UiT The Arctic University of Norway

Department of psychology, Faculty of Health Sciences

Structural differences in brain structure after trauma

An analysis based on The Tromsø Study

Maren Angel Christensen

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Supervisor: Matthias Mittner

Co-supervisor: Harald Bækkelund

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Foreword

The idea for this master's thesis came from an article by Bessel van der Kolk (2002) that I read when I wrote my bachelor thesis on trauma treatment for PTSD patients. When we were to write a review article in the autumn of 2020 on a separate desired topic, I contacted Matthias and asked if he would consider being my supervisor for this thesis as well as the desire to write a master's on brain changes associated with the diagnosis of PTSD. He replied that it was not really his field of study but that he could help with the review article first, and then see if he could contribute to my master's thesis.

When the time came to submit confirmation of the supervisor for the master's thesis, I contacted Matthias again. He had the same objection as in the review but said that if I got a co-supervisor who could guide the more clinical aspects related to trauma, he was up for it. I then contacted my supervisor on the bachelor thesis, Pål Kristian Molin, who again put me in contact with Harald Bækkelund at NKVTS. Harald said yes to the task, and we were soon in the process of getting the project up and running. The spring semester 2021 largely went to creating project protocols, applying to REK for ethical approval and DPU for access to the data from the Tromsø survey. At the beginning of the autumn semester 2021, we received the data for the project and large parts of the autumn were spent getting to know the data and learning how to use the statistics program R, which until then I barely knew the name of. After a lot of frustration and tearing of hair, as well as guidance from Harald after we thought we had found some beyond surprising findings (which turned out to be the result of a missing letter in an over 400 line R-script, but at least gave us all a very interesting discussion), we were finally confident that I was well enough acquainted with R and the data material that we could begin the analyzes of the task itself.

During the beginning of the spring semester 2022 Matthias guided me to run the analyzes in R and since we decided to change our analytical method to structural equational

modeling, he contributed parts of the R script (with much appreciated help from Mehmet Mehmetoglu from NTNU) used in our analysis. He then guided me so that I interpreted the findings correctly and saw them in a neurological perspective. When the analyzes were ready and the writing process was well underway, Harald helped us see the results in connection with the trauma data and gave us good input on what our findings may mean in that context. The end result is this master's thesis that I am honored that you are now reading. I want to thank my supervisors Matthias Mittner and Harald Bækkelund for all the guidance and motivation during this amazing journey. I also want to thank my parents Hanne and Rolf Harald for all the love and support, my boyfriend Kenneth who suddenly ended up in a long-distance relationship when I was accepted in a university on the other side of the country and has been a big motivator for me reaching my goals, and last but not least I want to thank my bonus son Odin for always believing in me. I hope you find this master thesis at least mildly as interesting as I have had working with it. Thank you for reading.

Best regards

Maren Angel Christensen

Maren Angel Christensen, master´s student

Matthias Mittner, supervisor

Harald Bækkelund, co-supervisor

Sammendrag

Forskning på traumepasienter har vist at noen lokale hjerneregioner hos pasienter diagnostisert med posttraumatisk stresslidelse (PTSD) er mindre enn hos personer som ikke er diagnostisert med PTSD. Derfor er ønsket vi å undersøke dette forskningsspørsmålet i denne masteroppgaven: Er det strukturelle hjerneforskjeller hos deltakere som har opplevd traumatiske hendelser i livet? Vi har også sett på angst og depresjon som en medierende variabel for å skille om reduksjoner i hjernevolum assosiert med PTE kan være forårsaket av depresjon/angst i stedet for de potensielt traumatiske hendelsene i seg selv. Vi har analysert data fra Tromsøstudien og studert en utvalgsstørrelse på 1864 deltakere (aldersspenn 40-87 år) som gjennomgikk magnetisk resonanstomografi (MRI). Vi brukte strukturell likningsmodell (SEM) med en sum-score av potensielt traumatiske hendelser (PTE) i barndommen og volumetriske målinger av hippocampus, amygdala, thalamus og corpus callosum kontrollert av intrakranielt volum. Vi fant ingen direkte effekt av PTE på strukturelle endringer i hippocampus, amygdala eller thalamus. I corpus callosum derimot fant vi en signifikant reduksjon i hjernevolum hos deltakerne som hadde opplevd PTE. Det var ingen evidens for indirekte effekter mediert av depresjon eller angst på noen av hjernestrukturene. Våre funn antyder at deltakerne fra Tromsø-studien som har opplevd PTE har strukturelle hjerneforandringer i corpus callosum og ikke i de undersøkte områdene av subcortex. Det ville vært interessant å undersøke dette nærmere for å se hvilken innvirkning dette kan ha på utviklingen av andre psykiske lidelser.

