Brain Microstructure of Subclinical Apathy Phenomenology in Healthy Individuals

Gianfranco Spalletta,^{1,*} Sabrina Fagioli,¹ Carlo Caltagirone,^{1,2}
and Fabrizio Piras¹

¹IRCCS Santa Lucia Foundation, Department of Clinical and Behavioral Neurology and Memory Clinic, Rome, Italy

²Tor Vergata University of Rome, Department of Neuroscience, Italy

Abstract: Although apathy has been extensively studied in relation to neuropsychiatric disorders, it is still unclear whether, in healthy people, it should be considered as a physiological phenomenon or whether it is a risk factor for progression to clinical disturbances. Here, we investigated subclinical apathy phenomenology and its brain microstructural correlates in healthy individuals. We submitted 72 participants to a comprehensive clinical assessment, a high-resolution structural MRI and a diffusion tensor imaging scan protocol. Data of individual microstructural (mean diffusivity and fractional anisotropy) variations were processed across genders in relation to the Apathy Rating Scale score. In females, subclinical apathy phenomenology was associated with microstructural variation of the bilateral thalami, the anterior thalamic radiation, the forceps major, and the corona radiata. These are white matter areas mostly connecting the thalami to the frontal and occipital cortices, regions that are known to be implicated in the expression of apathy in clinical samples. No significant relationship with brain microstructure was found in males who showed a positive correlation between subclinical apathy and somatic phenomenology of depression. In conclusion, our results show that in healthy individuals subclinical apathy phenomenology is associated with different mechanisms across genders, and raise the issue about whether brain microstructural changes associated with subclinical apathy in healthy females could be a precocious marker useful in the prediction of progression to more severe apathetic conditions. *Hum Brain Mapp* 34:3193–3203, 2013. © 2012 Wiley Periodicals, Inc.

Key words: apathy; thalamus; diffusion tensor imaging; healthy subjects; prefrontal cortex; sex differences

INTRODUCTION

Apathy is a frequent clinical feature in many neuropsychiatric disorders including stroke [Starkstein et al., 1993], Parkinson's disease [Starkstein et al., 1992], Huntington's disease [Craufurd et al., 2001], Alzheimer's disease (AD) [Starkstein et al., 2006], schizophrenia [Roth et al., 2008], and mood disorders [Marin et al., 1993]. However, it is still unclear whether apathy should be considered a dimension of these disorders or a discrete disorder.

The clinical dimension of apathy generally concerns the concept of "lack of motivation" not ascribable to a decreased level of consciousness, cognitive impairment, or emotional distress [Marin, 1990, 1991]. Accordingly, the

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*Correspondence to: Gianfranco Spalletta, IRCCS Santa Lucia Foundation, Neuropsychiatry Laboratory, Via Ardeatina, 306, 00179 Rome, Italy. E-mail: g.spalletta@hsantalucia.it

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clinical expression of apathy is characterized by a significant reduction of goal-directed behavior, goal-directed cognition, and the emotional concomitants of goal-directed behaviors [Marin, 1991; Starkstein and Leentjens, 2008]. The important question, however, is that concerning the functional meaning of subclinical apathy phenomenology in otherwise healthy participants (i.e., who have no neurological or psychiatric disorders). In fact, apathy can be viewed along a continuum ranging from subclinical apathetic-like expressions to more severe apathetic conditions.

Up until now, only a few studies have directly assessed the phenomenology and the putative structural correlates of subclinical apathy in otherwise healthy participants. In fact, the behavioral and structural correlates underlying the apathetic syndrome have been mainly studied in relation to neurodegenerative processes such as dementia, especially AD [Benoit et al., 2004; Marshall et al., 2006; Migneco et al., 2001] and Parkinson's disease [Drapier et al., 2006; Le Jeune et al., 2009] and a rather inhomogeneous picture has emerged, suggesting an involvement of different, but closely interconnected, subregions of the prefrontal cortex and of the basal ganglia [Bhatia and Marsden, 1994; Engelborghs et al., 2000; Mendez et al., 1989]. Moreover, apathy has also been found related to white matter (WM) microstructure in preclinical subjects with mild cognitive impairment who are at higher risk of developing AD [Cacciari et al., 2010]. Therefore, clarification of this issue requires a more thorough investigation.

