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Disinhibition in Alzheimer's Disease is Associated with Reduced Right Frontal Pole Cortical Thickness

Elizabeth Finger[a,b,*], Jing Zhang[b], Bradford Dickerson[c], Yves Bureau[b] and Mario Masellis[d,e,f] for the Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, University of Western Ontario, Parkwood Research Institute, London, Canada*
[b]*Lawson Health Research Institute, London, Canada*
[c]*Frontotemporal Disorders Unit, Department of Neurology, Alzheimer's Disease Research Center, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA*
[d]*Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Canada*
[e]*LC Campbell Cognitive Neurology Research Unit, Sunnybrook Research Institute, Toronto, Canada*
[f]*Department of Medicine, Division of Neurology, University of Toronto, Toronto, Canada*

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Abstract. Neuropsychiatric symptoms in Alzheimer's disease are among the most disabling and difficult aspects for caregivers and treating health professionals to manage. Despite the high prevalence of these behaviors, little is known about the factors which lead some patients to develop florid behavioral symptoms while others may progress to severe dementia without such phenomenon. We examined whether regional brain volumes as measured by cortical thickness would predict the presence or absence of disinhibition in patients with Alzheimer's disease. Using data from the ADNI, we identified 758 patients with caregiver ratings on the Neuropsychiatric Inventory and a volumetric MRI scan with cortical thickness measurements completed in FreeSurfer by the UCSF core. Of these, 177 patients were found to have disinhibition. Logistic regression models demonstrated that reduced cortical thickness in the right frontal pole was associated with the presence of disinhibition even when controlling for age, disease severity, total intracranial volume, gender, and *APOE* genotype. The results are considered in the context of leading models of the functions of frontopolar cortex.

Keywords: Alzheimer's disease, disinhibition, frontopolar cortex

*Correspondence to: Elizabeth Finger, MD, Parkwood Institute, 550 Wellington Rd. S, London, ON N6C 0A7, Canada. Tel.: +1 519 646 6032; Fax: +1 519 646 6226; E-mail: Elizabeth.Finger@lhsc.on.ca.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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.

INTRODUCTION

Behavioral and psychological symptoms of dementia are present in 60–80% of patients with Alzheimer's disease (AD) [1, 2]. Neuropsychiatric symptoms are financially costly; compared to AD patients with low scores on the Neuropsychiatric Inventory (NPI), patients with high scores cost an additional $10,670 to $16,141 annually [3]. While it has been shown that treatment with medications such as cholinesterase inhibitors or anti-psychotic medications can modestly reduce the presence of some of these behavioral disturbances [4], in many patients the symptoms persist or reemerge despite treatment. Approximately 30% of patients with AD display inappropriate social behaviors of disinhibition or euphoria, typically within 30–36 months of diagnosis [1]. The disinhibition ranges from impulsive decision-making and hypersexual comments or actions, to excessive jocularity and inappropriate approach of strangers. Such behaviors are a constant challenge for caregivers, and in the extreme, can result in criminal charges. Further, when patients with AD present with significant disinhibition and elation, they may be misdiagnosed with behavioral variant frontotemporal dementia (bvFTD) or other psychiatric disorders [5, 6].

The factors that cause a subset of patients with AD to develop these specific symptoms are yet undetermined. Comparison of patients with dysexecutive and frontal behavioral variants of AD to those with bvFTD demonstrated increased temporoparietal predominant atrophy, with limited atrophy in the frontal cortex (dorsolateral and insular cortex) when compared to controls [7]. In a combined sample of patients with FTD or AD, smaller volumes of ventromedial orbitofrontal cortex, temporal pole, and subgenual cingulate cortex were associated with more disinhibition as rated by caregivers [8]. In another combined sample of patients with AD ($n = 21$) and bvFTD ($n = 16$), disinhibition measured by the FrISBE was correlated with atrophy in the left anterior temporal lobe and right (caudal) orbitofrontal cortex [9]. There have been few dedicated studies of regional atrophy associated with disinhibition in AD. In one small study of 27 patients with AD, disinhibition measured by the NPI was associated with gray matter volume reductions in bilateral cingulate cortex and right middle frontal/precentral gyrus [10]. Given the striking atrophy hallmark of FTD, the extent to which the findings in combined samples reflect the neuroanatomic substrate of disinhibition in AD is unclear.

