Neuropsychiatric symptoms herald metabolic decline in Alzheimer’s disease

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Abstract

Background:

Neuropsychiatric symptoms (NPS) are increasingly recognized as early non-cognitive manifestations in the Alzheimer’s disease (AD) continuum. However, the role of NPS as an early marker of pathophysiological progression in AD remains unclear. Dominantly inherited AD (DIAD) mutation carriers are young individuals who are destined to develop AD in future due to the full penetrance of the genetic mutation. Hence, the study of DIAD mutation carriers enables the evaluation of the associations between pure AD pathophysiology and metabolic correlates of NPS without the confounding effects of co-existing pathologies. In this longitudinal study, we aim to identify regional brain metabolic dysfunctions associated with NPS in cognitively intact DIAD mutation carriers.

Methods:

We stratified 221 cognitively intact participants from the Dominantly Inherited Alzheimer’s Network according to their mutation carrier status. Regression mixed effect models with family-level random effects evaluated the interactions of NPS measured by the Neuropsychiatric Inventory-Questionnaire (NPI-Q), age and estimated years of onset (EYO) as a function of metabolism measured by $[^{18}\text{F}]$fluordeoxyglucose ($[^{18}\text{F}]$FDG) positron emission tomography in DIAD mutation and non-mutation carriers. An exploratory factor analysis was performed to identify the neuropsychiatric subsyndromes in DIAD mutation carriers using the NPI-Q sub-components. Regression mixed effect models then evaluated the interactions of specific neuropsychiatric subsyndromes with EYO and age on metabolism.

Results:

119 mutation and 102 non-mutation carriers were studied. The interaction of higher NPI-Q and shorter EYO was associated with greater global and regional $[^{18}\text{F}]$FDG uptake decline in the posterior cingulate and ventromedial prefrontal cortices, bilateral parietal lobes and right insula in DIAD mutation carriers. The neuropsychiatric subsyndrome of agitation, disinhibition, irritability and depression interacted with EYO to drive $[^{18}\text{F}]$FDG uptake decline in the DIAD mutation carriers. The interaction of NPI and EYO was not associated with $[^{18}\text{F}]$FDG uptake in DIAD non mutation carriers.

Conclusions:

NPS in cognitively intact DIAD mutation carriers are clinical indicators of subsequent metabolic decline in brain networks vulnerable to AD. Our findings further advanced the emerging conceptual framework that NPS represent early manifestations of neuronal injury in AD.

Background
Neuropsychiatric symptoms (NPS) are frequently observed in the mild cognitive impairment (MCI) and dementia stages of Alzheimer’s disease (AD) [1, 2] and are associated with greater functional impairment, poorer quality of life and accelerated cognitive decline [3–5]. In cognitively normal individuals, developing NPS later in life may potentially increase the risk of cognitive decline [6, 7]. Therefore, NPS are increasingly being proposed as non-cognitive manifestations in the early stages of AD when one is cognitively intact [8]. However, the role of NPS as early clinical manifestations of AD pathophysiological progression in cognitively normal individuals remains unclear. Our recent study showed that NPS in preclinical sporadic AD individuals preceded hypometabolism in the posterior cingulate cortex, a key brain region involved in the AD process [9]. Hence, further studies indicating NPS as an early manifestation of metabolic decline in an independent cognitively intact cohort known to have AD pathophysiology will further advance the emerging conceptual framework in which NPS constitute an early clinical manifestation of AD.

Dominantly inherited AD (DIAD) is a familial AD due to autosomal dominant mutations in the APP, PSEN1 or PSEN2 genes and cognitively intact individuals who are DIAD mutation carriers are destined to develop AD in future due to the full penetrance of the genetic mutation [10]. Similar to late-onset sporadic AD [11], the pathophysiology of DIAD begins to accumulate in the preclinical stage of the disease when carriers are cognitively normal [12, 13]. In DIAD, early behavioural changes are reported in mildly cognitively symptomatic mutation carriers in whom the NPS increase as their disease progresses [14]. Furthermore, DIAD mutation carriers are younger compared to individuals with sporadic AD and are less likely to have other medical conditions such as cerebrovascular disease [15]. Therefore, studying cognitively normal DIAD mutation carriers constitutes a valuable strategy to evaluate the associations between pure AD pathophysiology and the metabolic correlates of NPS in the preclinical stage of AD without the confounding effects of co-existing pathologies.

