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ORIGINAL ARTICLE

Resilience and corpus callosum microstructure in adolescence

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Background. Resilience is the capacity of individuals to resist mental disorders despite exposure to stress. Little is known about its neural underpinnings. The putative variation of white-matter microstructure with resilience in adolescence, a critical period for brain maturation and onset of high-prevalence mental disorders, has not been assessed by diffusion tensor imaging (DTI). Lower fractional anisotropy (FA) though, has been reported in the corpus callosum (CC), the brain's largest white-matter structure, in psychiatric and stress-related conditions. We hypothesized that higher FA in the CC would characterize stress-resilient adolescents.

Method. Three groups of adolescents recruited from the community were compared: resilient with low risk of mental disorder despite high exposure to lifetime stress ($n = 55$), at-risk of mental disorder exposed to the same level of stress ($n = 68$), and controls ($n = 123$). Personality was assessed by the NEO-Five Factor Inventory (NEO-FFI). Voxelwise statistics of DTI values in CC were obtained using tract-based spatial statistics. Regional projections were identified by probabilistic tractography.

Results. Higher FA values were detected in the anterior CC of resilient compared to both non-resilient and control adolescents. FA values varied according to resilience capacity. Seed regional changes in anterior CC projected onto anterior cingulate and frontal cortex. Neuroticism and three other NEO-FFI factor scores differentiated non-resilient participants from the other two groups.

Conclusion. High FA was detected in resilient adolescents in an anterior CC region projecting to frontal areas subserving cognitive resources. Psychiatric risk was associated with personality characteristics. Resilience in adolescence may be related to white-matter microstructure.

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Key words: Adolescence, corpus callosum, DAWBA, DTI, NEO-FFI, resilience, tractography.

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Introduction

One definition of resilience is the capacity of individuals to resist development of mental disorders despite exposure to stress (Davydov *et al.* 2010; Russo *et al.* 2012). Adolescence is the period of onset for most high-prevalence mental disorders (McLaughlin *et al.* 2012), many being influenced by stress. Little is known about neuroprotective factors underpinning resilience at that age. Throughout adolescence behavioral changes are related to life events and personality profile, as well as to neurobiological processes regulating emotions and cognitive function (Paus, 2010, 2013). Self-reported measures of life stressors have been used in the general population to predict the onset of psychological disturbance and poor school performance (Shaw *et al.* 2008). Positive affect contributes more than negative affect to build up resilience (Geschwind *et al.* 2010) implying that *negative* life events (NLE) are more representative of adversity (Newcomb *et al.* 1986). Resilience can thus be operationally defined as a history of NLE with a low probability of mental disorder.

Personality dimensions like Neuroticism build up markedly during adolescence, and might account for resilience in adolescents (Nakaya *et al.* 2006). Therefore, in a study of resilience, the influence of Neuroticism should be disentangled from an association with neural factors. While Neuroticism may engage widespread functionally related brain regions (Canli, 2008), authors have highlighted the association of personality dimensions with the white-matter (WM) microstructure in adults (Xu *et al.* 2012; Bjørnebekk *et al.* 2013), particularly at the level of the corpus callosum (CC), the largest WM fiber bundle, which connects homologous regions of the cerebral hemispheres.

The CC has been implicated in major psychiatric disorders by authors emphasizing abnormal interhemispheric communication in the etiology of mental disease. Most reports have used evidence from conventional structural magnetic resonance imaging (MRI) scans. CC volume has been found reduced in psychopathological conditions as in bipolar adults and adolescents (Lopez-Larson *et al.* 2010), in treatment-refractory depression and schizophrenia (Sun *et al.* 2009), attention deficit hyperactivity disorder (ADHD; Qiu *et al.* 2011) and post-traumatic stress disorder (PTSD; review by Jackowski *et al.* 2009; Chao *et al.* 2013). Smaller CC volumes have been reported in stress-related conditions, including early stress in children or adolescents (review in McCrory *et al.* 2011) and in childhood neglect (Teicher *et al.* 2004). The CC draws its importance from bihemispheric cortical projections, particularly to frontal areas controlling emotions and behaviors in illness and likely resilience (Vink *et al.* 2014).