Nøkkelord: barndomstraumer, hjernestruktur, angst, depresjon, Tromsøundersøkelsen

Abstract

Research conducted on trauma patients has shown that the local brain regions in patients diagnosed with post-traumatic stress disorder (PTSD) is smaller than in people who are not diagnosed with PTSD. Therefore, the research question we address in this master thesis is: Are there structural brain differences in participants that have experienced traumatic incidents in their lives? We also use anxiety and depression as a mediating variable to distinguish whether brain-volume reductions associated with PTEs may be caused by depression/anxiety rather than the potentially traumatic incidents themselves. We have analyzed data from the Tromsø Study and studied a sub-sample of 1864 participants (age span 40-87 years) that underwent magnetic resonance imaging (MRI). We used structural equational model (SEM) with a sum-score of childhood PTEs and volumetric measurements of the hippocampus, amygdala, thalamus and corpus callosum controlled for by intracranial volume. We found no direct effect of PTEs on structural changes in the hippocampus, amygdala or thalamus. In the corpus callosum on the other hand, we found a significant decrease in brain volume in the participants that had experienced PTEs. There was no evidence for indirect effects mediated by depression or anxiety on any of the brain structures. Our findings suggests that the participants from the Tromsø study that have experienced PTEs have structural brain changes in the corpus callosum and not in the investigated areas of the subcortex. It would be interesting to investigate this further to see what impact this can have on the development of other mental illnesses.

Keywords: childhood trauma, brain volume, anxiety, depression, the Tromsø study

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Introduction

About 10 years ago, my family helped start a youth center in Lesotho (inland state of South Africa). The stories we heard from the young people who came there can still haunt me to this day. The young people told stories of abuse, witnessing murder and mutilation. There is no doubt that the traumas these young people suffered inflicted permanent psychological damage. But is the damage purely psychological, or does it manifest in structural brain abnormalities?

This was the question we wanted to answer in this master thesis: Are there structural brain differences in participants that have experienced traumatic incidents in their lives? Some evidence for such a relationship comes from the study of clinical PTSD patient´s brains where in particular subcortical structures seemed to be affected. In this thesis, I wanted to investigate whether trauma-induced brain changes would manifest sub clinically. To do this we set out to investigate the relationship between the volume of specific brain structures and variables of Potentially Traumatic Events (PTEs) experienced in childhood.

Trauma and PTSD

The word trauma is Greek and means "wound". In this context, we see trauma as a mental wound after exposure to an unbearable experience (Bisson, 2015).

Potentially traumatic events PTEs generally refer to exposure to element of death or threatened death, serious injury or illness, or sexual violence (Thimm et al., 2021). In a study by Heir et al. (2019) conducted on the Norwegian population, they found that the prevalence of the experience of at least one PTE were 85% in men and 86% in women. Studies show that the experience of childhood PTEs leads to an increased risk of developing health problems in adulthood (Thimm et al., 2021).

In 1998, the Adverse Childhood Experiences (ACE) scale was developed at the Kaiser Permanente´s Sand Diego Health Appraisal Clinic (Felitti et al., 1998). The ACE study involved a questionnaire regarding potentially traumatic childhood experiences to examine the prevalence of childhood abuse and how childhood abuse can affect a later medical diagnosis and be predictive of specific causes of death in adulthood (see Appendix A for the full questionnaire). The motivation for the development of the ACE scale was to identify and prevent risk factors for mental illness and early death for people who experiences childhood abuse and live in dysfunctional households (Felitti et al., 1998).

Not everyone who experiences potentially traumatic incidents develops a trauma disorder afterwards. One of the most common trauma disorders is post-traumatic stress disorder (PTSD). The prevalence of being diagnosed with PTSD during a lifespan is between 1.9% and 8.8% and is 3 % for adults at any given time (Bisson et. al., 2015). In the Norwegian population the prevalence of PTSD is 3.8% for men and 8.5% for women (Heir et al., 2019). Santiago et al. (2013) wrote a systematic review that suggest that 37.1 % of all that experiences an intentional traumatic event, intentional trauma is where someone deliberately inflict harm on the person involved, develops PTSD afterwards. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) presents amongst others, these criteria for the diagnosis of PTSD: A) the person was either directly exposed to or witnessed death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. B) Intrusion symptoms. C) Persistent avoidance of stimuli associated with the trauma. D) Negative alterations in cognitions and mood that are associated with the traumatic event. E) Alterations in arousal and reactivity that are associated with the traumatic event (Friedman, 2014).