Here, in a longitudinal observation of cognitively normal DIAD mutation and non-mutation carriers from the Dominantly Inherited Alzheimer Network (DIAN) [16], we will test the hypothesis that the severity of NPS is associated with greater metabolic decline in cognitively intact DIAD mutation carriers as their disease progresses. We will further test the specific neuropsychiatric subsyndromes that drive the metabolic decline in the DIAD mutation carriers.

**Methods**

**Study Participants**

Data analysed in this study were obtained from the Dominantly Inherited Alzheimer’s Network (DIAN) Data Freeze 11. The DIAN observational study is an international multi-site study that enrolls biological adult children of a parent with a mutated gene known to cause DIAD [16]. Study participants may or may not be mutation carriers and they may or may not have cognitive symptoms. DIAN study participants undergo standardized clinical and cognitive testing, brain imaging, and biological fluid collection (blood, cerebrospinal fluid) with the goal of determining the sequence of changes in pre-symptomatic gene carriers who are destined to develop AD.

In this study, we selected cognitively normal DIAD mutation and non-mutation carriers from the DIAN cohort supported by clinical dementia rating (CDR) [17] score 0 and mini-mental state examination [18] score ≥ 24. Each participant’s first visit and subsequent yearly follow ups, if available, with completed neuropsychiatric
inventory-questionnaire (NPI-Q) and $[^{18}\text{F}]$Flurodeoxyglucose (FDG) positron emission tomography (PET) will be analyzed.

**Ethical Approvals and Patient Consents**

The DIAN study was approved by the Institutional Review boards of all of the participating institutions. Informed written consent was obtained from all participants at each site.

**Neuropsychiatric Assessments**

The NPI-Q is an informant-based assessment tool that measures the presence and severity of behavioural disturbances that represent a change from the baseline within the past month, in the 12 behavioural domains of agitation, anxiety, apathy, appetite changes, delusions, depression, disinhibition, abnormal elevated mood, hallucinations, irritability, repetitive motor behaviours, and sleep behaviour changes in clinical settings [19]. Higher NPI-Q scores represent greater severity of NPS.

**DIAN estimated years of onset (EYO)**

The estimated age of onset of cognitive impairment in cognitively normal individuals from the DIAN was calculated based on the mean mutation age of symptom onset and/or the parental age of symptom onset in the following ordered steps:

i. At any study visit, EYO equals to the visit age minus the mean mutation age of symptom onset if the individual’s mutation is known and the mean mutation age of symptom onset for this individual’s mutation is available in the master DIAN database.

ii. If the individual’s mutation is not available in the master DIAN database (e.g., the mutation has not been previously reported or other member age of onset not then at any study visit, EYO equals to the visit age minus the parental age of symptom onset.

The shorter the EYO, the closer the proximity of the individual’s time of clinical disease.

**Genetic analysis**

DNA sequencing of the $APP$, $PSEN1$ and $PSEN2$ genes was performed by the DIAN Genetics Core investigators as previously described [14] to establish the presence of disease-causing mutation in ADAD at-risk individuals.

**Cerebrospinal Fluid (CSF) Analysis**

CSF $\text{A}_\beta_{1-42}$, $\text{t-tau}$ and $\text{p-tau}_{181}$ were analysed by the DIAN Biomarker Core at the Washington University. The CSF levels of $\text{A}_\beta_{1-42}$, total tau and ptau$_{181}$ were measured by immunoassay using the Luminex bead-based multiplexed xMAP technology (INNO-BIA AlzBio3™, Innogenetics, Ghent, Belgium) as previously described [20].

