUX2+ Excitatory Neurons	0.057	0.059	0.331	0.634
Diagnosis	*VEGFA*	Inhibitory Neurons	-0.031	0.041	0.447	0.713

Diagnosis	*VEGFA*	Microglia	0.002	0.085	0.984	0.994
Diagnosis	*VEGFA*	Oligodendrocytes	0.079	0.082	0.334	0.634
Diagnosis	*VEGFA*	Oligodendrocyte Precursor Cells	-0.024	0.098	0.805	0.926
Diagnosis	*VEGFB*	Astrocytes	-0.004	0.032	0.908	0.963
Diagnosis	*VEGFB*	Endothelial Cells	0.091	0.064	0.156	0.467
Diagnosis	*VEGFB*	CUX2- Excitatory Neurons	-0.048	0.046	0.29	0.604
Diagnosis	*VEGFB*	CUX2+ Excitatory Neurons	-0.013	0.051	0.801	0.926
Diagnosis	*VEGFB*	Inhibitory Neurons	-0.068	0.038	0.074	0.292
Diagnosis	*VEGFB*	Microglia	-0.071	0.041	0.086	0.316
Diagnosis	*VEGFB*	Oligodendrocytes	0.082	0.039	0.039	0.192
Diagnosis	*VEGFB*	Oligodendrocyte Precursor Cells	0.003	0.033	0.925	0.975
Diagnosis	*VEGFC*	Astrocytes	0.072	0.055	0.193	0.522
Diagnosis	*VEGFC*	Endothelial Cells	0.048	0.095	0.61	0.819
Diagnosis	*VEGFC*	CUX2- Excitatory Neurons	0.180	0.066	0.007	0.086
Diagnosis	*VEGFC*	Inhibitory Neurons	0.017	0.061	0.777	0.926
Diagnosis	*VEGFD*	Astrocytes	-0.041	0.054	0.447	0.713
Diagnosis	*VEGFD*	Endothelial Cells	-0.197	0.127	0.12	0.4
Diagnosis	*VEGFD*	CUX2- Excitatory Neurons	0.027	0.022	0.224	0.55
Diagnosis	*VEGFD*	CUX2+ Excitatory Neurons	0.061	0.028	0.029	0.181
Diagnosis	*VEGFD*	Inhibitory Neurons	0.031	0.027	0.256	0.562
Diagnosis	*VEGFD*	Microglia	-0.019	0.109	0.862	0.944
Diagnosis	*VEGFD*	Oligodendrocytes	0.031	0.048	0.527	0.773
Diagnosis	*VEGFD*	Oligodendrocyte Precursor Cells	0.095	0.082	0.247	0.552
β-amyloid Burden	*FLT1*	Astrocytes	0.016	0.007	0.023	0.161
β-amyloid Burden	*FLT1*	Endothelial Cells	0.009	0.005	0.087	0.316
β-amyloid Burden	*FLT1*	CUX2- Excitatory Neurons	-0.008	0.007	0.3	0.605
β-amyloid Burden	*FLT1*	CUX2+ Excitatory Neurons	0.021	0.008	0.013	0.123
β-amyloid Burden	*FLT1*	Inhibitory Neurons	-0.001	0.004	0.799	0.926
β-amyloid Burden	*FLT1*	Microglia	0.053	0.011	0	0.001
β-amyloid Burden	*FLT1*	Oligodendrocytes	0.017	0.008	0.048	0.212
β-amyloid Burden	*FLT1*	Oligodendrocyte Precursor Cells	0.027	0.011	0.015	0.131
β-amyloid Burden	*FLT4*	Endothelial Cells	0.027	0.008	0	0.013
β-amyloid Burden	*KDR*	Endothelial Cells	-0.009	0.007	0.253	0.559
β-amyloid Burden	*KDR*	Inhibitory Neurons	-0.004	0.007	0.523	0.773
β-amyloid Burden	*KDR*	Oligodendrocytes	0.003	0.005	0.597	0.81
β-amyloid Burden	*NRP1*	Astrocytes	-0.012	0.006	0.056	0.238
β-amyloid Burden	*NRP1*	Endothelial Cells	0.013	0.006	0.026	0.177
β-amyloid Burden	*NRP1*	CUX2- Excitatory Neurons	-0.011	0.005	0.023	0.161
β-amyloid Burden	*NRP1*	CUX2+ Excitatory Neurons	0.006	0.003	0.045	0.202

β-amyloid Burden	*NRP1*	Inhibitory Neurons	0.004	0.003	0.233	0.55
β-amyloid Burden	*NRP1*	Microglia	0.008	0.005	0.075	0.292