The objective of the present study was to determine the relationship between the presence of disinhibition/euphoria and evidence of regional pathology based on volumetric analysis of magnetic resonance imaging (MRI) in AD using a large cohort of well characterized patients meeting criteria for AD from the Alzheimer's disease Neuroimaging Initiative (ADNI).

METHODS

Participants

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see http://www.adni-info.org.

Inclusion criteria were as follows: a diagnosis of AD at baseline or conversion to AD during the study, availability of UCSF Freesurfer volumetric measurements of a 1.5 T MRI scan in ADNI-1 from at least one time point when clinical diagnosis was AD, and available NPI ratings as of ADNI data available on 2 November 2015. Inclusion criteria for ADNI-1 were as follows for AD: patients meeting original NINDS/ADRDA criteria for probable AD which specify memory as the predominant deficit [11]; age 55 to 90; study partner to provide evaluation of function; speaks English; ability to undergo all testing, blood samples for genotyping and biomarkers, and neuroimaging procedures; completed 6 grades of education; for women- post-menopausal or surgically sterile, geriatric depression score <6 (not depressed), modified Hachinski score < or = 4 (not at risk of vascular dementia), and Mini-Mental State Examination (MMSE) between 20 and 26 and CDR score of 0.5 or 1. Patients initially enrolled as MCI met the above inclusion criteria except for MMSE score between 24 and 30 and Clinical Dementia Rating (CDR) score = 0. Exclusion criteria included the presence of psychiatric disorder (major depression, bipolar, schizophrenia, agitation, behavioral problems).

AD patients with disinhibition/euphoria present at baseline ADNI assessments based on the NPI ratings

and patients who developed disinhibition/euphoria over the course of ADNI who completed a follow up MRI when disinhibition symptoms were present were included in the "Disinhibition" group. Patients with AD who never developed disinhibition during the course of the ADNI studies (ADNI-1, ADNI-Go, ADNI-2) were included as the control "No Disinhibition" group. Exclusion criteria included the presence or occurrence of strokes or other neurologic or psychiatric conditions which could account for the neuropsychiatric symptoms (i.e., history of bipolar disorder, new brain tumor), or conversion to a non-AD diagnosis.

Demographic and behavioral data analysis

Disinhibition/euphoria domain scores from the NPI-Q and NPI data were extracted from the ADNI database for participants meeting the inclusion/exclusion criteria defined above on 11 November 2015. The original ADNI study (ADNI-1) used the NPI-Q, which reports the presence or absence of symptoms of the domain. Prompts for this domain on the NPI include reference to acting impulsively, to doing or saying things in public that are not normally done (i.e., discussion of private matters or touching behaviors), to talking to strangers, to saying things that are hurtful to others [12]. Additional demographic and cognitive data was extracted from the ADNI database included diagnosis, age, gender, and years of education, MMSE, composite memory and executive function scores [13, 14], and CDR-sum of boxes (CDR-SB) for the visits corresponding to the NPI and MRI data for each participant. For participants with multiple visits, data from the first ADNI visit in which disinhibition symptoms were present was included in the analysis. For participants in the "No Disinhibition" group, data from the first ADNI visit were included in the analysis, though follow up NPI scores and diagnosis from subsequent visits were reviewed to confirm membership in the "No Disinhibition" comparison group.

Neuroimaging data analysis

Sixty-three cortical and subcortical regions of interest (ROIs) from the UCSF Freesurfer ADNI data analysis were initially identified as being potentially relevant (Supplementary Table 1). Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite by the UCSF ADNI team (Co-I Norbert Schuff). FreeSurfer analysis was completed on high resolution anatomical T1 scans using Version 4.4 for ADNI1 cross-sectional data [UCSFFSX] according to protocols from the developer. Freesurfer procedures provide accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy, while minimizing geometric distortion, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface [15]. This analysis provides cortical thickness measurements from ROIs throughout the brain. To reduce the number of potential variables to be entered into a logistic regression model, a factor analysis was conducted on the cortical thickness and subcortical volume measurements of the 63 ROIs using a principal component analysis and varimax rotation with Kaiser normalization. A logistic regression analysis was then performed to ascertain the effects of the 6 factors by including the top four regions (cortical thickness measurements divided by total intracranial volume) from each factor as well as age, gender, years of education, and CDR-SB on the likelihood that patients displayed disinhibition based on the NPI disinhibition domain scores. Following the first logistic regression, for regions significantly contributing to the model, follow up logistic regressions were conducted that included all of the ROIs from the factor containing the significant ROI(s).

