Aβ-induced vulnerability propagates via the brain’s default mode network

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The link between brain amyloid-β (Aβ), metabolism, and dementia symptoms remains a pressing question in Alzheimer’s disease. Here, using positron emission tomography ([18F] flortetapir tracer for Aβ and [18F]FDG tracer for glucose metabolism) with a novel analytical framework, we found that Aβ aggregation within the brain’s default mode network leads to regional hypometabolism in distant but functionally connected brain regions. Moreover, we found that an interaction between this hypometabolism with overlapping Aβ aggregation is associated with subsequent cognitive decline. These results were also observed in transgenic Aβ rats that do not form neurofibrillary tangles, which support these findings as an independent mechanism of cognitive deterioration. These results suggest a model in which distant Aβ induces regional metabolic vulnerability, whereas the interaction between local Aβ with a vulnerable environment drives the clinical progression of dementia.
The relationship between regional cerebral amyloid-β (Aβ) aggregation and hypometabolism has been a topic of significant debate in Alzheimer’s disease (AD). Whereas some studies suggest an association,1-3 others refute that these pathological processes are directly related.4,5 The lack of association between these pathologies has been supported by studies, showing the absence of hypometabolism in some brain regions with high Aβ load, as well as the presence of hypometabolism in other areas with low Aβ concentrations.1,6-7 Notably, the lack of association between regional Aβ and hypometabolism contrasts with the idea of a direct deleterious effect of Aβ on disease progression, as initially proposed in the Aβ hypothesis.8

One possible explanation that links Aβ with disease progression and integrates the aforementioned conflicting observations is the idea that regional hypometabolism is caused by the toxic effects of Aβ aggregation from distant rather than topographically overlapping brain regions. Indeed, early observations using [18F] fluorodeoxyglucose ([18F]FDG) positron emission tomography (PET) support this notion, by showing that brain damage may lead to hypometabolism in remote, but metabolically connected cortical areas.9-11 These results highlight the possibility of a direct deleterious effect of Aβ on distant hypometabolism, which might be being overlooked by the current biomarker studies.

Regardless of the presence of a regional correlation between Aβ and hypometabolism, it is well established that the topographic coexistence of these pathologies in some brain regions such as the posterior cingulate cortex constitutes a signature of forthcoming dementia symptoms.12-15 Also, studies have shown that either Aβ or hypometabolism may be the first abnormality in these regions,16,17 and that cognitive changes may be potentiated by an interaction between these processes.18 Together, these results indicate that although regional Aβ may not be the cause of its overlapping hypometabolism, progression to dementia may be the result of local interactions between these pathologies.

Here, we tested the hypothesis that distant and local Aβ effects play a distinct role in the progression of AD. We find that distant Aβ determines the region’s metabolic vulnerability, whereas the synergy between this regional vulnerability with co-localized concentrations of Aβ determines dementia. These results were obtained in cognitively normal (CN) and mild cognitive impairment (MCI) individuals as well as transgenic rats that display Aβ single pathology in the absence of other brain human proteinopathies, such as neurofibrillary tangles. We therefore conclude that the deleterious effect of Aβ on the progression of AD occurs in a two-step process, in which distant Aβ determines regional vulnerability and local Aβ drives cognitive decline.

### Results

Aβ is unrelated to local hypometabolism. Demographics and key characteristics of the human population are summarized in Table 1. Voxel-wise analysis of covariance showed that compared with CN Aβ-negative individuals, CN Aβ-positive and MCI Aβ-positive had reduced gray matter density in the medial temporal cortex (Supplementary Fig. 1a, d). CN Aβ-positive and MCI Aβ-positive had reduced metabolism in the precuneus, posterior cingulate, inferior parietal, and temporal cortices (Supplementary Fig. 1b, e), and had widespread Aβ deposition (Supplementary Fig. 1c, f).

