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Understanding the link between childhood trauma and schizophrenia: A systematic review of neuroimaging studies

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ABSTRACT

Increasing evidence suggests that childhood trauma (CT) is a major risk factor for schizophrenia but the underpinning mechanisms of their association remain unclear.

Our aim is to review the literature on the association between CT and brain imaging measurements in adult schizophrenia subjects.

We conducted a systematic review of the existing neuroimaging literature on CT and schizophrenia. We reviewed studies considering adult subjects with schizophrenia, schizoaffective disorder or first episode schizophrenia.

A total of 15 studies were included. The most replicated result was the association in schizophrenia patients between CT and decreased total cerebral grey matter, particularly in the prefrontal cortex. In addition, studies suggest a different sensitivity to early stressors between schizophrenia subjects, their sibling and healthy unrelated subjects. In schizophrenia, CT is associated with alterations of white matter integrity in the inferior and superior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the forceps major. Functional connectivity studies suggest an association between CT and a network including the amygdala, the anterior cingulate cortex, the precuneus/posterior cingulate cortex region and the temporo-parietal junction.

1. Introduction

Recent literature suggests that childhood trauma represents an increased risk factor for schizophrenia, and many authors suggest even a causal relationship (for review, see (Morgan and Gayer-Anderson, 2016)). In fact, childhood trauma is more frequent in schizophrenic subjects than in the general population (van Os et al., 2010) and this association is found in both retrospective (Bebbington et al., 2011; Bendall et al., 2008; Cutajar et al., 2010; Janssen et al., 2004; Morgan and Fisher, 2007; Mullen et al., 1993; Spauwen et al., 2006) and prospective studies (Varese et al., 2012). Moreover, early life stress is associated with later occurrence of psychosis (van Nierop et al., 2013). There is a dose-response effect for childhood trauma in schizophrenia, i.e. the more severe the childhood trauma, the more severe the symptoms of schizophrenia (van Os et al., 2010; Heins et al., 2011). This link between early stress and psychosis has also been reported in studies controlling genetic risk factors (Janssen et al., 2004). Finally, the severity of childhood trauma is associated with increased susceptibility to stressful events in adults diagnosed with schizophrenia (Lardinois et al., 2011; Lataster et al., 2012). Therefore, early life stress does not only increase the risk of developing schizophrenia, but also influences the clinical presentation of the disease (Uçok and Bikmaz, 2007). Investigating the brain and clinical correlates of childhood trauma is essential to understand how early life events increase vulnerability to schizophrenia.

Several meta-analyses and literature reviews in healthy subjects have consistently identified multiple brain alterations associated to exposure to childhood trauma. This includes a decrease in total grey matter decrease, a decrease in dorsolateral and ventromedial prefrontal cortex grey and white matter, alterations in the hippocampus, amygdala and corpus callosum and connectivity alterations between these structures (Hart and Rubia, 2012; Paquola et al., 2016; Teicher et al., 2014).

Given the association between childhood trauma and brain

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alterations and the growing number of studies exploring the links between trauma exposure and schizophrenia, we examined the current brain imaging knowledge to better understand this link. Thus, we conducted a systematic review of neuroimaging literature in order to determine which brain alterations are associated with childhood trauma in schizophrenia?

This paper systematically reviews existing literature that discusses associations between childhood trauma and brain imaging measurements such as morphology, activity, brain connectivity or neurochemical variations, in adult schizophrenia subjects.

2. Methods

2.1. Search strategy

We performed a PubMed Medline database electronic search of articles published before July 2018. The keywords used were: 'name of the disorder' (schizophrenia OR psychosis) AND (mri OR fmri OR brain OR grey matter OR gray matter OR white matter OR neuroimaging) AND (child maltreatment OR childhood trauma OR early life stress OR adverse events). As a result of this search, we retrieved 654 items and the later similar search with the keywords "schizoaffective disorder" did not change the number of articles included in this review.

We then continue to complete our search manually. Three additional original articles were identified using the bibliography of the selected articles, the "related articles" function of PubMed Medline and via Google Scholar.

2.2. Studies identification

PRISMA recommendations (Moher et al., 2009) were followed in order to identify relevant studies. Two reviewers (AC, SD) independently screened titles and abstracts in a random order to identify the studies according to eligibility criteria. They also examined the full texts, assessed their eligibility. Any concerns were discussed amongst these authors and resolved through discussion and consensus. The identification, selection and inclusion process is detailed in Fig. 1.

A pre-selection of relevant articles was made after reading titles and abstracts, so as to ensure that: *i)* the articles were published after a peer review; *ii)* the studies reported original data (no review) in patients with a diagnosis of schizophrenia spectrum disorder as defined by the DSM-IV (American Psychiatric Association, 2000) or the DSM-5 (American Psychiatric Association, 2013) (schizophrenia, schizoaffective disorder or first episode schizophrenia); *iii)* the articles' findings included the links between childhood trauma and cerebral alterations in schizophrenia patients, using any MRI imaging method.

Eligible articles were verified after reading the complete texts. For studies that considered both schizophrenia and bipolar disorder patients, articles were excluded if the authors did not reported a subanalysis for patients with schizophrenia. In this case, we contacted the corresponding authors to retrieve the data for the subgroup of schizophrenia subjects. If these data were provided by the author, the article was included in our review.

In addition, when the authors did not report group comparisons between controls and schizophrenia patients or when the association between brain alterations and childhood trauma was not reported for controls, we contacted the corresponding author.

These unpublished results have been included in the review and are displayed in grey in Table 1.

2.3. Risk of bias assessment

For each study included in our review, we assessed the following risks of bias, reported in Table 1:

- Study population: presence of a control group, number of subjects included;
- Childhood trauma assessment tool: validated scale, validated cut-off considered when separating the population into subgroups according to the presence or absence of a history of childhood trauma;
- Quality of the imaging method: normalization method (linear, DARTEL …), visual inspection of the images (before or after automatic processing), motion correction, smoothing adapted to the structures of interest;
- Statistics: correction for multiple comparisons, statistical threshold, corrections for age, gender, treatment and if necessary for total intracranial volume.

If the authors computed both uncorrected and corrected results for multiple comparisons, only the results that remained significant after correcting for multiple comparisons were reported in this review.

3. Results

After title, abstract, full-text screening and removal of duplicates, the final sample comprised 15 studies exploring the associations between childhood trauma and brain alterations in schizophrenia. After contacting the authors, the unpublished results of four articles were included in this review (Cancel et al., 2017, 2015; Quidé et al., 2017a; Sheffield et al., 2013). Articles included in this review are described in Table 1.

Results are summarized in Table 2.