All data were analyzed using IBM SPSS Statistics for Windows, Version 24.0.

RESULTS

A total of 758 patients were identified from the ADNI database as meeting the inclusion/exclusion criteria. Of these, $n = 177$ had symptoms of disinhibition, and $n = 581$ patients were included in the "No Disinhibition" comparison group. Independent *t*-tests were conducted to compare the age, education and CDR-SB scores for the Disinhibition versus No Disinhibition groups (Means reported in Table 1). As predicted, this demonstrated a significant difference in CDR-SB scores, where patients with Disinhibition had higher scores on the CDR-SB indicative of greater disease severity in comparison to the No Disinhibition group ($t\ (756) = 14.4$, $p < 0.001$). There was a significant differences in age ($t(756) = -2.3$) with a mean difference of –1.3 years showing patients with disinhibition were younger

Table 1
Patient characteristics and cognitive testing profiles

	Disinhibition $n=177$		No Disinhibition $n=581$			
	Mean	(SD)	Mean	(SD)	t	p-value
Age	74.3	(7.4)	75.6	(6.6)	–2.2	0.03
Education (y)	15.2	(3.0)	15.7	(3.0)	–1.7	0.09
CDR-SB	3.9	(2.8)	1.5	(1.7)	14.4	<0.001
Sex (% female)	40%		42%			0.51
APOE4 % with 0/1/2 alleles	45/40/15		54/36/9			
ADAS11	16.99	(9.4)	10.88	(6.2)	–8.16	<0.001
ADAS13	25.49	(11.3)	17.12	(9.1)	–8.98	<0.001
MMSE	24.31	(4.7)	27.03	(2.6)	7.34	<0.001
RAVLT immediate	25.29	(10.2)	33.73	(11.8)	9.21	<0.001
RAVLT learning	2.41	(2.2)	3.93	(2.7)	7.57	<0.001
RAVLT forgetting	4.44	(2.1)	4.22	(2.4)	–1.09	0.241
RAVLT % forgetting	80.70	(27.8)	59.64	(35.3)	–8.15	<0.001
FAQ	11.90	(8.6)	3.85	(5.8)	–11.71	<0.001
Composite Memory (ADNI-MEM)	–0.46	(7.1)	0.15	(0.9)	8.07	<0.001
Composite Executive Function (ADNI-EF)	–0.55	(0.8)	0.50	(0.96)	7.06	<0.001

Table 2
Neuropsychiatric symptom frequency and severity

Total NPISCORE	Disinhibition $n=177$		No Disinhibition $n=581$	
		6.71 (1.1)		1.15 (1.0)
	% with symptom	Mean severity (SD)	% with symptom	Mean severity (SD)
Delusions	15%	0.25 (4.0)	1%	0.01 (1.9)
Hallucinations	5%	0.07 (0.6)	1%	0.01 (0.1)
Agitation/Aggression	51%	0.80 (0.3)	10%	0.13 (0.1)
Dysphoria/Depression	45%	0.58 (0.9)	15%	0.18 (0.4)
Anxiety	42%	0.66 (0.7)	12%	0.15 (0.5)
Euphoria/Elation	14%	0.18 (0.5)	1%	0.01 (0.4)
Apathy/Indifference	48%	0.72 (0.9)	11%	0.16 (0.4)
Disinhibition	100%	1.28 (0.5)	0%	0.00 (0.3)
Irritability/Lability	57%	0.91 (0.5)	18%	0.22 (0.1)
Aberrant Motor Behavior	22%	0.35 (0.4)	4%	0.05 (0.1)
Nighttime Behavior	37%	0.55 (0.9)	12%	0.15 (0.5)
Appetite/Eating	30%	0.39 (0.5)	6%	0.07 (0.3)

