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ALTERED FRONTAL AND INSULAR FUNCTIONAL CONNECTIVITY AS PIVOTAL MECHANISMS FOR APATHY IN ALZHEIMER'S DISEASE

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Running Title

Network correlates of apathy in AD

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Abstract

Background: Apathy is a common and early symptom in Alzheimer's disease (AD) and is linked to poorer prognosis. Theoretical interpretations of apathy implicate alterations of connections amongst fronto-striatal and limbic regions.

Objective: To test the association between presence of apathy and patterns of brain functional connectivity in patients with clinically-established AD.

Methods: Seventy AD patients were included. Thirty-five patients experienced apathy as defined by the screening question of the Neuropsychiatric Inventory, and thirty-five did not. All patients agreed to undergo an MRI protocol inclusive of resting-state acquisitions. The hemodynamic-dependent signal was extracted bilaterally from five regions of interest: ventromedial prefrontal cortices, anterior cingulate cortices, dorsolateral prefrontal cortices, insulae and amygdalae. *t* tests were run to compare connectivity maps of apathetic and non-apathetic patients. Age, education, Mini Mental State Examination score, gray matter volumes and gray matter fractions served as covariates.

Results: At a $p_{FWE} < 0.05$ threshold, apathetic patients had reduced connectivity between the left insula and right superior parietal cortex. Apathetic patients had also increased connectivity between the right dorsolateral prefrontal seed and the right superior parietal cortex. Patients with apathy were significantly more likely to experience other psychiatric symptoms.

Conclusion: Our findings support a role of frontal and insular connections in coordinating value-based decisions in AD. Both down-regulation and maladaptive up-regulation mechanisms appear to be at play in these regions.

Keywords

Functional connectivity; Resting-state; Neuropsychiatric inventory; MRI;

1. Introduction[1]

Apathy is the most common neuropsychiatric symptom in patients with Alzheimer's disease (AD) (Lyketsos, Lopez, Jones, Fitzpatrick, Breitner, & DeKosky, 2002). It has been found to have a significant impact on quality of life (Hongisto et al., 2018) and has been linked to early institutionalization (Bakker et al., 2013) and increased mortality (Lyketsos et al., 2002). An international task force defined apathy as decreased motivation present for at least four weeks with secondary functional impairment and at least two of the following: reduced goal-directed behavior, reduced goal-directed cognitive activity, or emotions (Robert et al., 2009).

AD may present with neuropsychiatric symptoms prior to the manifestation of cognitive impairment (Ismail et al., 2016). The presence of apathy in AD may also be a behavioral consequence of cognitive decline. Apathetic patients with mild cognitive impairment (MCI) are statistically more likely to convert to AD dementia than non-apathetic patients (Richard et al., 2012). The swifter cognitive decline in patients with AD and apathy suggests it could be a behavioral marker of a more severe clinical course (Starkstein, Jorge, Mizrahi, & Robinson, 2006). With this in mind, early detection and appropriate characterization of apathy would help clinicians provide appropriate support to patients and their carers. A better understanding of the neurobiological mechanisms implicated in apathy is required to achieve this goal.

Clinical research has investigated the anatomical, perfusion and metabolic correlates of this symptom in AD. Particularly, the anterior cingulate cortex (ACC), the prefrontal cortex, and sub-cortical regions such as amygdala, thalamus and basal ganglia have been reported as the

[1] LIST OF ABBREVIATIONS: ACC: anterior cingulate cortex; AD: Alzheimer's disease; DLPFC: dorsolateral prefrontal cortex; MCI: Mild cognitive impairment; MNI: Montreal Neurological Institute; NPI: Neuropsychiatric inventory; TFfMRI Task-free functional magnetic resonance imaging; VMPFC: ventromedial prefrontal cortex