Probing microstructure and connectivity of WM tracts in the CC makes diffusion-weighted imaging particularly relevant (Moseley *et al.* 1990). Using diffusion tensor imaging (DTI), Paul *et al.* (2008) found that fractional anisotropy (FA) was reduced at the level of the genu of the CC in cases of early life stress even in the absence of symptoms. They suggested that stress during a period of active WM development might compromise WM microstructure without reduction of CC volume. Thus, while vulnerability was addressed in the literature, little is known about neural aspects of resilience (Frodl *et al.* 2012). Reports concerned adults who had suffered stress during childhood, not adolescents whose negative experience was recent. Studies in non-clinical populations have not systematically assessed the risk of psychiatric disorders (Hart & Rubia, 2012). Hence, a DTI study of resilience in adolescents whose risk of mental disorders could be quantified might provide more straightforward evidence for a neuroanatomical marker of resilience.

We *a priori* hypothesized that in contrast with pathological and stress-related conditions characterized by lower FA values, resilience in adolescents would be associated with higher FA in the CC compared adolescents at risk of mental disorder and with control adolescents from the same community. These three groups are categories raised on operational criteria, while resilience is likely dimensional. Thus, should the primary hypothesis be confirmed, significant between-group differences in DTI measures were to be investigated to test the secondary hypothesis of a hierarchy of groups according to 'resilience capacity', i.e. resilient group>control group>at-risk group. In addition, we aimed to explore the WM cortical projections of the detected CC differences, using tractography. As regards personality traits, we expected that levels of Neuroticism would be lower in resilient youths than in the other two groups.

Method

The participants were 2224 healthy community adolescents (mean age 14.32, S.D. = 1.31 years) from the European IMAGEN cohort (Schumann *et al.* 2010) recruited from secondary schools. Written informed consent was obtained from all participants and from their legal guardians. The protocol was approved by local ethics committees and complied with the Helsinki Declaration. Participants with a medical condition or diagnosed neurodevelopmental disorders were excluded.

The psychometric characterization was partly conducted in participants' homes using the Psytools

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Table 1. *Sociodemographic characteristics, pubertal status and IQ scores of the three groups*

	Resilient ($n = 55$)	Control ($n = 123$)	At risk ($n = 68$)	Statistics	p value
Sex (F/M)	36/19	87/36	51/17	1.34	0.51[a]
Age, yr, mean (S.D.)	14.40 (0.42)	14.45 (0.40)	14.47 (0.43)	0.50	0.61[b]
NLE, mean (S.D.)	4.80 (1.06)	0.93 (1.08)	4.84 (1.10)	444.96	2.2×10^{-16} [bc]
PDS, mean (S.D.)	2.96 (0.48)	3.07 (0.48)	3.15 (0.49)	2.30	0.10[b]
IQ, mean (S.D.)	106.68 (11.29)	107.24 (11.54)	107.73 (11.78)	0.12	0.88[b]

NLE, Negative life events; PDS, Pubertal Development Scale; IQ, Intelligence Quotient.
[a] χ^2 test.
[b] F test.
[c] t test (resilient) *v.* at-risk (non-significant).

software (Delosis, UK). Pubertal status was self-assessed using the Pubertal Development Scale (PDS; Petersen *et al.* 1988).

NLE were identified by adolescents with the Life Event Questionnaire (LEQ; Newcomb *et al.* 1981), from a list of lifetime negative, neutral, and positive events. Participants rated each event to indicate how happy or unhappy it made them feel, and indicated whether or not the event had happened to them. Internal consistency of the LEQ is low, as there is no association between the independent events listed (Newcomb *et al.* 1986). Since our definition of resilience is based on the capacity to cope with NLE, we selected 16 LEQ items that are usually experienced as negative (see online Supplementary Table S1). A cut-off of four NLE was chosen to define significant exposure to stress, corresponding to the level of stress experienced by 15% of young adults followed since childhood (Caspi *et al.* 2003).

