



Cerebral microstructural abnormalities in impulsivity: a magnetic resonance study

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Abstract

Studies that investigated neurobiological parameters subtended to impulsivity trait found their relationship with structural and functional brain alterations. No studies investigated the white matter microstructural attributes of impulsivity in a large sample of healthy subjects. In the present study 1007 subjects from Human Connectome Project public dataset were divided in two groups, impulsive and not impulsive, basing on Delay Discounting task score. For both groups brain morphometric and microstructural characteristics were investigated. A t-test (correct for multiple comparisons) was performed for each brain parcel and impulsivity measure. Magnetic resonance diffusion images were pre-processed and selected to perform a voxelwise analysis on the fractional anisotropy (FA) maps between impulsive and not impulsive groups. Group analysis showed significant differences in morphometric brain data mainly for temporal and frontal lobes. The impulsive group presented higher FA values in four regions: bilateral medial lemniscus and midbrain reticular formation, right superior longitudinal fasciculus, left forceps major, right corticospinal tract. Not impulsive group showed higher FA values in two significant regions: right and left anterior thalamus radiation. Concluding, macroscopic and microstructural brain alterations were assessed, identifying new neuroanatomical substrates for multidimensional impulsivity construct in a large sample of healthy subjects.

Keywords Impulsivity · Delay discounting · Microstructure · Morphometry · Fractional anisotropy

Introduction

Impulsivity is a multi-dimensional construct referring to several self-regulatory capabilities that can be measured through different ways. Impulsivity main components are: personality trait, that means the ability in controlling prevailing aptitude and is measured by self-report questionnaires; response inhibition, that refers to faculty in inhibiting a dominant response in experimental tasks; decision making also measured by experimental tasks; motor impulsivity, reflecting outsourcing behaviors (Mackillop et al. 2016; Gray et al. 2018).

One of the most widely used indices of decision-making factor of impulsivity is the delay discounting task, a simple but effective paradigm where subject is requested to choose between a greater delayed reward and an immediate lesser reward (Madden and Bickel 2009; Amlung et al. 2017).

Several studies have investigated neuroanatomical pathways subtending impulsivity demonstrating that delay discounting mainly involves prefrontal cortex, primarily ventromedial division, orbitofrontal cortex and striatum (Kable and Glimcher 2007; Bartra et al. 2013; for a review see Peters and Buchel 2011). Differently, the preference for the immediate or delayed gains is more linked to activity in areas afferent to temporal pole and limbic system as insula, cingulate cortex and amygdala.

In healthy subjects, available studies on brain structural aspects of delay discounting have been conducted on relatively small samples, not providing unitary results. Wang et al. (2017) hypothesized correlations between delay discounting and smaller gray matter volume in dorsolateral prefrontal cortex and medial orbitofrontal cortices, parahippocampal and precentral gyri. Similarly, Pehlivanova et al. (2018) found that impulsive choice was associated with reduced cortical thickness in two networks including prefrontal and orbitofrontal cortices, core structures in reward-related decision-making.

Microstructural brain characteristics linked to impulsivity are poorly investigated in healthy subjects. Usually, diffusion tensor imaging (DTI) is suitable for detecting white matter

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microstructural differences (Basser et al. 1994; Alexander et al. 2007) and specifically the fractional anisotropy (FA) is the index that estimates fibers integrity. Ikuta et al. (2018) used probabilistic tractography to investigate the association between the accumbens tract integrity and impulsive tendencies (measured by the Urgency Premeditation Perseverance and Sensation Seeking impulsive behavior total score) in a sample of healthy subjects. They found that impulsive behavior is predicted by accumbens tract integrity.

In several types of abuse/dependence disorders structural, microstructural, functional and electrophysiological alterations, have been demonstrated. For example, in methamphetamine users Uhlmann et al. (2016) reported that high levels of self-report impulsivity were significantly associated to higher frontal white matter integrity and Andres et al. (2016) observed that white matter alterations in the striatum were positively related to greater impulsivity (measured by the Barratt Impulsiveness Scale); in cocaine abuser negative correlations between impulsivity and corpus callosum WM integrity (Moeller et al. 2005) and with inferior frontal WM (Romero et al. 2010) have been demonstrated. Horn et al. (2003) reported functional activation of paralimbic areas during response inhibition in impulsive subjects. Regarding electrophysiological alteration, a positive relationship between impulsive personality trait and motor system excitability during the preparation of self-initiated movements was found by Rossi et al. (2018).