**MRI and PET methods.**

MRI and PET standard acquisition protocols were described in the DIAN website. T1-weighted MRI images corrected for field distortions were processed with the CIVET image processing pipeline [21] and the PET images were processed with an established image processing pipeline previously described [22]. The pre-processed images from the DIAN database were spatially normalized to the Montreal Neurological Institute (MNI) 152 standardized space by using the transformations obtained for PET native to MRI native space and the MRI
native to the MNI 152 space. The $^{18}$F FDG PET standardized uptake value ratio (SUVR) maps were then generated using the pons as the reference region. The global brain glucose uptake was calculated by averaging the $^{18}$F FDG SUVR within several brain regions characteristic to the AD process, including the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices.

**Statistical Analysis**

Descriptive statistics and frequency distributions of baseline demographics, mutation characteristics and CSF AD biomarkers were summarized and compared between DIAD mutation and non-mutation carriers using family-level random-effect models for both continuous and categorical measurements using STATA 15.0. Principal components were derived for the variables NPI-Q, and EYO to resolve collinear relationships.

Linear mixed effect models with family-level random effects evaluated the interactions between NPI-Q, age and EYO on FDG SUVR in the mutation and non-mutation groups. We modelled FDG SUVR as a function of the interactions of NPI-Q, age and EYO and covariates, where FDG SUVR$_{ij}$ denotes the FDG uptake for the $j$th person from the $i$th family, NPI-Q$_{ij}$ indicates the severity of NPS, age$_{ij}$ indicates the age of participant at the time of study visit, EYO$_{ij}$ indicates the years to estimated age of symptom onset and $X_{ij}$ represents fixed effect covariates for gender, education, APOE ε4 status and family mutation type (APP, PSEN1 and PSEN2):

$$
\text{FDG SUVR}_{ij} = \beta_0 + \beta_1(\text{NPI-Q}_{ij}) + \beta_2(\text{EYO}_{ij}) + \beta_3(\text{Age}_{ij}) + \beta_4(\text{NPI-Q}_{ij} \times \text{EYO}_{ij}) + \\
\beta_5(\text{NPI-Q}_{ij} \times \text{Age}_{ij}) + \beta_6(\text{EYO}_{ij} \times \text{Age}_{ij}) + \beta_7(\text{NPI-Q}_{ij} \times \text{EYO}_{ij} \times \text{Age}_{ij}) + \beta_8(\text{X}_{ij}) + \\
F_i + \varepsilon_{ij}
$$

where $F_i$ represents a random effect for all individuals from family $i$, and $\varepsilon_{ij}$ is the residual error assumed independent and normally distributed for all individuals.

The family-level random effect term accounts for the correlations between individuals within the same family. Although correlations between family members might vary with the relationship type, due to the fairly small sizes of the families, this was modelled with a single random effect.

Voxel-based statistical analyses were then performed using the R Statistical Software Package version 3.3.0 with the RMINC library [23]. Voxel-based regression models tested the interactions of NPI-Q, age and EYO on FDG SUVR in the DIAD mutation and non-mutation carrier groups. All voxel-based regression analyses were corrected for multiple comparisons using random field theory [24] at $p < 0.001$.

Exploratory factor analysis was performed on the subcomponents of NPI-Q to identify the neuropsychiatric subsyndromes within the DIAD mutation carriers and verified using confirmatory factor analysis to assess the fit. Linear mixed effect models with family-level random effects then evaluated the interactions of specific neuropsychiatric subsyndromes and EYO and age on FDG SUVR in the mutation carrier groups.

**Results:**
Baseline demographics, mutation characteristics and CSF AD biomarkers

Two hundred and twenty-one (n = 221) cognitively intact individuals (102 (46.15%) non-mutation and 119 (53.85%) DIAD mutation carriers) were included in this study. 29 individuals had year 1, 24 had year 2, 46 had year 3, 7 had year 4, 4 had year 5 and 3 had year 6 follow-up data. Baseline demographics, \textit{APOE} \textit{\varepsilon}4 carrier status, and AD CSF biomarker characteristics were summarized in Table 1. The DIAD mutation and non-mutation carriers did not differ significantly in age, gender, education and \textit{APOE} \textit{\varepsilon}4 status. As expected, DIAD mutation carriers had lower CSF A\textsubscript{\textit{\beta}1−42}, higher CSF p-tau\textsubscript{181p} and CSF t-tau levels than non-mutation carriers.
Table 1
Baseline demographics and sample characteristics of cognitively intact DIAD mutation and non-mutation carriers