About twice as many women get diagnosed with PTSD as men. One likely cause is that women are more often exposed to sexual and/or violent assault than men. There have

also been findings that suggest that people with low IQ are more often diagnosed with PTSD after a traumatic event than people with high IQ. This is strongly correlated with highly educated in people (Sayed et al., 2015). As mentioned in the DSM-5 criterion, former trauma exposure is also a big implication for the development of PTSD. Childhood abuse is in addition a risk factor for the development of PTSD. Protective factors include a strong support system around the victim and access to social need resources (Sayed et al., 2015).

In addition to PTSD, childhood trauma is a risk factor for the development of anxiety and depressive disorders in adulthood (Hovens et al., 2010). Learned helplessness may be a contributing factor to alteration of the child´s belief system and development of cognitive vulnerability after a childhood trauma related to emotional abuse and relationally oriented peer victimization. Learned helplessness may be one mechanism which emotional abuse contributes to an increased risk of development of anxiety and depression disorders in adulthood (Hamilton et al., 2013).

Brain structures and their role in trauma

Research shows that some PTSD patients show structural differences in specific brain regions compared to healthy controls. Among other areas, the volume of the hippocampus (lat. “seahorse” because of its shape) and the amygdala (lat. “almond”) has consistently been found to be reduced (van der Kolk, 2002). One of the known functions of the hippocampus is that it is critical for declarative and episodic memory. That memory system is responsible for the accumulation and collecting of data and facts from a learning experience. Declarative memory is also essential for comparing, processing and encoding memory to other experiences (Eichenbaum et al., 1992). In other words, the hippocampus registers information, compares the information with experiences, and then reacts emotionally to this information, it thus stores our emotional memories and sets this into context. The amygdala receives sensory information from the thalamus and then activates the emotional system

accordingly to the association to the learned experience set into context by the hippocampus (Davis & Whalen, 2001). In other words, the amygdala elicits the "fear response" through the autonomic system and hormonal responses system (Toates, 2011). For example, distressing sensory-based involuntary memories of trauma, also called flashbacks, are a characteristic symptom of PTSD and is hypothesized to be mediated by specific brain areas i.e., the amygdala, the hippocampus and the thalamus (Vermetten & Bremner, 2003).

For patients diagnosed with PTSD, it has been suggested that there may have been issues with the processing of emotional information because of the decrease in hippocampal volume found in some patients diagnosed with PTSD (van der Kolk, 2002). The high density in glucocorticoid receptors in the hippocampus, which is an important factor in the regulation of the brains stress response (Seckl & Olsson, 1995), can support the theory that the hippocampus plays a role in emotional regulation, as glucocorticoids have a powerful impact on hippocampal neurons (van der Kolk, 2002).

Research conducted on trauma patients has shown that the hippocampus in patients diagnosed with post-traumatic stress disorder (PTSD) is smaller than in people who are not diagnosed with PTSD (Badura-Brack et al., 2020). However, other studies have found no difference in hippocampal volume (Bonne et al., 2001; Pederson et al., 2004; van der Kolk, 2002) and a final conclusion is still lacking.

The study by Badura-Brack et.al. (2020) found gender differences in brain volume in participants who had experienced severe trauma. The male participants who scored high on PTSD had less hippocampal volume than the male participants who scored low on PTSD. This effect was reversed for female participants: Those who scored high on PTSD, showed an enlarged hippocampus compared with the female participants who scored low on PTSD. The researchers suggested explanation to this find is that the limbic regions in males may be more

sensitive to the effect of stress and therefore are more prone to underdevelopment than females. This suggestion is based on prior rodent studies (Badura-Brack et al., 2020).

In an extensive systematic meta-analysis, Bromis et al. (2018) examined whether changes in brain volume were due to the diagnosis of PTSD or major depressive disorder. Merging data from all published studies, they compared three groups of participants: non-traumatized participants, traumatized participants without the diagnosis of PTSD, and traumatized participants with PTSD. They found that changes in hippocampal volume may be associated with the traumatic event itself and not to the diagnosis of PTSD and that a change in total brain volume may be associated with the diagnosis PTSD, and not necessarily the traumatic event itself. On the other hand, these authors did not find any correlation between changes in brain volume and depression (Bromis et al., 2018).