The association between impulsivity, alcohol dependence and brain alterations has been well investigated. Herting et al. (2010) reported a negative correlation of FA values in the inferior longitudinal fasciculus and the optic radiation with greater impulsivity assessed by a delay discounting task in youth with family history of alcohol abuse, which suggests that WM integrity may act as an intrinsic risk factor for alcohol use disorder (for a review see O'Halloran et al. 2017). Burnette et al. (2019) observed that functional neural activation in frontostriatal regions in response to alcohol cues was related with a measure of impulsivity trait. Increased blood oxygen level dependent signal in the mesolimbic reward system (Vollstädt-Klein et al. 2010), and increased spontaneous brain activity in the beta frequency band (Herrera-Diaz et al. 2016), were also described in alcohol dependent patients. Wang et al. (2016) in alcohol dependent patients have demonstrated both grey matter and white matter alterations in the mesocorticolimbic system also linked with abnormal impulsivity.

In adolescents with internet gaming disorder Du et al. (2017) demonstrated positive correlation between WM integrity and impulsivity, consistently with studies on delay discounting in healthy young subjects (Olson et al. 2009).

To the best of our knowledge, no studies specifically investigated the white matter abnormalities related to high

impulsivity, as assessed by an objective test, on a large sample of healthy participants. Therefore, the present study aims to investigate brain structural and microstructural abnormalities between high-scoring and low-scoring impulsivity groups, assessed by a Delay Discounting task examining the interplay between reward processing and temporal processing, in a large cohort of healthy subjects.

Materials and methods

Subjects

The Human Connectome Project (HCP) public is a dataset that includes high-resolution Magnetic Resonance Imaging (MRI) scans from healthy adults. Pre-processed structural and diffusion MRI as well as demographic, clinical and personality data from 1206 participants from the 'S1200 Subjects release' were obtained from the HCP public repository (<https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release>), informed consent was obtained for all participants (consent procedure detailed in Van Essen et al. 2013). All subjects were young and healthy adults (n: 1206; 656 females; mean age: 28.8 ± 3.5 ; age-range: 22–36). Sample size was filtered for left handedness, completion delay discounting test, and completion full structural and diffusion MRI sessions, determining a sample size of 1007 subjects (553 females, mean age 28.9 ± 3.6 ; 22–36 age-range). Impulsive and non-impulsive subjects have been defined according to their behavioral measures, as described in statistical analyses section.

MRI scanning and pre-processing

HCP structural MRIs were collected from a 3-Tesla Siemens Skyra unit (housed at Washington University in St. Louis) using an axial 3D-T1-weighted sequence (TR = 2400 ms, TE = 2.14 ms, flip angle = 8° , voxel-size $0.7 \times 0.7 \times 0.7$ mm). Diffusion MRI (dMRI) was performed using a Spin-echo EPI sequence (TR = 5520 ms, TE = 89.5 ms, flip angle = 78° , voxel-size $1.25 \times 1.25 \times 1.25$ mm, b-values = 1000, 2000 and 3000 s/mm²). Structural images were also reviewed for incidental brain abnormalities by a neuroradiologist. All MRI data were pre-processed using the Version 3 of the pre-processing pipelines. These pipelines are freely available from HCP public repository and Connectome Workbench image analysis suites that are discussed in detail in Glasser et al. (2013) and in the HCP Reference Manual, Chapter 4: HCP Processing Pipeline (Jenkinson et al. 2012; Glasser et al. 2013).

Brain morphometry

Brain morphological parameters including surface area and cortical volume were calculated using pre-processed and pre-segmented HCP data. To map all subjects' brains to a common space, reconstructed surfaces were registered to Desikan-Killiany atlas using a non-linear procedure that optimally aligned sulcal and gyral features across subjects (Fischl et al. 1999).