Our screening retrieved no studies using computed tomography or magnetic resonance spectroscopy.

Several articles reported data on the same population: two articles from our team (Cancel et al., 2017, 2015), four articles used data from the G.R.O.U.P. cohort (Genetic Risk and Outcome in Psychosis) (Domen et al., 2018; Frissen et al., 2018, Habets2011; Hernaus et al., 2014), and three articles published by Benedetti & Poletti used partially the same population (Benedetti et al., 2011; Poletti et al., 2016, 2015). In addition, the groups considered in the two articles of Quidé et al. are partly composed with the same subjects (Quidé et al., 2017b, 2017a).

3.1. Contribution of morphological imaging

In 1988 the use of MRIs were demonstrated as superior to computed tomography for psychiatric research (Cohen et al., 1988) and thus recent studies exploring the links between childhood trauma and brain morphology in schizophrenia rely on MRIs.

3.1.1. Total grey matter

Four studies reported an association between the severity of childhood trauma and an overall decrease in cerebral grey matter in schizophrenia (Cancel et al., 2015; Sheffield et al., 2013; Frissen et al., 2018; Habets et al., 2011). In a large sample of subjects form the G.R.O.U.P. cohort, Habets et al. (2011) and Frissen et al. (2018) found that childhood trauma was associated with decreased cortical thickness and total grey matter volume in schizophrenic subjects. The two VBM (voxel-based morphometry) studies included in this review reported an association between a total grey matter volume decrease and different subtypes of trauma, sexual abuse (Sheffield et al., 2013) and emotional neglect (Cancel et al., 2015).

In addition, the results from these studies suggest a different sensitivity to early stressors between schizophrenia subjects and healthy controls or healthy relatives to schizophrenia patients.

In the G.R.O.U.P. cohort, Habets et al. found that the association between childhood trauma and total cortical thickness was stronger in the schizophrenia group compared to the control group (Habets et al., 2011). In our previous study, the correlation between emotional neglect and a total grey matter decrease was lower in the control group than in the schizophrenia group (Cancel et al., 2015). Frissen et al. reported a difference between patients and healthy controls regarding the strength

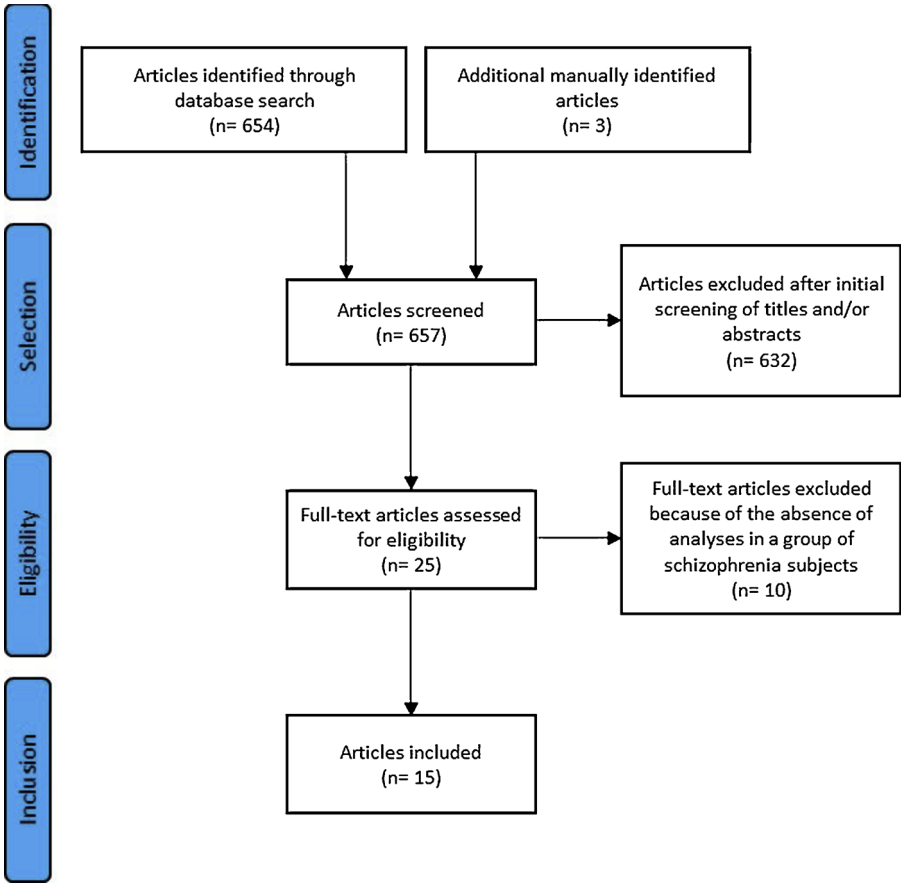

Fig. 1. Flow chart of article selection process.

of the association between early trauma and total grey matter volume (Frissen et al., 2018). Concerning the effects of early trauma in healthy siblings of schizophrenia subjects, Habets et al. reported that healthy relatives displayed an opposite effect to schizophrenia subjects with an increased cortical thickness linked to early trauma (Habets et al., 2011). In order to explain these volume increases in relatives, the authors suggested that trophic mechanisms linked to stress adaptation processes may be at play in resilient subjects spared from schizophrenia development. In the same G.R.O.U.P. cohort, Frissen et al. found that the strength of the association in siblings between early trauma and total grey matter volume significantly differed from schizophrenia subjects. Moreover, this significant association between childhood trauma and total grey matter volume had no such correlation in the sibbling's group (Frissen et al., 2018).

Although considering different dimensions of childhood trauma, these results are concordant: childhood trauma is associated with decreased grey matter volume and decreased overall cortical thickness in schizophrenia. In addition, the association between severity of trauma and decrease in grey matter is greater in schizophrenics than in unrelated controls. This result suggests a different sensitivity to early stressors, based on liability to illness, with schizophrenia subjects probably who probably have more genetic and environmental susceptibility factors than healthy control subjects.

3.1.2. Regional grey matter

We found five morphological studies that explored regional effects of childhood trauma in schizophrenia. Two of these were whole-brain studies in VBM (Cancel et al., 2015; Poletti et al., 2016), one was a whole-brain cortical thickness study (Habets et al., 2011), one was a VBM study focusing on regions of interest (Benedetti et al., 2011) and one was a genetic imaging study of hippocampal volume measured by surfacic method (Hernaus et al., 2014).