Focusing on the study of apathy in nonclinical samples of healthy subjects, this could be approached from two different perspectives: anthropological and clinical. The anthropological one concerns whether some aspects of apathy have physiological, constructive, or adaptive roles. The more challenging clinical perspective concerns whether subclinical apathy in healthy individuals constitutes a risk factor for progression to a clinical picture.

From a neurobiological perspective, diffusion tensor imaging (DTI) has proven to be a reliable tool for investigating the brain microstructural alterations associated with prodromal neuropsychiatric phenomenology in nonclinical samples. DTI measures the diffusion of water molecules in tissue and provides information about microstructural changes in the brain [Basser, 1995]; thus, it supplies physiological information that other MRI measures (such as voxel-based volumetry) cannot reveal, especially in populations with no signs of psychiatric or neurodegenerative diseases. In pathological conditions, low fractional anisotropy (FA) value in WM indicates similar diffusivity patterns in all directions, suggesting reduced fiber density, axonal diameter, and myelination [Basser and Pierpaoli, 1996]. Conversely, increased mean diffusivity (MD) in gray matter (GM) is linked to enlargement of the extracellular space due to altered cytoarchitecture, suggesting tissue immaturity or degeneration [Kantarci et al., 2005; Sykova, 2004]. In deep GM assemblies, this could reflect either direct primary pathological damage or secondary degeneration due to primary disruption of the WM tracts

that link them to other structures, possibly leading to cortical dysfunction [O'Sullivan et al., 2004]. In physiological states, extracellular water diffusion is influenced by different factors, such as the size of pores between cells, cellular structure, density, and surface [Le Bihan, 2007; Sykova and Nicholson, 2008], which, in turn, might modulate the efficacy of synaptic as well as extrasynaptic transmission [Sykova, 2004]. Therefore, in this study, we assessed the continuum of subclinical apathy phenomenology in healthy individuals and investigated its GM and WM microstructural correlates.

Specifically, if apathy in healthy individuals is a preclinical phenomenon associated with specific brain structural correlates, then its phenomenology expression should be significantly associated with microstructural variations in the GM and/or WM of the same brain structures involved in controlling apathy expression in clinical samples.

Furthermore, we will address the question about whether genders differ in the phenomenology of nonclinical apathy and in its association with brain microstructural data. This could be expected on the basis of the well-documented difference between males and females in the development of affective disorders [Kessler et al., 1993] and in emotion-related behaviors, such as emotion recognition from facial expression and regulation of emotional responses [Domes et al., 2010; Kret and De Gelder, 2012]. Intriguingly, brain imaging studies demonstrated that genders differ in emotional processing even at brain structural and functional level. Amygdala volume correlates positively with fearfulness in females but not in men [van der Plas et al., 2010], whereas aggressive and defiant behavior is associated with decreased right anterior cingulate cortex volume in boys [Boes et al., 2008] but not in girls. Moreover, a growing body of evidence demonstrated that the neural network involved in the processing of emotions is differently activated in males and females. Lee et al. (2005) and Carrè et al. (2012) found that individual differences in trait anger are positively correlated with bilateral dorsal amygdala reactivity to angry facial expressions, but only among men with elevated trait anxiety scores. Elevated activation in males versus females has also been observed in other brain areas than the amygdala. For example, Fine et al. (2009) showed greater male than female activation following photos and videos of positive and negative content in a range of frontal and temporal areas and in the cingulate cortex. Taken together, these findings support the idea that females are more "emotional" than males are, and that brain correlates of emotional processes are distinct among genders [Kret and De Gelder, 2012]. As a clinical implication, it may be expected that a number of psychological disorders involving emotional function occur at substantially different rates in men and women. Thus, it is reasonable to expect gender differences in the subclinical apathy phenomenology and in its associated neural correlates.

To avoid the influence of depression we excluded from the study sample all individuals with the minor forms of

TABLE I. Sociodemographic and clinical characteristics of the 72 healthy subjects

Variables	Males (<i>n</i> = 39) [mean (SD)]	Females (<i>n</i> = 33) [mean (SD)]	<i>t</i>	df	<i>P</i>
Age	34.21 (8.53)	33.52 (14.34)	−0.243	70	0.81
Educational level	15.95 (2.65)	15.15 (3.08)	−1.179	70	0.24
Apathy Scale score	5.59 (3.06)	6.42 (2.87)	1.19	70	0.24
Apathy Scale range	0–16	2–12			
BDI somatic subscore (BDI-SOM)	.95 (1.32)	2.06 (1.78)	2.96	70	<0.01*
BDI psychic subscore (BDI-PSY)	1.51 (1.65)	2.76 (2.18)	2.75	70	<0.01*
BDI total score	2.46 (2.61)	4.82 (3.39)	3.33	70	<0.01*
BDI range	0–9	0–15			

df, degrees of freedom; SD, standard deviation; BDI, Beck depression inventory.

