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Short Communication

Effect of Genetic Risk on the Relationship Between rs-fMRI Complexity and Tau and Amyloid PET in Alzheimer's Disease

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Abstract. Reduced functional magnetic resonance imaging (fMRI)-complexity in Alzheimer's disease (AD) progression has been demonstrated and found to be associated with tauopathy and cognition. However, association of fMRI-complexity with amyloid and influence of genetic risk (*APOE* ε4) remain unknown. Here we investigate the association between fMRI-complexity, tau-PET, and amyloid-PET as well as influence of *APOE* genotype using multivariate generalized linear models. We show that fMRI-complexity has a strong association with tau but not amyloid deposition and that the presence of an *APOE* ε4 allele enhances this effect. Thus fMRI-complexity provides a surrogate marker of impaired brain functionality in AD progression.

Keywords: Alzheimer's disease, amyloid, APOE, fMRI-complexity, tau

INTRODUCTION

Nonlinear statistical analyses of neural signals from resting state functional magnetic resonance imaging (rs-fMRI) that characterize the signal complexity within a brain area have been proposed as measures for the information processing capacity of brain areas and networks,[1–4] or indices of pathological brain function.[5–7] One of the most commonly used metrics is SampleEntropy (SampEn)[8] and its extension to multiple temporal frequencies, MultiScale Entropy (MSE).[9] SampEN and MSE both capture the randomness and predictability of a stochastic process. SampEn is calculated as the negative log of the likelihood that a pattern match at a specific length can be observed also at a length plus one. A match thereby is defined by a specific sensitivity threshold. MSE is an extension of SampEn to multiple frequency scales, which are formed by coarse sampling of the original time series to generate

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new time series with reduced frequency. Such fMRI-complexity analyses have demonstrated progressive decline in complexity from cognitively normal subjects (CN) to patients with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD).[10–12] fMRI-complexity is also associated with overall cognitive function and hippocampal fMRI-complexity specifically with memory deficits.[13,14] In sum, complexity was demonstrated to be related to worsening cognitive function with AD progression.

Amyloid has been shown to vary across as well as within diagnostic groups. Amyloid load can also be relatively high in individuals without cognitive impairments. Accordingly, recent hypotheses refer to amyloid as a prerequisite for AD but tau as the trigger that leads to cognitive decline as a result of neurotoxicity and hence loss of synapses, dendrites and ultimately neurons.[15,16] Furthermore, it has been shown that tau deposition is related to cognitive impairments in different domains in a region-specific manner and that these relations are only weakly related to amyloid burden.[17] Hence, there is increasing evidence for the relevance of tau pathology as the more critical pathophysiological index of neurodegeneration and subsequent cognitive decline than amyloid,[18] and AD therapy targeting tau being studied as potential interventions.[19] Since fMRI-complexity captures changes related to alterations in neuronal signaling, which is the basis for brain function, and these alterations in neuronal signaling and decline in cognition are strongly associated with tauopathy, it is reasonable to hypothesize that fMRI-complexity has a closer association to tau than amyloid. In a recent paper we showed that fMRI complexity in precuneus and medial temporal lobe is negatively associated with tau-PET uptake and that the relation between fMRI-complexity and cognitive function is mediated by tau deposition.[20] However, the effects of amyloid deposition or genetic risk (*APOE* ε4) on the relation between fMRI-complexity and tau remains unknown.

APOE ε4 has strong links to amyloid pathology and *APOE* ε4 is generally associated with greater risk of dementia.[21] Recently however, *APOE* ε4 has also been demonstrated as a critical regulator of tau pathology independent of amyloid in human[18] and animal studies.[22] It was demonstrated that the *APOE* ε4 allele is associated with more severe tau pathogenesis and tau related neuronal degeneration independent of amyloid pathology, particularly in medial temporal lobe.[23] *APOE* ε4 influences early regional tau PET burden, above and beyond effects related to cross-sectional amyloid PET burden.[24–26] Carriers of *APOE* ε4 also show accelerated amyloid-related tau spreading even at lower amyloid levels.[27] Finally, animal models demonstrate that the *APOE* ε4 genotype affects tau pathogenesis, neuroinflammation, and tau-mediated neurodegeneration independently of amyloid-β pathology.[22] Therefore, we hypothesize that the association between fMRI-complexity and tau-PET in areas of early AD pathology (posterior cingulate, precuneus, (para)hippocampal gyrus, and entorhinal cortex) is significantly modified by *APOE* status.