Four studies reported alterations of the prefrontal cortex (PFC) in relationship to childhood trauma in schizophrenic subjects. In our whole-brain VBM study, our team reported a negative association between the severity of emotional neglect experienced in childhood and the density of grey matter in the dorso-lateral prefrontal cortex (DLPFC), itself linked to the severity of the disorganization (Cancel et al., 2015). Sheffield et al. found a negative correlation between sexual abuse during childhood and the volume of the prefrontal part of the middle frontal gyrus and the volume of the mid cingular cortex (Sheffield et al., 2013).

Using the same VBM methodology, Poletti et al. described decreases in the volume of the orbitofrontal cortex (OFC) and the thalamus in schizophrenia patients compared to healthy controls (Poletti et al., 2016). However, when both groups were divided into high and low level of trauma exposure according to the median score of the Risky Familly Questionnaire or RFQ (Felitti et al., 1998), these differences in grey matter volumes between schizophrenia patients and controls were found only for subjects exposed to high levels of early stress. This suggests that usual morphological brain differences found between schizophrenic subjects and healthy subjects are present only in those with childhood trauma, while unexposed schizophrenia subjects are not different from healthy unexposed subjects.

Benedetti et al. published the first multimodal MRI study, with morphological and functional analyses (Benedetti et al., 2011). The functional results are detailed in paragraph 3.2. The VBM analyses included four regions of interest (ROI) selected for their simultaneous association with schizophrenia and early stressors: amygdala, hippocampus, anterior cingulate cortex (ACC) and PFC. Benedetti et al. analysed the ROI differences in grey matter volume between 10 schizophrenic patients with the lowest scores to RFQ and 10 schizophrenic

Table 1
Articles exploring the associations between childhood trauma and brain alterations in schizophrenia. Grey shaded results are unpublished results. *ACC: anterior cingulate cortex; AD, RD, MD: axial, radial and mean diffusivity; CECA: Childhood Experience of Care and Abuse; CT: childhood trauma; CTQ: Childhood Trauma Questionnaire; Ctrl: control; DTI: diffusion tensor imaging; FA: fractional anisotropy; MD: mean diffusivity; mPFC: medial prefrontal cortex; PCC: posterior cingulate cortex; PFC: prefrontal cortex; PPI: psychophysiological interaction; RFQ: Risky Families Questionnaire; ROI: region of interest; SCZ: schizophrenia; ToM: theory of mind; TPJ: Temporoparietal junction; VBM: voxel-based morphometry.*

Article	SCZ group (SCZ, first episode, affective or non-affective psychosis)	Ctrl group	CT evaluation	Imaging (MRI type, field strength, ± task, software, ± main measure, ROI or whole-brain)	Limitation, risks of bias	Main results
Asmal et al., 2019	77 (first episode SCZ)	51 Ctrl	CTQ short form	DTI 3.0T FSL software FA Whole-brain		Compared to Ctrl exposed to high levels of CT, SCZ exposed to high levels of CT had lower FA in: - inferior and superior longitudinal fasciculus (temporal part) - inferior fronto-occipital fasciculus - no significant results for CTQ sub-scales In SCZ patients sexual abuse was associated with reduced FA in: - right inferior fronto-occipital fasciculus - inferior longitudinal fasciculus - forceps major In SCZ patients emotional neglect was associated with higher FA in: - right superior longitudinal fasciculus No significant results in the Ctrl group for an association between CT and FA. No significant result in FA in SCZ group for Total CTQ.
Benedetti et al., 2011	20 (SCZ)	20 Ctrl	RFQ	fMRI and morphological MRI 3.0T fMRI: emotional task (faces) SPM5 ROI: amygdala, hippocampus, ACC and PFC Morphological MRI : SPM5 (VBM toolbox) VBM: grey matter volume ROI: amygdala, hippocampus, ACC and PFC	Small number of subjects No correction for age and gender No RFQ cut-off (high and low levels defined by the median score) No whole-brain analysis Control condition of the task is very different from the condition of interest (geometric forms vs faces) For fMRI analysis: primary threshold at $p < 0,005$ uncorrected For VBM : simple normalisation (no DARTEL), no visual inspection of the quality of segmentation Some subjects could have been included in other studies considered in this review (1,2)	Conjunction analysis (effects of both diagnostic and CT) : Hippocampus activity during the task (non-significant if adjusted for treatment) - SCZ had higher activity than Ctrl - Subjects with low CT had higher activity than with high CT exposure ACC activity during task (significant only if adjusted for treatment) - Ctrl had higher activity than SCZ - Subjects with high CT exposure had higher activity than with low CT ACC and PFC grey matter volumes: - SCZ had decreased ACC and PFC volumes compared to Ctrl - Subjects with high CT exposure had increased ACC and PFC volumes than subjects with low CT
Cancel et al., 2015	21 (SCZ)	30 Ctrl	CTQ	Morphological MRI 3.0T SPM8 VBM: grey matter density whole-brain	Small number of subjects Same population than Cancel et al., 2017 (3)	In both groups: Negative correlation between total grey matter volume and emotional neglect, with stronger correlation in SCZ group than in Ctrl group. In SCZ group: - Negative correlation between emotional neglect and grey matter density in dorso-lateral PFC. - Structural equation modelling: Emotional neglect predicts grey matter density in dorso-lateral PFC, which predicts severity of disorganization. In Ctrl group: no significant correlation between emotional neglect or total CTQ and grey matter density.

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Table 1 (*continued*)