However, these results were extracted from a diverse set of studies whose results were based on small sample sizes and who used different methodologies and inclusion criteria such that patients with different trauma experiences was included. Bromis et al. (2018) conclude that in order to substantiate their preliminary findings on the relationship between traumatic experiences and changes in brain volume, it is desirable and necessary to use data from large studies that use standardized recording protocols (both for MRI and trauma-related variables) such as, for example, the Tromsø study, in order to gain better insight into the relationship between brain structure and trauma.

In contrast, Head et al. (2012) conducted a study that investigated participants who were not diagnosed with PTSD but lived under strong pressure over time. Interestingly, the results from that study showed increased volume of the hippocampus in participants living under pressure.

Another brain structure that shows a systematic connection with mental disorders is the amygdala (Davidson et al., 2000). Differences in the size of the amygdala have been

related to patients having greater problems regulating emotions, especially the feeling of fear, behavioral activation and inhibition, as well as higher reactivity to emotional challenges (van der Kolk, 2002). It has also been shown that decrease in the size of the amygdala are associated with anxiety and mood disorders, including depression (Davidson et al., 2000). Differences in the size of the amygdala have been shown to be correlated with the context-dependent affective responsiveness, as well as the automated emotional processing ability, which may result in patients displaying emotional behavior patterns in inappropriate situations (Davidson et al., 2000).

Studies also show that in some patients diagnosed with PTSD, incidences of reduced volume of amygdala have been found Woon and Hedges (2008) conducted a meta-analysis that wanted to investigate whether the amygdala and hippocampal volume of children diagnosed with PTSD differed from healthy participants and investigate the development of hippocampal and amygdala volumes in children and adults diagnosed with PTSD after child maltreatment. The study showed that adults diagnosed with PTSD after experiencing childhood maltreatment had a smaller volume of the amygdala compared to a healthy control group (Woon & Hedges, 2008).

The thalamus (lat. “inner chamber”) receives sensory information and relays this information to other relevant brain structures (Pinel & Edwards, 2008). One example of this process is that the thalamus relays information from the sensory cortices to the amygdala during the processing of frightening stimuli (Flores et al., 2015). Another important role of the thalamus is to regulate sleep, alertness and wakefulness (Toates, 2011). Many patients diagnosed with PTSD suffers from insomnia and overactivation (Sinha, 2015). There have been findings that suggest that thalamus show structural brain changes in children that have experiences child maltreatment and early childhood stress (Teicher & Samson, 2016).

The corpus callosum (CC) is the prominent white-matter bundle that connects the right and left cerebral hemispheres with each other and enables the communication between them. Among others the corpus callosum connects the limbic lobes which includes the hippocampal formation and the amygdaloid complex (Shah, 2021). The corpus callosum is divided automatically into seven regions from the anterior to posterior. These regions are the rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium (De Bellis et al., 1999). Studies have found reduction in the corpus callosum in male children that have experienced child maltreatment and female children that have experienced sexual abuse. There are also findings of a decrease of the volume of the corpus callosum in orphans that have been raised in institutional care (Teicher & Samson, 2016).

Childhood physical maltreatment show association to affective and internalizing disorders in adulthood (i.e., anxiety and depression) and can have enduring effect on brain development and brain stress regulatory flow systems (Sheikh, 2018).

During health aging of the brain, the limbic system, including the hippocampus, the amygdala and thalamus, seem to be well preserved (Grieve et al., 2005). The corpus callosum shows aging effect most prominently in the posterior regions while healthy aging of the mid and anterior regions does not seem to show significant structural changes (Ota et al., 2006).

Anxiety and depression

Research show that patients who have developed anxiety and depressive disorder after experiencing childhood trauma is more likely to develop PTSD. This finding also increases if the patient has experienced childhood sexual and/or physical abuse (Spinhoven et al., 2014). Also, structural differences in brains structure in PTSD patients with major depressive disorder show a great overlap. Studies on these individuals have consistently show a reduction in local brain regions such as the hippocampus, the amygdala and the thalamus

(Kroes et al., 2011). Therefore, we wanted to investigate whether anxiety and depression is having a mediation effect on the trauma-brain relationship.

Our main hypotheses are:

Hypothesis 1. Can we find reduced volume of a) hippocampus, b) amygdala, c) thalamus or d) corpus callosum in participants who have experienced potentially traumatic events?

Hypothesis 2. Are those who experience PTEs more likely to get anxiety disorders, which in turn lead to changes in a) hippocampus, b) amygdala, c) thalamus or d) corpus callosum (mediation effect)?

