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Research paper

Effects of illness duration on cognitive performances in bipolar depression are mediated by white matter microstructure

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ABSTRACT

Background: Cognitive deficits are a core feature of bipolar disorder (BD), and persist during the euthymic phase. White matter (WM) microstructural abnormalities are widely considered a structural marker of BD. Features of illness chronicity, such as illness duration and number of mood episodes, have been associated with worsening of both clinical profile and brain structural alterations. This study examined the role of WM integrity as a possible mediator between illness duration and cognitive performances in a sample of BD patients.

Methods: We assessed 88 inpatients affected by a depressive episode in course of type I BD for verbal memory, visual memory, working memory, visuospatial constructional abilities, psychomotor coordination, executive functions, processing speed, and verbal fluency. White matter integrity was evaluated through FA measurements derived using the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA)-DTI protocol.

Results: The effect of illness duration on processing speed, verbal memory, and visual memory was mediated by the FA values of bilateral anterior corona radiata, bilateral corona radiata, genu of corpus callosum, and fornix, adjusting for age, sex, education and lithium treatment ($p < 0.05$).

Limitations: Potential interaction factors were not examined in this study.

Conclusions: This is the first study to show the role of WM integrity as a mediator of the negative effect of illness duration on cognitive performances. Our data provide new insight into the neuroprogressive hypothesis of BD.

1. Introduction

Cognitive impairment is a core feature of bipolar disorder (BD), especially in the domains of psychomotor speed, verbal memory and executive functions (Bora et al., 2009; Quraishi and Frangou, 2002; Glahn et al., 2007). These deficits affect social and vocational abilities of patients with BD, placing a significant burden on the global functioning (Depp et al., 2012). Cognitive abnormalities have been consistently observed during mood episodes and they are known to persist through remission (Mann-Wrobel et al., 2011; Sachs et al., 2007). Growing evidences support the temporal clinical progression of BD, characterized by an increase in frequency and severity of illness episodes and a decrease in response to treatments (Berk et al., 2011; Schneider et al., 2012; Gildengers et al., 2014; Berk, 2009). Features of illness progression such as illness duration and number of hospitalizations have been positively associated to worsening of neurocognitive performance, along with a shortening of the inter-episode interval, a poorer response to both pharmacological and psychosocial treatments and an increasing risk of suicide (Martinez-Aran et al., 2004; Bearden et al., 2006; Frangou et al., 2005; Delaloye et al., 2011). Several studies have marked the relationship between number of mood episodes and severity of cognitive deficits, suggesting underlying structural and neurophysiological changes (Hellvin et al., 2012; Cardoso et al., 2015a; Passos et al., 2016; Lebowitz et al., 2001). This is supported by the mounting evidence of stage-related structural abnormalities in BD, with cumulative episodes associated to higher white matter (WM) lesions load and ventricular enlargement (Strakowski et al., 2002; Birner et al., 2015) and disease duration with a loss of total grey matter (GM) volumes and thickness (Gildengers et al., 2014; Hallahan et al., 2011a; Lyoo et al., 2006).

Widespread signs of WM alterations in circuitries critical for emotional and cognitive processing are a core biological underpinning of BD psychopathology (Benedetti et al., 2011). Diffusion tensor imaging (DTI) is a MRI technique particularly suited for the study of WM microstructure, providing relevant information about fiber integrity and orientation (Heng et al., 2010). DTI studies have consistently reported subtle microstructural abnormalities of WM in BD, characterized by a loss of WM network connectivity involving not only prefrontal regions but also projection, associative and commissural fiber tracts (Nortje et al., 2013; Wise et al., 2016). Fractional anisotropy (FA) is a DTI derived measure that describes the degree of anisotropy of water diffusion in WM tracts. A diminished FA is thought to reflect compromised

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WM integrity, determined by microstructural changes in the features of the tissue, such as fiber diameter and density and the degree of myelination (Basser and Pierpaoli, 2011). A significant FA decline was reported in elderly patients with long-lasting BD (Haller et al., 2011) and several studies have observed a progressive reduction of FA measures with advancing age in healthy populations (Abe et al., 2002; Nusbaum et al., 2001; O'Sullivan et al., 2004; Sullivan et al., 2001). Thus, considering the above-mentioned findings on the effect of neuroprogression on brain structure, we can hypothesize that FA measures of WM alterations associate to illness duration in individuals affected by BD.