Voxel-wise models showed that Aβ was not locally associated with hypometabolism in CN Aβ-positive and MCI Aβ-positive individuals. On the other hand, these models showed that global Aβ was associated with hypometabolism in the posterior cingulate, precuneus, lateral temporal, and inferior parietal cortices in CN Aβ-positive (Fig. 1a, d; Supplementary Fig. 2a) and Supplementary Fig. 3a) and MCI Aβ-positive (Fig. 1b, e; Supplementary Fig. 2b; and Supplementary Fig. 3b). In addition, a bootstrap scheme supported that regional Aβ did not affect the stability of the global Aβ effect on hypometabolism in the models mentioned above (Supplementary Fig. 4).

We further replicated the results found in humans using a cohort of 20 rats (10 homozygous McGill-R-Thy1-APP rats overexpressing human Aβ precursor protein and 10 wild-type Wistar rats). They were 11-month-old, and the wild-type rats provided the means for determining that 11-month McGill-R-Thy1-APP transgenic rats presented mild cognitive symptoms, with a significant baseline genotype effect on the Morris Water Maze (MWM) (P = 0.03). In the transgenic Aβ rats, voxel-wise regressions supported that local Aβ and hypometabolism were unrelated to one another. On the other hand, the model revealed that global Aβ load was strongly associated with hypometabolism in the retrosplenial (which corresponds to the posterior cingulate in humans), medial and lateral temporal, and inferior parietal cortices (Fig. 1c, f).

Aβ leads to hypometabolism in functionally connected regions. In CN Aβ-negative (Fig. 2a), CN Aβ-positive (Fig. 2b), and MCI Aβ-positive (Fig. 2c) individuals, metabolic connectivity analysis showed that the regions comprising the brain’s DMN in the precuneus, posterior cingulate, lateral temporal, inferior parietal, and medial prefrontal cortices were highly correlated with each other.

Partial correlation matrices using anatomical segregated regions-of-interest revealed that Aβ was negatively associated...
with metabolism in distant, but metabolically connected brain regions in CN Aβ-positive (Fig. 2d) and MCI Aβ-positive (Fig. 2e–f; Supplementary Movie 1) individuals. Notably, the elements of the Aβ-glucose and glucose-glucose matrices were highly negatively correlated with one another in these individuals \((r = -0.5, \ P < 0.0001)\), which reinforced the link between metabolic connectivity and Aβ effect. Furthermore, the lack of correlation between the Aβ-glucose matrix elements and the Euclidean distance between regions \((r = 0.1, \ P = 0.3294)\) supported that regions’ proximity did not drive these correlations.

Voxel-wise network analysis showed that Aβ load in the precuneus, posterior cingulate, lateral temporal, inferior parietal, and medial prefrontal cortices were associated with distant, but within-DMN hypometabolism in CN Aβ-positive (Fig. 3) and MCI Aβ-positive (Fig. 3b–f) individuals. On the other hand, Aβ outside of the DMN either did not associate with hypometabolism or was associated with hypometabolism predominantly in
regions comprising other brain networks, such as the limbic and ventral attention networks (Fig. 4g, h).

In the transgenic Aβ rats, a voxel-wise regression analysis confirmed that Aβ was associated with distant, rather than co-localized, hypometabolism (Fig. 5). As expected, there were no associations between Aβ uptake and metabolism in the wild-type control rats.

Synergy of Aβ and local hypometabolism on cognitive decline. A voxel-wise interaction model showed that high local levels of Aβ and low local levels of glucose uptake in the precuneus, posterior cingulate, inferior parietal, and lateral temporal cortices synergistically determined subsequent cognitive decline up to 5.6 years in MCI Aβ-positive individuals (Fig. 6a, c; Supplementary Fig. 5; Supplementary Movie 2). In addition, a bootstrap analysis supported that the effect of the local interaction between Aβ and metabolism on cognitive decline was not influenced by a global Aβ effect (Supplementary Fig. 6). Moreover, analysis of variance reinforced that the models with the interaction term best described the relationship between overlapping biomarkers and cognitive decline as compared with reduced models assessing: (1) only Aβ, (2) only metabolism, and (3) Aβ plus metabolism, with a P < 0.0001 in all three cases. In CN Aβ-positive individuals, the aforementioned interaction was not significantly associated with cognitive decline.