*Statistically significant differences at $P < 0.05$.

depression. Further, we included subclinical depression phenomenology severity as a covariate of no interest in the multiple regression models in which we evaluated apathy scores as predictors of DTI-derived indices of microstructural variations separately for males and females.

METHODS

Participants

By means of local advertisement, 72 healthy adults (mean age $\pm$ standard deviation = 33.9 ± 11.47 , range = 19–67) were recruited from universities, community recreational centers, and hospital personnel by local advertisement.

Inclusion criteria were age between 18 and 70 years and suitability for MRI scanning. Exclusion criteria included (i) suspicion of cognitive impairment or dementia based on Mini Mental State Examination [Folstein et al., 1975] score ≤ 24 , and dementia diagnosis or cognitive deterioration further confirmed by a thorough clinical neuropsychological evaluation [Carlesimo et al., 1996]; (ii) subjective complaint of memory difficulties or any other cognitive deficits interfering with daily living activities; (iii) vision and hearing loss that could interfere with testing procedures; (iv) major medical illnesses; (v) current or reported psychiatric (assessed by the Structured Clinical Interviews for Diagnostic and Statistical Manual of Mental Disorders IV Edition Revised, Axis I and II, [First, 1997, 2002]) or neurological (assessed by a clinical-neurological evaluation) disorders; (vi) known or suspected history of alcoholism or drug dependence and abuse during lifetime; (vii) MRI evidence of focal parenchymal abnormalities or cerebrovascular diseases. We also investigated whether the apathy syndrome was present using Marin's (1991) modified criteria derived from Starkstein (2000) and excluded subjects who screened positive for clinically relevant apathy. Thus, none of the 72 subjects in the final sample had mental or neurological disorders, including clinical-relevant apathy.

The study was approved and carried out in accordance with the guidelines of the Istituto di Ricovero e Cura a Carattere Scientifico Santa Lucia Foundation Ethics Committee

and, in accordance with the Helsinki Declaration, each subject signed an informed consent form before enrollment.

Apathy Measurement

Degree of apathy was assessed by administering the Apathy Rating Scale (ARS) [Starkstein et al., 1995]. This is a 14-item questionnaire in which each item has four choices that are scored from 0 (no abnormality) to 3 (severe). Thus, apathy scale scores range from 0 to 42 points, and higher scores indicate more severe apathy. Clinical relevant apathy was diagnosed according to Starkstein's (2000) adaptation of Marin (1991) criteria, and apathetic subjects were excluded from this study.

Given the high frequency of the co-occurrence of depression and apathy, we administered the Beck depression inventory (BDI) to examine apathy separately from depression. The BDI is a 21-item multiple-choice inventory that measures severity of depressive symptoms [Beck, 1987]. Each response is assigned a score ranging from 0 to 3, which indicates severity of the symptom. The total test score (BDI-TOT) is defined as the sum of the individual item scores. We also calculated the psychic subscore (BDI-PSY) and the somatic subscore (BDI-SOM) by combining the first 14 items and the remaining seven items, respectively [Beck et al., 1988].

Image Acquisition and Processing

All 72 participants underwent the same imaging protocol, which included standard clinical sequences (Fluid Attenuated Inversion Recovery, DP-T₂-weighted), whole-brain T₁-weighted and diffusion-weighted scanning using a 3T Allegra MR imager (Siemens, Erlangen, Germany) with a standard quadrature head coil. All planar sequence acquisitions were obtained in the plane of the Anterior Commissure-Posterior Commissure line. Diffusion-weighted volumes were acquired using echo-planar imaging (Time of Echo/Time to Repeat = 89/8,500 ms, bandwidth = 2,126 Hz/vx; matrix size 128 × 128; 80 axial slices, voxel size 1.8 × 1.8 × 1.8 mm³) with 30 isotropically distributed orientations for the diffusion-sensitizing gradients at a *b* value of 1,000 s mm² and six *b* = 0 images. Scanning was repeated three

Figure 1.