NPI severity score range: 0–3.

than patients without). There was no significant difference in years of education between the Disinhibition and No Disinhibition groups. There was no significant association between sex and the presence of disinhibition ($\chi^2 = (1) = 0.44, p = 0.51$). To explore whether the disinhibition group was comprised of patients that might have a dysexecutive variant of AD, we examined composite memory and executive function scores for the two groups. A t-test comparing composite memory minus composite executive function scores showed no significant difference between the disinhibition groups ($t(756) = 0.2, p = 0.66$). Further, MANOVA comparing composite memory and executive function scores between the disinhibition groups with CDR-SB scores as a covariate demonstrated poorer performance for both executive function and memory in the disinhibition group relative to the no-disinhibition group, but no significant interactions ($F(1,755) = 0.02, p = 0.89$) (Fig. 1). Comparison of CNS active medications used by the disinhibition and no disinhibition groups is presented in Table 3.

Table 3
Comparison of frequency of CNS active medication use for Alzheimer's disease and neuropsychiatric symptoms in patients with and without disinhibition

	Disinhibition $n=177$	No Disinhibition $n=581$
Cholinesterase inhibitor	70%	34%
NMDA receptor agonist	31%	13%
SSRI	32%	17%
SNRI	8%	5%
Neuroleptic	3%	1%
Benzodiazepine	4%	2%

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

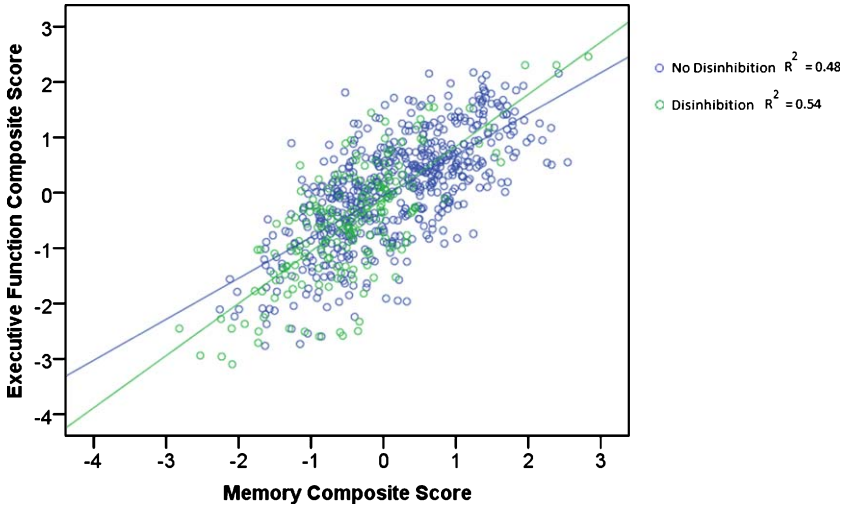

Fig. 1. Scatterplot of composite executive function and memory scores by participant according to the presence or absence of disinhibition symptoms. The correlations between composite memory and executive function scores were not significantly different for the disinhibition group compared to the no-disinhibition group ($z_{difference} = 1.31$, $p > 0.1$).

Neuroimaging data analysis

In the factor analysis conducted on the cortical thickness and subcortical volume measurements of the 63 ROIs using a principal component analysis and varimax rotation with Kaiser normalization, the rotation converged in 12 iterations. Inspection of the 6 most robust factors reflected identification of 1) motor and sensory cortices including dorsolateral prefrontal cortex prefrontal cortex and precuneus, 2) bilateral prefrontal cortex, 3) bilateral anterior temporal including hippocampus, 4) bilateral temporal and parietal regions, 5) posterior visual regions, and 6) cingulate cortex (Supplementary Table 1).