areas most often associated with the presence of apathy (see Theleritis, Politis, Siarkos, & Lyketsos, 2014; Kos, van Tol, Marsman, Knegtering, & Aleman, 2016 for recent reviews summarizing earlier neuroimaging findings). A theoretical model, however, suggest that network dysfunction among all these areas is responsible for the onset of this symptom through disruption of neural pathways that sustain motivational-affective-emotional processing. According to this view, the apathetic trait would be the result of prefrontal hypometabolism observed in AD patients, combined with reduced interactions among a distributed network of cortical and sub-cortical regions (Guimarães, Levy, & Teixeira, 2008). Disconnection between the amygdala, prefrontal cortex and nucleus accumbens would result in impaired dopaminergic function and reward response processing, and disconnection between the ACC and orbitofrontal cortex would affect the initiation of goal-directed behavior (Guimarães et al., 2008). Moreover, amygdala dysfunction is known to be associated with an inability to assign emotional valence to stimuli (Davis & Whalen, 2001).

The merit of this model is having provided an interpretative framework based on brain circuitry to account for the presence of apathy in AD. Aside from this model, another theoretical framework, however, could play a major role in the pathogenesis of apathy. The ACC's interplay with the insula forms the salience network, a major neurocircuital pathway. The anterior insula marks important events for additional processing while the ACC directs behavior via its connections to the motor system (Menon & Uddin, 2010). Moreover, the insula is also vital for emotional awareness (Gu, Hof, Friston, & Fan, 2013). Reduced connectivity within this network is associated with apathy in patients with depression (Yuen et al., 2014), therefore it is possible that insular circuitry plays a role in apathy in patients with AD.

Given the dynamic nature of brain function, examining functional connections between crucial regions to verify the involvement of brain areas in the pathogenesis of apathy is

highly likely to be more fruitful than examining structural or functional properties of single regions (Tisserand & Jolles, 2003). Task-free functional MRI (TFfMRI) allows the measurement of resting brain synchronized activity through the analysis of low frequency oscillations in the blood oxygen level dependent signal, and allows the testing of sets of predefined regions selected as "seeds". A number of studies have investigated functional connectivity of large-scale networks such as the default-mode network and attentional networks (Balthazar et al., 2014; Joo, Lee, & Lim, 2016; Munro et al., 2015). This study, however, is the first to have used TFfMRI to test apathy as a symptom linked to failure of selected theory-informed functional maps of connections in a sample of patients with mild AD. The pathways of connectivity involving major regions at the basis of the model by Guimarães and colleagues (2008) as well as those of a key region, the insula, at the core of the salience network, were investigated. The connectivity of these seed areas was compared between patients with and without apathy in a sample with very mild and mild AD.

2. Methods

2.1.Participants

All data included in this study were collected as part of the Virtual Physiological Human – DementiA RESearch Enabled by IT (VPH-DARE@IT; http://www.vph-dare.eu/) initiative, a multicentre project funded by the EU (Framework Programme 7). A total of 137 patients with a clinical diagnosis of either AD (the criteria by McKhann et al., 2011 were used) or MCI due to AD (Albert et al., 2011) were considered for inclusion. These were recruited from the memory clinic at the Royal Hallamshire Hospital, Sheffield (United Kingdom) and from the Institute of Clinical Medicine, Kuopio (Finland). Each patient had undergone a

brain MRI (see Section 2.3) and cognitive profiling. The cognitive domains characterized by the tests were selected based on their susceptibility to neurodegeneration of the AD type.

In the following paragraphs we report how we determined our final sample size (n = 70 patients), all data exclusions, all inclusion/exclusion criteria established prior to data analysis, all manipulations, and all measures in the study. Patients were not eligible if there was the potential for a non-degenerative cause of their cognitive symptoms (Winblad et al., 2004). For each MCI patient, probable AD was judged to be the most suitable etiology following consensus among senior clinicians, based on clinical, neuropsychological and neuroradiological evidence. Specific exclusion criteria were set as follows: medical diagnoses of clinical concern which could otherwise justify the potential presence of cognitive difficulties; MRI images showing abnormalities other than the effects of aging and/or neurodegeneration; medical or radiological evidence of acute or chronic cerebrovascular disease; history of transient ischemic attacks, cardiovascular disease, uncontrolled seizures, peptic ulcer, sick sinus syndrome, or neuropathy with conduction defects; abnormal levels of folate, vitamin B12, or thyroid-stimulating hormone; treatments with medications for research purposes or with significant toxic effects on internal organs; evidence of a psychiatric or psychological cause of cognitive impairment. These criteria resulted in the exclusion of thirteen patients.

