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Research Report

White matter abnormalities in the amputation variant of body integrity dysphoria

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ABSTRACT

"Body integrity dysphoria" (BID) is a severe condition affecting nonpsychotic individuals. In the amputation variant of BID, a limb may be experienced as not being part of the body, despite normal anatomical development and intact sensorimotor functions. We previously demonstrated altered brain structural (gray matter) and functional connectivity in 16 men with BID with a long-lasting and exclusive desire for left leg amputation. Here, we aimed to identify, in the same sample, altered patterns of white matter structural connectivity. Fractional anisotropy (FA), derived from diffusion tensor imaging data, was considered as a measure of structural connectivity. Results showed reduced structural connectivity of: (i) the right superior parietal lobule (rSPL) with the right cuneus, with the superior occipital and with the posterior cingulate gyri, (ii) the pars orbitalis of the right middle frontal gyrus (rMFGOrb) with the putamen, and (iii) the left middle temporal gyrus (lMTG) with the pars triangularis of the left inferior frontal gyrus. Increased connectivity was found between the right paracentral lobule (rPLC) and the right caudate nucleus. By using a complementary method of investigation, we confirmed and extended previous results from the same sample of individuals with BID, showing structural alterations between areas tuned to the processing of the sensorimotor representations of the affected leg (rPCL), and to higher-order components of bodily representation such as the body image (rSPL) and visual processing. Alongside this network for bodily awareness, other networks such as the limbic

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(rMFGOrb) and the mirror (lMTG) systems showed alterations in structural connectivity. These findings consolidate current understanding of the neural correlates of the amputation variant of BID, which might in turn guide diagnostics and rehabilitative treatments.

1. Introduction

"Body integrity dysphoria" (BID) represents a heterogeneous class of disorders characterized by dissatisfaction with the ordinal body morphology or functionality in nonpsychotic individuals (Brugger et al., 2016). In its most commonly researched form, one limb can be experienced as not being part of the body despite healthy anatomical development and intact sensorimotor functions (Stone et al., 2020). This feeling often leads to the desire for its amputation. While human beings commonly fear the idea of having a limb removed (Rozin et al., 2009), paradoxically, in BID individuals, the desired amputation would let them "*feel more complete*" (First, 2005). BID onset is typically in early childhood, or the desire has been lasting "for as long as the individual can remember" (Brugger et al., 2016). An exacerbation of the condition is sometimes seen at age 30–50 years, when the desire may be so distressing that the affected individuals might engage in hazardous behaviors like self-amputation (Sedda & Bottini, 2014). Individuals with BID often engage in the mimicking of the status of an amputee by moving in a wheelchair, using crutches, or binding up the affected limb (i.e., pretending behavior) (First & Fisher, 2012), which can result in harmful consequences such as reduced blood supply to the affected limb. The prevalence of the disorder in the general population is unknown. However, although systematic epidemiological and clinical studies on BID are still lacking, BID has been found to be more common in men than in women and to predominately affect only one side of the body, typically the left lower limb (Brugger et al., 2016). BID individuals may also exhibit unusual erotic attraction to amputees lacking the limb, which is not felt to be part of their own body (Ramachandran et al., 2009). They may be sexually aroused by picturing themselves as an amputee (Blom et al., 2017). This feature has led to the initial conception of BID as a paraphilia (see *apotemnophilia*; Money et al., 1977). BID has also been referred to as a neurological syndrome (*xenomelia*; McGeoch et al., 2011), a personality disorder (*BIID;* First, 2005), or an internet-induced madness (Charland, 2004). Only very recently, in the release of the 11th Revision of the International Classification of Diseases (ICD 11), BID has been included in an official diagnostic manual, where it is listed among the developmental disorders and labelled a "disorder of bodily distress or bodily experience" (ICD-11). As specific diagnostic criteria and effective treatments still await to be identified, and the suffering of BID individuals is persistently high, there is a pressing need for more research. Indeed, to date, psychotherapeutic treatments alone have proven ineffective or produced controversial effects on alleviating BID symptoms (Blom et al., 2012). In an online survey conducted in 54 BID individuals, Blom et al. (2012) found that psychotherapy was often supportive and that antidepressants (but not antipsychotics) acted to mitigate the BID-related depressive symptoms. Still, neither approach modulated the core symptoms of BID. The only treatment that, according to the authors, proved effective was actual amputation, as all those who underwent an amputation (7 out of the 54 examined cases) reported no longer experiencing BID symptoms. However, amputation of a healthy limb comes with certain health risks for the individual and constitutes a significant burden for the health system and society in general. The study of the neural correlates of BID can at the same time advance the understanding of BID and potentially inform new alternative treatments. For instance, by pinpointing altered neural patterns, it might be possible to tune these toward more neurotypical patterns through the application of noninvasive and nonharmful therapeutic intervention such as transcranial magnetic stimulation, brain-computer-interfaces, or neurofeedback (Chakraborty et al., 2021; Ros et al., 2014).