Brain diffusion

As a marker for white matter (WM) integrity, fractional anisotropy (FA) is a useful quantity to compare across subjects as it is computable voxelwise and is a scalar value that is independent of the local fibre orientation. For each subject, dMRI data were collected with both L/R and R/L phase encodings using the same gradient table, which were then merged into a single copy of dMRI data after the correction of distortions with the HCP pre-processing pipeline (Glasser et al. 2013). Diffusion tensor for the calculation of FA metric has been estimated using iteratively reweighted linear least squares (Veraart et al. 2013) implemented in MRTrix suite, version 3.0. All the brain diffusion data were normalized in MNI space as estimated within the freesurfer pipeline; FA maps with b-value 1000 were chosen as a default measure for every subject.

Behavioral measures

The HCP collects many behavioral measures developed for the NIH Toolbox Assessment of Neurological and Behavioral function and several additional measures to assess domains not covered by the NIH Toolbox. Delay Discounting test was selected, that describes the undervaluing of rewards that are delayed in time. A version of the discounting task that identifies 'indifference points' at which a person is equally likely to choose a smaller reward (e.g., \$100) sooner versus a larger reward later (e.g., \$200 in 3 years) was used. Based on the work of Green and Myerson (Estle et al. 2006; Green et al. 2007), they use an adjusting-amount approach, in which delays are fixed and reward amounts are adjusted on a trial-by-trial basis based on participants' choices. This approach has been repeatedly validated to provide reliable estimates of delay discounting (Estle et al. 2006). As a summary measure, we use an area-under-the-curve discounting measure (AUC) that provides a valid and reliable index of how steeply an individual discount delayed rewards (Myerson et al. 2001). AUC provides a score based on how quickly a subject switches to immediate smaller rewards as opposed to delayed larger rewards; the lower scores reflect an impulsive choice and the higher scores reflect non-impulsive

choice. HCP database provides delay discounting test with two rewards: 40.000\$ and 200\$.

Statistical analyses

A Shapiro-Wilk test was performed to assess normal distribution of the subjects in the two conditions; Only for 40.000\$ reward condition, subjects were normally distributed, and were chosen for the analyses in order to obtain homogeneous groups. In order to determine two groups of subjects, 40.000\$ test scores were progressively ordered from lower to higher (0–1), identifying impulsive group in the first quartile (0–0.25; $n = 224$), and not impulsive group in the third quartile (0.75–1; $n = 274$).

A Pearson correlation analysis was performed between the task score in all subjects with age, gender, brain surface areas and grey matter volumes. Furthermore, a two tailed two samples t-test, corrected for Bonferroni multiple comparisons (significant p value < 0.0004) was performed to compare brain morphological parameters in both groups. HCP database provides brain morphological parameters in pre-segmented parcel derived from freesurfer analysis, so in order to keep an original data from raw HCP database, no further voxel-wise analysis was performed with morphological parameters.

Regarding spatially normalized diffusion data, a voxel-wise analysis, two-sample t-test, corrected for family-wise error rate (FWE) (significant FWE p value < 0.05) was performed, with SPM toolbox (<https://www.fil.ion.ucl.ac.uk/spm/>), on FA maps derived from impulsive vs not impulsive group. A white matter mask containing voxels with WM probability greater than 0.3 was used to exclude voxels belonging to gray matter. The population-based, DTI cerebral WM tract atlas developed in John Hopkins University and distributed with FSL (Wakana et al. 2004) was used to anatomically localize significant clusters along major WM tracts.

Results

Brain morphometry & behavioral measures

In 40.000\$ condition, group analysis showed significant lower morphometric brain data in the impulsive compared to the not impulsive group: areas that survived at multiple comparisons test were left lingual, left and right middle temporal, left precentral, left and right superior parietal, right entorhinal, right inferior temporal; significantly decreased volumes were left and right entorhinal, left and right lingual left and right middle temporal, left postcentral, right banks of superior temporal sulcus, right fusiform, right inferior temporal, right lateral orbitofrontal, right parahippocampal, right superior

parietal (Table 1). No significant correlation was found between age, gender, area and volumetric data with task scores.