The presence of neuropsychiatric symptoms was verified by a questionnaire administered to a caregiver. Therefore, patients with no caregiver were not approached. One hundred and six patient-caregiver dyads were thus considered for inclusion.

A group of healthy controls were also recruited. These were of comparable age, education, and gender ratio as the groups of apathetic and non-apathetic patients.

This study was carried out on human subjects and received ethical approval from the Yorkshire and Humber Regional Ethics Committee, Ref No: 12/YH/0474 for the Sheffield cohort and from the ethics committee of the Northern Savonia Hospital District for the Kuopio cohort. The procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation and with the Helsinki Declaration of 1975, as subsequently revised in 1983. Written informed consent was obtained from all participants prior to enrolment. No part of these study procedures/analyses was pre-registered prior to the research being conducted.

2.2.Measurement of Apathy and Other Neuropsychiatric Symptoms

The Neuropsychiatric Inventory (NPI)[2] is a quantitative scale which estimates presence, frequency and severity of twelve psychiatric symptoms (listed in **Table 1**) from the point of view of a caregiver (Cummings, 1997). It is among the clinical instruments most often used to assess the presence of apathy in AD (Mohammad et al., 2018), and has adequate levels of test-retest reliability (Kaufer et al., 2000). The informants were asked to complete the entire NPI but, for the purpose of this study, only the apathy section of the questionnaire was used as predictor for inferential modelling. Any symptoms of apathy identified by the caregiver led to the patient being classified as "apathetic". In addition, as well as assessing the presence of apathy, the NPI detects the presence of possible other comorbid psychiatric symptoms, allowing the evaluation of potential ancillary psychiatric comorbities.

Although the NPI is a valid and reliable instrument, the typical "frequency × severity" score is not considered appropriate for parametric statistics (Lai, 2014). Based on this, we only

[2] This is a copyrighted scale, and the copyright is held by the author Professor Jeffrey Cummings

focused on the presence of apathy as a binary variable (present vs. absent) for statistical inference, as carried out in previous studies (Holthoff et al., 2005; Tunnard et al., 2011) rather than exploring its clinical characterisation more in detail. The response to the screening question on apathy was used for this purpose. This question is marked "yes" by the informant when the symptom is thought to be of clinical relevance. Three patients did not have the NPI administered. Thirty-eight (about 37%) of the remaining patients were classified as apathetic. One of the apathetic patients had an incomplete NPI, and two additional apathetic patients had evidence of MRI signal abnormalities. These three patients were excluded due to incomplete assessments, resulting in a final sample size of thirty-five apathetic patients. A group of thirty-five non-apathetic patients was thus selected. This group was matched for age, years of education, gender, disease severity, cognitive status and main neuroanatomical properties. A third group of thirty-five healthy controls matched for age, educational attainment and gender was also selected. To characterize the profile of cognitive deficits shown by patients, scores achieved on neuropsychological tests were compared between the two sub-groups (**Table 1**) and between each sub-group and the group of controls (**Table 2**).

--- Please insert **Table 1** and **Table 2** about here ---

All patients had their medication history documented. There was no significant difference in the numbers of patients on acetylcholinesterase inhibitors at recruitment (8/35 vs. 10/35; *chi-squared's p* = 0.584), memantine (1/35 vs. 1/35; *chi-squared's p* = 0.999), or antidepressants (6/35 vs, 3/35; *chi-squared's p* = 0.284) between patients with and without apathy,

respectively. Patients with MCI due to AD have been followed up at regular intervals for four years and their clinical diagnosis confirmed.