Article	SCZ group (SCZ, first episode, affective or non-affective psychosis)	Ctrl group	CT evaluation	Imaging (MRI type, field strength, ± task, software, ± main measure, ROI or whole-brain)	Limitation, risks of bias	Main results
Cancel et al., 2017	21 (SCZ)	25 Ctrl	CTQ	fMRI 3.0T Emotional task (faces and scenes) SPM8 PPI (functional connectivity) Whole-brain amygdala functional connectivity and whole-brain ACC functional connectivity	Small number of subjects High primary threshold for PPI ($p_{voxel} < 0,005$ uncorrected, then $p_{cluster} < 0,05$ FWE-corrected) Same population than Cancel et al., 2015(4)	In SCZ group: - Sexual abuse and physical neglect are both associated to a decreased connectivity between amygdala and precuneus/PCC in negative emotional valence condition. - Emotional neglect is associated to an increased connectivity between amygdala and TPJ in negative emotional valence condition. - Emotional abuse is associated to a decreased connectivity between ACC and precuneus/PCC in incongruent emotional condition. In Ctrl group : - Sexual abuse is associated to an increased connectivity between ACC and precuneus/PCC in incongruent emotional condition. No significant result for connectivity between ACC and precuneus/PCC in Ctrl group PCC in incongruent emotional condition No significant result for fMRI activation analysis. Connectivity between amygdala and precuneus/PCC is deceased in SCZ subjects compared to Ctrl in negative valence condition.
Domen et al., 2018	85 (non affective psychosis) (55 at 3-years follow-up)	80 Ctrl (49 at 3-years follow-up) 93 siblings (55 at 3-years follow-up)	CTQ short form	DTI 3.0T FSL Whole-brain mean FA	Mean FA and no regional results Results from the G.R.O.U.P. cohort : same population than Habets et al. (5), Hernaus et al. (6) and Frissen et al. (7)	At baseline : - Group x CT interaction was associated with decreased FA - In SCZ: decreased FA in subjects exposed to high CT - In Ctrl: no significant result At 3-years follow-up, in SCZ patients, high CT was associated with FA decrease. Decrease is different from Ctrl and siblings.
Frissen et al., 2018	89 (non affective psychosis)	87 95 Siblings	CTQ short form	Morphological MRI 3.0T Freesurfer Total grey matter volume Whole-brain (total grey matter volume)	No regional analysis No CTQ sub-scores (only total CTQ score) Results from the G.R.O.U.P. cohort: same population than Domen *et al.* (8), Habets *et al.* (5) and Hernaus *et al.*(6)	In the SCZ group: CT are associated with decreased total grey matter volume. No significant result in Ctrl or in sibling group for the association between CT and total grey matter volume. The strength of this association between CT and total grey matter volume is higher in the SCZ group than in Ctrl group and in siblings groups. Total grey matter volume is decreased in SCZ compared to the other groups.
Habets et al., 2011	88 (affective and non affective psychosis)	87 Ctrl 98 Siblings	CTQ short form	Morphological MRI 3.0T Freesurfer Cortical thickness Whole -brain	Results from the G.R.O.U.P. cohort: same population than Domen *et al.* (8), Hernaus *et al.* (6) and Frissen *et al.*(7)	Interaction group x CT: CT is associated with deceased cortical thickness, especially in SCZ group In SCZ group: CT is associated with decreased global cortical thickness In Ctrl group: Non significant results In Siblings group: CT is associated with an increased global cortical thickness No significant result for regional analysis.

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Table 1 (*continued*)

Article	SCZ group (SCZ, first episode, affective or non-affective psychosis)	Ctrl group	CT evaluation	Imaging (MRI type, field strength, ± task, software, ± main measure, ROI or whole-brain)	Limitation, risks of bias	Main results
Hernaus et al., 2014	89 (affective and non affective psychosis)	95 Siblings	CTQ short form	Morphological MRI 3.0T Freesurfer ROI : Hippocampal volume	No Ctrl group Results from the G.R.O.U.P. cohort : same population than Domen *et al.* (8), Habets *et al.* (5) and Frisen *et al.*(7)	Negative results: - Hippocampal volume is not dependent of the CT x group interaction - Hippocampal volume is not dependent of the CT x BDNF or FKBP5 interaction
Kasanova et al., 2016	12 (untreated non affective psychosis)	12 Ctrl	CECA	PET (dopamine system) 1.5T Social stress task SPM8 D2/D3 receptors ([^{18}F]fallypride) ROI: mPFC	Small number of subjects No limbic ROI	No significant result in the SCZ group In Ctrl group, CT is associated with an increased stress-related DA activity in mPFC (especially for early childhood trauma and in the ventral portion of mPFC)
Molina et al., 2018	19 (SCZ)	13 Ctrl	CTQ (probably short form)	DTI 3.0T FSL, Freesurfer and MRtrix FA ROI: tracks between right rostral lateral prefrontal and cingulate, caudate and tracts between left superior-medial prefrontal and hippocampus, thalamus, caudate (ROI from previous study (9))	Small number of subjects No information on the sub-group (from previous study (9) No whole-brain analysis No correction for multiple comparisons No correction for age, gender or treatment	In the SCZ group physical neglect is associated with decreased FA in left superior-medial prefrontal-hippocampus tract No significant result in the Ctrl group or for other types of CT in the SCZ group
Poletti et al., 2016	96 (SCZ)	136 Ctrl	RFQ	Morphological MRI 3.0T SPM8 (VBM toolbox) VBM: grey matter volume Whole-brain	No RFQ cut-off (high and low levels defined by the median score) No visual inspection of the grey/white matter segmentation VBM toolbox No correction for educational level when the groups differs for educational level Some subjects could have been included in other studies considered in this review (2,10)	In total groups as well as in sub-groups with high CT levels, SCZ subjects have decreased grey matter volume compared to Ctrl in: - Bilateral OFC - Left thalamus No significant result in groups with low CT levels.
Poletti et al., 2015	83 (SCZ)	0	RFQ	DTI 3.0T FSL FA, MD, AD and RD Whole brain	No Ctrl group No correction for multiple comparisons Some subjects could have been included in other studies considered in this review (1,10)	In SCZ, CT is associated with decreased FA in: - corpus callosum - left cingulum - left corona radiata - bilateral superior longitudinal fasciculus - left inferior longitudinal fasciculus - left anterior thalamic radiation In SCZ, CT is associated with increased MD in: - right superior fronto-occipital fasciculus - right inferior fronto-occipital fasciculus - right inferior longitudinal fasciculus - right corticospinal tract - anterior and posterior right thalamic radiation - forceps major - forceps minor - right cingulum - corpus callosum - right anterior, posterior and superior corona radiata - uncinate fasciculus

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Table 1 (*continued*)

Article	SCZ group (SCZ, first episode, affective or non-affective psychosis)	Ctrl group	CT evaluation	Imaging (MRI type, field strength, ± task, software, ± main measure, ROI or whole-brain)	Limitation, risks of bias	Main results
Quidé et al., 2017a	50 (affective and non affective psychosis)	45 Ctrl	CTQ short form	fMRI 3.0T Visual working memory task SPM8 and SPM12 Whole brain	No CTQ sub-scores (only total CTQ score) High primary threshold ($p_{voxel} < 0,005$ uncorrected, then $p_{cluster} < 0,05$ FWE-corrected)	In the context of the task, in SCZ group, exposition to CT is associated with increased activation (or decreased de-activation) in: - left superior temporal gyrus (including temporal pole and Heschl gyrus) - left posterior insula - left post-central gyrus and rolandic operulum In the context of the task and compared to exposed to CT Ctrl, exposed to CT SCZ have increased activation (or decreased de-activation) in: - right cuneus - bilateral TPJ - bilateral posterior insula No significant result for comparisons between unexposed SCZ and unexposed Ctrl No significant result for comparison between exposed Ctrl and unexposed Ctrl
Quidé et al., 2017b	47 (affective and non affective psychosis)	0	CTQ short form	fMRI 3.0T ToM task SPM8 Whole-brain and ROI	No CTQ sub-scores (only total CTQ score) No Ctrl group	In the context of the ToM task in SCZ, CT are associated with: - increased activation of PCC/precuneus (ROI analysis) - increased activation of the dorso-medial PFC (whole-brain analysis) - decreased activation of the right anterior TPJ (whole-brain analysis)
Sheffield et al., 2013	43 (affective and non affective psychosis)	26 Ctrl	CTQ short form	Morphological MRI 3.0T SPM8 (VBM toolbox) VBM: grey matter volume Whole-brain	VBM toolbox No correction for total intracranial volume or total grey matter volume	In SCZ group sexual abuse is associated with decreased total grey matter volume In SCZ group sexual abuse is associated with decreased grey matter volume in left middle frontal gyrus and in mid ACC

Table 2
Summary of the results: associations between childhood trauma (CT) and brain alterations in schizophrenia.