|                               | DIAD Non-Mutation Carriers (n = 102) | DIAD Mutation Carriers (n = 119) | P Value |
|--------------------------------|--------------------------------------|---------------------------------|---------|
| Age, mean, years (SD)          | 38.99 (10.75)                        | 36.45 (9.24)                    | 0.060   |
| Male, n (%)                    | 44 (43.13)                           | 58 (48.73)                      | 0.405   |
| Education, mean, years (SD)    | 15.15 (2.88)                         | 14.92 (3.05)                    | 0.566   |
| APOE carrier status            |                                      |                                 | 0.600   |
| APOE ε2/ε2, ε2/ε3, ε3/ε3 carriers, n (%) | 72 (70.06)                           | 83 (69.7)                       |         |
| APOE ε2/ε4 carriers, n (%)     | 6 (5.88)                             | 4 (3.36)                        |         |
| APOE ε3/ε4, ε4/ε4 carriers, n (%) | 24 (23.52)                           | 32 (26.89)                      |         |
| Parental age of onset, years, mean (SD) | 46.85 (6.37)                        | 48.32 (7.25)                    | 0.179   |
| EYO, years, mean (SD)          | -9.40 (11.92)                        | -11.51 (9.40)                   | 0.078   |
| DIAD Mutation Type             |                                      |                                 | 0.863   |
| APP, n (%)                     | 20 (19.60)                           | 20 (16.80)                      |         |
| PS1, n (%)                     | 69 (67.65)                           | 83 (69.75)                      |         |
| PS2, n (%)                     | 13 (12.75)                           | 16 (13.45)                      |         |
| MMSE, mean, (SD)               | 29.39 (0.83)                         | 29.08 (1.19)                    | 0.052   |
| CSF Aβ_{1−42}, mean, pg/ml (SD) | 461.14 (138.27)                     | 363.66 (166.72)                 | < 0.001 |
| CSF p-tau_{181p}, mean, pg/ml (SD) | 29.64 (11.96)                     | 53.44 (30.65)                   | < 0.001 |
| CSF t-tau, mean, pg/ml (SD)    | 54.86 (25.47)                        | 92.06 (62.16)                   | < 0.001 |

*P* values were assessed using family-level random-effects models for the continuous variables and categorical variables, taking into account the analysis of multiple family members within the families.

CSF: cerebrospinal fluid; EYO: estimated years of onset; MMSE: mini-mental state examination

^19 mutation carriers and 23 non-mutation carriers did not have CSF Aβ_{1−42} data for the visit.

^18 mutation carriers and 21 non-mutation carriers did not have CSF p-tau_{181p} & CSF t-tau data for the visit.

Interactions of NPI-Q, EYO and age on global \([^{18}F]FDG\) uptake

The interaction of NPI-Q and EYO was significantly associated with global \([^{18}F]FDG\) SUVR only in DIAD mutation carriers. We found that higher NPI-Q and shorter EYO were associated with greater global \([^{18}F]FDG\) uptake
decline ($\beta = -0.29$, 95% CI -0.054 to -0.003, $p = 0.024$) in DIAD mutation carriers but not in DIAD non-mutation carriers ($\beta = -0.008$, 95% CI -0.043 to 0.026, $p = 0.641$). We did not find a statistically significant interaction between NPI-Q and age on global $[^{18}\text{F}]$FDG uptake in either DIAD mutation or non-mutation carriers. We also did not find a statistically significant interaction between NPI-Q, age and EYO on global $[^{18}\text{F}]$FDG uptake in either DIAD mutation or non-mutation carriers.