Pioneering neuroimaging studies in individuals with BID described functional and structural alterations of the right superior parietal lobule (rSPL) and the left premotor cortex (lPMV; Hänggi et al., 2017; Hilti et al., 2013; McGeoch et al., 2011; van Dijk et al., 2013). We recently extended these findings in the most extensive neuroimaging BID study to date (Saetta et al., 2020). We gathered data on local structural changes and functional connectivity from 16 affected men with a homogenous manifestation of BID. That is, the long-lasting and exclusive desire to have the left leg amputated. The homogeneous and relatively large sample in our study allowed for the delineation of specific brain network anomalies associated with the lack of ownership over a single limb and the desire for its amputation, whereby previous studies focused on small samples of individuals with different limbs as targets of the amputation. The results led to the first comprehensive model for the neural underpinnings of BID, suggesting (i) reduced intrinsic functional connectivity of the primary sensorimotor area hosting the "to-be removed" leg representations and the right paracentral lobule (rPCL, Saetta et al., 2020), suggesting that the feeling of non-belonging relates to a deficit in transferring information from the primary sensorimotor regions to higher-level cortical hubs for body processing; (ii) anomalies of the lPMV (Blom et al., 2016; van Dijk et al., 2013; Saetta et al., 2020), which is thought to integrate the visual, motor, and tactile information about the affected limb into a coherent and unitary body representation (Ehrsson et al., 2005); (iii) structural and functional abnormalities of the rSPL as a crucial neural correlate of body image, that is, the conscious representation or visual template of one's body size and shape (Hilti et al., 2013; McGeoch et al., 2011; Ramachandran et al., 2009; Saetta et al., 2020). Outside of this network for sensorimotor and high-level bodily processing, a growing body of research suggests that the reward system and limbic circuitry may be altered in BID. Oddo-Sommerfeld et al. (2018) showed a heightened activity of the nucleus caudautus when individuals with BID looked at an image of themselves in the desired bodily state as compared to a control group. Moreover, the left orbito-frontal cortex (lOrbFG) as a key hub involved in both limbic and reward systems showed reduced intrinsic functional connectivity (Saetta et al., 2020). Other brain regions functionally altered in BID are the left superior and middle temporal gyri (lTG, Oddo-Sommerfeld et al., 2018; Saetta et al., 2020). These areas have often been linked to the mirror network. This network scaffolds the capacity to share others' actions and emotions by their simulation through one's own sensorimotor and affective systems (Gallese, 2007), and thus providing a potential neural basis for empathy (Bernhardt & Singer, 2012; Corradini & Antonietti, 2013; Gonzalez-Liencres et al., 2013; Pacella et al., 2017; Shamay-Tsoory, 2011).

However, as mentioned in a commentary by Longo (2020), even though our previous study (Saetta et al., 2020) had far-reaching implications for the understanding of BID, the analyses performed were primarily explorative. This calls for more hypothesis-driven neuroimaging studies spanning multiple methods of investigation to obtain a clearer picture of this multifaceted disorder. The current study takes a leap forward in this direction, identifying altered white matter structural connectivity (i.e., the anatomical connections between brain regions) in the same relatively large and homogenous sample of BID individuals. We quantified fractional anisotropy (FA) as a measure of structural connectivity derived from diffusion tensor imaging data (DTI, Pierpaoli et al., 1996).

Based on our own previous findings, we conceptualize BID as a network disorder, and hence warrant investigation of the physical connectivity between network components.