2.3.MRI Acquisition and Processing[3]

MRI scans were acquired on a Philips Ingenia 3T scanner in Sheffield and on a Philips Achieva 3T scanner in Kuopio using a shared image acquisition protocol. Each patient underwent a brain MRI scanning protocol which included T1-weighted, T2-weighted, Fluid Attenuated Inversion Recovery, and TFfMRI acquisitions. Anatomical images were reviewed clinically by a neuroradiologist to ascertain compliance with the inclusion criteria. T1-weighted and TFfMRI images were further processed for hypothesis testing. A T1-weighted volume was acquired using a Magnetization Prepared Rapid Acquisition Gradient Echo technique (voxel dimensions = $0.94 \times 0.94 \times 1.00$ mm^3, repetition time = 8.2 s, echo time = 3.8 ms, inversion time = 1 s, flip angle = 8°). Functional TFfMRI T2*-weighted dynamic datasets were obtained at rest (35 axial slices, reconstructed in-plane voxel dimensions = 1.8×1.8 mm^2, slice thickness = 4.0mm, repetition time = 2.6 s, echo time = 35 ms, number of temporal dynamics = 125). Each participant was asked to remain as still as possible with eyes closed for the entire duration of this acquisition (minimum 5 minutes and 25 seconds). Pre-processing and analyses pipelines were carried out with the Statistical Parametric Mapping 12 software (Wellcome Centre for Human Neuroimaging, London, UK) and the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) running in a Matlab R2014a (Mathworks Inc., UK) environment.

[3] The conditions of our ethical approval do not permit archiving of anonymised study data. All participants in this study gave permission for data sharing only with the consortium of investigators involved in the primary project. For this reason, no data supporting the conclusions of this research, other than those presented in the article, can be made available to any individual outside the author team under any circumstances.

T1-weighted images were segmented to separate maps of gray matter, white matter, and cerebrospinal fluid from the other tissue classes. The "get_totals" command line (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) was run to quantify the volume (expressed in ml) of each map in its native space. This served to extract the volume of gray matter, white matter, and cerebrospinal fluid, and to calculate the total intracranial volume (by summing the volume of the three tissue classes). Gray matter fraction (of the total intracranial volume) was also calculated to index global brain atrophy.

CONN was used to carry out all preprocessing and modeling pipelines. TFfMRI sequences were realigned to adjust for volume-to-volume spatial displacement and slice timed to homogenize slice-to-slice temporal specifications. During this stage, in-scanner movements made by patients or the imaging system were calculated and quantified as numerical vectors. These were inspected to rule out the presence of major abnormalities. No acquisition showed motions larger than 1 voxel in any of the directions. Scans were then normalized and registered to the Montreal Neurological Institute (MNI) echoplanar template and smoothed with a 6 mm^3 full-width at half maximum Gaussian kernel.

After pre-processing, first-level analyses were run to calculate individual maps of functional connectivity. A seed-based approach was adopted. Binary masks were created using the PickAtlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) based on anatomical landmarks identified with the IBASPM-116 atlas (http://www.thomaskoenig.ch/Lester/ibaspm.htm). The following regions were defined, maintaining left and right seeds separated (each atlas label is indicated below in italics): anterior cingulate cortex (ACC - "*Cingulum_Ant_L/R*"), dorsolateral prefrontal cortex (DLPFC – "*Frontal_Mid_L/R*"), ventromedial prefrontal cortex (VMPFC – "*Frontal_Mid_Orb_L/R*"), amygdala ("*Amygdala_L/R*") and insula ("*Insula_L/R*"). Maps of individual functional connectivity were calculated using the average time-course of the seed

to predict the time-course within each and every voxel included in the field of view. All maps were denoised regressing out: 1) the six rigid-body realignment motion parameters and their temporal derivatives; 2) the first five principal components estimated from the BOLD signal in the maps of white matter and cerebrospinal fluid (aCompCor procedure; Muschelli, Nebel, Caffo, Barber, Pekar, & Mostofsky, 2014). Although published studies and theoretical frameworks on apathy do not describe any underlying hemispheric lateralization, it was nonetheless decided to keep left and right seeds separated.