Brain diffusion

In 40,000\$ conditions significant differences were found in FA values voxelwise analysis between impulsive and not impulsive group. Impulsive group presents higher FA values in four significant clusters: brain stem, corresponding to bilateral medial lemniscus and midbrain reticular formation ($p = 1.2E-09$); right superior longitudinal fasciculus ($p = 0.008$); left forceps major ($p = 0.005$); right corticospinal tract ($p = 0.024$) (Table 2; Fig. 1). On the other hand, not impulsive group has higher FA values in two significant clusters: right and left anterior thalamus radiation ($p = 2.5E-07$ and 0.005) (Table 2; Fig. 2).

Discussion

The aim of the present study was to investigate morphometric and microstructural characteristics between high- and low-scoring impulsivity in a large sample of healthy subjects. According to the Delay Discounting task response participants were differentiated in impulsive and not impulsive groups. Similarly to previous research, age, gender and neuroanatomical measures produced no differences in impulsivity tendencies (Steward et al. 2017).

Differences in brain areas and volumes between the two samples of subjects were detected. Several previous studies have been conducted for investigating neurofunctional bases of impulsivity, but discordant results were presented. Both reduced gray matter volume (GMV) in prefrontal cortex (Bjork et al. 2009), superior frontal gyrus (Schwartz et al. 2010) and putamen (Dombrovski et al. 2012; Cho et al. 2013) and higher GMV in the ventral striatum, superior frontal gyrus (Schwartz et al. 2010), prefrontal cortex, and its medial portion, and anterior cingulate cortex (Cho et al. 2013; Wang et al. 2017) were reported in highly impulsive subjects. Here, more impulsive preference, as indexed by higher discounting, was associated with diminished brain areas and volumes of several regions. Relative to previous reports on brain structural volumes, the effects observed here were more widespread across the cortex, the use of larger sample of subjects could account for this heterogeneous and larger effect.

Impulsivity and decision making are complex processes involving interaction among multiple subsystems governed by different parameters. In particular, impulsive decision-making suggests not properly considering actions consequences, reflecting a process based on emotional and not on rational evaluation (Moeller et al. 2001). Decision-making has been found impaired in some pathologies as addiction (Hester and Garavan 2004), gambling (Cavedini et al. 2002) and some psychiatric disorders (Moeller et al. 2001; Alicata et al. 2009; Lederer et al. 2016).

Table 1 Brain morphological differences between impulsive (Q1) and not impulsive (Q3) groups; area values are expressed in mm^2 , volume values are expressed in mm^3

	Brain parcels	Q1 mean \pm SD	Q3 mean \pm SD	p
Surface Area	Left Precentral	4701 \pm 487	4883 \pm 571	0,0001
	Left Superiorparietal	5341 \pm 629	5564 \pm 716	0,0002
	Left Middletemporal	3057 \pm 396	3224 \pm 439	0,0000
	Left Lingual	3016 \pm 406	3151 \pm 446	0,0004
	Right Superiorparietal	5348 \pm 645	5573 \pm 667	0,0001
	Right Inferiortemporal	3165 \pm 490	3336 \pm 498	0,0001
	Right Middletemporal	3406 \pm 469	3557 \pm 460	0,0003
	Right Entorhinal	345 \pm 76	372 \pm 92	0,0003
Cortical Volume	Left Postcentral	10,258 \pm 1377	10,708 \pm 1361	0,0003
	Left Entorhinal	1751 \pm 338	1896 \pm 361	0,0000
	Left Middletemporal	11,193 \pm 1512	11,910 \pm 1657	0,0000
	Left Lingual	7256 \pm 1094	7681 \pm 1205	0,0000
	Right Lateralorbitofrontal	7929 \pm 1002	8257 \pm 1033	0,0004
	Right Superiorparietal	13,764 \pm 1817	14,325 \pm 1684	0,0004
	Right Fusiform	10,495 \pm 1434	11,040 \pm 1617	0,0001
	Right Inferiortemporal	11,150 \pm 1922	11,829 \pm 1868	0,0001
	Right Banks of Superiortemporal Sulcus	2638 \pm 451	2801 \pm 472	0,0001
	Right Entorhinal	1564 \pm 336	1712 \pm 389	0,0000
	Right Middletemporal	12,719 \pm 1911	13,434 \pm 1760	0,0000
	Right Parahippocampal	2053 \pm 301	2174 \pm 310	0,0000
	Right Lingual	7369 \pm 1039	7769 \pm 1164	0,0001