We expected structural connectivity abnormalities between the fronto-parietal hubs that we previously found to present with alterations in intrinsic functional connectivity in BID compared to controls: the rPCL, the rSPL, the lOrbFG, the lTG (Saetta et al., 2020). Additionally, given the implication in the limbic and reward systems (for a recent review, see Palomero-Gallagher & Amunts, 2021), which has been suggested to be fundamentally altered in BID, the right-hemisphere homologue of the lOrbFG was included.

2. Methods

2.1. Participants

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

The targeted number of participants consisted, in line with previous study (Saetta et al., 2020) and in view of the difficulties recruiting BID participants, of $n = 16$ for the BID group and $n = 16$ for the control group. Eligibility criteria were: (i) age range: 18–70 years; (ii) informed consent as documented by signature, gender: male, female, nonbinary; (iii) specifically for the BID group: individuals with a self-reported desire for unilateral amputation of the left leg (without having yet undergone an amputation); specifically for the healthy controls group: fully limbed, no desire for limb amputation.

The presence of any of the following criteria led to exclusion of the participant: presence of major psychiatric or neurological disorders (other than BID in the BID group). Known or suspected noncompliance, drug, or alcohol abuse (no objective test, but reliance on participants' report).

No participant was excluded. The BID sample was the same as that recruited for our previous study (Saetta et al., 2020), and consisted of 16 men with the specific desire for amputation of the left leg (Mean age = 44.38, SD = 12.32, range = 28–67; mean formal education in years = 16.06, SD = 2.28, range = 13–18). Recruitment of BID individuals was performed through advertisements published on this website: http://www.biid-dach.org/. Neuroimaging data from eight BID individuals were collected at the Department of Neuroradiology of the University Hospital of Zurich. Data from the other eight BID were collected at the Neuroradiology Department of the "ASST Grande Ospedale Metropolitano Niguarda" of Milan.

Sixteen healthy men functioned as controls (15/16 were the same recruited in the previous study, 1/16 was newly recruited as DTI data from one participant were not available). Controls were matched pair-wise to the BID individuals by age (mean age = 44.18, SD = 9.51, range = 30–62 sec, paired t-test: $t(15) = .06$, $p = .95$), years of formal education (mean formal education in years = 15.63, SD = 2.89, range = 9.5–18, paired t-test: $t(15) = .39$, $p = .70$), and by scanner used for neuroimaging data acquisition (see below).

Informed consent was provided by participants prior to participation in the study, which had been approved by the Ethics Committee of the University Hospital of Zurich and by the Ethical Committee Milano Area C. The study was carried out according to the Helsinki declaration guidelines. No part of the study procedures and study analysis was pre-registered prior to the research being conducted.

2.2. Clinical assessments and questionnaires

As described in our previous studies (Hilti et al., 2013; Saetta et al., 2020), the presence of any neurological, psychiatric, and neuropsychological disorders was formally assessed in all participants through standard examination and validated instruments. BID individuals additionally underwent the 2-h structured clinical interview for DSM-IV (Wittchen et al., 1997). Clinical examinations proved normal in both the control and the BID participants. A complete list of the performed tests is available in the supplementary materials.

The clinical features of the desire for amputation were formally assessed through the 12-items Zurich Xenomelia Scale and its three subscores (Aoyama et al., 2012): "pure desire" (i.e., identity restoration as the primary goal of the desired amputation), "erotic attraction" (i.e., sexual preference toward amputated bodies), and "pretending" (i.e., the habit to simulate the desired body state by binding upon the undesired leg or using wheelchairs or crutches for locomotion). Each of the three subscores is computed by the mean of four items. For each item, answers are provided on a six-points Likert-scale with 1 and 6 indicating, respectively, the least and greatest strong expression of the critical behavior or thought. Half of the items of each subscale are reverse-scored. The total score is the mean of all 12 items and represents the overall strength of the desire for amputation. Legal copyright restrictions prevent public archiving of the various assessment instruments and tests used in this study, which can be obtained from the copyright holders in the cited reference (Aoyama et al., 2012).