A decline in FA values has been previously found to be associated with processing speed, executive function and memory deficits in healthy controls in frontal, parietal and temporal lobes (Kochunov et al., 2010; Kuznetsova et al., 2016; Turken et al., 2008) and in other psychiatric disorders characterized by cognitive impairments, such as in schizophrenia (Kochunov et al., 2017; Karbasforoushan et al., 2015). Studies connecting DTI measures and cognitive decline in BD are limited, but consistent. Verbal and working memory performances positively correlate to FA values in forceps minor, anterior thalamic radiation and corona radiata (James et al., 2011). Reduced FA in the anterior limb of the internal capsule and uncinated fasciculus was significantly associated to higher number of errors during set shifting and increased risk taking (Linke et al., 2013). Finally, attention and information processing scores extensively associate to FA measures, with signal peaks in forceps major and anterior thalamic radiation (Poletti et al., 2015).

Despite these findings, the association between variables related to illness chronicity, brain structural alteration and cognitive deficits in BD is relatively understudied. More data are needed to disentangle the effects of illness chronicity on WM structure and cognition and the inter-relationship between brain and cognitive age-related trajectories in BD patients. The clinical relevance of these findings is elevated. It can offer a major contribution to define a staging model for BD which allows to deliver personalized treatments and to intervene in the early stages of the disorder with a proper management (Muneer, 2016; Kapczinski et al., 2009). Thus, with an exploratory approach, the aim of this study was to test the role of FA measure of WM integrity as a possible mediator between illness duration and cognitive performances in a sample of bipolar depressed patients.

2. Methods

2.1. Sample

The sample included 88 biologically unrelated inpatients with a diagnosis of Bipolar Disorder I (DSM-IV criteria, SCID-I interview) in course of a depressive episode. Exclusion criteria were: additional diagnoses on axis I, mental retardation on axis II, pregnancy, major medical and neurological disorders, history of drug or alcohol abuse or dependency. Forty-three per cent of patients were taking lithium medication for at least 6 months. Twenty-one per cent of patients had a history of previous delusional episodes but did not experience delusions at the time of the evaluation. Physical examination, laboratory tests and electrocardiograms were performed at admission. No patient received electroconvulsive therapy (ECT) within 6 months prior to study enrolment. After complete description of the study to the subjects, a written informed consent was obtained. All the research activities were approved by the local ethical committee.

2.2. Clinical and neuropsychological assessment

Severity of depression was rated on a modified version of the 21-item Hamilton Depression Rating Scale (HDRS). Cognitive functions have been assessed through the Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004), a broad battery evaluating several domains of cognition (verbal memory, working memory, psychomotor speed and coordination, selective attention, semantic fluency, letter fluency and executive functions). In order to investigate executive functions, the BACS battery employs the Tower of London Test. Visuospatial constructional abilities and visual memory were evaluated through the Rey-Osterrieth Complex Figure Test (Shin et al., 2006). All tests were administered by a trained psychologist.

Standardized domain scores were calculated for symbol coding (selective attention and processing speed), digit sequencing (working memory), verbal memory, token motor task (psychomotor coordination), verbal fluency and Tower of London (executive functions) and Rey-Osterrieth Complex Figure Test (visual-spatial abilities and memory). Normative Italian adjusted scores (Anselmetti et al., 2008) were used for the BACS subtests. To provide a standard metric for comparison across neurocognitive domains for each BACS subtest an equivalent score, ranging from 0 to 4, has been obtained where score 2, 3 or 4 reveal a good performance while score of 0 or 1 reveal a poor performance.

2.3. Image acquisition

Diffusion tensor imaging was performed on a 3.0 Tesla scanner (Gyroscan Intera, Philips, Netherlands) using SE Echo-planar imaging (EPI) and the following parameters: TR/TE = 8753.89/58 ms, FoV (mm) 231.43 (ap), 126.50 (fh), 240.00 (rl); acquisition matrix 2.14 × 2.71 × 2.31; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88 × 1.87 mm; SENSE acceleration factor = 2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value = 900 s/mm^2. Fat saturation was performed to avoid chemical shift artifacts. On the same occasion and using the same magnet 22 Turbo Spin Echo (TSE), T2 axial slices (TR = 3000 ms; TE = 85 ms; flip angle = 90°; turbo factor 15; 5-mm-thick, axial slices with a 512 × 512 matrix and a 230 × 230 mm^2 field of view) were acquired to rule out brain lesions.

