Title of the study (one request per article):
Childhood adversity and brain structure

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Wave (more options are possible):

- ☐ Rondom zw – 20 weeks
- ☐ Rondom zw – 30 weeks
- ☐ Rondom 0 – 5 mo
- ☐ Rondom 0 – 10 mo
- ☐ Rondom 3 (not available yet)
- ☐ Rondom 6 (not available yet)
- ☒ Rondom 9
- ☐ Rondom 12 (not available yet)
- ☐ Rondom 15 (not available yet)

We ask you to provide us with a clear background, methods section and data-analysis plan. These parts of the proposal will be publicly displayed for reference.

Background of the project (max. 500 words): Please provide a short background including the rational of your study as you would do in an introduction of the paper

During childhood the structure of the brain changes. Different brain regions mature following region-specific developmental trajectories (Mills et al., 2016; Foulkes et al., 2018). At the same time, the microstructure of the white matter tracts changes (Brouwer et al., 2012) resulting in reorganization of networks (Wierenga et al., 2018). The development in this period is so essential and time-sensitive, that experiences during childhood can shape brain development. Childhood adversity, including poverty, bullying, parental divorce and maltreatment, impacts brain structure and function (Teicher et al 2003; Lupien et al., 2009; McCrory et al., 2010; Pechtel & Pizzagalli, 2011; Hart & Rubia 2012). Although these alterations may be adaptive on the short-term, they are associated with cognitive deficits (De Bellis et al., 2009) and an increased vulnerability to develop a psychiatric disorder later in life (Kessler et al., 2010; Croft et al., 2019). Accumulated negative life events and chronic adversity have a higher impact than a singular negative life event (Evans et al., 2013). The negative effect of adversity can be buffered by protective factors, such as a closeness to grandparents (Flouri et al., 2010).

Magnetic resonance imaging (MRI) studies on childhood adversity started with a strong focus on the fronto-limbic network (frontal cortex, hippocampus and amygdala) (Teicher et al 2003; Andersen & Teicher, 2008; Lupien et al., 2009; Tottenham & Sheridan, 2009). Brain regions with a slow postnatal developmental trajectory and a high density of glucocorticoid receptors were hypothesized to be in particular sensitive to stress (Teicher et al., 2003). A decrease in frontal cortex volume is observed in multiple studies, but the affected sub-regions varied. There are mixed findings from studies comparing amygdala volume associated with childhood adversity (increased, decreased and not-affected). A reduction in hippocampal volume is observed in some adult-samples but not all (McCrory et al., 2010; Krugers et al., 2017). A recent meta-analysis pooling studies in adults that experienced childhood adversity concluded that there is no evidence for abnormalities in the amygdala and only weak evidence for a decrease in hippocampal volume (Calem et al., 2017).

These heterogenous results are explained in different ways. First, the effect of adversity can be non-detectable during childhood but get unmasked during adolescence explaining why hippocampal volume reductions are reported mostly in adult samples (Pechtel & Pizzagalli, 2011). Second, brain regions developing at the time of the adversity are thought to be more sensitive to stress-induced abnormalities (Andersen & Teicher, 2008; Andersen et al., 2008). Third, literature is confounded by small samples with (psychiatric) comorbidities (Hart & Rubia, 2012). Fourth, different types of adversity have a differential effect on the brain (Cassiers et al., 2018). This could explain why different types of adversity are related with specific psychiatric and cognitive problems. In contrast, impaired prefrontal cortex maturation appears to be a general effect observed after any time of childhood trauma (Cassiers et al., 2018). In conclusion, there is a need

for larger samples from the general population preferably during a specific developmental window in childhood.

Although above-described explanations may account for part of the heterogeneous results, it could also be that the fronto-limbic network is not the (only) network affected by childhood adversity. Whole-brain analyses reviewed by Hart & Rubia (2012) revealed abnormalities in brain regions outside the fronto-limbic network and failed to replicate abnormalities in the hippocampus and the amygdala. Instead, a decrease in gray matter was found in different frontal regions (including the anterior cingulate cortex), parietal lobe, the caudate and the thalamus. An increase in volume was found in the cerebellum, the cingulate cortex and a part of the prefrontal cortex. The described findings are based on medication-free samples of over 20 subjects controlled for comorbidities. In addition to abnormalities in gray matter volume, diffusion-weighted imaging (DWI) studies revealed abnormalities in white matter tracts in individuals exposed to childhood adversity. Most brain regions and white matter tracts implicated in childhood adversity are part of either the fronto-limbic or the fronto-striatal network (Hart & Rubia, 2012). These networks fit the functional deficits in emotion regulation and higher cognitive functioning observed in individuals that were exposed to childhood adversity (Hart & Rubia, 2012; Krugers et al., 2017). Thus, neuroimaging studies should not limit analyses to the fronto-limbic network only, but also include the fronto-striatal network or perform whole-brain analyses.