2.3. Diffusion weighted images data acquisition

Diffusion weighted images (DWI) were acquired at two separate sites: the Department of Neuroradiology of the University Hospital of Zurich [Zurich dataset, $n = 16$ (8 BID, 8 controls)], and the Neuroradiology Department of the "ASST Grande Ospedale Metropolitano Niguarda" of Milan [Milan dataset, $n = 16$ (8 BID, 8 controls)]. The Zurich dataset was acquired on a 3.0 T Philips Achieva whole-body MRI scanner with an eight-channel head coil. Two identical diffusion-weighted sequences were acquired with a spatial resolution of $2 \times 2 \times 2$ mm^3 (matrix: 112×112 pixels, 75 slices in transverse plane). Diffusion was measured along 32 noncollinear directions ($b = 1.000$ sec/mm^2) preceded by a non-diffusion—weighted volume (reference volume, $b = 0$ sec/mm^2). The field of view was 224×224 mm^2; echo time: 55.0 msec; repetition time: 13.010 sec; flip angle: 90°; SENSE factor: 2.1. Scan time was approximately 8 min 42 sec per sequence. The Milan dataset was acquired on a 1.5 T General Electric (GE) Signa HD-XT scanner. Diffusion was measured upon 35 noncollinear directions ($b = 700$ sec/mm^2) preceded by three non diffusion-weighted volumes (reference volume, $b = 0$ sec/mm^2) with a spatial resolution of $2 \times 2 \times 2$ mm^3.

2.4. DWI analysis

DWI data were processed using ExploreDTI (Leemans et al., 2009). Images were corrected for participant motion and eddy currents using the procedure described in Leemans and Jones (2009). Tensor estimation was then performed using the iteratively reweighted linear least-squares approach (Veraart et al., 2013). Whole-brain deterministic tractography was performed using DTI with a seed point resolution of $2 \times 2 \times 2$ mm, FA threshold of 0.2, maximum tracking angle of 30°, step size 1 mm, minimum fibre length 50 mm and maximum 500 mm. A restricted tractography analysis was performed subsequently in native space to reconstruct streamlines passing through pairs of ROIs that form part of the automated anatomical labelling (AAL) atlas (Rolls et al., 2015). By adopting a hypothesis-driven approach, we looked at reconstructed streamlines between selected ROIs and 90 regions of the AAL covering the whole cerebrum and subcortical structures excluding the cerebellum. These ROIs were: the rSPL (AAL label: 60, Parietal_Sup_R), the rPCL (AAL label: 70, Paracentral_Lobule_R), the left middle temporal gyrus (lMTG) (AAL label: 85, Temporal_Mid_L), the left inferior temporal gyrus (AAL label: 89, Temporal_Inf_L), the left and right inferior frontal gyri, pars orbitalis (AAL labels: 11, Frontal_Inf_Oper_L; 12, Frontal_Inf_Oper_R); and the left and right middle frontal gyri, pars orbitalis (AAL labels: 9, Frontal_Mid_Orb_L; 10, Frontal_Mid_Orb_R).

For each reconstructed streamline, FA was taken as the primary outcome measure. Additionally, the pairs of ROIs for which the number of participants presenting no streamlines was $n > 8$ were excluded from the analyses. This ensured that all the analyses included a minimum of $n = 24$ participants. Data were then manually checked to ensure an approximately equal distribution of missing values in the BID individuals and the control group (see Section 3 for the exact number of included BID and controls participants for each white matter bundle). The FA matrices for each participant are available on the open science forum (OSF, https://osf.io/bdmsr/).

Group analyses were performed in R studio V. 1.3.1093. Data analysis scripts and their associated dataset are available on the OSF (https://osf.io/bdmsr/). Due to ethical barriers preventing public archiving of the raw data, raw scans are not available and cannot be obtained upon request to the corresponding author.

Linear mixed models were fitted using R lme4 package (Bates et al., 2014) and estimated using REML and nloptwrap optimizer. The Wald approximation was used to compute the 95% confidence intervals (CIs) and p-values. A linear mixed model examined the FA values for each ROI pair as a function of the factor "*Group*" (BID individuals vs Controls). The factor "*Scanner*" defining the participants belonging to the Zurich or Milan dataset was modelled as a random factor to account for the data acquisition performed with different scanners (for a similar approach, see Saetta et al., 2020). The tested statistical model was the following:

$$FA = intercept + p + \beta_1(Group) + e$$

where "β_x" stands for the estimated parameter, "e" stands for the residuals, and "p" represents the random intercept for scanner. Importantly, exactly eight versus eight BID and control individuals (matched by sex, age, and formal education) were acquired with the 1.5 T, and eight versus eight BID and control individuals were acquired with the 3 T scanner. This allowed us to effectively control for the factor "scanner" in our statistical analyses.