2.4.Data Modelling

Group-level inferential models were run to compare the ten (five left, five right) maps of seed-based connectivity between apathetic and non-apathetic patients. Voxel-based analysis of gray matter volumes was also carried out to ascertain the absence of regional group differences in gray matter. Additionally, the default-mode network (estimated with an independent component analysis) was also compared between the two groups of patients to test for functional differences in the functional pathway that is most distinctively disrupted in AD. Between-sample *t-test* models were devised controlling for age, levels of education, Mini Mental State Examination, total gray matter volumes, and gray matter fractions. Levels of education were included as a proxy of cognitive reserve, while total gray matter volumes were selected as a proxy of brain reserve (Liu, Cai, Xue, Zhou, & Wu, 2013; Stern, 2009). Gray matter fractions were included to control for global atrophy, and scores on the Mini Mental State Examination served to control for disease severity. Threshold of significance was set at 0.0001 (uncorrected) at the set level. Only clusters surviving a cluster-level $p_{FWE} < 0.05$ were reported as significant. This setup is particularly conservative to decrease the risk of noise affecting the outcome of the analyses given the number of seeds used in our

analyses. Coordinates in the MNI space were converted into Talairach coordinates using a non-linear transformation (imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal-m), and were interpreted with the Talairach Daemon Client (Lancaster et al., 2000).

3. Results

3.1.Planned Analyses

Overall, when compared to healthy controls the group of patients showed extensive atrophy in temporal, parietal and prefrontal areas, and in the hippocampus, bilaterally. Moreover, analysis of functional connectivity within the default-mode network showed the typical AD-dependent down-regulation within the posterior cingulate cortex and precuneus. The neuropsychological assessment and the comparison of the cognitive profile seen in patients and in healthy controls also showed a range of cognitive impairments consistent with patients' clinical diagnoses for both the sub-group of apathetic patients and for the sub-group of non-apathetic patients (**Table 2**). The overall evidence from neuropsychological assessment, structural and functional imaging indicates that the sample (and sub-groups based on presence/absence of apathy) recruited in this study had a typical AD profile.

Apathetic and non-apathetic patients did not differ significantly demographically or cognitively, nor did they differ in their global neurostructural indices (**Table 1**). On average, apathetic patients tended to have significantly higher total NPI scores and more comorbid psychiatric symptoms, and there were significantly more individuals with irritability, anxiety, agitation or depression among apathetic patients. The two sub-groups, however, did not differ in the average severity of psychiatric symptoms. This is in line with previous studies that have found patients with dementia suffer from multiple behavioral symptoms (Srikanth, Nagaraja, & Ratnavalli, 2005). When patterns of atrophy of the two patient sub-groups were

compared, no anatomical differences emerged from the voxel-by-voxel analysis of gray matter of the two AD sub-groups. Similarly, no between-group differences emerged from the analysis of the default-mode network.

Significant results were found in two out of the ten patterns of functional connectivity (**Table 3**, **Figure 1**). Apathetic patients had reduced connectivity between the left insula and the right parietal cortex, in a region covering part of the sensory cortex (BA5) and associative sensory areas (BA7-40). In addition, apathetic patients showed increased connectivity between the right DLPFC seeds and the right superior parietal lobe (BA7).

--- Please insert **Table 3** and **Figure 1** about here ---

3.2.Post Hoc Analyses

Confirmatory *post hoc* analyses were run using the frequency × severity score, by converting the two clusters with significant results into binary seeds. The average cluster connectivity, in the form of a *beta* score, was extracted for the corresponding network from the map of each of the seventy patients. Nonparametric correlation models (Spearman's ρ) confirmed the presence of a significant association between each pathway of connectivity and individual frequency × severity apathy scores, in the same direction as emerged in the main models (both ρ values greater than ±0.4). Conversely, no significant associations were found between the functional connectivity of these regions and the cognitive variables included in **Table 2**.

In order to characterize these findings more in detail, *post hoc* analyses were run to compare each sub-group of patients with the group of matched healthy controls, who did not differ

from patients in demographic factors or level of education. Functional connectivity was extracted in the form of a *beta* score from binarized clusters as described above, significant differences emerged between sub-groups of patients and healthy controls. Apathetic patients had less connectivity than both non-apathetic patients and controls in the pathway between the left insula and the superior parietal cluster. Conversely, it was non-apathetic patients that had less connectivity than both apathetic patients and healthy controls in the other pathway (**Figure 2**).