Morphological imaging	
Grey matter (GM)	
Benedetti et al. (2011)	CT is associated with: ↓ GM in SCZ compared to Ctrl in ACC and PFC ↑ GM in subjects with high CT compared to low CT exposure in ACC and PFC
Habets et al. (2011)	CT is associated with: ↓ cortical thickness in the interaction analysis (Group x CT) ↓ cortical thickness in SCZ ↑ cortical thickness in siblings NS in Ctrl
Sheffield et al. (2013)	Sexual abuse associated with: ↓ total GM volume in SCZ ↓ GM in SCZ left middle frontal gyrus and mid cingular cortex
Cancel et al. (2015)	Emotional neglect associated with: ↓ total GM volume in SCZ and Ctrl ↓ GM in SCZ right DLPFC (associated with disorganization)
Frissen et al. (2018)	CT is associated with: ↓ total GM volume in SCZ NS in Ctrl, siblings
White matter (WM)	
Poletti et al. (2015)	CT is associated with: ↓ FA in SCZ corpus callosum, left cingulum, left corona radiata, bilateral superior longitudinal fasciculus, left inferior longitudinal fasciculus and left anterior thalamic radiation ↑ MD in SCZ right superior fronto-occipital fasciculus, right inferior fronto-occipital fasciculus, right inferior longitudinal fasciculus, right corticospinal tract, anterior and posterior right thalamic radiation, forceps major, forceps minor, right cingulum, corpus callosum, right anterior and posterior and superior corona radiata, uncinate fasciculus
Molina et al. (2018)	Physical neglect associated with: ↓ FA in SCZ left superior-medial prefrontal-hippocampus tract NS in Ctrl
Domen et al. (2018)	CT is associated with: ↓ FA in the interaction analysis (group X CT) ↓ FA in SCZ NS in Ctrl ↓ FA in SCZ at 3 years follow-up
Asmal et al. (2019)	CT is associated with: ↓ FA in SCZ compared to Ctrl in inferior and superior longitudinal fasciculus (temporal part) and inferior fronto-occipital fasciculus NS in Ctrl Sexual abuse associated with: ↓ FA in SCZ in right inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and forceps major Emotional neglect associated with: ↑ FA in SCZ in right superior longitudinal fasciculus
Functional imaging	
Benedetti et al. (2011)	CT is associated with: ↑ hippocampus activity during emotional task in SCZ compared to Ctrl ↓ hippocampus activity during emotional task in subjects with high CT compared to low CT exposure ↓ ACC activity during emotional task in SCZ compared to Ctrl ↑ ACC activity during emotional task in subjects with high CT compared to low CT exposure
Cancel et al. (2017)	Sexual abuse and Physical neglect associated with: ↓ connectivity between amygdala and precuneus/PCC in SCZ (negative emotional valence condition) Emotional neglect associated with: ↑ connectivity between amygdala and TPJ in SCZ (negative emotional valence condition) Emotional abuse associated with: ↓ connectivity between ACC and precuneus/PCC in SCZ (incongruent emotional condition) Sexual abuse associated with: ↑ connectivity between ACC ans precuneus/PCC in Ctrl (incongruent emotional condition)
Quide et al. (2017a)	CT is associated with: ↑ activation in working memory task in SCZ in left superior temporal gyrus (including temporal pole and Heschl gyrus), left posterior insula, left post-central gyrus and rolandic operulum CT exposed SCZ compared to CT exposed Ctrl have: ↑ activation in working memory task in right cuneus, bilateral TPJ and bilateral posterior insula NS for unexposed SCZ compared to unexposed Ctrl NS for exposed Ctrl compared to unexposed Ctrl
Quide et al. (2017b)	CT associated with: ↑ activation in TOM task in SCZ in precuneus/PCC and in DLPFC ↓ activation in TOM task in SCZ in right anterior TPJ
Molecular imaging	
Kasanova et al. (2016)	CT associated with: ↑ stress-related dopamine activity in Ctrl in mPFC NS in SCZ

ACC: anterior cingulate cortex; CT : childhood trauma; Ctrl: controls subjects; DLPFC: dorsolateral prefrontal cortex; FA: fractional anisotropy; GM: grey matter, SCZ: schizophrenia patients; MD: mean diffusivity; mPFC: medial prefrontal cortex; NS: non significant results; PCC: posterior cingulate cortex; PFC: prefrontal cortex; TOM: theory of mind; TPJ: temporo-parietal junction.

patients with the highest scores. There was an interaction effect between early stress and diagnosis on the volumes of the PFC and the ACC. Schizophrenia was associated with reductions in ACC and PFC volumes and, unlike the other studies in this section, exposure to childhood trauma was associated with increases in volume. To the best of our knowledge this result has not been replicated and it also contradicts the latter literature that applies more recent methodological standards in neuroimaging (Barnes et al., 2010).

None of the article included in our review mentioned any significant hippocampal results. Benedetti et al. did reported no significant results for the limbic system structures included in the ROIs: the amygdala and the hippocampus (Benedetti et al., 2011). Whole-brain studies from Cancel et al., Habets et al., Poletti et al. and Sheffield did not report a significant result in the hippocampus (Cancel et al., 2015; Sheffield et al., 2013; Habets et al., 2011; Poletti et al., 2016).

Many studies reported decreases in the volume of the hippocampus, linked on one hand to trauma in healthy subjects (Frodl and O'Keane, 2013) or to BDNF variants associated with genetic vulnerability for schizophrenia (Carballedo et al., 2013; Frodl et al., 2014), or, on the other hand, being linked to schizophrenia (Haijma et al., 2013; Shepherd et al., 2012). These results may have suggested that the effect of childhood trauma on hippocampal volume was mediated by genetic vulnerability. The authors who worked on the G.R.O.U.P. cohort performed a Genes x Environment interaction study on the volume of the hippocampus, measured by the surfacic method (Hernaus et al., 2014). This study evaluated the effect of childhood trauma on hippocampal volume interacting i) with the group effect (schizophrenia patient compared to healthy siblings) and ii) with the effect of the expression of genes of interest, BDNF and FKBP5. Here again, they did not report significant results.