β-amyloid Burden	*NRP1*	Oligodendrocytes	0.014	0.007	0.029	0.181
β-amyloid Burden	*NRP1*	Oligodendrocyte Precursor Cells	0.018	0.006	0.002	0.046
β-amyloid Burden	*NRP2*	Astrocytes	0	0.01	0.967	0.988
β-amyloid Burden	*NRP2*	Endothelial Cells	0.008	0.004	0.051	0.224
β-amyloid Burden	*NRP2*	CUX2- Excitatory Neurons	0	0.003	0.897	0.963
β-amyloid Burden	*NRP2*	CUX2+ Excitatory Neurons	0.005	0.004	0.188	0.522
β-amyloid Burden	*NRP2*	Inhibitory Neurons	0	0.003	0.88	0.958
β-amyloid Burden	*NRP2*	Microglia	0.007	0.004	0.035	0.183
β-amyloid Burden	*NRP2*	Oligodendrocytes	0.005	0.005	0.379	0.647
β-amyloid Burden	*NRP2*	Oligodendrocyte Precursor Cells	0.006	0.007	0.383	0.647
β-amyloid Burden	*PGF*	Astrocytes	0.007	0.01	0.5	0.768
β-amyloid Burden	*PGF*	Endothelial Cells	0.018	0.007	0.015	0.131
β-amyloid Burden	*VEGFA*	Astrocytes	-0.003	0.007	0.687	0.882
β-amyloid Burden	*VEGFA*	Endothelial Cells	-0.001	0.009	0.908	0.963
β-amyloid Burden	*VEGFA*	CUX2- Excitatory Neurons	-0.01	0.005	0.056	0.238
β-amyloid Burden	*VEGFA*	CUX2+ Excitatory Neurons	-0.006	0.006	0.289	0.604
β-amyloid Burden	*VEGFA*	Inhibitory Neurons	-0.012	0.004	0.003	0.056
β-amyloid Burden	*VEGFA*	Microglia	0.006	0.008	0.503	0.768
β-amyloid Burden	*VEGFA*	Oligodendrocytes	-0.001	0.008	0.935	0.977
β-amyloid Burden	*VEGFA*	Oligodendrocyte Precursor Cells	-0.019	0.009	0.04	0.192
β-amyloid Burden	*VEGFB*	Astrocytes	0.005	0.003	0.144	0.443
β-amyloid Burden	*VEGFB*	Endothelial Cells	0.002	0.006	0.772	0.925
β-amyloid Burden	*VEGFB*	CUX2- Excitatory Neurons	-0.005	0.004	0.217	0.55
β-amyloid Burden	*VEGFB*	CUX2+ Excitatory Neurons	0	0.005	0.936	0.977
β-amyloid Burden	*VEGFB*	Inhibitory Neurons	-0.012	0.004	0.001	0.019
β-amyloid Burden	*VEGFB*	Microglia	0.009	0.004	0.026	0.177
β-amyloid Burden	*VEGFB*	Oligodendrocytes	0.014	0.004	0	0.009
β-amyloid Burden	*VEGFB*	Oligodendrocyte Precursor Cells	0.007	0.003	0.029	0.181
β-amyloid Burden	*VEGFC*	Astrocytes	0.013	0.005	0.008	0.091
β-amyloid Burden	*VEGFC*	Endothelial Cells	-0.001	0.009	0.946	0.98
β-amyloid Burden	*VEGFC*	CUX2- Excitatory Neurons	-0.004	0.006	0.571	0.789
β-amyloid Burden	*VEGFC*	Inhibitory Neurons	-0.01	0.006	0.101	0.352
β-amyloid Burden	*VEGFD*	Astrocytes	0.016	0.005	0.001	0.029
β-amyloid Burden	*VEGFD*	Endothelial Cells	0.015	0.011	0.181	0.522
β-amyloid Burden	*VEGFD*	CUX2- Excitatory Neurons	0.001	0.002	0.674	0.872
β-amyloid Burden	*VEGFD*	CUX2+ Excitatory Neurons	0.005	0.002	0.031	0.181
β-amyloid Burden	*VEGFD*	Inhibitory Neurons	0.002	0.003	0.387	0.647

β-amyloid Burden	*VEGFD*	Microglia	0.015	0.01	0.114	0.384
β-amyloid Burden	*VEGFD*	Oligodendrocytes	0.01	0.004	0.033	0.181
β-amyloid Burden	*VEGFD*	Oligodendrocyte Precursor Cells	0.015	0.008	0.057	0.238