--- Please insert **Figure 2** about here ---

4. Discussion

A few studies of apathy in AD have investigated large-scale networks that support certain cognitive statuses such as the default mode network or the attentional networks (Balthazar et al., 2014; Joo et al., 2016; Munro et al., 2015). This study of apathy in patients with clinically-established AD was based on testing the relevance of disruption of specific maps of connectivity informed by theoretical frameworks proposed in previous studies. We found altered functional connectivity aligned with the anatomical, perfusion and metabolic correlates as previously reported (Bruen, McGeown, Shanks, & Venneri, 2008; Huey, Lee, Cheran, Grafman, & Devanand, 2016; Kos et al., 2016; Stanton, Leigh, Howard, Barker, & Brown 2013; Theleritis et al., 2014). Although the dysfunctional nature of these regions as emerging from these studies hinted that apathy might be consequential to a network failure rather than alterations of individual brain areas, our findings provide direct interpretative

evidence. Consistency across neuroimaging techniques clearly indicates that a strong statistical effect linked to apathy exists in these regions.

A cluster of reduced connectivity was found in apathetic patients between the insula and parietal areas involved in somatosensory and attentional processing. Structural connectivity exists between the insula and the superior parietal lobe (Ghaziri et al., 2017). Regions functionally coupled with the insula form the salience network, a neural pathway responsible for integrating external and interoceptive stimuli for decision making (Menon & Uddin, 2010). The insula is also thought to play a major role in assigning priorities to neural processes for subsequent elaboration (Michel, 2017). On this note, reduced interplay between the insula and the right superior parietal lobe would result in reduced priority allocated to the outcome of sensory-attentional processing (an interpretation of cognitive significance). However, emotional and sensory components might also be at play. In a study of patients with autonomic failure, those with reduced activation of the right insula during an interoceptive task identified with the statement "*I have lost my ability to feel emotions*" (Critchley, Mathias, & Dolan, 2001). Other studies have indicated a role for the insula in emotional awareness (Gu et al., 2013) and interoception (Terasawa, Shibata, Moriguchi, & Umeda, 2013). Of relevance in this respect is the classification of apathy into sub-types. Of these, corticosensory apathy is due to the inability to assign motivational significance to sensory information (Duffy, 2000), and would be consistent with our finding, and with apathy being the result of reduced motivation stemming from the inability to assign emotional status to sensory information. Apathetic patients had lower levels of connectivity than non-apathetic patients and healthy controls, indicating that retaining strength of certain connections might have an adaptive function in AD, preventing/being associated with the onset of apathy.

Sensory-attentional areas were also characterized by increased connectivity. Clusters within the right superior parietal cortex, (located adjacent to an area in which we found decreased connectivity) were found to show increased connectivity with the right dorsolateral seeds in apathetic patients. The DLPFC is one of the main structures that controls the normal generation of behaviors (Guimarães et al., 2008) by contributing to response inhibition (Blasi et al., 2006). Since apathy may result from excessive inhibition (Jahanshahi, Obeso, Rothwell, Obeso, 2015), hyper-connectivity of the right DLPFC is a feature consistent with a global failure of behavioral control. We argue that the disconnection intrinsic to limbic-cortical circuits may cause the DLPFC to be deprived of the modulation offered by other structures like the ACC and exerts excessive inhibition that contributes to the apathetic trait. Interestingly, *post hoc* analyses revealed that it was non-apathetic patients who had "abnormally" reduced levels of connectivity, lower than apathetic patients, and lower than healthy controls as well. This suggests that volitional control of motivated behavior is a complex behavioral trait sustained by a balanced interplay among multiple regions that might be altered by reductions as well as increases of connectivity.

Beyond an interpretation that accounts for the specific role played by individual brain structures flagged in theories of apathy, it is also interesting to focus on the concept of cross-hemispheric connectivity. A prominent hypothesis is that of cerebral specialization pursued via lateralization of function (Gazzaniga, 2000). Apathy resulting from impaired inter-hemispheric communication is consistent with evidence emerging from diffusion tensor imaging. AD patients with apathy have reduced fractional anisotropy in voxels rich in commissural fibers, particularly in the genu of the corpus callosum, that is the portion that radiates to the forebrain (Hahn, Lim, Won, Ahn, Jung, & Lee, 2013). The onset of a behavioral trait following inter-hemispheric failure is also consistent with reduced

performance levels of aging adults who do not show reduced asymmetry during cognitive processing (Cabeza, 2002).