Thus, contrary to the results on global grey matter reductions in relationship to childhood trauma in schizophrenia, the results concerning grey matter in specific regions are mostly inconsistent. Three out of five reviewed studies suggest that a decrease in the volume of the PFC is associated with the severity of childhood trauma in schizophrenia (Cancel et al., 2015; Sheffield et al., 2013; Poletti et al., 2016). One study had non-significant results for PFC (Habets et al., 2011) and one study (even if less methodologically rigorous) reported contradictory results with decreasing CPF volume in schizophrenia but increased volume in subjects with high levels of childhood trauma (Benedetti et al., 2011). No study, with whole-brain or ROI approach, found an association with hippocampus volume and childhood trauma in schizophrenia. Finally, in schizophrenia subjects, only one study reported an association between trauma and decreased thalamus volume (Poletti et al., 2016) and one study between trauma and increased ACC volume (Sheffield et al., 2013).

These discrepancies may be due to different imaging methodologies which include covariates that significantly modify brain morphological measurements, such as age, gender, total intracranial volume and treatments. Another source of divergent findings are confounding factors, particularly the genetic or environmental vulnerability factors associated with schizophrenia such as the socio-economic level, urbanicity or substance abuse such as cannabis.

3.1.3. White matter

We included in this review four studies which explored links between childhood trauma and white matter in schizophrenia (Domen et al., 2018; Poletti et al., 2015; Asmal et al., 2019; Molina et al., 2018). All four studies used diffusion tensor imaging (DTI). Poletti et al. reported results for parameters that reflects the integrity of axons and myelin sheaths (axial diffusivity, AD), myelination disruption (radial diffusivity, RD), membrane density (mean diffusivity, MD) and more generally the integrity of white matter fibers (fractional anisotropy, FA) (Poletti et al., 2015). The three other studies reported results only for FA, in whole brain analysis (mean FA for Domen et al. (2018), and whole brain regional analysis for Asmal et al. (2019) or in ROI (Molina et al., 2018).

Domen et al. reported a decrease in mean cerebral FA associated with high levels of trauma in schizophrenia subjects (Domen et al., 2018). More specifically, in a group of 83 schizophrenia patients, the severity of childhood trauma was negatively correlated with the FA and positively to the MD in many bundles, suggesting diffuse alterations in white matter (Poletti et al., 2015). These abnormalities were found in the corpus callosum, cingulum, superior and inferior longitudinal fasciculi, thalamic radiation, superior and inferior fronto-occipital fasciculus, previously described as altered in schizophrenia (Ellison-Wright and Bullmore, 2009), but also in the corona radiata, the cortico-spinal tract, the major and minor forceps, and the uncinate fasciculus.

Alterations in white matter integrity associated with childhood trauma is also found reported by Asmal et al. (2019). In schizophrenia subjects exposed to severe trauma and in comparison to exposed controls, trauma was associated with abnormalities in inferior and superior longitudinal fasciculi (temporal part) and in inferior fronto-occipital fasciculus. Additionally, in the schizophrenia group, sexual abuse was associated with reduced FA in right inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and forceps major and emotional neglect was associated in higher FA in right superior longitudinal fasciculus. All these alterations were found in the schizophrenia group but not in the control group.

The It should be noted that this study is the only one of our review (with that of Domen et al. whose results are limited to a measure of average total FA) whose methodology does not seem exploratory (group size over 50, corrections for multiple comparisons, whole-brain analysis, covariates such as age, gender and educational level of parents, etc.).

Molina et al. reported an association between physical neglect and white matter tracts connecting the superior-medial prefrontal cortex and the left hippocampus (Molina et al., 2018). These results were post-hoc and centered on ROI issued from a previous study (Molina et al., 2017) and we note that the authors did not report the whole-brain results.

Thus, despite the very recent interest in exploring the white matter alterations linked to childhood trauma in schizophrenia, some results have already been replicated. This is the case of the alterations of the following bundles: inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculus and forceps major. These tracts were found to be altered in schizophrenia subjects exposed to high levels of childhood trauma and are different from the abnormalities found in controls or unexposed subjects.

3.2. Contribution of functional imaging

Three functional imaging articles reported changes in brain activity related to childhood trauma in schizophrenia and one article reported changes in functional connectivity. We note that the tasks used in these studies were different.

Only one study reported changes in hippocampal activity linked to trauma (Benedetti et al., 2011). The fMRI task consisted of an emotional visual task and the contrast of interest was the condition "faces" (where the subjects had to recognize the negative expression of faces that were presented to them) versus the control condition (recognition of geometric shapes). The methods were identical to that used in the same article exposing morphological findings i.e. groups divided into high and low level of exposure depending on median score of RFQ and ROI analysis. Hippocampal activity was modified by the group x trauma interaction. Schizophrenia subjects showed increased hippocampal activation compared to controls, whereas high levels of childhood trauma were associated with a decreased activation. This indicates that schizophrenia and exposure to trauma were associated with inverse modification in hippocampal activation. However, the result was no longer significant after adjusting for antipsychotic treatment. The authors reported inverse results in this same condition in ACC: a decreased ACC