Behavioral and emotional disturbances in adolescents were self-reported using the Development and Well-Being Assessment (DAWBA; Goodman *et al.* 2000). Definite symptoms were identified by structured questions to child and parent. Diagnoses were generated according to probability bands, i.e. 'DAWBA' bands, ranging from low- to high-risk levels. The DAWBA predictions contain specific bands for the diagnostic criteria of ICD-10 and DSM-IV, as well as a general band that gives a global probability of mental illness. Clinical diagnoses were validated by experienced clinicians from the IMAGEN Consortium, after discussion if a decision was questionable.

We chose an operational definition of resilience: the exposure to an important level of lifetime stress ($\geqslant 4$ NLE) coupled with a low risk ($\leqslant 0.5\%$) of mental disorders (levels 0–1 of DAWBA general and specific bands). To avoid false positives, the records of all resilient adolescents were screened individually by a child psychiatrist from the IMAGEN Consortium. One subject with a body mass index <18, and three with a clinical diagnosis (DSM-IV-TR), were not included after file review. Four participants fulfiling DSM-IV-TR PTSD criteria were excluded from the resilient group.

Within the IMAGEN database, 55 resilient adolescents (Table 1) were eligible for analysis. Sixty-eight adolescents at risk were defined by a significant level of stress ($\geqslant 4$ NLE) coupled with a higher than 15% risk of mental illness (level $\geqslant 3$ of DAWBA general band). A control group was constituted from 123 adolescents scoring at DAWBA general band levels <3 and exposed to a low number of NLE ($\leqslant 3$), randomly selected from the IMAGEN database to match the two other groups for sex, PDS and Intelligence Quotient (IQ) (Table 1).

Behavioral assessment

With the French, German and English standardization norms for the respective populations, the Wechsler Abbreviated Scale of Intelligence (WASI; Axelrod, 2002) provided an estimate of the full-scale IQ based on vocabulary, similarities, block design and matrix reasoning subtests of the WAIS. The IMAGEN database also included neuropsychological assessments with CANTAB (Cambridge Neuropsychological Test Automated Battery) modules (detailed in Schumann *et al.*, 2010).

Personality dimensions were assessed with the NEO Five-Factor Inventory (NEO-FFI). This shortened 60-item form of the Revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992) questionnaire measures five broad personality dimensions (Neuroticism, Extraversion, Openness to Experience, Agreeableness, Conscientiousness).

MRI data acquisition

Diffusion tensor images were obtained on 3 T scanners (Siemens, Philips, General Electric, Bruker). The imaging protocols' comparability in the different scanners

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Table 2. *Personality dimensions of resilient, control and at-risk adolescents*

NEO-FFI	Resilient ($n = 55$) mean (S.D.)	Control ($n = 123$) mean (S.D.)	At risk ($n = 68$) mean (S.D.)	Test statistic[a]
Neuroticism	22.40 (6.32)	22.95 (7.00)	29.54 (8.01)	$F_{2,240} = 19.35$, $p = 1.61 \times 10^{-8}$ [b]
Extraversion	32.12 (5.30)	30.46 (5.41)	29.56 (6.47)	$F_{2,240} = 3.52$, $p = 0.03$[c]
Openness to experience	25.56 (5.12)	26.69 (5.58)	26.75 (6.06)	$F_{2,240} = 0.61$, $p = 0.54$
Agreeableness	30.44 (5.03)	30.02 (4.67)	26.63 (5.64)	$F_{2,240} = 12.72$, $p = 5.64 \times 10^{-6}$ [d]
Conscientiousness	30.73 (6.51)	28.46 (65)	26.37 (7.40)	$F_{2,240} = 5.46$, $p = 0.005$[e]

NEO-FFI, NEO Five-Factor Inventory.

[a] ANCOVA with sex, Pubertal Development Scale and IQ covariates.

[b] Linear effect: $p = 8.72 \times 10^{-7}$. Pairwise t test: resilient *v.* control ($p = 0.65$); resilient *v.* risk ($p = 5.6 \times 10^{-7}$); control *v.* risk ($p = 4.7 \times 10^{-8}$).

[c] Linear effect: $p = 0.009$. Pairwise t test: resilient *v.* control ($p = 0.14$); resilient *v.* risk ($p = 0.04$); control *v.* risk ($p = 0.30$).