In the transgenic Aβ rats, a voxel-wise interaction model supported the synergy between Aβ and overlapping hypometabolism in the retrosplenial, inferior parietal, and mediolateral temporal cortices as a determinant of cognitive decline over 8 months (Fig. 6b, d). This interaction was absent in the wild-type control rats.

Distant and local Aβ effects on hypometabolism. Structured equation modeling (SEM) showed that the construct in which Aβ occurring in distant regions drives hypometabolism, whereas the interaction between this hypometabolism and the co-localized Aβ determines cognitive decline well describe AD progression (Fig. 7).

Discussion
In summary, our results suggest that Aβ is related to vulnerability in distant brain regions functionally connected by the DMN, whereas the synergy between this vulnerability with local Aβ levels is associated with the clinical progression to dementia (Fig. 8). Remarkably, similar results in transgenic Aβ rats, which do not form neurofibrillary tangles20, supported this model as an independent mechanism of cognitive deterioration.

Our results suggest that the regional hypometabolism observed in AD may derive from distant Aβ effects within brain regions connected by the DMN. This observation is supported by early studies showing that lesions in remote brain regions are associated with DMN hypometabolism9–11. For instance, studies in non-human primates show that localized surgical lesions lead to hypometabolism in metabolically connected brain areas, and that the severity of the inflicted lesion correlates with the degree of remote hypometabolism11. These studies suggest that this occurs due to a synaptic disconnection between the damaged and the remote brain region11. Based on these observations, one may
argue that the regional patterns of hypometabolism in AD derive from a decreased synaptic input from distant, but DMN connected brain areas affected by Aβ. Also, we have shown that global Aβ load, rather than local, is associated with regional DMN hypometabolism, which is in line with previous studies. Expanding upon these studies, our findings indicate that this might be explained by the fact that Aβ from several distant brain regions contributes to regional hypometabolism. Therefore, it
seems reasonable that a global Aβ composite contemplating all distant brain regions shows a better association with regional hypometabolism than merely local Aβ levels. Altogether, our results corroborate the deleterious effects of Aβ on the DMN as previously suggested by the network neurodegeneration hypothesis of AD\textsuperscript{15,21,22}, by showing that Aβ leads to hypometabolism in distant brain regions interconnected by the DMN, rather than locally, as inferred from the traditional view\textsuperscript{22}.

On the other hand, our results support the synergy between Aβ and topographically overlapping DMN vulnerability as a driving force behind dementia symptoms. It is well known that individuals might respond differently to Aβ based on their capacity to compensate through the reconfiguration or re-occupation or recruitment of alternative synapses using the DMN\textsuperscript{22,23}. Moreover, DMN hypometabolism has been repeatedly suggested to represent underlying network

[Diagram of brain regions and associated graphs showing distribution of Aβ-hypometabolism across networks.]
dysfunction, and metabolic connectivity has been shown to represent synaptic pathways in the human brain. Thus, the hypometabolism in our results may indicate the dysfunction of the DMN in recruiting alternative synapses in the face of toxic effects of Aβ. As such, our model could be understood to mean that the toxic effects of Aβ and the underlying local levels of DMN dysfunction in handling these toxic effects synergistically determine the severity of the subsequent cognitive deterioration. Together, these findings support that regional vulnerability to Aβ plays an important role in the progression to AD and that this occurs through the decrease of the capacity of the DMN to compensate for the deleterious effects of Aβ.