The first logistic regression included the cortical thickness measurements divided by total intracranial volume for the top four regions from each of the 6 factors, as well as age, sex, education, and CDR-SB scores. The logistic regression model was statistically significant, $\chi^2(29) = 92.7$, $p < 0.0001$. The model explained 33.9% (Nagelkerke R^2) of the variance in disinhibition and correctly classified 83% of cases. The Wald criterion demonstrated that cortical thickness of the right frontal pole ($p = 0.05$), left temporal middle gyrus ($p < 0.05$), left inferior parietal ($p = 0.05$), CDR-SB scores ($p < 0.0001$), and age ($p < 0.05$) made significant contributions to the prediction. Specifically, smaller right frontal pole and left middle temporal gyrus cortical thickness, larger left inferior parietal cortical thickness, younger age, and higher CDR-SB scores were associated with increased likelihood of exhibiting disinhibition. When correction for whole brain volume was used in place of total intracranial volume, the pattern of results was similar (smaller right frontal pole $p < 0.055$; left middle temporal gyrus $p < 0.075$; left inferior parietal $p < 0.075$; all other regions $p > 0.1$).

A second logistic regression analysis was then performed to further ascertain whether other ROIs in the pre-frontal and temporal regions would better predict likelihood of disinhibition. Bilateral frontal pole, temporal pole, lateral and medial orbitofrontal, pars opercularis, pars triangularis, rostral anterior cingulate, rostral middle frontal, superior frontal, middle temporal, and insula cortical thickness divided by intracranial volume averages, amygdala and nucleus accumbens volumes divided by intracranial volume, and age, CDR-SB, APOE4, and gender were included as variables. The logistic regression model was statistically significant, $\chi^2(30) = 187.71$, $p < 0.001$. The model again explained 33% (Nagelkerke R^2) of the variance in disinhibition and correctly classified 80% of cases. The Wald criterion demonstrated that only right frontal pole cortical thickness ($p < 0.05$), CDR-SB scores ($p < 0.0001$), and age ($p < 0.05$) made significant contributions to the prediction. When the analysis was repeated correcting for whole brain volume in lieu of total intracranial volume, CDR-SB ($p < 0.001$), the right frontal pole ($p < 0.05$), and the left rostral middle frontal gyrus ($p < 0.05$)

made significant contributions to the prediction of disinhibition.

Finally, a *post-hoc* sensitivity analysis was performed to examine whether the above findings would persist in the subset of ADNI patients diagnosed with AD who had confirmation of amyloid positivity, either by CSF amyloid/tau analysis conducted by the UPENN biomarker core or by florbetapir PET, as per prior established cutoffs of CSF $A\beta_{1-42}$, t-tau, and p-tau autopsy validated positivity cutoffs of 192 pg/mL, 93, and 23 [16] or 4 region average SUVr for the PIB amyloid ligand ≥ 1.5 (https://adni.loni.usc.edu/wp-content/uploads/2012/08/instruction-about-data.pdf). Of the 758 patients included in the original analysis, 207 had CSF analysis or PIB PET scan. Of the 207, $n = 196$ (95%), were found to have amyloid positivity based on CSF and/or PET scans, while $n = 11$ were amyloid negative. Of the 196 amyloid positive patients, $n = 62$ were in the Disinhibition group and $n = 134$ were in the "No Disinhibition" group. A logistic regression analysis including these 196 patients with the right frontal pole cortical thickness measurement, age, CDR-SB, and gender included as variables. Again, the Wald criterion demonstrated that of these variables, smaller frontal pole cortical thickness ($p = 0.06$), age ($p = 0.05$) CDR-SB scores ($p < 0.0001$) made significant or near-significant contributions to the prediction of disinhibition. Similarly, when the $n = 11$ patients who were amyloid negative by CSF and florbetapir PET criteria were excluded from the analysis of the whole cohort of $n = 758$, in the $n = 747$ patients that were amyloid positive or amyloid not tested the pattern of findings described for the initial regression and follow up frontal and temporal region regression remained.