Research question

The main question of the proposed study is: Is there an association between childhood adversity and brain structure in typically developing children? We hypothesize white matter integrity abnormalities and a reduction of gray matter volume in children that experienced negative life events compared to children that did not have these experiences. We expect these structural alterations in brain regions and white matter tracts that are part of the fronto-striatal and fronto-limbic network, but not in regions outside of these networks.

Within the group of children that experienced adversity, we expect more pronounced effects in children that were exposed to chronic aversity or accumulated negative life events, compared to children exposed to a single life event. Furthermore, we hypothesize that different types of adversity result in specific brain abnormalities, but frontal cortex abnormalities across the different types as a more general feature.

Image reprinted from: "Neuroimaging of child abuse: a critical review"
Hart and Rubia, 2012. Front. Hum. Neurosci.

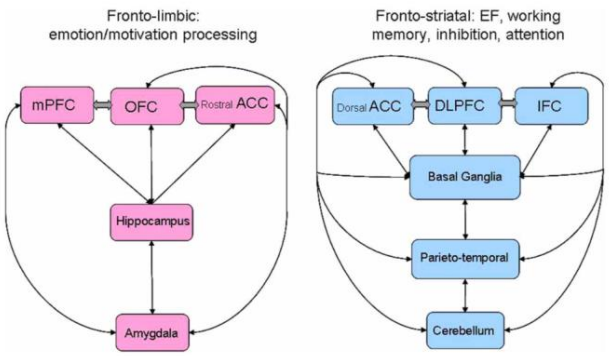

FIGURE 2 | Schematic representation of the brain regions and networks that have been implicated childhood maltreatment in functional and structural imaging studies. Deficits of fronto-limbic regions and networks have most consistently been associated with childhood abuse. However, there is some evidence from more recent studies, including whole brain imaging analyses, for deficits in fronto-striatal and fronto-cerebellar networks.

Methods Describe the methods as in the paper in which the data will be presented, according to the categories below, with a total **maximum** of 1500 words. For a description of task, methods etc. refer to the website, if possible.

Design of the study (for instance cross-sectional, longitudinal etc.; substantiate your choices)

We will use the cross-sectional data of the 8- to 10-year old children in YOUth. Information on the child's environment will be gathered based on questionnaires filled in by the parents as proxy (see data selection template). Below a list of different types of adversity that were selected because they are often studied in relation to stress or trauma. The life events and stressors are followed by the YOUth's Experiment Name were we expect to extract this information from.

- Bullying < Bullying
- Child's economic situation < Demographics
- Changes in financial situation, household or housing < Major life events & List of longterm stressful life events
- Death in family < Major life events & List of longterm stressful life events
- Child's exposure to violence < Major life events & List of longterm stressful life events
- (Mental) health problems of a first-degree family member < Family illness - medical & family illness – psychiatric & Substance (ab)use & Adult self report
- Child's health problems (only significant or chronic illnesses) < Child health

The following structural brain measures will be studied: (sub)cortical brain measures extracted from anatomy MRI scans (https://www.uu.nl/sites/default/files/smri.pdf) and characteristics of white matter tracts extracted from DWI-scans (https://www.uu.nl/sites/default/files/diffusion_weighted_imaging.pdf). Age, sex and intelligence quotient (IQ) will be used as covariates in the analyses (see *Planned sensitivity analyses* below).

Study population and sample-size (entire population or a subset; substantiate your choices e.g. Provide a rationale for the requested sample-size, for instance using a power calculation)

Based on the literature we expect small effects and therefore we will need all available data to have sufficient power.

Data processing and preparation (including necessary recoding of data etc.)

<u>Environmental, cognitive and descriptive data</u>

Categorical data (e.g. on life events, sex, economic situation) will be recoded to binary variables. Scalar data (e.g. intellectual ability and age) will remain continuous (no cut-offs).