Cognition Trajectory	*FLT1*	Astrocytes	0.455	0.343	0.184	0.522
Cognition Trajectory	*FLT1*	Endothelial Cells	-0.771	0.248	0.002	0.041
Cognition Trajectory	*FLT1*	Inhibitory Neurons	0.44	0.164	0.007	0.086
Cognition Trajectory	*FLT1*	Microglia	-1.964	0.504	0	0.009
Cognition Trajectory	*FLT1*	Oligodendrocyte Precursor Cells	0.666	0.527	0.207	0.539
Cognition Trajectory	*FLT1*	CUX2- Excitatory Neurons	0.167	0.343	0.626	0.829
Cognition Trajectory	*FLT1*	CUX2+ Excitatory Neurons	-0.022	0.401	0.957	0.987
Cognition Trajectory	*FLT1*	Oligodendrocytes	0.449	0.388	0.247	0.552
Cognition Trajectory	*FLT4*	Endothelial Cells	-1.089	0.373	0.004	0.056
Cognition Trajectory	*KDR*	Endothelial Cells	0.093	0.346	0.787	0.926
Cognition Trajectory	*KDR*	Inhibitory Neurons	-0.381	0.316	0.228	0.55
Cognition Trajectory	*KDR*	Oligodendrocytes	0.044	0.256	0.862	0.944
Cognition Trajectory	*NRP1*	Astrocytes	0.825	0.286	0.004	0.06
Cognition Trajectory	*NRP1*	Endothelial Cells	-0.29	0.287	0.311	0.606
Cognition Trajectory	*NRP1*	Inhibitory Neurons	0.1	0.146	0.493	0.768
Cognition Trajectory	*NRP1*	Microglia	-0.269	0.213	0.208	0.539
Cognition Trajectory	*NRP1*	Oligodendrocyte Precursor Cells	0.209	0.284	0.462	0.732
Cognition Trajectory	*NRP1*	CUX2- Excitatory Neurons	0.495	0.232	0.033	0.181
Cognition Trajectory	*NRP1*	CUX2+ Excitatory Neurons	-0.15	0.146	0.306	0.606
Cognition Trajectory	*NRP1*	Oligodendrocytes	0.004	0.304	0.99	0.994
Cognition Trajectory	*NRP2*	Astrocytes	0.747	0.437	0.087	0.316
Cognition Trajectory	*NRP2*	Endothelial Cells	-0.169	0.195	0.384	0.647
Cognition Trajectory	*NRP2*	Inhibitory Neurons	0.289	0.143	0.043	0.202
Cognition Trajectory	*NRP2*	Microglia	0.484	0.165	0.003	0.056
Cognition Trajectory	*NRP2*	Oligodendrocyte Precursor Cells	0.347	0.33	0.294	0.605
Cognition Trajectory	*NRP2*	CUX2- Excitatory Neurons	0.095	0.156	0.545	0.775
Cognition Trajectory	*NRP2*	CUX2+ Excitatory Neurons	-0.391	0.166	0.019	0.146
Cognition Trajectory	*NRP2*	Oligodendrocytes	0.217	0.246	0.378	0.647
Cognition Trajectory	*PGF*	Astrocytes	0.853	0.499	0.087	0.316
Cognition Trajectory	*PGF*	Endothelial Cells	-0.327	0.35	0.35	0.639
Cognition Trajectory	*VEGFA*	Astrocytes	-0.223	0.337	0.508	0.772
Cognition Trajectory	*VEGFA*	Endothelial Cells	-0.934	0.396	0.018	0.146
Cognition Trajectory	*VEGFA*	Inhibitory Neurons	0.175	0.183	0.339	0.637
Cognition Trajectory	*VEGFA*	Microglia	0.256	0.391	0.512	0.773
Cognition Trajectory	*VEGFA*	Oligodendrocyte Precursor Cells	0.623	0.413	0.131	0.423
Cognition Trajectory	*VEGFA*	CUX2- Excitatory Neurons	0.315	0.241	0.192	0.522

Cognition Trajectory	*VEGFA*	CUX2+ Excitatory Neurons	-0.102	0.266	0.702	0.893