DISCUSSION

In this large sample of well characterized patients with probable AD, we report that the right frontal pole was the main brain region significantly predicting the presence or absence of symptoms of disinhibition. The disinhibition domain score on the NPI reflects a range of behaviors from impulsivity to socially inappropriate actions that may arise from several aspects of cognition. Clinically, a subset of patients with AD become disinhibited during their illness, and may begin to share overly personal information with strangers, to spend more money than they would normally, to hug or kiss acquaintances. Based on further parcellation of this construct of disinhibition, behaviors scored in this domain could derive from deficits in a variety of cognitive processes and thus potential neuroanatomic localizations. For example, impulsivity may reflect impairments in response inhibition, expected value representation, reversal learning, temporal discounting, or prediction error processing that typically involve frontostriatal circuits. Inappropriate social behavior can arise from deficits in theory of mind processing, empathy and facial expression recognition, and response inhibition and may be localized to the amygdala, temporal poles, medial prefrontal cortex, orbitofrontal cortex and temporoparietal junction. The current finding that right frontopolar cortical thickness predicted disinhibition in AD raises the question of how dysfunction in this region may relate to these processes.

The functional contributions of frontopolar cortex have been the object of much interest, as this region is significantly expanded in human brains relative to other species [17]. The frontal pole describes the anterior tip of the frontal lobe and is comprised of the rostral region of Brodmann area 10. In addition to its large size in humans, other features of the frontal pole that have furthered interest in its potential role in advanced aspects of human cognition and integration of inputs include its long maturation period [18, 19] and high density of dendritic spines [17, 20, 21]. Frontopolar cortex is well connected to other regions of prefrontal cortex but does not have direct connections to temporal or parietal cortex [21–23]. Part of the difficulty in ascertaining the role of frontopolar cortex is the finding that this region is activated in humans across a wide range of cognitive tasks including executive tasks, mentalizing tasks, and recall of actual events [24].

Several hypotheses or models of frontopolar cortex function have been proposed to account for its apparent role in this diverse range of activities. Noting functional MRI (fMRI) activation of this region during tasks requiring consideration or representation of multiple rules, Rahmnani and Owen have proposed that this region of frontopolar cortex is involved in the coordination of information processing and information transfer between multiple cognitive operations [21]. Based on experiments using single cell recording in macaques, Tsujimoto and colleagues have proposed that frontopolar cortical neurons may encode goals at the time of feedback, particularly for correct trials, thereby facilitating learning of which goals result in specific

behavioral outcomes [17]. In this model, frontopolar cortex activity results in retrospective monitoring that affects future choices. Rushworth and colleagues have proposed a slightly different unifying function based in part on findings that in an fMRI decision making task, lateral frontopolar cortex activity was active during both decision making and feedback phases, and was associated with forecasting the reward potential of the best option not selected, and the associated costs of the non-selections [25]. In this model it is suggested that such computations in frontopolar cortex promote behavioral flexibility by preparing the organism to take the best pending option in the future [25]. A caudal-rostral distinction of frontopolar cortex function has been delineated by Burgess, Gilbert and colleagues to account for the seeming ubiquitous activity in frontopolar cortex in diverse fMRI tasks. Based on meta-analysis of fMRI studies activating frontopolar cortex and then confirmed in studies examining two tasks and directly comparing activation peak location within this region, rostral regions of frontopolar cortex were found to be active during studies requiring coordination of multiple tasks while caudal regions of frontopolar cortex were active during mentalizing tasks [26]. A potential medial/lateral axis was also proposed where lateral frontopolar cortex is engaged during working memory/episodic retrieval and medial frontopolar cortex during mentalizing [27]. These findings have led to their proposed model of frontopolar cortex where this region may modulate or bias attentional processes between stimulus oriented cognition or watchfulness of the environment (rostral frontopolar cortex) and stimulus-independent cognition such as mind wandering (caudal frontopolar cortex) [26, 28].