Spatial localization of the correlation between mean diffusivity and Apathy Rating Scale score. **A:** Representative axial slice showing significant results ($P < 0.05$, FDR correction) of the voxel-based correlation between mean diffusivity and Apathy Rating Scale score in the whole sample of healthy individuals. In this figure, right is right and left is left. **B:** Results are superimposed over the Oxford Thalamic Connectivity Atlas (Available at: <http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#-thal>), which shows thalamic regions that are color-coded according to their white-matter connectivity to cortical areas. **C:** Voxels showing significant correlation between mean diffusivity

and Apathy Rating Scale score superimposed over an axial thalamic section from a cytoarchitectonic atlas (Morel et al., 1997) showing thalamic nuclei and cortical projections. VA, ventral anterior nucleus; VLd, ventral lateral anterior nucleus; VLp, ventral lateral posterior nucleus; VPL, ventral posterior lateral nucleus; LP, lateral posterior nucleus; Pu, pulvinar; MD, medial dorsal nucleus. Red: prefrontal cortex; green: posterior parietal cortex; blue: premotor cortex; yellow: temporal cortex. **D:** Focusing on thalamic regions that are significant in A, scatter plots in D show the relationship between mean diffusivity and Apathy Rating Scale score separating female and male subjects.

times to increase the signal-to-noise ratio. Whole-brain T_1 -weighted images were obtained in the sagittal plane using a modified driven equilibrium Fourier transform [Deichmann et al., 2004] sequence (Time of Echo/Time to

Repeat = 2.4/7.92 ms, flip angle 15° , voxel size $1 \times 1 \times 1 \text{ mm}^3$).

Image processing was performed using FMRIB Software Library (FSL) 4.1 (www.fmrib.ox.ac.uk/fsl/). Image distortions

Figure 2.

Spatial localization of the correlation between mean diffusivity and Apathy Rating Scale score in female subjects. **A:** Representative axial slices showing significant results ($P < 0.05$, FDR correction) of the voxel-based correlation between mean diffusivity and Apathy Rating Scale score. In this figure, right is right and left is left. **B:** Results are superimposed over the Oxford Thalamic Connectivity Atlas. **C:** Three-dimensional rendering of the

correlation between mean diffusivity and Apathy Rating Scale score. Statistically significant results corrected for multiple comparisons are indicated in blue. A three-dimensional thalamic model is also reported (in dark grey). **D:** Voxels showing significant correlation between mean diffusivity and Apathy Rating Scale score superimposed over an axial thalamic section from Morel's cytoarchitectonic atlas (see Figure 1 for details).

induced by eddy currents and head motion in the DTI data were corrected by applying a 3D full affine (mutual information cost function) alignment of each image to the mean no diffusion weighted (b_0) image. After these corrections, DTI data were averaged and concatenated into 31 ($1b_0 + 30b_{1000}$) volumes. A diffusion tensor model was fitted at each voxel to generate FA and MD maps. The FA maps were registered to brain-extracted whole-brain volumes from T₁-weighted images using a full affine (correlation ratio cost function) alignment with nearest-neighbor resampling because the spatial distribution of signal intensities of FA and T₁-weighted images are similar. The calculated transformation matrix was applied to the MD maps with identical resampling options.

Finally, MD and FA maps were normalized to the Montreal Neurological Institute template and subsequently smoothed with a Gaussian kernel with a full-width half maximum of 8 mm. The normalized and smoothed images were then used in the analyses.

Statistical Analyses

Behavioral

Statistical analyses were performed with Statview Software v5.0.1 (SAS Institute). To determine the significance of the correlations between continuous variables,

TABLE II. Anatomical regions of positive correlation between mean diffusivity and the Apathy Rating Scale score in females

Anatomical region	Label for peaks	Cortical projection	Extent (mm ³)	P (FDR-cor)	T	equivZ	^a Coordinates x, y, z (mm)
L thalamus and internal capsule	Thalamus	Premotor (57%)	290	0.04	5.15	4.38	-16, -20, 6
	Thalamus	Prefrontal (87%)		0.04	4.89	4.21	-14, -10, 8
	Internal capsule (posterior limb)			0.04	4.44	3.90	-22, -4, 14
R thalamus and internal capsule	Internal capsule (posterior limb)		216	0.04	5.11	4.36	24, -16, 14
	Thalamus	Prefrontal (84%)		0.04	4.43	3.89	14, -8, 8
	Thalamus	Premotor (71%)		0.05	4.14	3.69	16, -16, -2

For voxels located inside the thalami, a percentage of probability of anatomical connection to cortical areas is reported (see Methods section).