[d] Linear effect: $p = 2.56 \times 10^{-5}$. Pairwise t test: resilient *v.* control ($p = 0.61$); resilient *v.* risk ($p = 8.6 \times 10^{-5}$); control *v.* risk ($p = 4.0 \times 10^{-5}$).

[e] Linear effect: $p = 0.001$. Pairwise t test: resilient *v.* control ($p = 0.09$); resilient *v.* risk ($p = 0.02$); control *v.* risk ($p = 0.09$).

was ensured through a thorough standardization (Schumann *et al.* 2010). All participants were instructed to close their eyes and keep as steady as possible during image acquisition. The diffusion tensor images were acquired using an Echo Planar imaging sequence (four $b = 0$ and 32 directions with $b = 1300$ s/mm^2; 60 near-axial slices, aligned with the line between the anterior and posterior commissures; echo time ≈104 ms; 128 × 128 matrix; voxel size 2.4 × 2.4 × 2.4 mm), adapted to tensor measurements [e.g. FA, mean diffusivity (MD)] and tractography analysis.

Preprocessing of diffusion data

Diffusion data preprocessing was performed using FMRIB Diffusion Toolbox (FDT) in FSL software (http://www.fmrib.ox.ac.uk/fsl) and consisted of affine registration to the first $b = 0$ image for head motion and eddy current correction, brain extraction using the brain extraction tool (BET; Smith, 2002), and voxel-wise diffusion tensor fitting to obtain FA, MD, axial diffusivity (AD) and radial diffusivity (RD) images. Voxelwise statistical analysis of the FA data was carried out using tract-based spatial statistics (TBSS), part of FSL (Smith *et al.* 2006). All participants' FA data were aligned into a common space using the nonlinear registration tool FNIRT (Andersson *et al.* 2007), which uses a b spline representation of the registration warp field (Rueckert *et al.* 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. This skeleton was then thresholded to FA > 0.2 to keep only the main tracts. Each adolescent's aligned FA, MD, AD and RD data were then projected onto the skeleton and the resulting data fed into voxelwise cross-individual statistics.

Data quality control and randomization

DTI datasets were discarded in case of head movement, poor tensor computation or defective spatial normalization. Among 96 resilient and 120 at-risk adolescents, 56 and 72 had eligible DTI datasets, respectively. Five participants were discarded because of missing IQ or PDS values (resilient, 1; at-risk, 4). Among 725 potential controls with available DTI, 123 (all of whom had eligible DTI data) were randomly matched by sex, PDS and IQ with participants of the two other groups. Thus, 55 resilient subjects, 68 at-risk subjects and 123 controls were available for TBSS analysis.

Statistical analysis

Statistical analyses for non-voxel-based data were conducted using R software (http://www.R-project.org/). The normality of variable distribution was assessed by the Shapiro-Wilk test. Between-group comparisons were performed using analysis of variance (ANOVA) with sex, PDS, IQ and neuroticism (except for NEO-FFI results) scores as confounding covariates. *Post-hoc* pairwise comparisons between groups were made using the Student t test. Sex distribution difference between resilient, at-risk and control subjects was tested with the χ^2 test.

DTI data analysis

Voxelwise group comparisons on FA, RD, AD and MD maps were tested in the framework of the general linear model (GLM) using a randomization based method (5000 permutations). We included Neuroticism score, PDS and DTI acquisition type (i.e. scanner manufacturers and/or software level) as confounding covariates. Analyses were restricted to voxels on the skeleton within the CC, based on the JHU-ICBM