Cognition Trajectory	*VEGFA*	Oligodendrocytes	-0.531	0.387	0.17	0.498
Cognition Trajectory	*VEGFB*	Astrocytes	-0.163	0.146	0.266	0.579
Cognition Trajectory	*VEGFB*	Endothelial Cells	-0.244	0.28	0.384	0.647
Cognition Trajectory	*VEGFB*	Inhibitory Neurons	0.266	0.174	0.126	0.411
Cognition Trajectory	*VEGFB*	Microglia	-0.046	0.187	0.804	0.926
Cognition Trajectory	*VEGFB*	Oligodendrocyte Precursor Cells	-0.098	0.155	0.527	0.773
Cognition Trajectory	*VEGFB*	CUX2- Excitatory Neurons	0.065	0.206	0.754	0.912
Cognition Trajectory	*VEGFB*	CUX2+ Excitatory Neurons	-0.361	0.235	0.123	0.407
Cognition Trajectory	*VEGFB*	Oligodendrocytes	-0.561	0.166	0.001	0.019
Cognition Trajectory	*VEGFC*	Astrocytes	-0.169	0.234	0.469	0.74
Cognition Trajectory	*VEGFC*	Endothelial Cells	0.61	0.417	0.143	0.443
Cognition Trajectory	*VEGFC*	Inhibitory Neurons	-0.185	0.273	0.499	0.768
Cognition Trajectory	*VEGFC*	CUX2- Excitatory Neurons	-0.754	0.291	0.01	0.099
Cognition Trajectory	*VEGFD*	Astrocytes	0.241	0.227	0.288	0.604
Cognition Trajectory	*VEGFD*	Endothelial Cells	0.619	0.57	0.277	0.594
Cognition Trajectory	*VEGFD*	Inhibitory Neurons	-0.076	0.119	0.523	0.773
Cognition Trajectory	*VEGFD*	Microglia	0.108	0.472	0.819	0.935
Cognition Trajectory	*VEGFD*	Oligodendrocyte Precursor Cells	-0.192	0.361	0.595	0.81
Cognition Trajectory	*VEGFD*	CUX2- Excitatory Neurons	-0.08	0.099	0.42	0.684
Cognition Trajectory	*VEGFD*	CUX2+ Excitatory Neurons	-0.125	0.12	0.296	0.605
Cognition Trajectory	*VEGFD*	Oligodendrocytes	-0.041	0.208	0.844	0.941
Last Cognition before Death	*FLT1*	Astrocytes	-0.004	0.033	0.91	0.963
Last Cognition before Death	*FLT1*	Endothelial Cells	-0.089	0.024	0	0.009
Last Cognition before Death	*FLT1*	Inhibitory Neurons	0.034	0.016	0.031	0.181
Last Cognition before Death	*FLT1*	Microglia	-0.176	0.046	0	0.009
Last Cognition before Death	*FLT1*	Oligodendrocyte Precursor Cells	0.073	0.052	0.158	0.468
Last Cognition before Death	*FLT1*	CUX2- Excitatory Neurons	-0.001	0.033	0.964	0.988
Last Cognition before Death	*FLT1*	CUX2+ Excitatory Neurons	-0.013	0.038	0.731	0.901
Last Cognition before Death	*FLT1*	Oligodendrocytes	0.004	0.038	0.906	0.963
Last Cognition before Death	*FLT4*	Endothelial Cells	-0.102	0.035	0.003	0.056
Last Cognition before Death	*KDR*	Endothelial Cells	-0.032	0.032	0.31	0.606
Last Cognition before Death	*KDR*	Inhibitory Neurons	-0.058	0.031	0.058	0.242
Last Cognition before Death	*KDR*	Oligodendrocytes	0.008	0.024	0.746	0.909

Last Cognition before Death	*NRP1*	Astrocytes	0.01	0.027	0.716	0.901
Last Cognition before Death	*NRP1*	Endothelial Cells	-0.025	0.028	0.357	0.645
Last Cognition before Death	*NRP1*	Inhibitory Neurons	0.005	0.014	0.729	0.901
Last Cognition before Death	*NRP1*	Microglia	-0.018	0.021	0.381	0.647