In this study, we investigate the association between fMRI-complexity, tau-PET and amyloid-PET as well as influence of *APOE* status.

METHODS

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). From the ADNI phase 3 (ADNI3), we identified participants that had amyloid PET (florbetapir, ^{18}F-AV-45), tau PET (flortaucipir, ^{18}F-AV-1451), an fMRI resting state scan and an anatomical scan (MPRAGE) at the same timepoint. We collected the tabulated SUVR values for amyloid and tau from the ADNI database for ROIs within the FreeSurfer Desikan-Killiany atlas. We also downloaded the ADNIMERGE table, containing demographic information (age, sex, number of *APOE* ε4 alleles), and diagnostic labels (CN/MCI/AD). Raw structural and functional MRI data was downloaded for each identified subject. The rs-fMRI data were preprocessed using Matlab and SPM12, and included motion realignment, regression of white matter, cerebrospinal fluid, and head motion related signal fluctuations, coregistration to anatomical scan and normalization into MNI standard space. FMRI-complexity was then calculated by Multiscale Sample Entropy (MSE) (LOFT complexity toolbox)[28] with pattern sensitivity threshold $r = 0.5$, pattern matching length $m = 2$ and temporal scale 6 (for low signal fluctuations at 0.05 Hz). MSE maps were then parcellated into regions of interest using the same FreeSurfer Desikan-Killiany atlas resulting in ROI specific average MSE values. Finally, we defined a set of bilateral ROIs associated with early AD pathology: posterior cingulate, precuneus, (para)hippocampal gyrus, and entorhinal cortex. For each ROI we thus had indices for amyloid, tau and fMRI-complexity (see

Supplementary Figure 1 for example of ROI specific values for diagnostic groups). A multivariate generalized linear model was used to investigate the adjusted independent effects of amyloid and tau in relation to fMRI-complexity (Model1). Furthermore, we were interested whether such effects were modified by genetic risk, e.g., *APOE* ε4 status (carriers versus non-carriers). These effects were tested using the interaction terms in the multivariate model. Age and gender were controlled for in all models. We also tested a second model that accounted for diagnostic group as there likely is an association between disease severity and physiological markers of the disease (Model2). Data normality was visualized by histogram. Model integrity was assessed by residual plots. SAS 9.4 was used for statistical analyses. The global α level was set to 0.05, with Bonferroni correction for multiple comparisons (number of ROIs tested). Thus, the adjusted α for overall association and interaction test is 0.0125 and for strata specific (*APOE* ε4 carrier or non-carrier) effect is 0.006.

RESULTS

The final cohort consisted of 127 subjects (Table 1). For Model1 (not including information for diagnostic group), we observed statistically significant negative associations between complexity and tau in parahippocampal gyrus (–0.07 95% CI: (–0.13, –0.02); $p = 0.01$) and precuneus (–0.05 95% CI: (–0.08, –0.01); $p = 0.01$) with a trend in posterior cingulate cortex (–0.06 95% CI: (–0.12, 0); $p = 0.07$) (Table 2A). No statistically significant relationships with amyloid were found. *APOE* ε4 status was found as a statistically significant effect modifier on the association between tau and complexity ($p = 0.006$) in posterior cingulate gyrus (Table 2B). This strata specific effect showed that *APOE* ε4 carriers have a statistically significantly stronger negative association between tau and complexity of –0.26 95% CI: (–0.42, –0.1); $p = 0.002$ compared to non-carriers with the effect of 0.09 95% CI: (–0.09, 0.28), p: 0.33. A similar trend was found in precuneus with effect in *APOE* ε4 carriers of –0.14 95% CI: (–0.24, –0.05); $p = 0.004$ and non-carriers of –0.02 95% CI: (–0.13, 0.08), p: 0.68 with an interaction test $p = 0.1$. For amyloid no statistically significant interaction effect was found nor was there a main effect (Table 2B). For Model2 that accounts for diagnostic group, the main effects between fMRI-complexity and tau disappeared, but the interaction effect with *APOE* ε4 in posterior cingulate cortex remained. Since the data were slightly skewed to the left, we conducted sensitivity analysis with cubed data transformation, which resulted in a close-to-perfect bell shape distribution and no extreme outlier was observed in Cook's distance plot. All statistical significance remained after data transformation.