<u>Anatomy MRI scans</u>

MRI scans will be quality checked for artefacts and severe motion. Anatomy scans will be processed with FreeSurfer's automatic segmentation pipeline (Fischl et al., 2002). FreeSurfer version 6.0 will be used to extract regional and global brain measures. These brain measures thereafter will be available for other researchers that hand in a data request on brain structure.

<u>DWI scans</u>

The YOUth MRI team is currently working on an automated quality control method for the DWI scans. In general, DWI processing consists of corrections for susceptibility artefacts, Eddy-current distortions and movement. This will be done creating a distortion map and realigning all images to the diffusion unweighted images. A diffusion tensor model will be fitted to create maps with information on the microstructure of the white matter tracts, like measures of fractional anisotropy and mean diffusivity. Fibers will be reconstructed. Next, the DWI-scans will be realigned to the anatomy MRI scans using the anatomical segmentation output of the same subjects and all fibers will be warped into model space. Fiber bundles within the fronto-striatal and fronto-limbic network will be traced using a region-of-interest approach in model space.

Handling missing data (describe how you will detect and handle missingness in the data)

We need available data from all children (collected between March 14th, 2016 and March 29th, 2019, N>1000) to test if there are differences between the full sample and our selected sample (for example different number of life events in the children without MRI data). For the main analysis we will include participants of which the following data is available: a good quality anatomy MRI scan and data on life events reported by father and/or mother and/or guardian. In the sensitivity analyses we will use only the participants with data on intellectual ability. We will estimate IQ from the WISC data

(https://www.uu.nl/sites/default/files/wisc_more_information_9-12-15_years.pdf). If only one subtask of the WISC is missing, we will base the IQ estimate on the available subtasks.

Data analysis methods (including statistical design and statistical analysis plan. If it is not possible to provide a detailed statistical plan, as this does not fit in with the research questions formulated above, please explain.)

Regression analyses will be done with R software (https://www.r-project.org). Adversity (any type of negative life event or stressor described in our selection), age and sex will be modelled as independent variables. Despite having a hypothesis on the regions of interest, we will do a whole-brain analysis looking at the effect of these variables on each brain measure in separate models. It is important to test whether hypothesized abnormalities in the regions of interest are region-specific or more global. In the main analysis we will use adversity as a binary variable (any type of adversity / no adversity). We will correct our p-values using the false discovery rate (FDR; Genovese et al., 2002) to correct for the multiple models corresponding to different brain measures. The effect of accumulated life events will be investigated in an exploratory analysis just as the comparison between different type of life events.

Planned subgroup analyses (if applicable. Substantiate your choices)

None

Planned sensitivity analyses (if applicable. Substantiate your choices)
Sensitivity analyses are analyses that you plan beforehand to test whether certain factors have a major influence on your results.

IQ

Among the strongest determinants of individual differences, a part from age and sex, is intelligence. There is consistent evidence for the link between intelligence and cortical surface and thickness (Schnack et al., 2015), total brain volume (McDaniel et al., 2005) and white matter characteristics (Schmithorst et al., 2005; Koenis et al., 2018). IQ can be compromised (temporarily) by childhood adversity (De Bellis et al., 2009). For these reasons, we will do an additional analysis with IQ as an additional independent variable. Differences in IQ can be seen as confounder but also as part of the real effect of adversity. The current study design and data do not suffice to model the interaction between IQ, childhood adversity and brain structure. Comparing the results from the main analysis with the results from this additional analysis will tell us to which extent our effects can be explained by IQ. We expect to keep some effect after controlling for IQ. De Bellis et al. (1999) found a significant lower IQ in pediatric PTSD patients compared to healthy children and found brain abnormalities after controlling for these differences in full-scale IQ. In the IQ analysis we will add an extra covariate to correct for version of the WISC (III or V).

Regional specificity

We will repeat the analyses with a correction for global measures (intracranial volume and average fractional anisotropy).

Literature

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1. **Timeline and milestones (including dates of when to analyze/write up):**
   April – May 2019 – Processing all MRI data (anatomy and DTI)
   June – July 2019 – Data analyses
   August – September 2019 – Preliminary results
   October 2019 – First draft
   December 2019 – Submitting article

2. **Output (e.g. article, report, etc.):**
   Article

3. **Proposed authors + affiliations (please note that the YOUth data access committee can request certain authors to be included):**
   Elizabeth Buimer (first author), Pascal Pas, Rene Mandl, Rachel Brouwer, Hilleke Hulshoff Pol

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