Last Cognition before Death	*NRP1*	Oligodendrocyte Precursor Cells	0.001	0.027	0.979	0.993
Last Cognition before Death	*NRP1*	CUX2- Excitatory Neurons	0.045	0.022	0.045	0.202
Last Cognition before Death	*NRP1*	CUX2+ Excitatory Neurons	-0.009	0.014	0.532	0.773
Last Cognition before Death	*NRP1*	Oligodendrocytes	-0.018	0.03	0.553	0.78
Last Cognition before Death	*NRP2*	Astrocytes	-0.002	0.04	0.967	0.988
Last Cognition before Death	*NRP2*	Endothelial Cells	-0.024	0.019	0.19	0.522
Last Cognition before Death	*NRP2*	Inhibitory Neurons	0.016	0.013	0.222	0.55
Last Cognition before Death	*NRP2*	Microglia	0.042	0.016	0.008	0.09
Last Cognition before Death	*NRP2*	Oligodendrocyte Precursor Cells	0.019	0.032	0.544	0.775
Last Cognition before Death	*NRP2*	CUX2- Excitatory Neurons	0.001	0.015	0.943	0.98
Last Cognition before Death	*NRP2*	CUX2+ Excitatory Neurons	-0.035	0.016	0.028	0.181
Last Cognition before Death	*NRP2*	Oligodendrocytes	-0.03	0.023	0.188	0.522
Last Cognition before Death	*PGF*	Astrocytes	0.027	0.045	0.545	0.775
Last Cognition before Death	*PGF*	Endothelial Cells	-0.03	0.034	0.377	0.647
Last Cognition before Death	*VEGFA*	Astrocytes	-0.035	0.03	0.246	0.552
Last Cognition before Death	*VEGFA*	Endothelial Cells	-0.105	0.038	0.005	0.073
Last Cognition before Death	*VEGFA*	Inhibitory Neurons	0.007	0.017	0.691	0.883
Last Cognition before Death	*VEGFA*	Microglia	-0.035	0.037	0.343	0.637
Last Cognition before Death	*VEGFA*	Oligodendrocyte Precursor Cells	0.022	0.036	0.542	0.775
Last Cognition before Death	*VEGFA*	CUX2- Excitatory Neurons	0.004	0.022	0.859	0.944
Last Cognition before Death	*VEGFA*	CUX2+ Excitatory Neurons	-0.031	0.024	0.201	0.535
Last Cognition before Death	*VEGFA*	Oligodendrocytes	-0.076	0.037	0.04	0.192
Last Cognition before Death	*VEGFB*	Astrocytes	-0.01	0.014	0.484	0.759
Last Cognition before Death	*VEGFB*	Endothelial Cells	-0.044	0.027	0.107	0.365

Last Cognition before Death	*VEGFB*	Inhibitory Neurons	0.02	0.016	0.228	0.55
Last Cognition before Death	*VEGFB*	Microglia	-0.009	0.018	0.605	0.816
Last Cognition before Death	*VEGFB*	Oligodendrocyte Precursor Cells	-0.009	0.015	0.554	0.78
Last Cognition before Death	*VEGFB*	CUX2- Excitatory Neurons	0.007	0.02	0.738	0.904
Last Cognition before Death	*VEGFB*	CUX2+ Excitatory Neurons	-0.027	0.023	0.231	0.55
Last Cognition before Death	*VEGFB*	Oligodendrocytes	-0.038	0.016	0.017	0.139
Last Cognition before Death	*VEGFC*	Astrocytes	-0.027	0.023	0.241	0.552
Last Cognition before Death	*VEGFC*	Endothelial Cells	0.008	0.038	0.832	0.937
Last Cognition before Death	*VEGFC*	Inhibitory Neurons	-0.023	0.026	0.368	0.647
Last Cognition before Death	*VEGFC*	CUX2- Excitatory Neurons	-0.074	0.028	0.007	0.086