Table 1
Cohort Demographics

	CN	MCI	AD
N	79	42	6
age (mean/SD)	71.1/5.6	68.6/7.8	69.7/10.0
gender (F/M)	47/32	17/25	2/4
APOE ε4 (0/1/2 alleles)	54/20/5	24/16/2	3/1/2

Supplementary Figure 1 exemplifies amyloid, tau and fMRI-complexity values for each diagnostic group in precuneus and parahippocampal gyrus.

DISCUSSION

The observations of a negative association between fMRI-complexity and tau-PET in medial temporal and parietal cortices from this study confirmed previously reported statistically significant inverse relationships in these areas. While the cohort was largely overlapping with the ADNI cohort in our previous paper, here we used a different cortical parcellation and thus present evidence that the reported relationship is robust to atlas selection and small alterations in the subject sample. Furthermore, while fMRI complexity is robustly found to be associated with tau, we could for the first time demonstrate that this is independent of amyloid, and that fMRI-complexity shows no association with amyloid deposition in areas affected early in the progression of AD. Hence, fMRI-complexity appears to be indicative of dysfunction of neuronal signaling in the presence of tauopathy. This aligns with the notion that tau-PET imaging correlates more closely with neuronal injury and associated cognitive decline. It is conceivable that fMRI-complexity assesses dynamic fluctuations of rs-fMRI signals that possess clinically meaningful information and is sensitive to alterations in these dynamics in the process of tau related synaptic neurodegeneration.[29,30] In addition to the general effect we observed, we further found that the increased risk conferred by the *APOE* ε4 allele had a strong modifying effect leading to a stronger negative relationship between fMRI-complexity and tau-PET values in posterior cingulate cortex (PCC) and precuneus. The PCC has been discussed as an

Table 2

Test statistics of Multivariate Generalized Linear Model. A, B) Main and interaction effect for multivariate model without accounting for diagnostic groups. C, D) Main and interaction effects for multivariate model including diagnostic group. The adjusted α for overall association and interaction test is 0.0125 and for strata specific effect (by APOE ε4 carries or non-carries) is 0.006. Results with statistical significance after correction for multiple testing are highlighted in bold