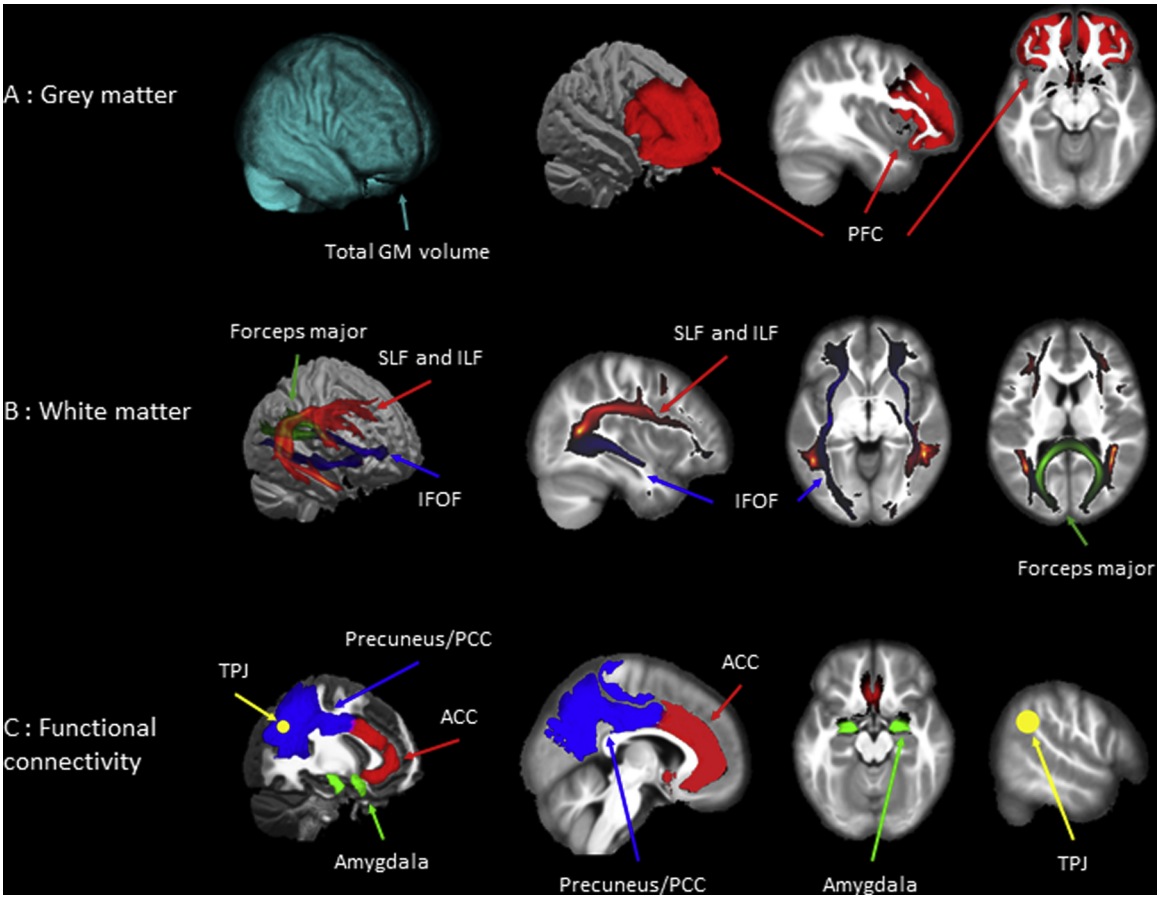

Fig. 2. Graphic summary of brain regions with replicated results showing association between childhood trauma and neuroimaging alterations in schizophrenia. Childhood trauma in schizophrenia is associated with A) decreased total grey matter volume and decreased prefrontal cortex grey matter volume/density; B) alterations of the white matter integrity in the inferior and superior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the forceps major; C) functional connectivity alterations in a network including the amygdala, the anterior cingulate cortex, the precuneus/posterior cingulate cortex region and the temporo-parietal junction.
GM: grey matter; PFC: prefrontal cortex; SLF: superior longitudinal fasciculus; ILF: inferior longitudinal fasciculus; IFOF: inferior fronto-occipital fasciculus; TJP: temporo-parietal junction; PCC: posterior cingulate cortex; ACC: anterior cingulate cortex.

activation in patients compared to controls, but an increased activation with higher levels of childhood trauma, significant only in the adjusted model for doses of antipsychotic treatment.

Quidé et al. published two studies on the same sample (Quidé et al., 2017b, 2017). Their first study concerned the effect of childhood trauma on whole brain activity during a visual task involving working memory. In the group of schizophrenia patients and under demanding working memory conditions, childhood trauma was associated with an increased activation (in fact, a decreased de-activation) in a fronto-temporo-parietal and insula cluster (see Table 1 for details). Comparisons between schizophrenia subjects exposed to trauma and exposed control subjects revealed an increased activation in regions largely overlapping those found in schizophrenia exposed versus unexposed. This large cluster included the insula, the temporo-parietal junction (TPJ) and the right cuneus which are regions involved in the treatment of sensory impulses. No results were significant for the other group comparisons (between unexposed schizophrenia patients versus unexposed controls and between exposed and non-exposed controls). These results suggest that the activation increase in the fronto-temporo-parieto-insular cluster were mainly found in schizophrenia subjects exposed to childhood trauma.

In their second study Quidé et al. investigated the associations between childhood trauma and brain activity in a group of schizophrenia subjects during a theory of mind task (Quidé et al., 2017b). Early trauma was negatively correlated with activation of the right TPJ and was positively correlated with activation of the precuneus/posterior cingulate cortex (PCC) region and the dorsolateral prefrontal cortex (DLPFC).

These regions have already been linked to deficits in theory of mind in schizophrenia (Bosia et al., 2012) and have also been linked to childhood trauma in these patients in the only functional connectivity study in this review (Cancel et al., 2017). Cancel et al. reported that, in schizophrenia subjects and in relation to the negative emotional valence condition, sexual abuse and physical neglect were associated with decreased connectivity between the amygdala and the precuneus/PCC region. There was also an association between emotional neglect and increased connectivity between amygdala and TPJ. In addition, during an emotional incongruency task, emotional abuse was associated with decreased connectivity between ACC and the precuneus/PCC region.

These results echo those from Quidé et al. (2017b) and highlight, in schizophrenia patients, a link between various types of childhood trauma and a network including the amygdala, the ACC, the precunus/PCC region and the JTP. Although the tasks were different, these two whole-brain studies, reported alterations in similar regions previously involved in social cognition. However, the designs of these studies did not allow us to compare these associations between schizophrenia subjects and controls and to understand whether this is a general effect of childhood trauma or a specific effect of these traumas only present in schizophrenia subjects.

3.3. Contribution of molecular imaging

Our review contains a single study that explored the modification of dopaminergic activity linked to childhood trauma in schizophrenia patients never having received antipsychotic treatments (Kasanova et al., 2016).

Kasanova et al. measured dopamine release in the medial PFC during a social stress task in 12 schizophrenia subjects and 12 matched control subjects. Their results were negative in schizophrenia subjects, where no correlation was found between childhood trauma and dopamine release in mPFC, whereas there was a positive correlation in the control group between trauma and dopaminergic activity in this region, especially for early childhood trauma and in the ventral portion or mPFC. This negative result, although gathered from a single study, suggests that the impact of trauma on the pathophysiology of schizophrenia would not be associated with altered prefrontal dopaminergic activity.

4. Discussion

Since the first study in 2011, links between childhood trauma and brain alterations in adult schizophrenia patients have been explored in more than 15 articles. Imaging studies have been conducted with morphological imaging techniques using VBM, surfacic method or DTI, and functional imaging consisted in activation as well as functional connectivity. Only one study was conducted with molecular imaging method.

Replicated results are reported in Fig. 2.