Last Cognition before Death	*VEGFD*	Astrocytes	0.024	0.022	0.292	0.605
Last Cognition before Death	*VEGFD*	Endothelial Cells	0.097	0.057	0.085	0.316
Last Cognition before Death	*VEGFD*	Inhibitory Neurons	-0.009	0.011	0.447	0.713
Last Cognition before Death	*VEGFD*	Microglia	0.019	0.045	0.67	0.872
Last Cognition before Death	*VEGFD*	Oligodendrocyte Precursor Cells	-0.033	0.034	0.325	0.629
Last Cognition before Death	*VEGFD*	CUX2- Excitatory Neurons	-0.01	0.01	0.307	0.606
Last Cognition before Death	*VEGFD*	CUX2+ Excitatory Neurons	-0.01	0.011	0.393	0.647
Last Cognition before Death	*VEGFD*	Oligodendrocytes	-0.006	0.019	0.763	0.918
Tau Burden	*FLT1*	Astrocytes	0	0.005	0.979	0.993
Tau Burden	*FLT1*	CUX2- Excitatory Neurons	-0.004	0.004	0.347	0.637
Tau Burden	*FLT1*	CUX2+ Excitatory Neurons	0.008	0.005	0.153	0.463
Tau Burden	*FLT1*	Endothelial Cells	0.003	0.003	0.384	0.647
Tau Burden	*FLT1*	Inhibitory Neurons	-0.003	0.002	0.233	0.55
Tau Burden	*FLT1*	Microglia	0.02	0.007	0.006	0.077
Tau Burden	*FLT1*	Oligodendrocytes	0.001	0.005	0.797	0.926
Tau Burden	*FLT1*	Oligodendrocyte Precursor Cells	0.002	0.007	0.725	0.901
Tau Burden	*FLT4*	Endothelial Cells	0.011	0.005	0.016	0.134
Tau Burden	*KDR*	Endothelial Cells	-0.001	0.005	0.818	0.935
Tau Burden	*KDR*	Inhibitory Neurons	0.003	0.004	0.496	0.768
Tau Burden	*KDR*	Oligodendrocytes	0	0.003	0.935	0.977
Tau Burden	*NRP1*	Astrocytes	-0.014	0.004	0	0.009
Tau Burden	*NRP1*	CUX2- Excitatory Neurons	-0.003	0.003	0.358	0.645

Tau Burden	*NRP1*	CUX2+ Excitatory Neurons	0.001	0.002	0.733	0.901
Tau Burden	*NRP1*	Endothelial Cells	0.004	0.004	0.345	0.637
Tau Burden	*NRP1*	Inhibitory Neurons	0.001	0.002	0.568	0.788
Tau Burden	*NRP1*	Microglia	0.002	0.003	0.561	0.782
Tau Burden	*NRP1*	Oligodendrocytes	0.001	0.004	0.837	0.937
Tau Burden	*NRP1*	Oligodendrocyte Precursor Cells	-0.001	0.004	0.847	0.942
Tau Burden	*NRP2*	Astrocytes	-0.006	0.006	0.27	0.583
Tau Burden	*NRP2*	CUX2- Excitatory Neurons	-0.001	0.002	0.797	0.926
Tau Burden	*NRP2*	CUX2+ Excitatory Neurons	0.005	0.002	0.039	0.192
Tau Burden	*NRP2*	Endothelial Cells	0.001	0.003	0.79	0.926
Tau Burden	*NRP2*	Inhibitory Neurons	-0.004	0.002	0.019	0.147
Tau Burden	*NRP2*	Microglia	-0.004	0.002	0.105	0.362
Tau Burden	*NRP2*	Oligodendrocytes	-0.002	0.003	0.647	0.845
Tau Burden	*NRP2*	Oligodendrocyte Precursor Cells	-0.002	0.004	0.729	0.901
Tau Burden	*PGF*	Astrocytes	-0.015	0.007	0.04	0.192
Tau Burden	*PGF*	Endothelial Cells	0.007	0.005	0.137	0.435
Tau Burden	*VEGFA*	Astrocytes	-0.001	0.005	0.894	0.963
Tau Burden	*VEGFA*	CUX2- Excitatory Neurons	-0.002	0.003	0.623	0.829
Tau Burden	*VEGFA*	CUX2+ Excitatory Neurons	0.002	0.004	0.576	0.792