Although our results suggested that regional metabolic vulnerability depends on distant Aβ, other factors may potentiate this vulnerability in AD. Determinants of such vulnerability might include inflammatory agents and pathology related stressors that might lead to biochemical dysregulations, resulting in decreased synaptic exchanges and therefore hypometabolism. Other factors may include cerebral vascular diseases, systemic metabolic disorders, and allele variants implicated in brain plasticity and resilience. Also, previous studies have proposed that APOE ε4 may lead to hypometabolism independently of Aβ. Recently, it has been shown that astrocytes play an important role in [18F]FDG signal since astrocytes have been associated with numerous mechanisms involving neuronal plasticity and transmission.

**Fig. 4** Amyloid-β (Aβ) in DMN is predominantly associated with distant within-network hypometabolism in MCI Aβ positive. a In the 3D brain, the dots represent the regions-of-interest in which Aβ values were obtained. The regions in which Aβ values were obtained are also shown in white, superimposed on the structural MRI templates in panels b–h. Statistical parametric maps, overlaid on a structural MRI template, show the brains regions where voxel-wise glucose metabolism was negatively associated with Aβ load in the (b) precuneus (green), (c) posterior cingulate (yellow), (d) lateral temporal (red), (e) inferior parietal (blue), (f) medial prefrontal (pink), (g) anterior cingulate (light blue), and (h) paracentral (orange) cortices in MCI Aβ positive (n = 170). The bar graphs show the distribution of the significant voxels in the aforementioned statistical parametric maps across seven functional brain networks (DM default mode, FP frontoparietal, DA dorsal attention, VA ventral attention, limbic visual, SM somatomotor). Thus, the sum of the seven bars in each graph is 100%. Aβ in the orbitofrontal, insular, and occipital pole cortices did not significantly associate with hypometabolism. Parametric images were FWER corrected at P < 0.05 and adjusted for age, gender, education, APOE ε4 status, p-tau, and gray matter density.

**Fig. 5** Amyloid-β (Aβ) is associated with distant within-network hypometabolism in transgenic Aβ rats. a 3D brain representation of the regions-of-interest in which the Aβ values were obtained. Statistical parametric maps, overlaid on a structural MRI template, show the brains regions where voxel-wise glucose metabolism was negatively associated with Aβ load in the (b) retrosplenial (yellow), (c) medial temporal (green), (d) lateral temporal (red), (e) inferior parietal (blue), (f) frontoparietal (light blue), (g) olfactory bulb (pink), and (h) cerebellar (orange) cortices in transgenic Aβ rats (n = 10). Aβ in the somatosensory cortex did not significantly associate with hypometabolism. Parametric images were FWER corrected at P < 0.05 and adjusted for age, gender, and gray matter density.
Astrocytic dysfunction may be involved in the DMN vulnerability reported here. As previously reported by our group and others, interactions between Aβ and tau proteins determine AD progression34,41,42. Since glucose metabolism is proposed to be closely linked to tau pathology36, the regional effects of hypometabolism in this study could be merely inferred as a proxy of neurofibrillary tangles. Therefore, we used the McGill-R-Thy1-APP rats overexpressing human Aβ pathology to clarify our results. Remarkably, the similar results in our transgenic Aβ rats, which do not form tangles20, supported the associations between Aβ and DMN vulnerability as a tau-independent mechanism of cognitive deterioration. It is worth to mention that, although independent, this model is likely to be highly potentiated by neurofibrillary tangles, which is supported by the more markedly cognitive deterioration found in humans as compared with the transgenic Aβ rats. Indeed, it is probable that the Aβ-induced metabolic vulnerability reported here will create a favorable environment, also for neurofibrillary tangles to determine cognitive decline. Importantly, the DMN is an evolutionarily conserved feature involved in the integration of cognitive abilities in humans and rodents19,43.