Table 2 Significant clusters in FA group analysis with p value corrected, number of voxels for each cluster, T-score and MNI coordinates of the cluster peak

Q1 > Q3	p (FWE-corr)	N. voxels	T-score	Peak coordinates		
Medial Lemniscus	1,2E-09	543	5738	6	-28	-17
R_SLF	0,008	130	4266	30	15	24
L_FM	0,005	140	4266	-23	-59	18
R_CT	0,024	109	4088	16	-21	53
Q3 > Q1						
R_ATR	2,5E-07	383	5483	9	-10	11
L_ATR	0,005	138	4815	9	-6	12

R_SLF = right superior longitudinal fasciculus; L_FM = left forceps major; R_CT = right corticospinal tract; R_ATR = right anterior thalamus radiation; L_ATR = left anterior thalamus radiation

We found reduced area and volume in impulsive subjects for the orbitofrontal cortex (OFC), one of the core structures in impulsivity, being site, together with the striatum, of mental representation of the incentive values of different kinds of reward (Kable and Glimcher 2009; Chib et al. 2009; Peters and Buchel 2010). The OFC plays a crucial role in reward and punishment processing (O'Doherty et al. 2001; O'Doherty 2004) and in top-down control (Elliott and Deakin 2005) and its alteration might be a shared neural substrate underlying impulsivity (Blair, 2004). This finding, in line with previous data that reported association between the OFC and delayed

reward discounting (Jiang et al. 2015; Bjork et al. 2009; Mohammadi et al. 2015; Wang et al. 2017) confirms the pivotal role in controlling impulsive behavior and in monitoring and updating the representation of the expected rewards. Indeed, OFC reduced volume could be responsible for a less accurate evaluation of reward.

We also found that parahippocampal volume was reduced in impulsive subjects relative to not impulsive subjects. Recent evidences by Gupta et al. (2010) reported impaired decision-making following hippocampal damage and stated that hippocampal-prefrontal cortex interaction results in a

Fig. 1 Significant clusters in FA group analysis overlaid with 2 mm T1 normalized in MNI space