**Interactions of NPI-Q and EYO on regional $[^{18}\text{F}]$FDG uptake**

The voxel-based analysis indicated that the interaction between higher NPI-Q and shorter EYO was associated with regional $[^{18}\text{F}]$FDG uptake decline in the posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC), bilateral parietal lobes and right insula in DIAD mutation carriers (Fig. 1). There was no statistically significant interaction between NPI-Q and EYO on regional $[^{18}\text{F}]$FDG uptake in DIAD non-mutation carriers. There was no statistically significant interaction between NPI-Q and age, and NPI-Q, age and EYO on regional $[^{18}\text{F}]$FDG uptake, in both DIAD mutation and non-mutation carriers.

**Factor analysis of NPI-Q subcomponents**

A 4 factor solution was applied to the NPI-Q subcomponents, which explained 70% of the variance. Cross-loading of the 4 factors resulted in a good fit of comparative fit index (CFI) = 0.837. The neuropsychiatric subsyndromes derived from the factor analysis were 1) agitation, disinhibition, irritability and depression; 2) anxiety, apathy, depression, motor behaviours, and sleep behaviour changes; 3) delusion, sleep behaviour changes and irritability; 4) appetite and anxiety (Table 2). In DIAD mutation carriers, we found that only the interaction of the neuropsychiatric subsyndrome agitation, disinhibition, irritability and depression and shorter EYO was associated with global $[^{18}\text{F}]$FDG uptake decline ($\beta = -0.044$, 95% CI -0.071 to -0.017, $p = 0.001$). The interaction of the same neuropsychiatric subsyndrome and higher age was also associated with global $[^{18}\text{F}]$FDG uptake decline ($\beta = -0.049$, 95% CI -0.078 to -0.020, $p = 0.001$) in DIAD mutation carriers.
| Neuropsychiatric Subsyndromes | 1 | 2 | 3 | 4 |
|-----------------------------|---|---|---|---|
| Agitation                   | 0.867 | | | |
| Anxiety                     | 0.477 | 0.421 | | |
| Apathy                      | 0.785 | | | |
| Appetite                    | | 0.929 | | |
| Delusion                    | | | 0.908 | |
| Depression                  | 0.456 | 0.577 | | |
| Disinhibition               | 0.822 | | | |
| Irritability                | 0.692 | 0.410 | | |
| Motor                       | | 0.797 | | |
| Sleep changes               | | 0.489 | 0.564 | |

Principal component analysis of a 4 factor solution identified the above 4 components which explained 70% of the variance. Cross-loading of the 4 factors resulted in a good fit of comparative fit index (CFI) = 0.837.

**Discussion:**

The present study showed that the emergence of NPS heralded metabolic dysfunction in brain regions susceptible to AD pathophysiology in cognitively intact DIAD mutation carriers. In these individuals who were destined to develop AD, the more severe the NPS and the shorter the EYO to AD dementia onset, the greater the metabolic decline in the PCC, vmPFC, bilateral parietal lobes and right insular. We found that the metabolic dysfunctions were driven by the neuropsychiatric subsyndrome of agitation, disinhibition, irritability and depression.

Accumulating evidence have demonstrated the importance of NPS as predictors of cognitive decline in cognitively normal individuals. In the population-based Mayo Clinic Study of Aging, the presence of NPS at baseline increased the risk of incident MCI compared to those without NPS [6]. In the Alzheimer’s Disease Cooperative Study (ADCS) Prevention Instrument Project, anxiety and depression at baseline predicted CDR conversion to ≥ 0.5 in cognitively intact older subjects over a 4-year follow-up [25] while in the National Alzheimer’s Coordinating Center (NACC) cohort, cognitively normal participants who developed CDR > 0 during follow up had a significantly earlier presence of NPS [7]. NPS among cognitively normal individuals may also represent an early manifestation of progressive metabolic dysfunction. In cognitively normal persons aged > 70 years, depressive and anxiety symptoms were associated with decreased FDG uptake in AD-related regions [26].

In a recent study of preclinical sporadic AD individuals, we found that NPS were associated with metabolic dysfunctions in the limbic network and predicted hypometabolism in the PCC [9]. Our present findings in a cohort of preclinical familial AD mutation carriers who are destined to develop AD in future further support the emerging
conceptual framework that NPS are early non-cognitive manifestations of AD pathophysiology and herald subsequent metabolic decline.