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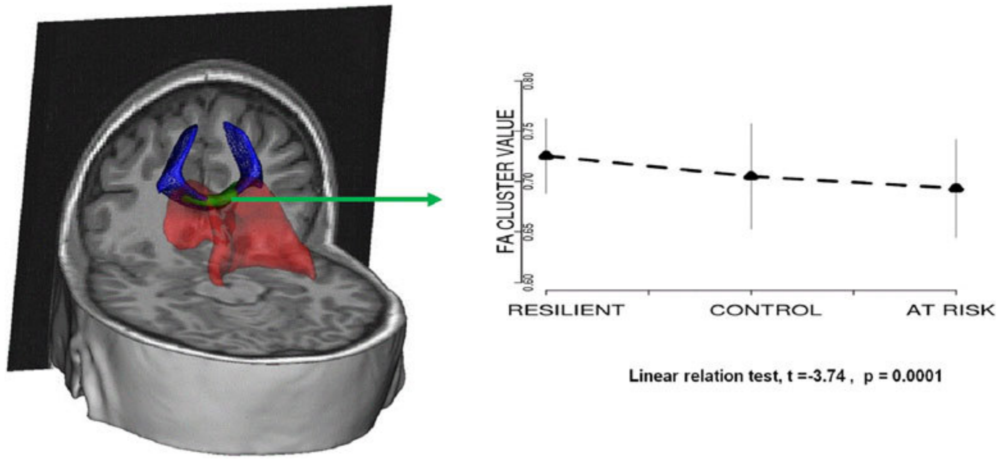

Fig. 1. Fractional anisotropy 3D rendering of between-group difference ($F = 10.44$, $p < 0.02$, family-wise error-corrected) denoting a significant cluster (green) within the corpus callosum (red) [FA (mean ± S.E.) in at-risk <FA in control <FA in resilient groups, linear effect, $t = -3.74$, $p = 0.0001$] and probabilistic tractography from that cluster [streamlines (in blue) were detected towards frontal and cingulate regions].

atlas (Mori *et al.* 2008). Statistical thresholds were set at $p < 0.05$ FWE (family-wise error) corrected and threshold-free cluster enhancement-corrected (Smith & Nichols, 2009). In order to test our secondary hypothesis, analyses on the extracted CC tensor values were performed considering groups as an ordered factor (e.g. resilient>control>at-risk) and searching for significant linear effects.

Tractography

The CC cluster identified in intergroup comparison of FA (see online Supplementary Table S3) was used as a seed mask to perform probabilistic diffusion tractography (PDT; Behrens *et al.* 2003, 2007). PDT estimates a probability distribution function of fiber direction and allows modeling multiple fiber orientations of each voxel. The warp fields of nonlinear registration and their inverses were used for the translation between the original space and the MNI 152 standard space. We then generated 5000 samples from each seed voxel to target 45 cortical and 15 subcortical regions based on the Harvard-Oxford atlases (Desikan *et al.* 2006). We used the numbers of samples reaching the target region from all seed voxels as a proxy of connectivity between the seed and each target region. For the number of streamlines, we investigated the interaction between group and neuropsychological scores only if between–group differences in neuropsychological scores were significant.

Results

Resilient, at-risk and control adolescents did not differ with respect to age, sex, years of education, PDS, IQ (Table 1), or neuropsychological performance (see online Supplementary Table S2). Controls differed from the other two groups in the number of NLE, but resilient and at-risk subjects had faced the same number of NLE ($t = 0.53$, $p = 0.60$).

Personality profile

Groups differed on four NEO-FFI factor scores, notably Neuroticism (Table 2). The *post-hoc* comparison between resilient and at-risk adolescents showed lower scores on Neuroticism ($p = 5.6 \times 10^{-7}$) and higher scores on Extraversion ($p = 0.04$), Agreeability ($p = 8.6 \times 10^{-5}$) and Conscientiousness ($p = 0.02$) in resilient adolescents. No difference appeared between resilients and controls.

DTI analyses

There was a between-group difference in FA within the genu and the anterior body of the CC ($F = 10.44$, $p < 0.02$, FWE-corrected for multiple comparisons, cluster size $k = 380$; peak voxel $x = 7$, $y = 14$, $z = 21$ MNI coordinates) (Fig. 1). *Post-hoc* pairwise t tests showed higher FA in resilient *v.* at-risk ($t = 4.33$, $p < 0.05$), and in resilient *v.* control ($t = 3.77$, $p < 0.05$) adolescents. All other pairwise comparisons were non-significant.