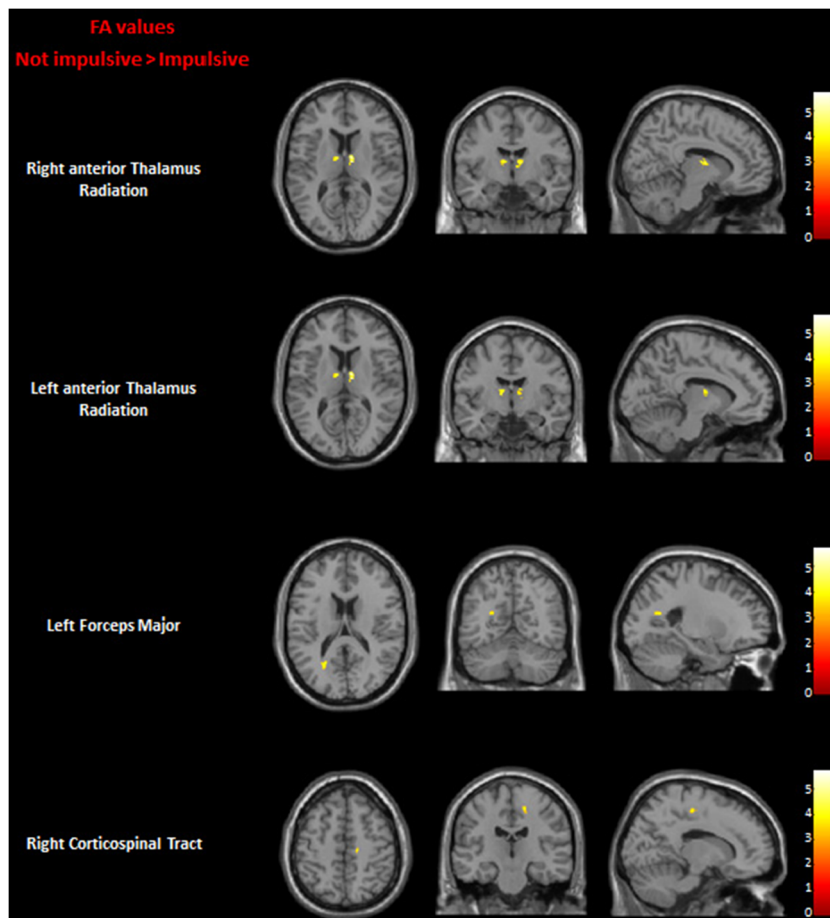
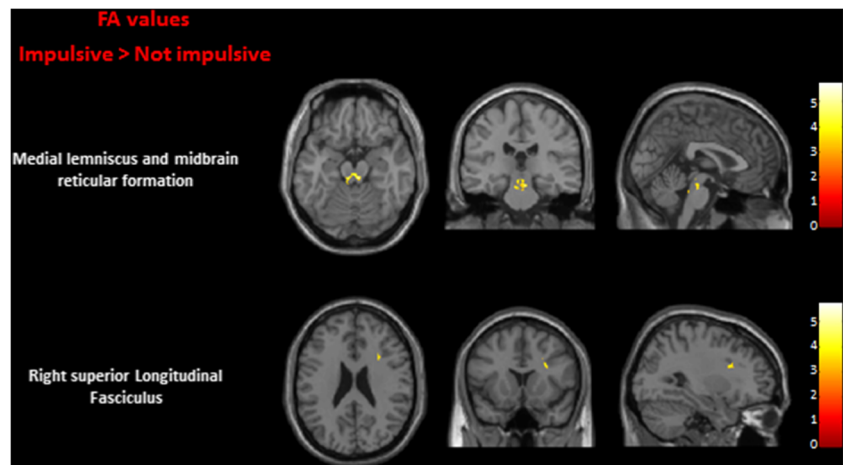


Fig. 2 Significant clusters in FA group analysis overlaid with 2 mm T1 normalized in MNI space



prospection network (Peters and Buchel 2010). The diminished volume of both regions in impulsive subjects sustains the idea about a responsibility for impaired evaluation of future-rewards and difficulty in making a more conservative choice. These data support that striatal interactions with the prefrontal cortex and the hippocampus are central to impulsivity. OFC and hippocampus (among ventral striatum posterior cingulate) are part of those areas more activated by choices with immediate rewards according to McClure et al. (2004). The authors hypothesized that short-run impatience is driven by the limbic system which preferentially responds to immediate rewards and is less sensitive to the value of future rewards. Conversely, long-run patience is mediated by the lateral prefrontal cortex and associated structures, able to evaluate trade-offs between rewards, including those in the more distant future. Results of Jiang et al. (2015) indicated that cortical thickness of the OFC, fusiform and parahippocampal gyri was associated with higher level of impulsivity.

The ability to postpone rewards in a more distant future is expression of cognitive control, a process based on goal-directed behavior and supported by brain interactions as fronto-parietal network, related with decision-making processing (Sanfey et al. 2006). Reduced bilateral superior parietal volume evidenced in the present study probably contribute to the difficulty in inhibiting the impulse to choose smaller more immediate rewards instead of a greater later one.

Owens et al. (2017) reported in delayed reward discounting decision making atrophy in precentral and postcentral regions, entorhinal cortex, lingual and fusiform gyri. Jiang et al. (2015) found that callous-unemotional personality trait was inversely related with fusiform and lingual gyri, they found diminished volume of the inferior temporal cortex including the fusiform gyrus as well as the precentral area. Also, Kubera et al. (2018) in a sample of non-demented patients with Parkinson disease reported that cortical thickness in precentral area was significantly associated with the Barratt Impulsiveness Scale, probably due to impaired inhibitory cognitive control that leads to a proactive impulse control. A recent study by Gavazzi et al.

(2019) explored with fMRI the “readiness” period (subjects were waiting and preparing a motor response) during a GoNoGo task. They found a positive correlation between motor impulsivity scores and the activation of motor cortices. This result indicates that motor impulsivity trait might be associated with a disinhibition of the motor system in impulsive people.