The altered patterns of FA were exploratively correlated with the Zurich Xenomelia Scale scores through Spearman correlations, given the non-normality of questionnaire data distribution.

3. Results

3.1. DWI analysis

Compared to controls, BID individuals showed significantly reduced FA values for the fibre bundles connecting the right superior parietal lobule and (i) the right cuneus (mean FA BID = .41, $n = 15$, mean FA controls = .49, $n = 15$, $b = .072$, SE = .012, $t(27) = 5.707$, $p < .0001$); (ii) the right superior occipital gyrus (mean FA BID = .42, $n = 16$, mean FA controls = .46, $n = 16$, $b = .049$, SE = .013, $t(29) = 3.742$, $p = .0008$); (iii) right posterior cingulate gyrus (mean FA BID = .47, $n = 12$, mean FA controls = .50, $n = 14$, $b = .029$, SE = .013, $t(24) = 2.119$, $p = .045$). Other ROI pairs with reduced FA values in BID were the following: the pars orbitalis of the middle frontal gyrus and the putamen in the right hemisphere (mean FA BID = .43, $n = 14$, mean FA controls = .45, $n = 15$, $b = .026$, SE = .01, $t(27) = 2.543$, $p = .017$), and the pars triangularis of the inferior frontal gyrus and the middle temporal gyrus in the left hemisphere (mean FA BID = .42, $n = 13$, mean FA controls = .44, $n = 13$, $b = .025$, SE = .011, $t(23) = 2.413$, $p = .024$).

Conversely, BID individuals showed increased FA values for the fibre bundles connecting the rPCL and the right caudate (mean FA BID = .43, mean FA controls = .39, $b = -.034$, SE = .012, $t(22) = -2.812$, $p = .010$).

Results are displayed in Fig. 1 and summarised in Table 1.

Correlations with the Zurich Xenomelia Scale

The mean sub-scores were: pure desire: mean = 5.47, SD = .57; erotic attraction: mean = 4.45, SD = 1.19; pretending: mean = 4.24, SD = .66. Mean total score was 4.70, SD = .58.

The FA values for the fibre bundles connecting the pars triangularis of the inferior frontal gyrus and the middle temporal gyrus in the left hemisphere negatively correlated with the strength of the pure desire for amputation (Spearman's; $r(11) = -.63$; $p = .002$) and the erotic attraction (Spearman's correlation coefficient; $r(11) = -.58$; $p = .036$) as assessed by the Zurich xenomelia scale (see Fig. 2). All the other correlations were not significant.

4. Discussion

The results of the present DTI study, obtained in a homogenous and so far the most substantial sample of BID individuals (Longo, 2020), showed reduced structural connectivity of (i) the rSPL with the cuneus, the superior occipital and posterior cingulate gyri in the right hemisphere; (ii) the rOFC with the putamen, and (iii) the triangular part of the left inferior frontal gyrus with the middle temporal gyrus. Increased structural connectivity was found between the rPCL and the right putamen. These results point to the presence of altered structural connectivity of cortical hubs previously found in the same sample to be functionally altered (Saetta et al., 2020).

In this discussion, we address the altered structural connectivity within different hubs starting with those classically associated with sensorimotor processing and bodily consciousness, before moving to those predominantly involved in other cognitive processes.