FDR, false discovery rate; R, right; L, left.

^aCoordinates are in Montreal Neurological Institute (MNI) space.

correlational analyses and Fisher's r to z transformation were performed. Unpaired t -tests were used to assess differences between males and females on the scores of the BDI and the ARS. The level of statistical significance was defined as $P < 0.05$.

Neuroimaging

The statistical significance of the correlations between MD and FA values and ARS scores were tested at the voxel level using SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5). To identify the brain regions in which all subjects showed MD and FA variations associated with subclinical apathy severity, two distinct multiple-regression models were used (i.e., separating MD and FA maps) using the ARS score as the regressor and age, education, and BDI score as covariates of no interest. Then, in order to assess sex differences in the relationship between brain structure and apathy, four other multiple-regression analyses were run, separating MD and FA maps in male and female subjects. All the FA analyses were restricted for those voxels having a value greater than 0.2, to exclude cortical GM from the analyses. The voxels were deemed statistically significant at $P < 0.05$ with false discovery rate (FDR) correction for multiple comparisons, and if they were part of a spatially contiguous cluster size of a minimum of 20 voxels.

Finally, to obtain fine localization of statistical results, four different brain atlases (all part of the FSL 4.1 software library) were used: (i) the Harvard-Oxford cortical and subcortical atlases, provided by the Harvard Center for Morphometric Analysis (www.cma.mgh.harvard.edu/); (ii) the ICBM-DTI-81 WM labels atlas (including 50 WM tract labels created by hand segmentation of a standard-space average of diffusion MRI tensor maps from 81 subjects); (iii) the John Hopkins University white-matter tractography atlas (including 20 structures identified probabilistically by averaging the results of deterministic tractography in 28 normal subjects); and iv) the Oxford thalamic connectivity atlas [Johansen-Berg et al., 2005] (including seven

subthalamic regions segmented according to their WM connectivity to cortical areas).

RESULTS

Behavioral

No significant relationship between ARS scores and sociodemographic variables of age and educational attainment emerged. No differences between males and females for age, educational attainment, or ARS scores were found. It should be noted that females obtained higher scores on the ARS than males (53% vs. 35%, when considering a sample-based estimate of the mean score weighted on its own range of variation); although differences between these values (ca. 20%) are not significant, they can be considered relevant with reference to our *a priori* hypothesis, thus justifying separate analyses across genders. Furthermore, the analysis revealed that females obtained higher scores on the depression dimension, as measured by the three BDI indexes here considered (Table I). To further explore the role of the depressive dimension in the continuum of subclinical apathy and provide a fuller picture of the data, we performed a linear multiple regression analysis (enter model; probability of P to enter = 0.05) separately on each gender to evaluate the impact of the BDI score on the ARS score. We considered the three indexes of the BDI as independent variables and the score on the ARS as dependent variable. In males, a significant model emerged [$F(2,36) = 4.353$; $P < 0.05$; adjusted $R^2 = 0.15$], in which the BDI-SOM was a significant predictor of the ARS score ($\beta = 0.41$; $P = 0.028$). No significant model emerged for female participants. The sample characteristics are presented in Table I.

Neuroimaging

As reported in Figure 1, we found a positive correlation between MD values and ARS scores in the whole sample, mainly located in right and left thalamus.

Figure 3.

Spatial localization of the correlation between fractional anisotropy and Apathy Rating Scale score. **A:** Representative axial slices showing statistically significant results ($P < 0.05$ FDR correction) of the voxel-based correlation between fractional anisotropy and Apathy Rating Scale score in the whole sample of healthy individuals. White matter labels and tracts (when available) are based on

the John Hopkins University DTI-based white-matter atlas (Available at: <http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#wm>). In figure, right is right and left is left. **B:** Focusing on regions that are significant in A, scatter plots in B show the relationship between mean fractional anisotropy and Apathy Rating Score separating female and male subjects.

When separate analysis was run for male and female subjects, we found a positive correlation between MD and ARS in the left and right thalamus and the internal capsule in female subjects (Fig. 2 and Table II). We found no significant clusters showing a relationship between MD values and ARS score in male participants, even when the statistical threshold was lowered to $P < 0.001$ uncorrected for multiple comparisons.