2.4. ENIGMA-DTI processing

Whole-brain tract-wise average FA values were extracted for each subject according to ENIGMA-DTI protocols (available online at http://enigma.ini.usc.edu/protocols/dti-protocols/). DTI images were preprocessed using FSL tools (http://www.fmrib.ox.ac.uk/fsl). By FSL's "eddy correct" command, all volumes were corrected for eddy current induced distortions and subjects' movements (Horsfield, 1999). A brain mask was then created using FSL's Brain Extraction Tool (BET) (Smith, 2002), which deletes non-brain tissues from the image. Next, by FSL's DTIFIT command, included in FMRIB's Diffusion Toolbox (FDT) (Behrens et al., 2003), a voxel-wise diffusion tensor model was fit to the data to obtain parametric maps of FA. Whole brain statistical analyses of all subject's FA images were conducted using FSL's Tract-Based Spatial Statistics (TBSS; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) analytic method. All subject's FA data were aligned to the Montreal Neurological Institute (MNI) space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT) (www.fmrib.ox.ac.uk/fsl/fnirt/index.html). The mean of all aligned FA images was then created, and a "thinning" process was applied to create a skeletonized mean FA image representing the centers of all common tracts. A threshold of 0.2 was set to this image to control for inter-subject variability and reduce the likelihood of partial volume effect. Quality control, including inspections of data, vector gradients, registration, and average skeleton projection distance, were performed according to the ENIGMA-DTI protocol. Finally, all individual FA image was projected onto the skeleton by searching perpendicular from the skeleton for maximum FA values (Smith et al., 2006). Average FA values, for each fiber tract, were calculated from voxels in each subject's white matter skeleton within 43 tract-wise regions of interest (ROIs), derived from the Johns Hopkins University (JHU) white matter parcellation atlas (Mori et al., 2008).

2.5. Statistical analyses

All statistical analyses were performed with the statistical package SPSS software package version 23.0. The average FA measures of WM tracts extracted using the ENIGMA-DTI protocol were included as dependent variables in a Multivariate Regression within the context of the general linear model, (McCulloch et al., 2008; Timm and Kim, 2006), with illness duration as independent factor. We accounted for the effects of nuisance covariates which could influence WM structure: age (Kochunov et al., 2007), sex (Herting et al., 2012), and lithium treatment within the past six months (Benedetti et al., 2013). Levels of significance of the observed regressions were corrected for multiple comparisons with the method of the adaptive linear step-up procedures that control the False Discovery Rate (FDR) (Benjamini et al., 2006).

FDR corrected FA measures of WM tracts were then used as predictor variables for each score in cognitive performances. Given that a high inter-correlation of white matter tracts was expected, multicollinearity was diagnosed by calculating the variance inflation factor (VIF). In the presence of an average VIF substantially > 1, that indicates that predictors have linear relationships among themselves that might bias regression (Bowerman and O'Connell, 1990), multicollinearity was corrected by principal component analysis (PCA) (Lafi and Kaneene, 1992; Dormann et al., 2013). PCA was performed to identify orthogonal directions of maximum variance in the original data, and to project the data into a lower-dimensionality space formed of a sub-set of the highest-variance component(s), detected according to the least squares criterion. In the presence of significant effects, and eigenvalues for the component(s) > 1, the score of the component was then extracted and used as predictor variable to test the combined effect of the original collinear factors on cognitive performances. Univariate tests were conducted to test the significance of the effect on each dependent variable, using a multiple comparison correction (pFDR < 0.05, Table 2). To test the hypothesis of WM tracts mediating the possible effects of illness duration on cognitive functions, we performed a multiple regression mediation analysis with the PROCESS macro for SPSS and SAS, version 3.0 (Hayes, 2013), with 10.000 bootstrap resamples to generate 95% confidence percentile intervals, and with age, sex and education as nuisance covariates. The R^2 was calculated as mediation effect size measure (Fairchild et al., 2009), while the completely standardized indirect effect was used to evaluate the effect size of the indirect effect (Preacher and Kelley, 2011).

3. Results

Clinical, demographic and neuropsychological characteristics of the sample are resumed in Table 1.