![Fig. 6](image-url)
Methodological strengths of this study include the use of continuous biomarkers analyzed with a robust voxel-wise approach and the use of an animal model in a controlled experimental setting, which permitted assessing the effects of Aβ on metabolism independent of possible confounding factors, such as neurofibrillary tangles. This study has methodological limitations. Our studied population represents a self-selected group of elderly individuals motivated to participate in an AD study. Therefore, these individuals may not represent a general elderly population. Importantly, the model proposed in this study should be confirmed by future studies using different populations and long-term sequential biomarkers and clinical observations performed at multiple time points. In a heterogeneous population such as MCIs, some individuals have early Aβ deposition and may present a positive association between Aβ and metabolism, while others in later disease stages may present a negative association. Thus, these opposing phenomena in the same population

**Fig. 7** Structured equation modeling showed that the distant and local amyloid-β (Aβ) effects on hypometabolism well describe AD progression. This model represents the hypothesis that distant and local Aβ effects (yellow) on posterior DMN hypometabolism (red) are associated with cognitive decline. The model used CN Aβ-positive and MCI Aβ-positive individuals, and the associations were adjusted for age, gender, education, APOE ε4 status, p-tau, and gray matter density. Negative associations are shown in solid lines, whereas dashed lines show positive associations. Notably, Aβ showed positive association with its overlapping metabolism but negative associations with distant metabolism. The hypothesized model fitted the data well ($n = 223, X^2 = 81$, degrees of freedom $= 21, P < 0.01$, standardized root mean square residual (SRMR) $= 0.092$, and Comparative Fit Index (CFI) $= 0.966$)

**Fig. 8** Schematic representation of the distant and local amyloid-β (Aβ) effects on metabolism. Aβ from distant brain regions leads to regional metabolic vulnerability, whereas the synergy between this vulnerability with local Aβ effects drives the clinical progression of dementia. Importantly, either Aβ or metabolic vulnerability as a single abnormality is insufficient to determine dementia.
may obscure the regional association between these biomarkers. Although we restricted our analyses to Aβ-positive individuals and adjusted the models for p-tau levels, we cannot exclude that other pathological processes than Aβ—such as tau aggregates, neuroinflammation, cholinergic depletion, cerebrovascular disease, α-synuclein, and TDP-43—have influenced the interpretation of these results\(^4\). Also, the lack of tau PET images is an important limitation of these results. McGill-R-Thy1-APP rats develop Aβ plaque and oligomeric species\(^4\). Since regional Aβ load is highly associated with regional oligomeric Aβ, the deleterious effects of Aβ on metabolism reported here might reflect oligomers rather than fibrillar conformations. Also, there are large pathophysiological differences between human AD and transgenic models overexpressing Aβ. However, it is important to mention that the less aggressive progression of Aβ in rats, compared with mice, makes this model more similar to the insidious disease progression of elderly with sporadic AD. For instance, McGill-R-Thy1-APP mice and rats express exactly the same mutations, but rats present plaques at 6–9 months while mice do as early as at 4 months\(^4\). Importantly, the much larger brain size of rats (approximately five times bigger than mice) makes the identification of specific brain structures using techniques with low spatial resolution, such as PET, possible to be performed in this study\(^4\).

To conclude, our results suggest that within the brain’s DMN, regional vulnerability is associated with distant Aβ, while the interaction between this vulnerability with local Aβ is associated with dementia.

**Methods**

**Human subjects.** The data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database, phases GO, and 2 (adni.info.org). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, M.D. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. ADNI study was conducted according to Good Clinical Practice guidelines, US 21CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards, and pursuant to state and federal HIPAA regulations and was approved by the Institutional Review Board of each participating site (adni.info.org). Written informed consent for the study was obtained from all participants and/or authorized representatives. We studied participants who had \(^1^8\)F FDG PET, \(^1^8\)Fflorbetapir PET, MRI, and cerebrospinal fluid (CSF) p-tau at baseline, as well as cognitive assessments at baseline and follow-up. Cognition was assessed with Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test 30-min delayed recall, Trail Making Test Part A and B, and Boston Naming Test. For this study, we selected CN individuals and MCI Aβ-positive individuals. CN individuals had an MMSE score of 24 or higher, and a clinical dementia rating (CDR) of 0. MCI had MMSE scores equal to or greater than 24, a CDR of 0.5, subjective and objective memory impairments, essentially normal activities of daily living, and were not demented (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for probable AD\(^4\)). Individuals did not present other neuropsychiatric disorders (further information about ADNI cognitive tests and inclusion/exclusion criteria may be found at www.adni-info.org).