Hypothesis 3. Are those who experience PTEs more likely to get depressive disorders, which in turn lead to changes in a) hippocampus, b) amygdala, c) thalamus or d) corpus callosum (mediation effect)?

Method

Analysis plan

To investigate the potential of structural changes in brain structure on the hippocampus, the amygdala, the thalamus, and the corpus callosum in trauma patients in more detail, we chose to conduct a quantitative analysis on data from the Tromsø study using the structural equational model (Hindenes et al., 2020). Our goal was to investigate whether there was correlation between those who had experience with PTEs in their childhood and their MRI measurements of relevant brain structures including the hippocampus, the amygdala, the thalamus, and the corpus callosum. The Tromsø Study with its large sample size of older participants and a standardized recording protocol for MR images make these data ideal for investigating this issue. It was also necessary to control for additional other variables in order to rule out potentially confounding other causes behind a possible local reduction in brain volume due to PTEs. To analyze our data, we used R Studio (4.1.2) and R

Studio (2022.02.2). RStudio is an integrated development environment for R, a programming language for statistical data processing (R Core Team, 2021; RStudio Team, 2020).

We used structural equational model (SEM) as our method, hereunder the confirmatory factor analysis (CFA), because it allows us to specify and estimate the relationship between the different factors at the same time.

This study was approved by the Regional Committee of Medical and Health Research Ethics (ref. 263082).

The Tromsø Study

The Tromsø study started in 1974 and is Norway's biggest and most comprehensive population study. The study was started after an epidemic of cardiovascular diseases in the north of Norway to map the cause of the high mortality of cardiovascular disease, survey the risk factors and prevent illness (Hindenes et.al., 2020). The Tromsø Study consists of seven waves to date (with an eight wave in preparation) with over 45 000 participants where the research ranges across a large number of public health issues such as cancer, lung disease, mental health, chronic pain, diabetes, dementia, musculosketal diseases, dental health, antibiotic resistance, etc. (Hindenes et al., 2020). The study also includes variables mapping habits such as alcohol intake, drug use, physical activity, tobacco, diet, use of health services, etc. (Sheikh 2018; Thimm et al., 2020).

The variables we analyze include general information such as age and sex, responses to a questionnaire on experiences with mental trauma and MRI data. We also considered as relevant confounding or mediating variables, anxiety and depression and cognitive data.

Based on previous published studies (Bromis et al, 2018; van der Kolk, 2002), we focused on the volume of the following brain regions extracted from both hemispheres separately: The thalamus, the hippocampus, the amygdala, the corpus collosum, as well as intracranial volume to control for overall differences in brain size across individuals.

In the following, is a description of the variables that were requested from the Tromsø Study to give a justify their inclusion:

Demographic variables

We use general information about sex and age of the participants. Differences between the sexes is important as previous research shows that there may be systematic differences in the relationship between brain volume and trauma in women and men (Badura-Brack et al., 2020). We want to look at age as a covariate to control for healthy aging-effect of reduced brain volume with age.

Outcome variables

Of the brain and circulation measurements from the MRI scans we mainly focus on right, left and total brain volume the hippocampus, the amygdala, the thalamus and the corpus callosum (Bromis et al., 2018: van der Kolk, 2002), controlled for by using the measurement of intracranial volume (De Bellis et al., 1999).

We look at the total brain volume to be able to distinguish whether any differences in may be based on different brain sizes (Stewart et al., 2011).

Predictor variables

Information from the class of mental trauma variables is essential to calculate if a participant has experienced one or more PTEs and one that has not experienced PTEs in childhood. We look at information about the participants who have undergone MRI scans and who have experienced PTEs, and whether these show changes in brain volume compared to healthy people (Bromis et al., 2018).

In the Tromsø study participants were asked about whether and when they had experienced specific PTEs during their life. More specifically, for each PTE, they were asked whether they experienced it during childhood, adulthood, or during last year. In our analysis, we chose to focus on the participants who experienced PTEs in childhood. The reason why

we chose to focus on childhood trauma is a considerable body of evidence that childhood trauma has a more profound effect on developmental changes in brain structure (Carrion & Wong, 2012; Nemeroff, 2004; Teicher et al., 2016). There is also evidence for the fact that many who experiences childhood trauma will develop an anxiety and/or depressive disorder afterwards (Nemeroff, 2004). This also emphasise our choice to look at anxiety and depression as mediating variables for the trauma-brain relationship.