A) Overall				Amyloid		Tau	
				test statistic	*p*	test statistic	*p*
Entorhinal				0.01 95% CI: (–0.02, 0.03)	0.64	–0.01 95% CI: (–0.05, 0.03)	0.6
Parahippocampus				0.01 95% CI: (–0.01, 0.03)	0.27	**–0.07 95% CI: (–0.13, –0.02)**	**0.01**
Posterior Cingulate				0.01 95% CI: (–0.01, 0.02)	0.6	–0.06 95% CI: (–0.12, 0)	0.07
Precuneus				0.00 95% CI: (–0.02, 0.01)	0.83	**–0.05 95% CI: (–0.08, –0.01)**	**0.01**
B) *APOE* ε4		Interaction Test		Amyloid		Tau	
	carrier	Amyloid p	Tau p	test statistic	*p*	test statistic	*p*
Entorhinal	no	0.75	0.17	0.01 95% CI: (–0.05, 0.06)	0.85	–0.07 95% CI: (–0.19, 0.04)	0.21
	yes			0.02 95% CI: (–0.05, 0.09)	0.57	0.04 95% CI: (–0.08, 0.16)	0.5
Parahippocampus	no	0.02	0.64	–0.02 95% CI: (–0.07, 0.04)	0.54	–0.19 95% CI: (–0.35, –0.03)	0.02
	yes			0.08 95% CI: (0.02, 0.15)	0.01	–0.13 95% CI: (–0.3, 0.03)	0.12
Posterior Cingulate	no	0.05	**<0.006**	–0.03 95% CI: (–0.08, 0.02)	0.29	0.09 95% CI: (–0.09, 0.28)	0.33
	yes			0.05 95% CI: (–0.01, 0.11)	0.09	**–0.26 95% CI: (–0.42, –0.1)**	**<0.002**
Precuneus	no	0.23	0.1	–0.02 95% CI: (–0.07, 0.02)	0.28	–0.02 95% CI: (–0.13, 0.08)	0.68
	yes			0.02 95% CI: (–0.03, 0.07)	0.53	**–0.14 95% CI: (–0.24, –0.05)**	**<0.004**
C) Overall (with DDX)				Amyloid		Tau	
				test statistic	p	test statistic	p
Entorhinal				0.00 95% CI: (–0.02, 0.03)	0.75	0.01 95% CI: (–0.04, 0.05)	0.7
Parahippocampus				0.01 95% CI: (–0.01, 0.03)	0.22	–0.03 95% CI: (–0.09, 0.03)	0.41
Posterior Cingulate				0.01 95% CI: (–0.01, 0.03)	0.35	–0.02 95% CI: (–0.08, 0.04)	0.51
Precuneus				0.00 95% CI: (–0.01, 0.02)	0.83	0.00 95% CI: (–0.03, 0.04)	0.89
D) *APOE* ε4 (with DDX)		Interaction Test		Amyloid		Tau	
	carrier	Amyloid p	Tau p	test statistic	*p*	test statistic	*p*
Entorhinal	no	0.9	0.24	0.00 95% CI: (–0.05, 0.06)	0.88	–0.04 95% CI: (–0.15, 0.08)	0.56
	yes			0.01 95% CI: (–0.06, 0.08)	0.78	0.07 95% CI: (–0.06, 0.2)	0.31
Parahippocampus	no	0.04	0.55	–0.01 95% CI: (–0.06, 0.04)	0.72	–0.11 95% CI: (–0.27, 0.05)	0.19
	yes			0.08 95% CI: (0.01, 0.14)	0.02	–0.04 95% CI: (–0,22, 0.14)	0.67
Posterior Cingulate	no	0.05	**<0.01**	–0.02 95% CI: (–0.07, 0.03)	0.44	0.13 95% CI: (–0.05, 0.32)	0.15
	yes			0.06 95% CI: (0.00, 0.11)	0.05	–0.18 95% CI: (–0.35, –0.02)	0.03
Precuneus	no	0.29	0.09	–0.06 95% CI: (–0.06, 0.03)	0.45	0.07 95% CI: (–0.04, 0.17)	0.21
	yes			–0.03 95% CI: (–0.03, 0.06)	0.47	–0.04 95% CI: (–0.14, 0.05)	0.36