Reduced structural connectivity was observed between the rSPL and the right cuneus, the superior occipital gyrus and the posterior cingulate gyrus. Combined tractography and postmortem dissections evidence converge in showing that the connecting pathways between these regions, involved in visual and sensorimotor processing, are the inferior fronto-occipital, longitudinal and the ventral occipital fasciculi, as well as the short association U-fiber (Lin et al., 2021). Our result is compatible with recent accounts regarding BID as a clinical condition that might ensue from unsual visual and sensorimotor processing which instantiate a discrepancy between the body image represented in the rSPL (in BID individuals lacking a limb) and the actual visually perceived "fully-limbed" functional body (McGeoch et al., 2011; Saetta et al., 2020). Accordingly, the binding up of the undesired leg frequently observed during pretending in BID individuals would temporarily solve this discrepancy and alleviate the desire through the adjustment of the *visual* information about the actual body to the body image represented in the rSPL. This conceptual framework might be substantiated by previous correlative evidence showing that the lower the concentration of gray matter in rSPL, the stronger an individual's amputation desire and pretending behaviour (Saetta et al., 2020). In line with this, it has been shown that BID individuals experience a temporary relief from the desire for amputation, when the undesired leg is experimentally made to fade off from visual awareness (i.e., disappearing limb trick, Stone et al., 2018) or while undergoing augmented or virtual reality to transiently adapt the appearance of illusory embodiment to the desired body opening the way for noninvasive therapeutics (Turbyne et al., 2021). We thus suggest that reduced white matter connectivity between the rSPL and visual areas might be linked to the experienced mismatch between phenomenal and physical body.

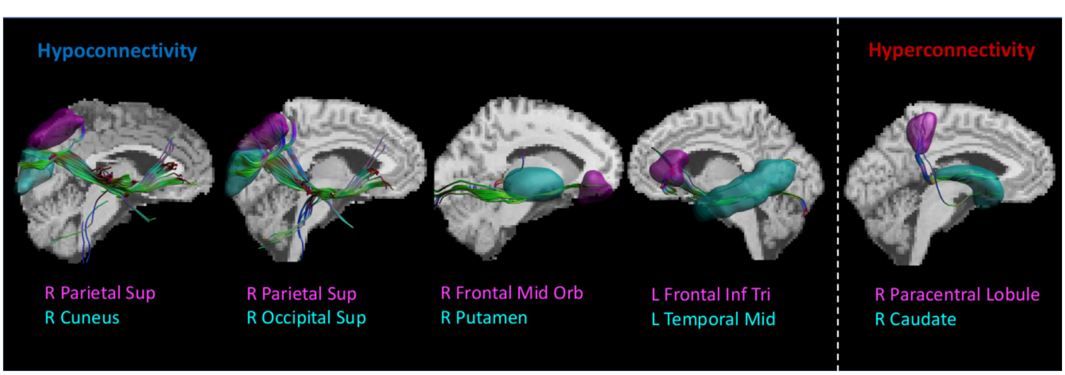

Fig. 1 – White matter pathways significantly altered in BID relative to controls. Reconstructed streamlines superimposed on anatomical white matter template warped to individual subject data. Shown are tract visualizations for a representative healthy control participant. Hypoconnectivity: reduced FA in BID relative to controls; hyperconnectivity: increased FA in BID relative to controls.

Table 1 – Altered fractional anisotropy (FA) in BID compared with controls. Mean FA values and results of the linear mixed model procedure.

White matter fiber bundle	Mean FA in BID	Mean FA in Controls	*b*	SE	*t*	df	*p*
Reduced FA in BID							
Right superior parietal lobule—right cuneus	.41	.49	.072	.012	5.707	27	$p < .0001$
Right superior parietal lobule—right superior occipital gyrus	.42	.46	.049	.013	3.742	29	$p = .0008$
Right superior parietal lobule—right posterior cingulum gyrus	.47	.50	.029	.013	2.119	24	$p = .045$
Right middle orbitofrontal gyrus—right putamen	.43	.45	.026	.01	2.543	27	$p = .017$
Left inferior frontal gyrus, pars triangularis—left middle temporal gyrus	.42	.44	.025	.011	2.413	23	$p = .024$
Increased FA in BID							
Right paracentral lobule—right caudate nucleus	.43	.39	−.034	.012	−2.812	22	$p = .010$