Mediation variables

Anxiety and depression are essential variables in relation to our research question, as many who suffer from trauma disorders also experience anxiety and depression (Hovens, 2010). In studies comparing brain volume in PTSD patients and patients suffering from major depression, brain images show that those suffering from PTSD have a greater degree of changes in brain volume than patients suffering from deep depression (Bromis et al, 2018). Studies done on patients diagnosed with anxiety disorders also show reductions in brain volume such as the hippocampus, midbrain, thalamus, insula and superior temporal gyrus (Moon et al., 2014). Therefore, it is essential to disentangle the underlying causes of the putative PET-brain volume effect to determine whether any changes in brain volume are due to the actual potentially traumatic events and possible associated disorders or depression and anxiety disorders that also can occur as a consequence of a potentially traumatic experience.

Exclusion criteria

We also include cognitive data collected as a part of the Tromsø study as these can tell us if any of the participants suffer from dementia or incipient dementia. Dementia is associated with brain atrophy, and this may interfere with our task to determine smaller effects on local brain structures. Research also shows that patients who report mental failure and memory problems early are more likely to be diagnosed with dementia later, because it is easier to identify hidden risk factors for dementia and compare this with changes in brain

volume such as lesions in the white matter, general brain volume. in low regions and especially change in the hippocampus (Stewart et al., 2011).

Mini-Mental State (MMS) form is a short and easy to use cognitive test performed on participants to examine elderly patients for dementia or cognitive disorders. If the participants score below 24, there is a high probability that the participant suffers from cognitive disorders that may affect brain structure (Folstein et al., 1975), therefore, we have chosen to exclude participants that have scored below 24 on MMS in the Tromsø Study wave 7 (See Appendix B for full questionnaire).

Participants

In our study we use data from subjects participating the MR module from the Tromsø Study wave 7. That sub-sample consisted of a total of N=1864 participants, 874 men, mean age 65.4, range 40-87 years (Hindenes et al., 2020).

MR Data collection

In Hindenes et al. (2020) they explain how the MR images collected from the Tromsø Study in this examination where pre-processed and the volume of individual brain regions was calculated. Participants were scanned at the University Hospital North Norway with the same 3T Siemens Skyra MR scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil. T1-weighted (T1w) images were acquired with a 3D magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (flip angle=9°, TR/TE/TI=2300 ms/4.21 ms/996 ms). T2-weighted fluid-attenuated inversion recovery (FLAIR) images were acquired with a 3D turbo spin-echo sequence with variable flip angle (TR/TE/TI = 5000 ms/388 ms/1800 ms, partial Fourier = 7/8). The T1w and FLAIR scans were acquired sagittally with 1 mm isotropic resolution, GRAPPA parallel imaging acceleration factor 2, FOV = 256 mm, 176 slices, 1 mm slice thickness, 256 x 256 image matrix. Time-of-flight (TOF) angiography images were acquired with a 3D transversal fast

low angle shot (FLASH) sequence with flow compensation (TR/TE = 21/3.43 ms, GRAPPA parallel imaging acceleration factor 3, FOV 200 x 181 mm, slice thickness 0.5 mm, 7 slabs with 40 slices each). Reconstructed image resolution was 0.3 x 0.3 x 0.5 mm. Susceptibility weighted images (SWI) were acquired transversally (flip angle = 15°, TR/TE = 28/20 ms, GRAPPA parallel imaging acceleration factor 3, partial Fourier = 7/8, FOV = 220 x 220 mm, slice thickness 1.3 mm, 88 slices). Reconstructed image resolution was 0.6 x 0.6 x 1.6 mm. Slice prescription was automatically aligned to a standardized brain atlas to ensure consistent slice prescription across examinations. Total scan time was 22 minutes (Hindenes et al., 2020; van der Kouwe, 2005).

The volume calculations for the brain structures based on the structural MR images were conducted with the use of FreeSurfer v 6.0. To that purpose, the freesurfer sub-program "recon-all" (with default settings) was applied to the T1-weighted images. Participants for whom it was evident that they had experienced brain pathology (stroke, tumors etc.) were excluded from the study (Hindenes et al., 2020).

Measurement of traumatic life-events

The survey of occurrences of potentially traumatic events (PTEs) included questions considering experiences of life-threatening illness or serious accidents, exposure of violence, exposure of sexual abuse or sexual actions against their will, exposure of bullying, witnessing violence or sexual abuse, experiencing frightening situation such as warfare, natural disasters, terror attacks or kidnapping, experiences of complicated sorrow after the loss of a close one, experiencing painful hospital treatments or dental treatment, witnessing life-threatening illness or serious accidents of a close one, experiencing child maltreatment and if they experienced at least one of this events, if they still think about what happened (see Table 1 for specific items). All questions included information on whether if the participant had

experienced the mental trauma before or after the age of eighteen or whether they have experienced the trauma during the previous year (Thimm et al, 2021).