As the thalamus is a complex structure composed of several nuclei, each interconnected with different cortical

areas, we established the precise location of the correlational results. They were mainly located in the medial dorsal, ventral-anterior, ventrolateral anterior and posterior, and ventral-posterior lateral nuclei. Moreover, when our results were superimposed over probabilistic maps based on DTI [Johansen-Berg et al., 2005], the greater percentage of voxels showing significant correlations between ARS score and MD values was localized in thalamic portions projecting mainly to the prefrontal cortices and the premotor areas.

TABLE III. Anatomical regions of negative correlation between fractional anisotropy and Apathy Rating Scale score in females

Anatomical region	Label for peaks	White matter tract	Extent	P (FDR-correction)	T	equivZ	^a Coordinates x, y, z (mm)
L cerebellum and R parietal	Middle cerebellar peduncle	Corticospinal	11,795	<0.01	5.82	4.80	-12, -38, -36
	Middle cerebellar peduncle	Cerebellum		<0.01	5.48	4.59	-16, -58, -36
R Occipital lobe	Supramarginal gyrus BA 40	Sup long fasc	376	<0.01	5.33	4.49	40, -32, 36
	Calcarine BA 19	Forceps major		<0.01	4.75	4.12	22, -76, 14
	Calcarine BA 18	Forceps major		<0.01	3.95	3.55	22, -86, 2
	Calcarine BA 19	Forceps major		0.01	3.67	3.34	26, -50, 10
Corpus Callosum	Splenium	Forceps major	364	0.01	3.69	3.35	-4, -34, 10
	Precuneus BA 29	Forceps major		0.01	3.55	3.24	-12, -42, 6
	Precuneus	Forceps major		0.01	3.51	3.21	-4, -44, 12
L Occipital lobe	Middle occipital area BA 18	Inf long fasc	203	0.01	3.56	3.25	-26, -84, 2
	Precuneus BA 19	Forceps major		0.01	3.47	3.18	-22, -58, 10
	Superior occipital area BA 19	Forceps major		0.02	3.00	2.80	-16, -82, 14
R Parietal lobe	Supramarginal gyrus	Ant thal rad	63	0.02	3.14	2.92	22, -36, 28
L Temporal lobe	Superior temporal area BA 20	Inf front-occ fasc	60	0.02	2.88	2.70	-40, -16, -8

White-matter tracts based on deterministic tractography are reported (see Methods section).

Ant thal rad, anterior thalamic radiation; inf front-occ fasc, inferior frontooccipital fasciculus; FDR, false discovery rate; R, right; L, left.

^aCoordinates are in Montreal Neurological Institute (MNI) space.

In addition, in the whole sample of healthy individuals we found negative correlations between FA and ARS scores in several areas located in the corpus callosum, internal capsule, anterior thalamic radiations, and superior longitudinal fasciculi (Fig. 3).

When separate analyses were carried out for male and female individuals, we found significant negative correlations in females between FA and ARS scores in several WM tracts located in the left middle cerebellar peduncle, internal capsule, anterior thalamic radiations right supramarginal gyrus, right and left occipital lobe, corpus callosum, and left superior temporal area (Table III, Fig. 4). However, we found no significant clusters showing a significant relationship between FA values and ARS scores in males.

DISCUSSION

In this study, we investigated whether subclinical apathy is associated with microstructural variations of brain GM and WM in healthy participants who were completely free of mental and neurological disorders, including apathy and depression. Bilateral thalamic microstructure, along with the microstructural variability of the corpus callosum and WM tracts connecting these subcortical structures to frontotemporal and occipital areas (i.e., the anterior thalamic radiation, the forceps major, and the corona radiata) predicted subclinical apathy only in female subjects. The thalamic result was located in subportions mainly projecting to the prefrontal and premotor cortices, that is, to those brain areas strictly involved in clinical apathy in patients suffering from neuropsychiatric illnesses.

Our results raise the important question about whether subclinical apathy has a preclinical prognostic significance and whether gender differentiates these outcomes in healthy individuals.