The most reproduced result is the association between childhood trauma severity and an overall decrease in cerebral grey matter in schizophrenia. This association between trauma severity and grey matter decrease is stronger in schizophrenia subjects than in unrelated controls. This increased sensitivity to early stressors in patients may be due to genetic vulnerability but also to other environmental risk factors for schizophrenia and raises the question of multiple interactions between different risk factors. Future studies on the impact of childhood trauma in schizophrenia should consider these interactions, with Genes x Environment or Environment x Environment models or by adjusting the results for the other environmental risk factors. Indeed, there is an important co-occurrence of these factors, some subgroups of the population combining genetic vulnerability, urbanicity, childhood trauma, migration, cannabis use in adolescence, etc. (van Os et al., 2010).

In addition, when the authors included healthy sibblings related to schizophrenia patients, they found either no significant results (Habets et al., 2011) or an inverse result in this population compared to patients (Benedetti et al., 2011). In healthy relatives, the severity of trauma was associated with increased grey matter volumes. This result, which needs to be replicated, may be related to different genetic makeup, to different environmental factors or to the effect of the pathology itself. However, they may also be effects of mechanisms of resilience and individual coping in vulnerable but non-developing subjects who are the healthy relatives of schizophrenic subjects (Feder et al., 2009). Future studies comparing schizophrenia subjects, healthy controls and healthy siblings of schizophrenia patients need to be conducted in order to explore the difference of sensitivity to early life stress in these groups.

Several authors suggest that the association between early stress and brain alterations in schizophrenia would be present only in patients with significant trauma, exceeding the thresholds considered as significant in the assessment scales. This observation raises the question of identifying subgroups of schizophrenia patients, vulnerable to early environmental risk factors, exhibiting specific brain alterations, and even different clinical pictures from other subgroups of patients with low level of environmental vulnerability. This hypothesis, developed by Martin Teicher, states that for the same diagnostic category, individuals exposed to trauma are clinically, neurobiologically and genetically distinct from unexposed individuals (Teicher and Samson, 2013). Teicher also suggests that the neurodevelopmental impact of early trauma is so strong that its signal in imaging studies may be more intense than the signal associated with schizophrenia itself. Childhood trauma is therefore a major confounding factor in studies of psychiatric disorders, whether they are clinical, genetic or imaging studies. It seems possible that authors have observed effects of differences in the prevalence of trauma between groups of patients and controls rather than differences related to the pathology studied, which would partly explain the great variability of the imaging results. Thus, we believe that childhood trauma should therefore be systematically considered as a confounding factor in biological psychiatry studies.

This review did not allow us to draw conclusions about the specificity of the different types of trauma. Most of the authors considered childhood trauma as a whole or considered exposure to at least one type of trauma, without reporting results by subtypes. The studies reporting results for trauma subtypes showed alterations in similar regions for various types of childhood trauma or for total trauma exposure. These elements would be consistent with the common end-pathways hypothesis of the effects of early stressors (Morgan and Gayer-Anderson, 2016).

The underpinning mechanisms explaining the association between childhood trauma and brain alterations in schizophrenia have been widely discussed in literature. The main hypothesis is that repeated childhood trauma could cause chronic hypothalamic-pituitary-adrenal (HPA) axis hyperactivation, which leads to neurobiological alterations. Many authors have highlighted long-term biological alterations associated with childhood trauma, based on various observations in animals and in humans. Childhood trauma is associated with higher stress reactivity in adulthood (Eckenrode, 1984; Glaser et al., 2006), with higher stress sensitivity in psychotic subjects, and with higher severity of symptoms when they are exposed to stressors (Lardinois et al., 2011). Blood cortisol and inflammatory markers are increased in subjects with a history of childhood trauma (Carpenter et al., 2010). In schizophrenia patients, cortisol release is associated with more severe symptoms and altered cognition (Halari et al., 2004; Hempel et al., 2010). Early life stress is associated with lifelong HPA axis alterations. The HPA axis stress response is increased in rodents exposed to early life stress (Liu et al., 1997). In humans childhood trauma is associated with modifications of HPA axis in healthy subjects (Heim et al., 2000; Pruessner et al., 2004) and in schizophrenia subjects (Braehler et al., 2005). Moreover, in schizophrenia subjects, such HPA axis alterations are associated with symptoms severity (Belvederi Murri et al., 2012). An exposure to acute stress is associated with more important striatal dopamine release in adults exposed to childhood trauma than in non-exposed subjects (Pruessner et al., 2004), striatal dopamine release being associated with positive symptoms in schizophrenia. Childhood trauma is associated with prefrontal cortex dopamine release modifications in acute stress in healthy subjects but not in schizophrenia subjects, and could be an adaptive response to childhood trauma (Kasanova et al., 2016).

It is noteworthy that oxytocin might play a protective role towards early life stress and its consequences on the HPA axis alterations (Feder et al., 2009).

We identified limits in neuroimaging studies that explored the links between childhood trauma and schizophrenia. Thus, researchers who wish to disentangle the brain alterations consecutive to childhood trauma from alteration linked to the illness should be particularly attentive to a number of methodological issues:

- Comparison with a group of healthy subjects, or even a group of healthy relatives.
- Recruiting a group of schizophrenia patients as homogeneous as possible.
- Systematic adjustment of results for the most documented

environmental risk factors of schizophrenia: urbanicity, migration, early and heavy cannabis use, obstetric factors or obstetric complications. The adjustment to the socio-economic level should also be considered because of its interaction with the majority of these risk factors.
- Documentation of the periods of childhood at which the trauma was experienced.
- Recruitment of large samples to allow performing Genes x Environment or Environment x Environment interaction models, with other co-occurring risk factors that interact with childhood trauma.
- Publication of results, even non-significant, or available data concerning the different subtypes of childhood trauma.
- Perform replication studies.

5. Conclusion

Our review of the literature on the association between childhood trauma and neuroimaging alterations in schizophrenia rendered multiple replicated results that included childhood trauma being associated with: i) decreased total cerebral grey matter, particularly in prefrontal cortex, ii) alterations of the white matter integrity in the inferior and superior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the forceps major, iii) functional connectivity alterations in a network including the amygdala, the anterior cingulate cortex, the precuneus/posterior cingulate cortex region and the temporo-parietal junction.

Because of the increased vulnerability of schizophrenia patients and the alteration of regions and networks implicated in high level and social cognition, this review suggests specific and long term impacts of early life stress in the physiopathology of schizophrenia.

Additionally, our findings encourage investigators to conduct wider explorations focusing on the interactions between childhood trauma and schizophrenia in future studies while taking into account the methodological issues identified in our review.

Declaration of interest

The authors have no declared conflict of interest in relation with this article.

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