Table 1

Questions regarding PTEs in the Tromsø Study, wave 7

Item
Have you ever experienced one of the following events?
A life-threatening illness or a serious accident (for example, fire, work accident, or car accident).
Been exposed to violence (for example, hit, kicked, beaten, robbed, or threatened with a firearm).
Been exposed to sexual abuse, i. e. sexual actions against your will.
Experienced something else that was frightening, dangerous, or violent (for example, natural disaster, war, terror attack, held captive).
Witnessed someone close to you being exposed to violence or sexual abuse (for example, hit, kicked, beaten, robbed, or threatened with a firearm).
Been called negative things, marginalized, threatened or bullied by schoolmates, fellow students, or coworkers over a longer period.
Death of a close one and difficulty accepting the loss, yearning for the deceased, and intense emotional pain related to the loss.
Received painful medical treatment when in hospital due to sickness or serious injury.
Received painful medical treatment at the dentist.
That someone close to you had a life-threatening illness or was exposed to a serious accident.

Note. The list of research question includes all the trauma related questions from the Tromsø Study wave 7. We decided to use a sum-score of the first five questions in our analysis. The remaining last five questions is included to show the to show the scope of the questions related to trauma experiences in the Tromsø Study wave 7.

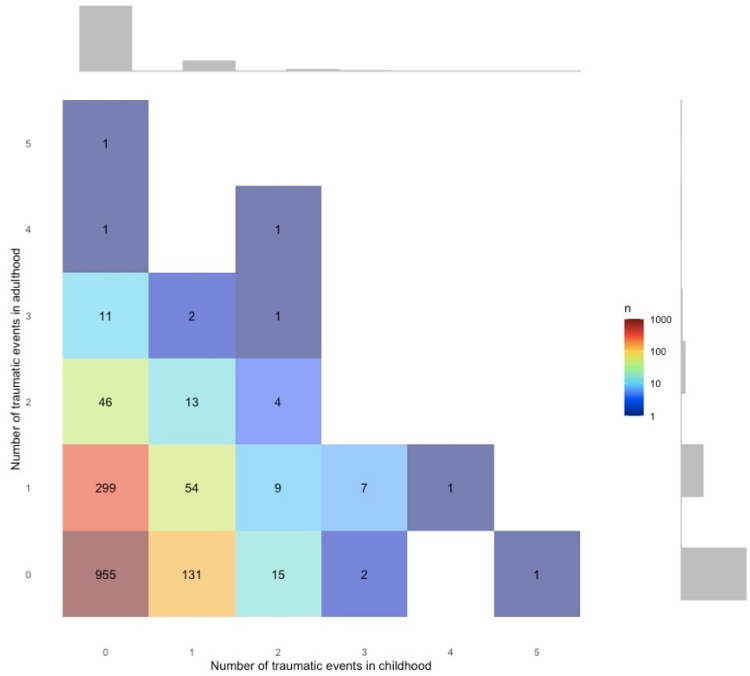
It is usually reported that PTEs that involve harm inflicted by other humans have more severe consequence and lead more often to a post-traumatic stress disorder (van der Kolk, 2000). Based on these considerations, we chose to focus only on the subset of the items used in the PTE questionnaire: Whether the participant had experienced a dramatic and

potentially deadly accident or illness, experienced sexual abuse, had been exposed to violence, had been exposed to a frightening experience (for example kidnapping, natural disaster, war) or whether they have witnessed someone have been exposed to extreme violence or an accident. Based on these five variables, we calculated a single sum-scores reflecting the number of PTEs experienced during childhood by each individual.

The motivation for calculating sum-scores is that it is commonly observed that the likelihood of developing a post-traumatic stress disorder increases with the number of traumatic events (Kolassa et al., 2010). We decided to investigate events experienced during childhood because they are typically more harmful regarding mental health and because their effect on the development of brain structure is potentially more severe (Dye, 2018). We also wanted to investigate how childhood trauma effect the structural brain in older participants. The motivation behind the use of childhood PTEs in our analysis is illustrated in Figure 1 were we see how many of the participants who had experienced PTEs in childhood and adulthood. In Table 2 we see an overview over the participants prevalence of PTEs in childhood and adulthood. We wanted to include adulthood to show a descriptive description of the participants collected from the Tromsø Study, but in the model, we only focus on those who experienced PTEs in childhood.