Considering equivalent scores, in our sample 40% of patients present a poor performance in verbal memory, 55% in working memory, 60% in psychomotor coordination, 35% in verbal fluency, 66% in selective attention and processing speed scores and 37% in executive functions. No multivariate effect was observed (Pillai's Trace = 0.45), however, univariate results showed that illness duration significantly predicts FA measures of several WM tracts: bilateral anterior corona radiata (ACR), bilateral corona radiata (CR), genu of corpus callosum (GCC) and fornix (FX) (pFDR < 0.05, Table 2). The 6 WM tracts significantly correlated among themselves, and all showed a VIF > 1 (ACR-L = 10.82; ACR-R = 10.66; CR-L = 11.19; CR-R = 11.99.14; FX = 1.48; GCC = 2.18), yielding a mean VIF = 9.66. A PCA was then conducted on the 6 factors. The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis (KMO = 0.69) which is above the acceptable limit of 0.05 (Field, 2013). Given that only one component had an eigenvalue over Kaiser's criterion of 1 (Eigenvalue = 4.29) a single component was extracted which explained 73.7% of variance. The single WM factor significantly predicts all cognitive performances, except visual-spatial abilities (pFDR < 0.05, Table 3). Mediation analysis revealed a significant indirect negative effect of illness duration on verbal memory, visual memory and processing speed mediated by the FA component extracted (p < 0.05, Fig. 1. a-c).

Table 1
Clinical and demographic characteristics of the sample (N = 88). For cognitive functions mean standardized scores have been reported.

	Bipolar patients (N = 88)
Age	48.02 ± 11.97
Sex (M/F)	28/60
Education (yrs at school)	11.87 ± 3.77
Age at onset of illness (yrs)	30.53 ± 10.76
Illness duration (yrs)	16.97 ± 10.01
N° of previous depressive episodes	6.32 ± 5.23
N° of previous manic episodes	3.16 ± 2.91
Severity of depression (HDRS)	20.51 ± 7.42
Lithium treatment in the past 6 months (yes/no)	38/50
Verbal fluency	0.03 ± 0.94
Verbal memory	0.07 ± 0.93
Working memory (digit sequencing task)	0.05 ± 0.96
Visuo-spatial abilities (ROCF)	0.05 ± 0.98
Visuo-spatial memory (ROCF)	0.08 ± 0.95
Psychomotor coordination (Token Motor task)	−0.03 ± 1.02
Attention and information processing (symbol coding)	0.06 ± 0.89
Executive functions (ToL)	0.12 ± 0.95

We observed initial significant negative relationships between illness duration and processing speed (total effect: b = −0.0393, 95% CI −0.0572 to −0.0213), verbal memory (total effect: b = −0.0316, 95% CI −0.0496 to −0.0135), and visual memory (total effect: b = −0.0385, 95% CI −0.0585 to −0.0185), which were reduced, but still significant, after controlling for FA (direct effects, respectively: b = −0.0297, 95% CI −0.0482 to −0.112; b = −0.0236, 95% CI −0.0424 to −0.0047; b = −0.0305, 95% CI −0.0514 to −0.0095); in turn, FA was significantly decreased by illness duration (b = −0.038, 95% CI −0.0588 to −0.0164) and significantly increased cognitive performances (processing speed: b = 0.2547, 95% CI 0.0768 to 0.4325; verbal memory: b = 0.2130, 95% CI 0.0316 to 0.3944; visual memory: b = 0.2138, 95% CI 0.0120 to 0.4155). The analyses suggest then a partial mediation of FA on the effects of illness duration on processing speed (whole model: R^2 = 0.27, $F_{4,83}$ = 7.84, p < 0.05), on verbal memory (whole model: R^2 = 0.32, $F_{4,83}$ = 9.67, p < 0.05) and on visual memory (whole model: R^2 = 0.21, $F_{4,83}$ = 5.45, p < 0.05) indicating that cognitive performances variance attributable to the indirect effect of illness duration trough WM integrity ranged from 21% to 32%. The completely standardized indirect effect was −0.0107 (95% CI = −0.0107 to −0.0192) in processing speed, −0.0862 (95% CI −0.01680 to 0.0.0211) in verbal memory and −0.0084 (95% CI = −0.0171 to −0.0010) in visual memory scores, indicating that for every SD increase in illness duration, cognitive performances score were expected to decrease in a range from 0.0084 to 0.0107 indirectly via FA measures. No other significant mediation effect was detected.