The default mode network (DMN), which comprises of the PCC, vmPFC and inferior parietal lobes, plays a vital role in episodic memory processing and decreased metabolism in the DMN is observed early in the course of AD [27, 28]. The salience network (SN) which is critical in detecting and integrating behavioural and emotional stimuli, has key nodes in the insular cortex and modulates the switch between the DMN and the central executive network [29, 30]. The impairment of the SN can lead to numerous neuropsychiatric disorders such as psychosis [31] and depression [32]. Brain metabolic dysfunctions within the SN are also related to NPS in AD [33]. Therefore, our finding of NPS heralding greater FDG uptake decline in the PCC, vmPFC, parietal lobes, and right insula in DIAD mutation carriers with shorter EYO to onset of AD dementia supports the link between early NPS, limbic structures and brain regions involved in early AD pathophysiology.

While there is heterogeneity in the neuropsychiatric manifestations in AD, certain NPS tend to co-express. Hence, several neuropsychiatric sub-syndromes have been identified to characterise the clustering of NPS [34] in AD. In our study, an exploratory factor analysis revealed four neuropsychiatric subsyndromes (Table 3) and among them, only the neuropsychiatric subsyndrome “agitation, disinhibition, irritability and depression” was associated with regional metabolic decline in cognitively intact DIAD mutation carriers with shorter EYO to onset of AD dementia. This neuropsychiatric subsyndrome is consistent with findings from a systemic review of behavioural and psychological subsyndromes among elderly individuals with sporadic AD, where 34 different clusters were found and the quartet of agitation/aggression, depression, anxiety and irritability were most commonly clustered together [35]. In addition, delusion and hallucinations, depression and anxiety, agitation and irritability and euphoria and disinhibition tend to be frequently associated symptoms. Hence, our finding is consistent with the current evidence of neuropsychiatric subsyndromes in AD. In addition, given that currently reported subsyndromes are mostly defined among elderly individuals with sporadic AD, our results further advanced the field by identifying specific neuropsychiatric subsyndromes among younger cognitively intact DIAD mutation carriers who are destined to develop AD.

The neurobiology of agitation, disinhibition, irritability and depression is closely linked to dysfunctions within the PCC, vmPFC, bilateral parietal lobes and right insular. The vmPFC enables the use of emotional signals to guide decisions towards the advantageous direction, regulates behavioural responses such as changing reinforcement contingencies and emotional processing and regulation [36, 37]. The manifestation of irritability is linked to abnormal emotional processing associated with vmPFC and PCC, while behavioral disinhibition and prominent emotional lability are linked to lesions in the vmPFC. Dysfunctions within the vmPFC and PCC, which are part of the neural network involved in the modulation of normal emotional behaviour, also lead to affective disorders and depressive symptoms [38]. The insular plays a key role in producing appropriate behavioral responses in a person by integrating affective, homeostatic, and higher-order cognitive processes [39]. Irritability is associated with dysfunctions within the insular [40] while AD patients with agitation also appear to have dysfunctions within the frontal cortex, anterior cingulate cortex (ACC), orbitofrontal cortex, amygdala, and insula [41]. While the neuropsychiatric subsyndrome of agitation, disinhibition, irritability and depression is linked to regional metabolic decline in cognitively normal DIAD mutation carriers, further studies are needed to evaluate if the neuropsychiatric subsyndrome also identifies cognitively normal individuals with an increased risk of pathological progression in sporadic AD.
The main strength of the present longitudinal study is the inclusion of preclinical DIAD mutation carriers who have AD pathology and are destined to develop AD in future. This allows the study of the associations between NPS, metabolism and effects of increasing AD pathology over time (EYO). Furthermore, given that individuals may be susceptible to NPS presentations due to genetic, family and environmental factors, or being at risk for DIAD, studying both DIAD mutation and non-mutation carriers enables the control of these factors.