In the context of such models, how then would reduced cortical thickness, atrophy, or dysfunction in right frontopolar cortex give rise to disinhibited behavior in patients with AD? Real world social behaviors require consideration of multiple rules when approaching any goal. For example, a patient may desire a donut, but in addition to representing the goal of satisfying one's hunger, rules on when and where eating a donut is appropriate, and the number of donuts one may take from a communal box depending on the context must also be represented. Patients with disinhibition in the setting of neurodegenerative disease often lose the ability to plan for the future and to make intermediate or long term goals. If frontopolar cortex is critical for reinforcing goals at the time of feedback, disruption of goal reinforcement may be expected to impair goal setting and adherence. Alternatively, their choices may appear impulsive because they have lost the ability to delay gratification or attainment of a reward. Similarly, if consideration of initially unselected alternative options is disrupted, patients may exhibit perseverative behavior, repeating their initial choice even if its reward value diminishes relative to other options. Finally, impaired switching between attention to external cues in the environment and internal mentalization could result in disinhibition from lack of integration of a behavior or choice (i.e., buying lottery tickets when spotted at the checkout display) with internal reflection on one's resources or financial goals (money should be saved for groceries or rent). Alternatively, consideration only of one's internal state could result in inappropriate social behavior if external cues are not attended to (i.e., acting on a desire to kiss someone despite their body language and facial expression). Future study using cognitive tasks targeting these specific cognitive processes may help to inform these models and elucidate which of these mechanisms may underlie the association of frontopolar cortex cortical thickness and disinhibition in patients with AD.

The finding of right frontal polar cortex accounting for the largest variance predicting caregiver rated disinhibition in patients with AD differs from prior reports, most likely due to differences in sample composition and power. Comparison of composite executive function and memory scores as well as NPI scores to those in other published cohorts suggests most of participants in the present disinhibition and no-disinhibition cohorts did not meet recently used criterion for the dysexecutive or frontal variants of AD, who were found to have mainly temporoparietal atrophy and mild dorsolateral prefrontal cortex and insular cortex volume reductions relative to controls [7]. Both composite memory and executive function scores were worse in our disinhibition group relative to the no-disinhibition group, as would be expected with the greater disease severity as represented by CDR-SB scores in this group. MANOVA with CDR-SB scores included as a covariate did not reveal any significant interaction between the composite memory and executive scores in the disinhibition versus no disinhibition groups. Direct comparisons of NPI severity were limited as other studies we could identify reported NPI domain scores (frequency $\times$ severity) rather than severity alone from the NPI-Q (where frequency is not available). Based on comparison of the NPI disinhibition severity scores with our local cohort of patients with bvFTD, the

severity of disinhibition based on NPI severity scores in this AD cohort (mean 1.28) is lower than that in patients with bvFTD (mean disinhibition severity score 1.7) (unpublished data from [29]). This pattern is consistent with studies comparing NPI disinhibition domain scores (severity × frequency) in patients with AD and bvFTD, where bvFTD scores are significantly higher [30, 31]. The region of right frontal polar cortex is rostral to the right caudal orbitofrontal cortex region associated with disinhibition in the combined FTD/AD samples from Pohlak et al. [9] and to the subgenual region of orbitofrontal cortex identified in the combined FTD/AD cohort of Hornberger et al. ($n = 15$, AD + $n = 15$ FTD) [8]. Both studies used voxel-based morphometry rather than cortical thickness measurements. These differences may also be in part due to effects driven by patients with FTD in combined samples, as well as limitations of assessing this symptom in a small sample of patients with AD. In Pohlak et al., patients with AD showed low increases in disinhibition from their baseline (pre-morbid) disinhibition ratings to current levels of disinhibition, the primary variable used [9]. We did not find an association of disinhibition with the region of dorsomedial prefrontal cortex reported by Serra et al. in a study limited to patients with MCI and AD, though notably only approximately $n = 9$ patients with disinhibition were included in that cohort [10]. A potential limitation to the present study is the difference in CDR-SB scores between the disinhibition and no disinhibition groups. While inclusion of CDR-SB as a predictor in the model aimed to correct for differences due to greater disease severity in the disinhibition cohort, it is possible that our findings could still be due to severity differences. When the analyses were restricted to a subset of patients from the above cohort with matched CDR-SB scores >2 and <5, no brain regions predicted the presence of disinhibition, though the reduced sample size may result in under powering of the analyses.

In summary, we report an association between cortical thickness in the right frontopolar cortex and the presence of disinhibition in patients with AD. Future analysis using ADNI-2 and ADNI-3 cohorts when available, and examination of FDG-PET data would be of benefit to confirm the present findings in an independent sample and across methodologies. Further, examination of genotypes that may be associated with or interact with frontopolar cortex thickness to give rise to these symptoms may further elucidate the mechanisms for individual differences within AD and identify potential symptom based treatment targets.

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SUPPLEMENTARY MATERIAL

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