Given that an association between number of previous illness episodes and worsening of cognitive deficits was observed in literature (Cardoso et al., 2015b), we checked if in our sample illness duration correlated to the total number of mood episodes. Even though a significant result was found (r = 0.26, p = 0.02), no other association between number of previous episodes and cognitive performances or FA measures was observed. Moreover, to gain more insight on the nature of the relationship between illness duration, FA, and cognitive measures we tried to disentangle the effect of age and Illness duration. A significant correlation between age and illness duration was observed in our sample (R = 0.38, p < 0.05). Thus, in a mediation model we tested the effect of age as a possible predictor of cognitive performances scores mediated by FA, but the whole model was not significant. Indeed, age was negatively associated to FA measures (b = −0.04, p < 0.05), but did not associate to cognitive performances. Considering this result, we tested the role of age as possible mediator or moderator of the effect of

Table 2
FDR-adjusted *p*-values of the effect of illness duration on FA measures of 43 WM tracts according to the adaptive linear step-up multiple testing procedure. * significant *q* values < 0.05.

Input area		Output area				Classical one-stage method	
Hypothesis name	*p*-values	Unique rank	Order	Ascending *p*-values	Hypothesis name	FDR-derived significance thresholds	FDR-adjusted *p*-values a.k.a. *q*-values
ACR-L	0,000006	2	1	0,00000	FX	0,00116279*	3,24863E-05
ACR-R	0,000152	3	2	0,00001	ACR-L	0,00232558*	0,00013235
ALIC-L	0,627417	34	3	0,00015	ACR-R	0,00348837*	0,002179118
ALIC-R	0,774217	38	4	0,00025	CR-L	0,00465116*	0,002672892
BCC	0,042054	9	5	0,00131	GCC	0,00581395*	0,011289925
CC	0,167663	16	6	0,00181	CR-R	0,00697674*	0,012938876
CGC-L	0,398724	26	7	0,01207	EC-R	0,00813953	0,074141085
CGC-R	0,190873	17	8	0,02026	EC-L	0,00930233	0,108920721
CGH-L	0,737274	37	9	0,04205	BCC	0,01046512	0,181478793
CGH-R	0,346912	23	10	0,04235	PCR-R	0,01162791	0,181478793
CR-L	0,000249	4	11	0,04642	PCR-L	0,0127907	0,181478793
CR-R	0,001805	6	12	0,12217	SCR-L	0,01395349	0,431335317
CST-L	0,644098	35	13	0,13040	FX/ST-R	0,01511628	0,431335317
CST-R	0,382559	25	14	0,14636	PTR-R	0,01627907	0,449529932
EC-L	0,020264	8	15	0,16727	FX/ST-L	0,01744186	0,450595132
EC-R	0,012069	7	16	0,16766	CC	0,01860465	0,450595132
FX	0,000001	1	17	0,19087	CGC-R	0,01976744	0,469491963
FX/ST-L	0,167274	15	18	0,19653	PTR-L	0,02093023	0,469491963
FX/ST-R	0,130404	13	19	0,25829	RLIC-L	0,02209302	0,55575215
GCC	0,001313	5	20	0,25849	SLF-L	0,02325581	0,55575215
IC-L	0,885008	42	21	0,29984	SCR-R	0,0244186	0,613959255
IC-R	0,780710	39	22	0,33398	SLF-R	0,0255814	0,648574079
IFO-L	0,906160	43	23	0,34691	CGH-R	0,02674419	0,648574079
IFO-R	0,543874	33	24	0,37941	SCC	0,02790698	0,658002261
PCR-L	0,046425	11	25	0,38256	CST-R	0,02906977	0,658002261
PCR-R	0,042348	10	26	0,39872	CGC-L	0,03023256	0,659428364
PLIC-L	0,485915	30	27	0,46707	PLIC-R	0,03139535	0,69647857
PLIC-R	0,467068	27	28	0,46903	UNC-L	0,03255814	0,69647857
PTR-L	0,196532	18	29	0,47417	SFO-R	0,03372093	0,69647857
PTR-R	0,146359	14	30	0,48592	PLIC-L	0,03488372	0,69647857
RLIC-L	0,258290	19	31	0,50622	SFO-L	0,03604651	0,702179731
RLIC-R	0,531963	32	32	0,53196	RLIC-R	0,0372093	0,70868418
SCC	0,379413	24	33	0,54387	IFO-R	0,03837209	0,70868418
SCR-L	0,122170	12	34	0,62742	ALIC-L	0,03953488	0,791320481
SCR-R	0,299841	21	35	0,64410	CST-L	0,04069767	0,791320481
SFO-L	0,506223	31	36	0,70478	SS-R	0,04186047	0,837531195
SFO-R	0,474172	29	37	0,73727	CGH-L	0,04302326	0,837531195
SLF-L	0,258489	20	38	0,77422	ALIC-R	0,04418605	0,837531195
SLF-R	0,333981	22	39	0,78071	IC-R	0,04534884	0,837531195
SS-L	0,798576	41	40	0,78148	UNC-R	0,04651163	0,837531195
SS-R	0,704777	36	41	0,79858	SS-L	0,04767442	0,837531195
UNC-L	0,469034	28	42	0,88501	IC-L	0,04883721	0,90607961
UNC-R	0,781482	40	43	0,90616	IFO-L	0,05	0,906160003