**Animal use.** We imaged and cognitively assessed 20 rats, 10 homozygous McGill-R-Thy1-APP rats overexpressing human Aβ precursor protein\(^2\) with the Swedish...
double mutation (K670N, M671L) and the Indiana mutation (V177P), along with 10 wild-type Wistar rats. Half of the rats in each group were males. The rats performed behavioral tasks [18F]NAV4694 PET and [18F]FDG at baseline (11-month-old SD 0.14), as well as the MWM test at baseline and at 8 months follow-up. The MWM was performed with four trials per day, over 4 consecutive days. The rats were placed on the platform if they failed to find it within 90 s, and we assumed a maximum trial length of 90 s. The time to find the platform was measured with over 90% accuracy and was water ad libitum. All procedures involving rats were performed according to the ethical regulations for animal testing and research from the Canadian Council on Animal Care and the National Institutes of Health and received ethical approval from the Animal Care Ethics Committee of the McGill University.

**Human imaging methods.** MRI and PET acquisitions followed ADNI protocols (http://adni.loni.usc.edu/methods). T1-weighted MRIs were corrected for field distortions, non-uniformity corrected, brain masked, segmented, and non-linearly transformed to the MNI reference space using the CIVET pipeline. Subsequently, partial volume effects using region-based voxel-wise (RBV) method were corrected for scattering, dead time, and decay. [18F]NAV4694 non-displaceable binding images were reconstructed using a maximum a posteriori algorithm and corrected for global Aβ deposition and hypometabolism between regions-of-interest. The matrices were corrected for multiple comparisons using Bonferroni at P < 0.05. FDG-FDG and FDG-Aβ matrix elements were further corrected using Pearson’s correlation. We also tested the correlation between the matrix elements and the Euclidean distance between nodes (mm) to ensure that the results were not driven by regions’ proximity.

In humans, we further performed a voxel-wise connectivity analysis using Aβ values within the 10 regions-of-interest mentioned above as independent predictors and glucose metabolism at every voxel as the outcome accounting for age, gender, education, APOE ε4 status, p-tau, and gray matter density. In addition, a brain network could provide the matrix elements that assessed the overall brain functional networks (default mode, frontoparietal, dorsal and ventral attention, limbic, visual, and somatomotor network). In rats, a voxel-wise connectivity analysis was performed using Aβ values in eight regions-of-interest, based on previous literature, in retrosplenial, medial temporal, lateral temporal, inferior parietal, frontoparietal, occipital, cerebellum, and somatomotor cortices as independent predictors and glucose metabolism at every voxel as the outcome for accounting for age, gender, and gray matter density.

The association between image biomarkers and cognitive changes was tested in humans with a voxel-wise model using the slope of change in cognitive performance as the dependent variable and the main and interactive effects of [18F]NAV4694 BPND and [18F]FDG SUVR at every voxel as independent predictors. The slope of change in cognitive performance was defined using all available MMSE evaluations for each subject with a mean of 4 (SD: 0.96) evaluations spanning up to 5.6 years (mean of 3.4 years). The analysis was adjusted for global Aβ, age, gender, education, APOE ε4 status, p-tau, gray matter density, and follow-up duration. The voxel-wise interaction model was built as follows:

\[
\Delta \text{MMSE} = \beta_0 + \beta_1 (\text{NAV4694 BPND}) + \beta_2 (\text{FDG SUVR}) + \beta_3 (\text{Flurbiprofen SUVR} + \text{FDG SUVR}) + \epsilon
\]