Our findings are in line with a multi-dimensional view of apathy. Our results show that apathy in AD reflects insular and prefrontal function influencing a number of computational routes, and resulting in altered cognitive, sensory, and emotional processing and integration. At present, the only studies of apathy that have explored the role of long-range pathways of connectivity in AD have provided limited evidence. A study of the apathetic syndrome (inclusive of apathy and appetite and eating abnormalities, as measured by the NPI) showed no significant associations with the default-mode network or the salience network in a sample of 20 AD patients (Balthazar et al., 2014). A negative association was found in a sample of 42 patients with a diagnosis of MCI between apathy and a global index of functional connectivity within a bilateral fronto-parietal network (Munro et al., 2015). A third study investigating a sample of 50 MCI patients with an amnestic presentation was conducted with a seed-based methodology to investigate the main large-scale networks. In this study apathy was associated with increased functional connectivity between the middle frontal gyrus (chosen as seed region for the computation of the executive-control network) and a series of frontal and inferior parietal regions (Joo et al., 2016), supporting the idea of apathy emerging in concomitance with increased connectivity of the DLPFC. Together with these three studies, our findings contribute to lay out the principle that apathy can be the result of disrupted connectivity among regions. Future studies will have the opportunity to disentangle the contribution of each apathy sub-type by using appropriate clinical instruments, which give more detail than the NPI. Although the NPI is among the scales most often used to assess apathy in AD, other validated instruments relying on a different methodology exist, such as the Apathy Evaluation Scale (Mohammad et al., 2018). Three versions of this scale exist, and a study carried out in healthy adults and patients with MCI

found a significant association between clinician-rated levels of apathy and thickness of the inferior temporal cortex (Guercio et al., 2015), a region that is not part of the theoretical frameworks this study is based upon. On this note, it is important to be aware of the operational and methodological nuances that are at play when apathy is measured. Other than the source of information (e.g., patient vs. informant), one such nuance might be represented by the degree of severity of the symptom. This study focused on the presence/absence of a general apathetic trait without any further clinical characterization. Although the NPI does not offer a full characterization of the apathetic symptom, it does screen for possible comorbidities with other psychiatric symptoms and is quickly and conveniently administrable in secondary-care settings. In all likelihood, however, combining multiple instruments could be useful to capture the multidimensionality of the clinical trait.

The two groups of patients were well matched for demographic characteristics, cognitive profile, and overall severity of neuropsychiatric profile. The only exception was a tendency to show other symptoms such as irritability, anxiety, agitation or depression. Irritability is a complex symptom that may result from other variables linked to traits (e.g., mood) or states (e.g., hunger, pain (Koenig, Arnold, & Streim, 2016)) and may also be secondary to apathy (e.g., part of the patient's reactions to the carer's attempt to increase motivation). For a similar reason some degree of agitation might be expected as secondary to the apathetic state and contingent to situational triggers. We conclude, therefore, that, as far as this study indicates, the difference in irritability and agitation symptoms between groups is negligible. Greater anxiety and depression, however, is not an unusual occurrence in association with apathy and there is evidence of a frequent association between apathy with depression and anxiety in a non-neurodegenerative population (Batail et al., 2019). Comorbidity of depression and anxiety with apathy, therefore, might be intrinsic to the apathetic trait. Reserve was also controlled for. To date, only one study has found a protective effect of

cognitive reserve against apathy in another condition (Shapiro, Mahoney, Peyser, Zingman, & Verghese, 2014). Although apathy was unrelated to indices of reserve, this link deserves more attention in future research.