illness duration on FA, but still no significant result was observed.

4. Discussion

This is the first study to show that individual DTI measures of WM microstructure mediate the association between illness duration on cognitive performance. Our data also confirm prior observations that duration of illness affects both cognitive functions (Cardoso et al., 2015a) and brain structure, as reported in Major Depressive Disorder, where length of illness has a detrimental effect on FA (de Diego-Adelino

Table 3
FDR-adjusted *p*-values of the effect of FA component on cognitive performances according to the adaptive linear step-up multiple testing procedure. * significant *q* values < 0.05.

Input area		Output area				Classical one-stage method	
Hypothesis name	*p*-values	Unique rank	Order	Ascending *p*-values	Hypothesis name	FDR-derived significance thresholds	FDR-adjusted *p*-values a.k.a. *q*-values
Visual-spatial abilities	0,15315	8	1	0,00015	Processing Speed	0,00625*	0,00116
Visual-spatial memory	0,00211	3	2	0,00162	Verbal memory	0,0125*	0,004284
Verbal memory	0,00162	2	3	0,00211	Visual-spatial memory	0,01875*	0,004284
Working memory	0,01137	5	4	0,00214	Executive function	0,025*	0,004284
Psychomotor coordination	0,02915	7	5	0,01137	Working memory	0,03125*	0,0181904
Verbal fluency	0,02507	6	6	0,02507	Verbal fluency	0,0375*	0,0333188
Processing speed	0,00015	1	7	0,02915	Psychomotor coordination	0,04375*	0,0333188
Executive function	0,00214	4	8	0,15315	Visual-spatial abilities	0,05	0,153147

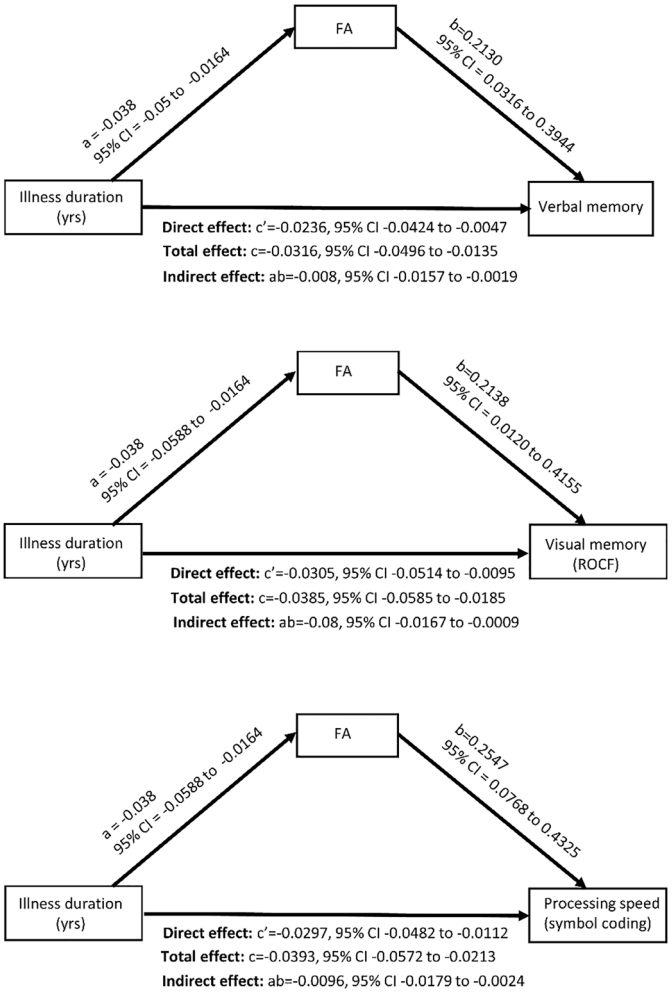

Fig. 1. a–c Mediation model for the effect of illness duration on verbal memory, visual memory, and processing speed performances through PCA composite scores for FA measures of WM tracts. a, b, c and c' are path coefficients representing unstandardized regression weights. * Significant confidence intervals at 95%.

et al., 2014) and hippocampal volume (Sheline et al., 2003; Bell-McGinty et al., 2002).