Apathy is considered a negative symptom in schizophrenia [Roth et al., 2008] and has been associated with a number of brain alterations in neuropsychiatric diseases [Cacciari et al., 2010; Starkstein et al., 1993]. Furthermore, it has been suggested that apathy in AD patients may be a behavioral marker of a more severe subtype of dementia, with faster functional and motor decline [Starkstein et al., 2006, 2009], whereas even in preclinical dementia apathy increases the risk of developing AD [Palmer et al., 2010]. Actually, our finding of a relationship between subclinical apathy and brain microstructure of regions typically involved in the expression of clinical apathy suggests that in healthy females subclinical forms may be a risk factor for progression to more severe forms of apathy. In fact, the finding of increased MD in both portions of the thalamus, projecting mainly to the prefrontal and premotor cortices and in the internal capsule, and of decreased FA in the anterior thalamic radiation suggests that women's apathy-like phenomenology even in the absence of neuropsychiatric disorders is associated with changes in pathways known to be implicated in the apathetic disorder [Levy and Dubois, 2006]. Accordingly, we found that females tended to show more apathy-like symptoms than men (53% vs. 35%, respectively). In fact, even if the difference between these values was not statistically significant, it should be noted that since we eliminated all subjects who scored positive for clinically relevant apathy symptoms, the apathy phenomenology was varied by a more restricted range, which probably explains why our analysis

Figure 4.

Spatial localization of the correlation between fractional anisotropy and Apathy Rating Scale score in female subjects. **A:** Representative axial slices showing statistically significant results ($P < 0.05$ FDR correction) of the voxel-based correlation between fractional anisotropy and the Apathy Rating Scale score. In this figure, right is right and left is left. **B:** Three-dimensional rendering of the negative correlation between fractional anisotropy and Apathy Rating Scale score.

failed to reveal significant differences between the two genders on the ARS scores.

Intriguingly, we found no significant relationship with brain correlates in males, suggesting that apathy phenomenology is driven by different mechanisms across genders. Indeed, although subclinical apathy is linked to more biologically driven characteristics in females, it seems to reflect a depression-like state in males, who showed a relationship between subclinical apathy and the somatic dimension of depression, in the absence of variations in the brain microstructure. This suggests that the subclinical apathy in males could be linked to the behavioral/motor mechanism of apathy (e.g., quantitative reduction of voluntary actions) associated with cognitive inertia [Levy and Dubois, 2006]. Leaving speculation aside, further longitudinal studies in healthy people should be carried out to confirm these hypotheses by verifying the different impact of subclinical apathy in males and females.

Finally, our results suggest a putative role of the thalamus in the pathogenesis of apathetic symptomatology in women. The thalamus is a nuclear complex located in the diencephalon that operates as a relay station for most sensory and motor pathways and acts as a source of information for the frontal and motor areas [Herrero et al., 2002]. It is connected to the cerebral cortex by the thalamic radiation; the fibers run obliquely through the internal capsule towards the cerebral cortex. Indeed, our finding of an association of subclinical apathy with microstructure changes in those thalamic nuclei that mainly project to prefrontal and premotor cortices may justify our consideration of this structure as crucial for the genesis and development of apathetic symptomatology in women. In fact, due to its dense and reciprocal interconnections with the regions that form the prefrontal-subcortical circuit, which are known to be involved in the control of clinical apathy [Levy and Dubois, 2006], it can be argued that early changes in these structures might constitute a risk factor

for the development of clinical apathy in females. Of course, further research should address this challenging hypothesis.

Although this is a novel study examining the brain microstructural correlates of subclinical apathy phenomenology, limitations should be considered. As our sample was homogeneous with regard to race and recruitment source, our results could be limited in extendibility to different populations and future research is needed to deepen this issue. Further, the cross-sectional structure of the study might also be a limitation. In fact, longitudinal data collection might allow to establish if female subclinical apathy expression and the associate brain microstructural variations are predictive of later development of affective disorders.

In conclusion, subclinical apathy is accounted for by different mechanisms across genders. Brain microstructure variation of the prefrontal-thalamic network was found in females, therefore suggesting that subclinical apathy could represent a precocious marker of progression to a more severe clinical outcome only in this gender. Importantly, our results highlight that the thalamus is a key structure in the pathogenesis of apathetic symptomatology in the absence of depression.

Conversely, variation in male subclinical apathy is related to motor or behavioral processes involved in the reduction of voluntary actions associated with the somatic dimension of nonclinical depression.

These findings indicate that the continuum of subclinical apathy phenomenology may be ascribable to different mechanisms across genders in healthy individuals, thus confirming not only that apathy is a multiple, heterogeneous entity, but also that it is subserved by different neural mechanisms [Levy and Dubois, 2006]. Nevertheless, as this is the only evidence reported to date on subclinical apathy phenomenology in healthy individuals, future research should be dedicated to definitively confirm the hypotheses derived by our results.

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