In rats, we built the same voxel-wise model performed in humans using the slope of change in the MWM as the dependent variable and the main and interactive effects of [18F]NAV4694 BPND and [18F]FDG SUVR as independent predictors. A slope of change in cognitive performance was defined for each rat using the MWM' changes in average (four trials) latency to find the platform over 8 months. The model was adjusted for global Aβ, age, gender, and gray matter density. The voxel-wise interaction model was built as follows:

\[
\Delta \text{AMMM} = \beta_0 + \beta_1 (\text{NAV4694 BPND}) + \beta_2 (\text{FDG SUVR}) + \beta_3 (\text{NAV4694 BPND} + \text{FDG SUVR}) + \epsilon
\]

Statistical parametric maps were corrected for multiple comparisons, and the statistical significance was defined using a family-wise error rate (FWER) threshold of P < 0.05.

The presence of collinearity between regional and global Aβ PET values could inflate the variance of estimates, potentially leading to incorrect the statistical results of significance when both effects are used in the same model. To assess whether such case occurred in our analysis, we investigated the statistical estimates by measuring the variance based on a resampling scheme repeated 10,000 times. The model could be used for the overlap between the results was further assessed with an analysis of variance comparing the interaction model with each reduced model: (1) Aβ, (2) metabolism, and (3) Aβ plus metabolism.

The relationship between Aβ metabolism, and the longitudinal cognitive decline was further assessed via SEM using the R package lavaan. SEM was built to test the specific hypothesis demonstrated in the figure’s meta-model. SEM was classified as satisfactory whether: comparative fit index (CFI) > 0.95 and standardized root mean-square residual (SRMR) < 0.14.
Data availability

All human data used in this study were downloaded online at the Alzheimer’s Disease Neuroimaging Initiative database (adni.loni.usc.edu). The locally processed human brain images (MRI and PET) and the animal data are not publicly available for download, but might be retrieved from the correspondennt author on a request.

Received: 19 June 2018 Accepted: 16 April 2019
Published online: 04 June 2019

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**Acknowledgements**

The data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI; National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica; Biogen; Bristol-Myers Squibb Company; Cerebral; Eisai Inc.; Elan Pharmaceuticals; Eli Lilly and Company; Euroimmun; F. Hoffmann-La Roche and its affiliated company Genentech; Fujirebio; GE Healthcare; IXICO; Janssen Alzheimer Immunotherapy Research & Development; Johnson & Johnson Pharmaceutical Research & Development; Lumosity; Lundbeck; Merck; Meso Scale Diagnostics; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer; Piramal Imaging; Server; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This work was supported by the Canadian Institutes of Health Research (CIHR) (MOP-11-51-31, PR-N.), Weston Brain Institute (P.R.-N.), the Canadian Institutes of Health Research (MOP-11-51-31, P.R.-N.), the Alzheimer’s Association (NIRG-12-92090 and NIRP-12-259245, P.R.-N.), the Alzheimer Society Research Program and the Canadian Consortium on Neurodegeneration in Aging (CCNA) (T.A.P.). A.C.C. has been supported by the CIHR. A.C.C., S.G., and P.R.-N. are members of the CIHR/CCNA.

**Author contributions**

T.A.P., S.G. and P.R.-N. performed the conception of the study and interpreted the data. T.A.P., S.Ma., A.L.B., S.Mo., M.S.K., M.C. and J.T. performed the processing, analysis, and quality control of the image data. M.S.K., M.S. and M.I.P. performed the acquisition of the animal data. A.C.C. developed the transgenic rat model. B.M. assisted in the metabolic network analysis. A.Y.P., J.A.D.A. and H.H. assisted in the statistical analysis. T.A.P., J.P.S., A.C.C., S.G. and P.R.-N. prepared figures, table, and drafted the paper. All authors revised and approved the final paper draft.

**Additional information**

Supplementary Information accompanies this paper at https://doi.org/10.1038/s41467-019-10217-w.

**Competing interests:** The authors declare no competing interests.

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