Here, we observed a significant negative association between illness duration and FA in anterior corona radiata, fornix, and genu of corpus callosum, suggesting that in these areas the damage to WM progresses with chronicity, as confirmed by other studies (Squarcina et al., 2017). The corpus callosum is known to play a crucial role by modulating inter-hemispheric cross-talk and cognitive processes (Perlini et al., 2012; Duncan and Owen, 2000). In particular, the fibers running through the genu interconnect the frontal association cortical areas involved in several cognitive domains such as attention, memory and executive functions (Prunas et al., 2018), which are frequently impaired in BD (Brambilla et al., 2009). The fornix connects the hippocampal formation with sites beyond the temporal lobe. The importance of this tract in memory function has been indicated by several studies (Tsivilis et al., 2008; Vann et al., 2008; Metzler-Baddeley et al., 2011) and fornices degeneration has been considered a predictor of incipient cognitive decline among healthy elderly individuals (Fletcher et al., 2013). The anterior corona radiata (ACR) is part of the limbic-thalamo-cortical circuitry and includes both ascending and descending thalamic projections from the internal capsule to the cortex. The alteration of connectivity provided by ACR fibers between brainstem and neocortex may contribute to the fronto-striatal dysfunctions frequently observed in BD (Pavuluri et al., 2009), associated to cognitive abnormalities in the domain of executive function (Kozicky et al., 2013) processing speed, task switching (Sasson et al., 2012) and cognitive flexibility (Birdsill et al., 2014) and to impaired top-down emotion regulation systems (Blond et al., 2012; Vargas et al., 2013; Vai et al., 2014; Brambilla et al., 2005).

In healthy subjects timing and rates of FA development and degradation vary regionally. A general trend was observed in which FA values increase from childhood to adulthood, reach a peak and decrease at slower rate during later adulthood. The genu reaches its FA peaks around 21 years and, together with the fornix, which reaches its peak before age 20 years, it's among the first WM matter tract to maturate, while corona radiate reaches its peak around age 26 years. However, the fornix and callosal tracts, after completing their development, present the earliest trend reversals and first start to decline (Yap et al., 2013).

FA measures are known to reflect regional myelination levels, axonal density and diameter and the degree of intra-voxel fiber crossing (Beaulieu, 2002; Budde et al., 2007). However, evidences showed that during normal aging, changes in regional FA are principally ascribable to the change in the local axonal myelination levels (Abe et al., 2002; Gao et al., 2009). Myelin breakdown and repair processes, which occurs repeatedly over neural networks, are slowed down in older age as a result of the progressive overtaking of myelin breakdown on the repair processes. This determines an accelerated rate of decline in brain networks average performances (Bartzokis et al., 2004; Bartzokis et al., 2007; Sloane et al., 2003; Peters et al., 2001). Moreover, in healthy aging, a decline in myelin content and integrity was found to follow the same trajectory of cognitive processing speed (Bartzokis et al., 2010), suggesting a decreased efficiency of communication among the neural circuitry involved in these cognitive domain. With respect to healthy controls, bipolar patients present a strong downregulation of key oligodendrocyte and myelination genes (Maletic and Raison, 2014; Bartzokis, 2012) and a significant oligodendrocyte cell loss (Hercher et al., 2014; Savitz et al., 2014; Haroutunian et al., 2014), as pointed out by several morphometric postmortem studies. It can be hypothesized that neurocognitive disorder, such as bipolar depression, by progressively affecting myelination and remyelination processes in specific brain circuitry, ultimately modulate cognition.