There are limitations to our study. Firstly, while NPI-Q is commonly used to detect NPS in AD patients, the NPI-Q was not developed for patients with prodromal or preclinical AD. Hence, the sensitivity of NPI-Q in identifying early NPS in cognitively intact individuals remains unclear. In addition, given that the NPI is based on responses from an informed caregiver, the NPI scores may not accurately reflect the NPS of study participants. In this regard, the mild behavioral impairment checklist (MBI-C) [42] which is a 34-item instrument completed by either the patient, close informant, or clinician, has been developed to assess mild behavioral impairment (MBI), a construct that characterises the emergence of sustained and impactful neuropsychiatric symptoms (NPS) in pre-dementia populations as a precursor to cognitive decline and dementia. Given that the MBI-C is sensitive in detecting MBI in people with MCI [43], future studies of NPS in pre-dementia individuals should also include the MBI-C.

Conclusions:

Our findings further support the emerging conceptual framework that NPS, characterised by agitation, disinhibition, irritability and depression, are early clinical presentations of AD pathophysiology progression. Given that early NPS may contribute to the characterization of the preclinical AD stage, cognitively intact individuals presenting with NPS can be identified earlier so as to allow a personalized and timely preventive intervention.

Abbreviations

anterior cingulate cortex (ACC); Alzheimer's disease (AD); Alzheimer's Disease Cooperative Study (ADCS); clinical dementia rating (CDR); comparative fit index (CFI); Cerebrospinal fluid (CSF); Dominantly inherited AD (DIAD); Dominantly Inherited Alzheimer's Network (DIAN); estimated years of onset (EYO); $[^{18}F]$Flurodeoxyglucose (FDG); mild behavioral impairment (MBI); mild behavioral impairment checklist (MBI-C); mild cognitive impairment (MCI); National Alzheimer's Coordinating Center (NACC); neuropsychiatric inventory-questionnaire (NPI-Q); Neuropsychiatric symptoms (NPS); posterior cingulate cortex (PCC); positron emission tomography (PET); standardized uptake value ratio (SUVR); ventral medial prefrontal cortex (vmPFC)

Declarations

Ethics approval and consent to participate

The DIAN study was approved by the Institutional Review boards of all of the participating institutions.

Consent for publication

Informed written consent was obtained from all participants at each site.
Availability of data and materials

The datasets used and/or analysed during the current study are available from the Dominantly Inherited Alzheimer Network on reasonable request.

Competing interests

Not Applicable

Funding

Not Applicable

Authors' contributions

Kok Pin Ng study concept, design, analysis and interpretation of data, compose figures and manuscript draft.

Tharick A. Pascoal analysis and interpretation of data and manuscript draft.

Sulantha Mathotaarachchi image data processing, analysis and interpretation of data and manuscript draft.

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Monica Shin image data processing, manuscript draft.

Nagaendran Kandiah analysis and interpretation of data and manuscript draft.

Celia M.T. Greenwood analysis and interpretation of data and manuscript draft.

Pedro Rosa-Neto study concept, design, study supervision, and critical review of manuscript for intellectual content.

Serge Gauthier study concept, design, study supervision, and critical review of manuscript for intellectual content.

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**Figures**

**Figure 1**

Higher NPI-Q and shorter EYO to onset of AD is associated with higher [18F]FDG uptake decline in DIAD mutation carriers Figure Legend: Statistical parametric map overlaid on a structural MRI scan shows regions in the PCC, vmPFC, bilateral parietal lobes and right AI where higher [18F]FDG uptake decline was found in cognitively normal DIAD mutation carriers with higher NPI-Q scores and shorter EYO to onset of AD. The analysis was corrected for gender, education, APOE ε4 status and family mutation type (APP, PSEN1 and PSEN2) and multiple comparisons were corrected using random field theory at p < 0.001. AD: Alzheimer disease; AI: anterior insula;
DIAD: dominantly inherited Alzheimer's disease; EYO: estimated years of onset; [18F]FDG: [18F]fluorodeoxyglucose; NPI-Q: Neuropsychiatric Inventory; PCC: posterior cingulate cortex; vmPFC: ventromedial prefrontal cortex.