Regarding RD, a between-group difference was observed in the same region ($F = 8.83$, $p < 0.05$, FWE-corrected, cluster size $k = 371$; same peak voxel MNI coordinates). *Post-hoc* pairwise t tests showed higher RD in at-risk *v.* resilient ($t = 3.96$, $p < 0.05$) and in control *v.* resilient ($t = 3.50$, $p < 0.05$) adolescents. All other pairwise comparisons were non-significant.

No between-group differences were found in AD or MD.

Considering the group factor as rank-ordered, a higher mean FA in this region was associated with higher resilience capacity (at-risk<control<resilient groups, linear effect, $t = -3.74$, $p = 0.0001$, Fig. 1). Similarly, lower mean RD in this region was associated with higher resilience capacity (at-risk>control>resilient groups, linear relation test, $t = 3.327$, $p = 0.001$).

No group per Neuroticism interaction was detected with the FA values extracted from this region ($F = 1.62$, $p < 0.20$), nor group per other NEO-FFI dimensions (Extraversion: $F = 2.59$, $p < 0.08$; Agreeability: $F = 0.38$, $p < 0.68$; Conscientiousness: $F = 0.40$, $p < 0.92$).

Tractography

Using the anterior CC cluster as a seed mask for probabilistic tractography, we found a high number of cortical streamlines (sample >1000) targeting the anterior cingulate, middle frontal, frontal pole, superior frontal, and paracingulate regions (Fig. 1). There was no between-group difference in the number of streamlines to any of these regions (see online Supplementary Table S3).

Discussion

In this first neuroimaging study of resilient adolescents, diffusion tensor images of 246 adolescents divided into three groups (resilient, controls, at risk for mental disorders) showed that FA values within the anterior body of the CC and the adjacent part of the genu were significantly higher in the resilient than in the at-risk adolescents and controls. Moreover, in agreement with our secondary hypothesis of linearity, these values increased with resilience capacity. Analysis of DTI parameters showed reduced RD in the same region according to resilience capacity. Tractography evidenced streamlines from this callosal region to anterior cingulate as well as superior and middle frontal gyri.

Due to the lack of neuroimaging studies of resilient adolescents, previous reports from the literature are only relevant for our at-risk group. CC abnormalities have been reported in MRI studies of adults and youths with major psychiatric disorders suggesting they may be present early in the course of illness. In stress-related conditions reflecting the role of life events, volume of medial and posterior, but not anterior, parts of the CC has been found reduced in children and adolescents with PTSD (Jackowski *et al.* 2009) or childhood neglect (Teicher *et al.* 2004), as well as in adults (Teicher *et al.* 2006).

However, DTI analysis follows a different paradigm and the results may differ from volumetric measures; e.g. TBSS methodology does not depend on local volumetry since it is restricted to assessment within 'skeletonized' WM bundles (Smith *et al.* 2006). Calculating water diffusivities parallel and perpendicular to axons, several DTI studies have reported CC abnormalities in mental disorders. As in the present at-risk group, lower FA values were observed in the CC of adults and adolescents with bipolar disorder (Barnea-Goraly *et al.* 2009), and lower FA and higher RD in the anterior part of the CC in schizophrenic subjects (Whitford *et al.* 2011; Knöchel *et al.* 2012). In pediatric ADHD, DTI was characterized by a global FA decrease involving the CC anterior parts as well as other brain structures (Qiu *et al.* 2011). Thus both volumetric and DTI studies in pediatric or adult samples with psychiatric conditions report CC alterations consistent with abnormalities detected in the present at-risk adolescents.

Evidence of resilience in adults was indirectly produced by Frodl *et al.* (2012) in healthy relatives of patients. In line with our resilient participants, they showed higher FA values after exposure to stressful events, albeit in the CC splenium rather than the genu. In non-clinical adults exposed to various early life stressors, Paul and co-workers' (2008) report of decreasing FA values in the genu of the CC with a growing number of early life stressors is also consistent with our findings, although their subjects were adults, and risk of mental disease was not assessed. The same remarks apply to Teicher *et al.* (2010), who showed that past peer verbal abuse was associated with increased RD in the body and splenium of the CC and demonstrated a trend for decreased FA in the right corona radiata of normal adults. The present result of higher FA and lower RD in a more anterior part of the CC in 14-year-old resilient adolescents compared with at-risk adolescents is consistent with their suggestion (Andersen *et al.* 2008) that according to windows of vulnerability life stressors actively impact the maturing brain structures, such as the CC before age 14. DTI studies have shown that the anterior CC intensively develops until age 12, thus promoting cognitive abilities (Snook *et al.* 2005). Moreover in the present sample, tractography from the anterior CC cluster reconstructed a frontal-anterior cingular network, i.e. between regions providing cognitive resources to adolescents.