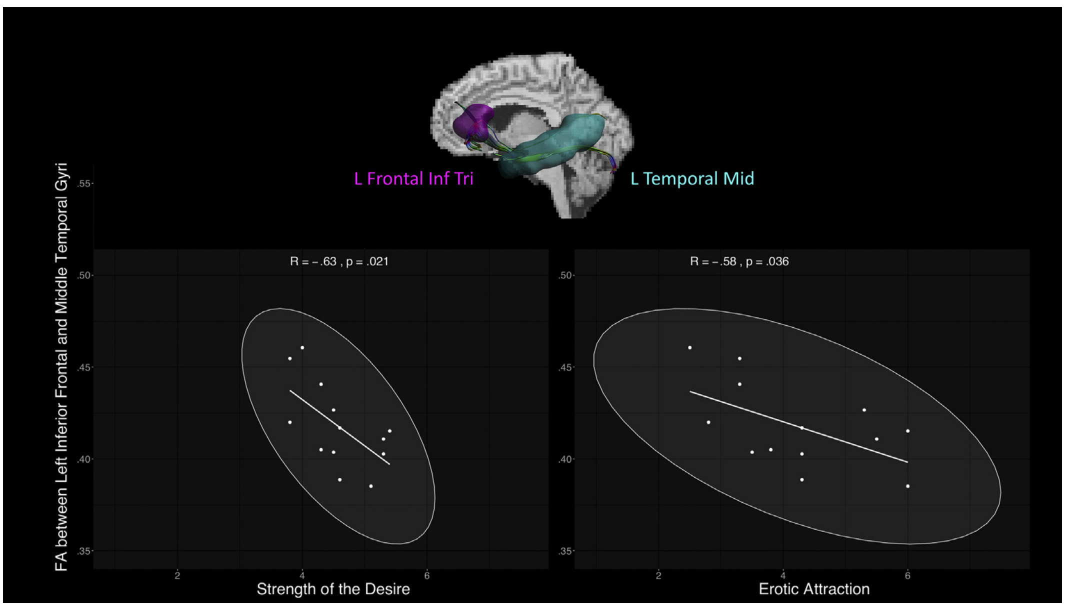

Fig. 2 – Brain-behavior correlation plots. Correlations in the BID sample between fractional anisotropy values between the left inferior frontal gyrus, pars triangularis and the lMTG and: (i) the strength of the desire for amputation (left panel); (ii) the erotic attraction to own and other amputated bodies (right panel).

Alongside this parieto-occipital network's alteration, we found in BID reduced structural connectivity between the middle rOFC and the putamen. This cortico-striatal pathway has been described as the neural substrate for reward-related behaviors (review in Ongür & Price, 2000). Also from an anatomical standpoint both regions present extensive connections with other limbic structures (Ongür & Price, 2000; Price, 2007; Yakovlev & Locke, 1961). Our findings suggesting a coupling with altered structural connectivity between rSPL and visual and extrastriate areas and alterations within the limbic system might be compatible with a compelling, yet speculative, model proposed by Ramachandran et al. (2009). According to this model, the body image in the rSPL would predispose an individual to be more sexually attracted by bodily shapes congruent with this template. The sexual preference would be mediated by the limbic and extrastriate areas, and the connection between them. Thus, on a phenomenal level a body image lacking a limb as observed in BID individuals would determine a sexual preference to amputated bodies. Also in line with Ramachandran's model, in the current study we also found reduced FA in BID in the left uncinate fasciculus traditionally considered, by virtue of its location and connectivity (Von Der Heide et al., 2013) to be part both of the limbic (Hasan et al., 2009) as well as of the mirror systems (Wang et al., 2018), and, more specifically, of a fiber bundle connecting the left inferior frontal gyrus and the middle temporal lobe. Interestingly, while a growing body of research reveals a tight association between the integrity of the left uncinate fasciculus and individual levels of emotional empathy (Parkinson & Wheatley, 2014), alterations in empathic responsivity have been discussed as a social co-determinant of BID. Specifically, an excessive merging of BID individuals' bodily self with that of individuals with an amputation could arguably lead to an overidentification with amputated bodies, a process supposedly mediated by the mirror system (Brugger & Lenggenhager, 2014; Hilti et al., 2013; Macauda et al., 2017). Accordingly, introspective reports of BID individuals show specific differences in the quality and quantity of emotional experiences with others who have a disability during childhood (Money et al., 1977; Obernolte et al., 2015). A large number of BID individuals describe a "trigger event" for their desire for amputation, that is, the sight of an amputee (Brugger, 2011; Hilti et al., 2013; Aoyama et al., 2012). They also report a significantly higher exposure to disabled people in their childhood environment (Obernolte et al., 2015) and eventually start to experience the kind of erotic attraction frequently accompanying BID (Money et al., 1977; Obernolte et al., 2015). One possible explanation for the link between empathic admiration and erotic attraction is tentatively offered in the psychodynamic perspective by Money et al. (1977), who suggested the existence of a "non-erotic imagery of masculine overachievement as providing an erotic turn-on in their amputee fantasies. The over-achievement imagery primarily consisted of amputees overcoming the adversity of a handicap" (p. 125). However, self-report reconstruction of early childhood memories should generally be treated with caution as they could represent an attempt of later rationalization (Gallo, 2010). Still, the negative correlation we found between reduced FA values of a left fronto-temporal bundle, the desire for amputation and, of special interest, also the erotic attraction, may potentially constitute the first neural correlate for the abovementioned link.