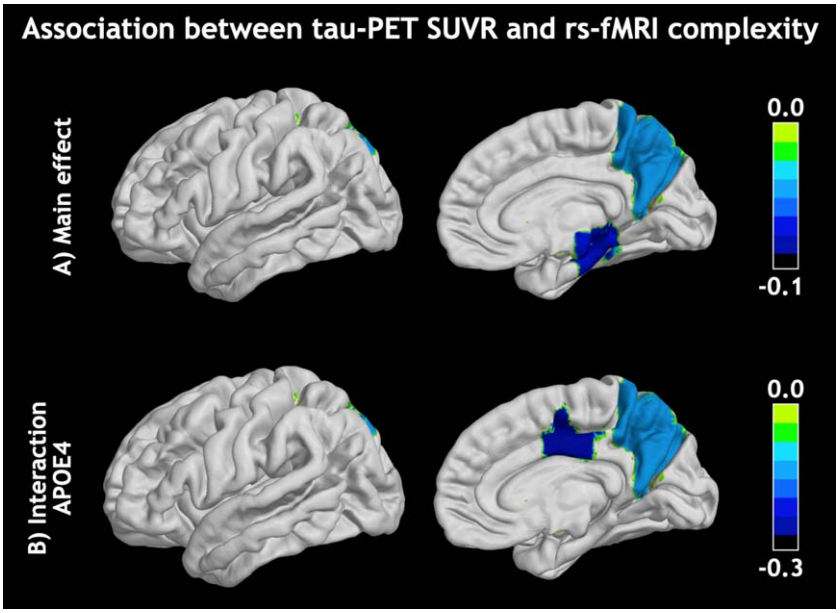

Fig. 1. Visualization of A) main effect on the association between fMRI-complexity and tau-PET SUVR and B) *APOE* ε4 presence enhanced this association. There were no associations with amyloid-PET SUVR.

early epicenter of AD and that changes in PCC gray matter[31] and glucose metabolism[32] predicts AD progression. Additionally, postmortem tissue analysis in PCC showed reduced synaptic numbers already during prodromal stages of AD.[33] Following this line of thought, we propose that fMRI-complexity might be a novel marker to assess tau-related alterations in neuronal signaling and subsequent cognitive deficits in the progression of AD. This hypothesis also considers why there were no association or interactions with amyloid, since while the presence of amyloid increases risk for cognitive decline it is the occurrence of tau that leads to synaptic deficits, neurodegeneration and consequently cognitive decline. Furthermore, amyloid can largely vary across diagnostic groups since even with high amyloid load there might not be severe cognitive impairment. However, longitudinal studies will be needed to investigate whether subjects with higher genetic risk and/or amyloid burden show faster decrease of fMRI-complexity which the current cross-sectional observations indicate. Our data also showed that amyloid is more variable and a less robust predictor of diagnosis than tau or fMRI-complexity (Supplementary Figure 1).

When including information about diagnostic group in the statistical model, the main effects disappeared which suggests a complete mediation effect of diagnostic group on the relation between fMRI-complexity and tau. This finding is not surprising, since with increased load of amyloid and specifically tau there is likely higher cognitive impairment and thus more severe diagnosis. We believe that the initial model is important as it compares purely physiological markers which all are capturing different aspects of AD pathology that are used to classify diagnostic groups: fMRI-complexity, amyloid and tau are all to some degree associated with diagnostic group.

To conclude, we observed a significant inverse relationship between fMRI-complexity and tau-PET markers, specifically in medial temporal lobe and precuneus and that this relationship was modified by genetic risk. Therefore, fMRI-complexity might provide a surrogate index of the information processing capacity of regional neuron populations and is sensitive to tau-related neuronal injury and cognitive decline in the course of AD pathogenesis.

AUTHOR CONTRIBUTIONS

Kay Jann (Conceptualization; Data curation; Formal analysis; Funding acquisition; Software; Visualization; Writing – original draft); Steven Cen (Formal analysis; Writing – review & editing); Mariella Santos (Data curation; Formal analysis); Leon Aksman (Data curation; Writing – review & editing); Dilmini Wijesinghe (Data curation; Software; Writing – review & editing); Ru Zhang

(Data curation; Formal analysis; Writing – review & editing); Kirsten Lynch (Data curation; Visualization; Writing – review & editing); John M. Ringman (Supervision; Writing – review & editing); Danny J. Wang (Conceptualization; Funding acquisition; Supervision; Writing – review & editing).

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CONFLICT OF INTEREST

Kay Jann is an Editorial Board Member of this journal but was not involved in the peer-review process of this article nor had access to any information regarding its peer-review.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

Data is publicly available and managed by the ADNI consortium.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-240459.

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