TFfMRI functional connectivity was chosen as an investigational method for multiple reasons. The risk of biased results secondary to the specifications of a task was avoided, as was the effect of the participants' ability to engage in such a task. Secondly, it is acknowledged that neurodegenerative diseases affect brain function by down-regulating long-scale brain networks (Seeley, Crawford, Zhou, Miller, & Greicius, 2009), which can be assessed using measures of functional connectivity. Thirdly, it is well established that it is these networks that sustain high-order cortical function (including behavior generation) rather than a set of single areas working independently from one another (Tisserand & Jolles, 2003). Fourth, the model by Guimarães and coworkers specifically characterizes behavior generation as the result of interplay and mutual control enacted by the set structures at play (Guimarães et al., 2008). Based on these factors, modelling of TFfMRI functional connectivity was the most suitable method to explore the neural changes associated with the presence of apathy.

This study is not free from limitations. The NPI relies on caregiver observation of the presence or absence of neuropsychiatric symptoms. Reliance on caregiver ratings for diagnosing neuropsychiatric symptoms has been both criticized for lacking clinical operativeness (Moretti & Signori, 2016) as well as promoted, as patients with dementia may lack insight into their symptoms (Honigsto et al., 2018). The binary scoring of the NPI allowed us to circumvent the problems the typical "frequency × severity" scores have in inferential statistical models (Lai, 2014). This scoring, however, has prevented us from looking for correlations between severity and changes in connectivity. Our findings are limited to the study of the presence of "general apathy" without providing any insight on the

variability of its clinical significance. An instrument that measures severity as a continuous variable should be considered in future studies. Furthermore, the use of other instruments would allow a separation of the various sub-types of apathy, to investigate the specific features that accompany this symptom. More generally, further studies on apathy in AD are still warranted. Specifically, studies that investigate the neural correlates in large cohorts such as the Alzheimer's Disease Neuroimaging Initiative might provide greater statistical power and give additional insight on the brain circuital breakdowns fostering the appearance of this behavioral symptom. In particular, longitudinal studies are needed to determine whether presence or absence of apathy is a stable behavioral trait or is subjected to fluctuations over time.

Two clinical implications can be extrapolated from our findings. First, since abnormal connectivity is the result of AD neuropathology, the variants of AD that target prefrontal areas, i.e., the frontal variant of AD, are likely to result in more severe apathy (Ossenkoppele et al., 2015). Although none of the patients included in this study presented with a frontal-variant onset, reduction of function in prefrontal circuits was found in concomitance with apathy. As a consequence, AD patients presenting with a frontal onset (and thus, with intense prefrontal deposition of AD pathology) would suffer from a more severe disruption of prefrontal connectivity, and, plausibly, more severe apathy. Second, since the pathways of connectivity involved in this symptom are partly dopaminergic circuits, this could be a therapeutic target for the treatment of apathy. This concurs with findings that patients with Parkinson's disease and apathy have reduced connectivity between the limbic striatum and prefrontal cortex suggesting dopamine deficits in the frontostriatal pathways as the cause (Alzahrani, Antonini, & Venneri, 2016; Baggio et al., 2015).

5. Conclusions

In conclusion, we have found alterations of specific frontal and insular circuits in AD patients with apathy. While confirming the role of the regions emerging from studies of brain anatomy and metabolism, these results offer data-driven insight on apathy as potentially due to network disruption and abnormal synaptic activity.

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DISCLOSURES

The authors have no conflict of interest to report.

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FIGURE LEGEND

Figure 1.

The pattern of group differences found between apathetic and non-apathetic patients. The seeds are reported in green on the left. Significant differences are illustrated in the MNI space. Significant differences in functional connectivity of the left insula (A) are illustrated in red (slice coordinates: y = -52, x = 30). The difference in the functional connectivity of the right DLPFC (B) is colored in blue (slice coordinates: y = -66, x = 36).

Figure 2.

Post hoc analyses (A for the left insula and B for the right dorsolateral prefrontal seeds) comparing the cluster-level *beta* score of functional connectivity among the three sub-groups included in this study (non-apathetic patients, apathetic patients and healthy controls). One-way *ANOVA*s were run, controlling for age and education levels, followed by Bonferroni-corrected *t* tests. Significant differences and differences approaching significance are indicated. Uncorrected *p-values* are indicated.