Aberrant cortical motor regions, like the precentral cortex, may weaken the control-motor circuit, thereby resulting in a poor regulation of impulsive behavior. As for microstructural analysis, impulsive subjects displayed higher FA values in midbrain regions, including ascending reticular formation and bilateral medial lemniscus tracts. Ascending reticular activating system also known as extrathalamic control modulatory system, is crucial to maintain behavioral arousal and consciousness, mediating various levels of alertness (Jones 2008). Although its role has not clearly been identified, midbrain reticular formation dysregulation has been postulated in many neurological and psychiatric diseases characterized by arousal disturbances (GarciaRill 1997). Moreover, compulsive behavior seems linked to excessive stimulation of arousal and reticular formation (Mills 1985; Siegel and Victoroff 2009). The highly significant alteration detected in microstructural properties of midbrain reticular formation can sustain an altered communication within impulsivity network circuitry. Instead, medial lemniscus tract is involved in somatosensory perception and responsible of transferring sensory information of proprioception (Navarro-Orozco and Bollu 2019). These data, together with higher FA values in impulsive subjects also in the corona radiate, part of cortico-spinal tract, and probably with the reduced grey matter in the primary motor and sensory cortices, could reflect the motor hyperactivity manifestation of impulsivity trait. Correlation between impulsivity and FA values of the cortico-spinal tract has also been observed in adolescents with internet gaming disorder, that could reflect potential WM microstructural changes associated to greater impulsivity in this disorder (Du et al. 2017).

In addition to the sensory and motor systems involvement, also visuo-spatial abilities seem to be involved, since higher FA values were found in the superior longitudinal fasciculus and in the left forceps that connects visual occipital areas. By contrast, not impulsive subjects had higher FA values in the anterior thalamic radiation projecting to frontal lobes, that could reflect greater ability to reduce action triggered by impulsive stimuli; this was in agreement with a previous paper on the correlation between accumbo-frontal projections and impulsivity trait (Ikuta et al. 2018). Our data contribute to address the question about if the maturation of prefrontal-striatal white matter connections contributes to predict future oriented choices across development. Investigating white matter, Achterberg et al. (2016) suggested that stronger prefrontal-striatal interaction can mediate and predict the ability in delay gratification, leading to less impulsive choices. Since higher fronto-striatal WM integrity is associated with increased preference for delayed rewards in adults (Peper et al. 2013) and adolescents (van den Bos et al. 2015), our results support the idea that an alteration of this white matter tract integrity could result in the de-generation of ability in preferring delayed rewards.

The present study has several limitations. Firstly, impulsivity is a multi-faced construct and here we investigated only impulsive decision-making measured through the delay discounting task. Therefore, our findings cannot be generalized to encompass all impulsivity components. Nevertheless, neuroimaging studies have investigated the neural bases of the other components, demonstrating neural correlates of motor impulsivity (Hampton et al. 2017), response inhibition (Bari and Robbins 2013) and impulsivity trait (McDonald et al. 2017). Secondly, literature provides a poor characterization of brainstem areas and functions, probably due to the limited MR spatial resolution for these very small and few outlined structures, mainly for functional studies, thus limiting our interpretation results. Furthermore, the present study evaluates specifically microstructural data, not providing functional results. Even if this could be considered a limitation, it should be taken into account that functional analyses are more frequently used, in fact, a lot of studies provide functional data instead of those that investigate microstructural alterations. In order to a better understanding of how neurofunctional mechanisms subtend to impulsivity, it could be useful to focus future studies on the correlation between functional and structural data, together with behavioral information. Among structural analyses, it could be interesting to use the tractography, in order to study potential alterations of connections across the different impulsivity-related disorders.

Concluding, magnetic resonance imaging data support the hypothesis that impulsivity manifestations, namely behavioral, motor and cognitive, result from an alteration of different cortical and brainstem areas. These differences include macroscopic and microstructural brain modifications, identifying

new neuroanatomical substrates for multidimensional impulsivity construct in a large sample of healthy subjects.

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Compliance with ethical standards

Conflict of interest The authors declare that they had no financial or non-financial conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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