Tau Burden	*VEGFA*	Endothelial Cells	0.008	0.006	0.147	0.448
Tau Burden	*VEGFA*	Inhibitory Neurons	0.001	0.002	0.732	0.901
Tau Burden	*VEGFA*	Microglia	0.003	0.005	0.591	0.808
Tau Burden	*VEGFA*	Oligodendrocytes	0.005	0.005	0.306	0.606
Tau Burden	*VEGFA*	Oligodendrocyte Precursor Cells	0.003	0.006	0.617	0.825
Tau Burden	*VEGFB*	Astrocytes	-0.001	0.002	0.755	0.912
Tau Burden	*VEGFB*	CUX2- Excitatory Neurons	-0.001	0.003	0.837	0.937
Tau Burden	*VEGFB*	CUX2+ Excitatory Neurons	0.005	0.003	0.095	0.337
Tau Burden	*VEGFB*	Endothelial Cells	0.004	0.004	0.334	0.634
Tau Burden	*VEGFB*	Inhibitory Neurons	-0.003	0.002	0.142	0.443
Tau Burden	*VEGFB*	Microglia	0	0.003	0.992	0.994
Tau Burden	*VEGFB*	Oligodendrocytes	0.006	0.002	0.013	0.123
Tau Burden	*VEGFB*	Oligodendrocyte Precursor Cells	-0.001	0.002	0.629	0.829
Tau Burden	*VEGFC*	Astrocytes	0.004	0.003	0.204	0.538
Tau Burden	*VEGFC*	CUX2- Excitatory Neurons	0.009	0.004	0.013	0.123
Tau Burden	*VEGFC*	Endothelial Cells	-0.012	0.006	0.034	0.181
Tau Burden	*VEGFC*	Inhibitory Neurons	0.001	0.004	0.687	0.882
Tau Burden	*VEGFD*	Astrocytes	0.003	0.003	0.382	0.647
Tau Burden	*VEGFD*	CUX2- Excitatory Neurons	0	0.001	0.71	0.9
Tau Burden	*VEGFD*	CUX2+ Excitatory Neurons	0.001	0.002	0.342	0.637

Tau Burden	*VEGFD*	Endothelial Cells	-0.006	0.008	0.432	0.7
Tau Burden	*VEGFD*	Inhibitory Neurons	0.001	0.002	0.368	0.647
Tau Burden	*VEGFD*	Microglia	-0.005	0.006	0.413	0.677
Tau Burden	*VEGFD*	Oligodendrocytes	0.003	0.003	0.231	0.55
Tau Burden	*VEGFD*	Oligodendrocyte Precursor Cells	0.005	0.005	0.3	0.605

*logFC values for diagnosis is gene expression change in AD over normal cognition controls

Supplemental Table 2. Communication Strength Comparison of Enriched VEGFA-Receptor Pair within 10 VEGFs Between AD and Cognition Normal Groups

Receptor	Original Probability	Adjusted Probability*	Source -> Target	Group	P Value
FLT1	1.888854e-06	0.07587518	Astrocytes -> Endothelial Cells	Normal Cognition	<= 0.01
FLT1	1.138895e-06	0.07307029	Astrocytes -> Endothelial Cells	AD	<= 0.01
NRP1	1.180536e-07	0.06268756	Astrocytes -> Endothelial Cells	Normal Cognition	<= 0.01
NRP1	1.180536e-07	0.06268756	Astrocytes -> Excitatory Neurons	Normal Cognition	<= 0.01
NRP1	1.180536e-07	0.06268756	Astrocytes -> Microglia	Normal Cognition	<= 0.01
NRP1	4.745401e-08	0.05929965	Astrocytes -> Endothelial Cells	AD	<= 0.01
NRP1	4.745401e-08	0.05929965	Astrocytes -> Excitatory Neurons	AD	<= 0.01
NRP1	4.745401e-08	0.05929965	Astrocytes -> Microglia	AD	<= 0.01
NRP2	1.180536e-07	0.06268756	Astrocytes -> Endothelial Cells	Normal Cognition	<= 0.01
NRP2	4.745401e-08	0.05929965	Astrocytes -> Endothelial Cells	AD	<= 0.01

*Adjusted Probability = -1/log(Original Probability)