RD values in the three groups mirrored FA results along the continuum of resilience capacity. RD values reflect several aspects of WM properties (Paus 2010; Jones *et al.* 2013) including microstructure of myelin sheaths (Song *et al.* 2002) that may provide adaptative advantage if observed in meaningful frontal areas.

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Faster cognitive processing in aging humans has been correlated with higher myelination in the genu of CC (Lu *et al.* 2013). The CC region identified in our sample projected to cognitive more than emotional areas of the brain: anterior cingulate and paracingulate, middle and superior frontal cortices (Fig. 1, online Supplementary Table S3). These cortices are involved in the executive functions and in the selection of action programs, whereas the anterior cingulate cortex has a fundamental role in relating actions to their consequences, either success or error (Bush *et al.* 2000), thus guiding decisions about future actions (Rushworth *et al.* 2004). These cognitive areas are also involved in the reappraisal of negative emotions (Etkin *et al.* 2011), which is appropriate when facing NLE.

Scores on four NEO-FFI dimensions including Neuroticism (Table 2) differed between the three groups. A specific personality profile, with high Neuroticism, typified adolescents at risk in this sample, as NEO-FFI scores differentiated at-risk adolescents from the other two groups but not resilient individuals from controls contrary to our expectations. Consistently, Neuroticism has been prospectively linked with risk for depression (Kendler *et al.* 1993) and other psychiatric disorders (Jylhä *et al.* 2010; Rosellini & Brown, 2011), and associated with functional activity of widespread brain regions (Canli, 2008; Wright *et al.* 2006).

Here, lower levels of Neuroticism did not explain the association of resilience with higher FA in our sample. Indeed the resilient group had higher FA than controls despite comparable Neuroticism scores. Thus, resilience link to anterior CC WM does not appear as a trivial opposite of at-risk personality concomitants.

Limitations

There are some limitations to this study. Lower probability of mental disorder means absence of negative outcome in the context of an adverse environment, and is a common denominator across definitions of resilience (Compas & Reeslund, 2009). Somatic conditions were not taken into account, although in adults as well as in children they may also result from a stressful environment (Vila *et al.* 2012).

Although questionnaires concerned more recent memories than studies in adults, they were retrospective. Questions were not designed to identify events of early childhood that may also play an important role in mental illness.

The present sample was mostly female (Table 1). Myelination of the CC is an on-going process until adulthood and is influenced by hormonal status (Peper *et al.* 2011). However, controls were matched for sex and PDS scores, and these variables were used as covariates in between-group comparisons.

Finally, our findings give no insight into a causal relationship between CC microstructure (Assaf & Pasternak, 2008) and resilience. A modification of brain microstructure may be a consequence of overcoming NLE. Myelination, a process often estimated by RD (Song *et al.* 2002), has been shown to be sensitive to stress in animals (Carlyle *et al.* 2012). At the same time it should be underlined that FA and RD are not measures specific enough to distinguish axon- and myelin-related processes (Paus, 2010). Similarly, tractography identifying projections to frontal and cingulate regions cannot fully characterize actual fiber structure of WM (Jones *et al.* 2013).

Conclusion

This study of 123 community adolescents exposed to earlier stressful life events showed higher WM integrity of resilient youths. This CC region projects to frontal and anterior cingulate areas subserving cognitive resources. Resilience when facing negative emotions may depend on properties of the WM connecting those brain regions.

Appendix. IMAGEN Consortium (http://www.imagen-europe.com) (other members)

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Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715000239.

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Declaration of Interest

R.G. is the owner of Youthinmind, which provides no-cost and low-cost software and websites related to the Development and Well-Being Assessment. The remaining authors declare no conflict of interest.

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