Increased FA in BID was found between a cortical-striatal bundle connecting the rPCL and the right caudate nucleus. While the rPCL is involved in the leg sensorimotor processing of the affected limb, the latter region has been consistently found to be implicated in the reward system (review in Grahn et al., 2008). Increased FA in the right caudate and cortical regions has been observed in individuals with an obsessive-compulsive disorder (Lochner et al., 2012; Cannistraro et al., 2007; Fontenelle et al., 2009), a severe condition characterized by recurrent intrusive thoughts, ideas, and impulses also known as "obsessions." We speculate that the desire for an amputation of one's left leg, initially a consequence of a functional disconnection between rPCL and rSPL (Saetta et al., 2020), might develop in to obsessive features through continuous reinforcement induced by the hyperconnectivity of rSPL and the right caudate nucleus. Such assumption remains however speculative, and active-task fMRI studies are needed to test further test such hypothesis.

To summarize, the results of the previous and current studies suggest that BID might reflect multiple alterations of distinct but interconnected neural networks for body processing (including limb representation, multisensory integration, and body image), for emotional and social processing as well as of the reward system.

Our study comes with several limitations. First, the sample size is relatively small. This is due to the rarity and secrecy of the disorder. Only after a decade of cooperation between different international research centers has it been possible to put together a relatively substantial and homogenous database of individuals willing to participate in BID research. Second, and again relating to the challenges and timescale for data acquisition with this rare cohort, the DTI dataset was acquired between 2013 and 2018. Methodology for quantifying white matter microstructure has improved vastly in the intervening time period, meaning that FA is no longer considered the gold standard measure (Alexander et al., 2001; Jeurissen et al., 2013; Tuch et al., 2002). In particular, FA estimates are unreliable in regions that contain crossing fibres, such as the most lateral projections of the corpus callosum (Ruddy et al., 2017) where low FA values may paradoxically reflect densely packed (but directionally incoherent) fibre pathways. This may raise questions regarding the validity of some of our findings using tractography from cortical regions of interest as we were unable to use alternative more high resolution approaches to measure fiber density, limited by the fairly low number of diffusion directions in which data was acquired. Finally, the FA analyses were performed on an already existing dataset of BID individuals. We can not be certain whether these results would generalize from the examined sample to the general BID population.

Also, the focus of the present study was on the amputation variant of BID and therefore, results may not be extended to other BID variants. Future comparative studies between different variants of BID would be desirable.

To conclude, our empirical approach was deliberately limited to uncover the neural mechanisms of BID and relate them to individual phenomenal experience. A more comprehensive approach would consider all the possible nonlinear interactions between biological, psychological, and social factors of this aberrant condition. Only an integrative, cross-disciplinary view that includes the brain, the mind, and society as equally important levels of analysis will eventually lead to further essential advances in understanding a multifaceted disorder such as BID.

Author contributions

Gsae wrote the manuscript. Gsae, BLen, Pbru, Gbot conceptualized the project. BLen, PBru, GBot, acquired fundings. Gsae, Mgan, Lzap, Gsal, Msbe collected the neuroimaging data. Pbru, Gbot, Gsae, Mgan, Blen performed the clinical interview. Gsae, Krud performed data analyses. All authors revised and the manuscript and approved the final version.

Conflict of interest

The authors declare no competing interests.

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Supplementary data

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