Some explanatory models that could justify a neuroprogressive disease course have been described. According to a recent hypothesis, the high overlap between neuropathological changes in BD and aging suggests that the disorder may be linked to a process of accelerated brain aging (Rizzo et al., 2014). Both conditions are associated to significant brain structural alterations, including brain atrophy, hippocampal volume loss and increased number of WM hyperintensities (Raz and Rodrigue, 2006; Allen et al., 2005; Hallahan et al., 2011b; Lisy et al., 2011). Moreover, BD and aging commonly share substantial molecular and cellular changes, linked to cumulative oxidative stress (Kong et al., 2014; Andreazza et al., 2009), decline of the regulatory immunological response to inflammatory factors (Brietzke et al., 2009; Franceschi et al., 2007) and reduction in neurotrophins levels, notably BDNF (Fernandes et al., 2011; Perovic et al., 2013). Increased production of proinflammatory cytokines and immune-mediated mechanisms seem to play a major role in the neuroprogression of BD (Barbosa et al., 2014). According to the concept of allostatic load in BD (i.e. the neural and bodily "wear and tear" that emerge in the context of chronic stress), ilness chronicity, through multiple biochemical factors involved in stress sensitization process, associates to a disruption of the homeostasis between inflammatory and neuroprotective mechanisms and oxidative processes with a toxic effect on neurons and glia (Berk et al., 2011). In adult clinical populations, increasing levels of pro-inflammatory cytokines, in the absence of active somatic immune diseases, is usually observed in a subgroup of patients. These pro-inflammatory phenotypes were associated with worse outcomes of mood disorders, including poor response to antidepressant treatment (Benedetti et al., 2017b) and with MRI signs of white matter disruption

(Benedetti et al., 2016) Moreover, a crucial role in neuroprogression may be exerted by sleep loss and circadian rhythms disruption which are core features of BD (Dallaspezia and Benedetti, 2009; Gonzalez, 2014). Preclinical studies in animal models showed that sleep promotes myelination and oligodendrocyte precursor cells proliferation (Cirelli et al., 2004; Bellesi et al., 2013) and sleep disturbances are associated with measures of neuroinflammation, such as increased secretion of pro-inflammatory cytokines (Fernandes et al., 2017) increased blood-brain barrier permeability (Hurtado-Alvarado et al., 2018) and activation of microglia (Wisor et al., 2011). Thus, prolonged circadian rhythms alterations could hamper brain homeostasis with a detrimental effect on WM microstructure, as previously observed in BD (Benedetti et al., 2017a)., our results seem to align more to the concept of allostatic load in BD (i.e. the neural and bodily "wear and tear" that emerge in the context of chronic stress) according to which illness itself, through multiple biochemical factors involved in stress sensitization process, such as cortisone, inflammatory processes, oxidative stress, and changes to neurotrophins including BDNF, is linked to the observed structural changes and the associated cognitive decline

Here we observed that WM integrity in early myelinating tracts mediate the effect of illness duration on cognitive functions. As suggested by the neuroprogressive hypothesis, neuroinflammation and a reduced cellular resilience to stress characterise BD. It can be surmised that such processes may accelerate the natural decrease of FA showing their effect particularly on those tracts which are already declining when the onset occur.

Strengths of the present study include a focused research question, sample size and state-of-the-art imaging methods, but our results must be viewed in light of some limitations. The lack of a healthy control group for DTI limits generalizability to the general population. No patient was drug-naive, and the drug treatments administered during the course of the illness, including antidepressant and antipsychotic drugs, could have influenced MRI measures. Recruitment was in a single center and in a single ethnic group, thus raising the possibility of population stratifications. Finally, the cross-sectional design of our study did not allow us to examine direct causative mechanisms of the effects of progression of illness and future longitudinal studies would be needed to confirm our speculation.

These limitations, however, do not bias the main finding of an association between of illness duration, WM integrity and cognitive functions, correcting for age. These provide new insights about the neuroprogression hypothesis in BD which may be relevant in stratifying psychiatric patients into clinically relevant illness stages and eventually translating into individual tailored functional remediation therapeutic interventions.

Conflict of interest

The authors of this paper report no biomedical financial interests or other potential conflicts of interest. All authors have approved the final article.

Contributors

All individuals included as authors of papers contributed substantially to the scientific process leading up to the writing of the paper. FB designed the study. CC and FB obtained the funding. EM, SP, IB and BV were involved in participants' recruitment and selection and collected the clinical data. EM designed the data analyses and carried it out. EM wrote the draft of the manuscript with the supervision of FB and SP. All authors take final responsibility for the decision to submit for publication. FB had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors are entirely responsible for the scientific content of the paper.

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