Figure 1

Number of PTE occurrence in childhood and adulthood in The Tromsø Study wave 7



Note. This figure illustrates how many participants from the Tromsø Study have experienced, none, one or more than one type of PTE in both adulthood and childhood.

Table 2

Prevalence regarding PTEs an MR data in the Tromsø Study wave 7

	Before age of 18			After the age of 18		
	Overall	Women	Men	Overall	Women	Men
PTEs	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Serious illness or accident	75	35 (3.06)	40 (3.63)	305	142 (10.43)	163 (16.46)
Violence	59	31 (0.63)	28 (0.61)	125	62 (5.80)	63 (7.63)
Sexual Abuse	94	76 (4.84)	18 (1.21)	33	32 (4.11)	1 (0.36)
Another frightening, dangerous or violent event	69	37 (2.00)	32 (1.82)	51	19 (2.00)	32 (3.15)

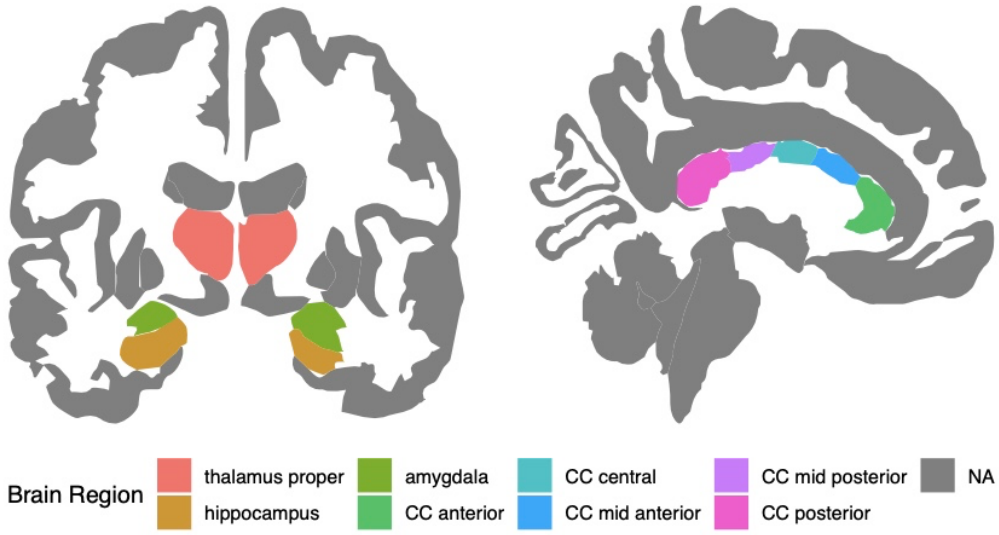
Brain regions

We want to investigate the brain regions displayed in Figure 2: Hippocampus, Amygdala, Thalamus and Corpus Callosum. We adjust the volume of these regions by using intracranial volume, age and sex as a covariate as all of these factors are known to contribute to brain volume and we wish to investigate relative changes caused by PTEs. Each brain region is modeled as a reflective factor-model where the volume of the structure in both hemispheres are the observables. Furthermore, since both the hippocampus and the amygdala are subcortical structures, we capture the shared variance from that fact by a second-level model where the first-level variables Hippocampus, Amygdala and Thalamus are reflectively modeled by the common factor "Subcortex" (see Figure 3a).

Previous studies have shown that the volume of the corpus callosum (CC) can show trauma-related changes, where the changes have been found across the different sub-regions of the CC (De Bellis et al., 1999). As a consequence, we initially planned to model the five variables measured by the Tromsø study (corpus callosum anterior, corpus callosum posterior, central corpus callosum, mid anterior corpus callosum and mid posterior corpus callosum) as reflective measurements of a single underlying factor. However, based on our empirical findings from an exploratory factor analysis, we found that this assumption was not supported by our data (see Results below) and we finally decided to split model the CC on two levels with separate first-level factors for the inner and outer corpus callosum (see Figure 3b).

Figure 2

Illustration of the brain structures investigated from the Tromsø Study wave 7



Note. In this figure we see an overview of the different brain regions investigated in this study. On the left we see the local brain regions from the Subcortex. On the right we see the regions from the Corpus Callosum.

Figure 3.a

Structural Equational Model Illustration of the measurement model of subcortex

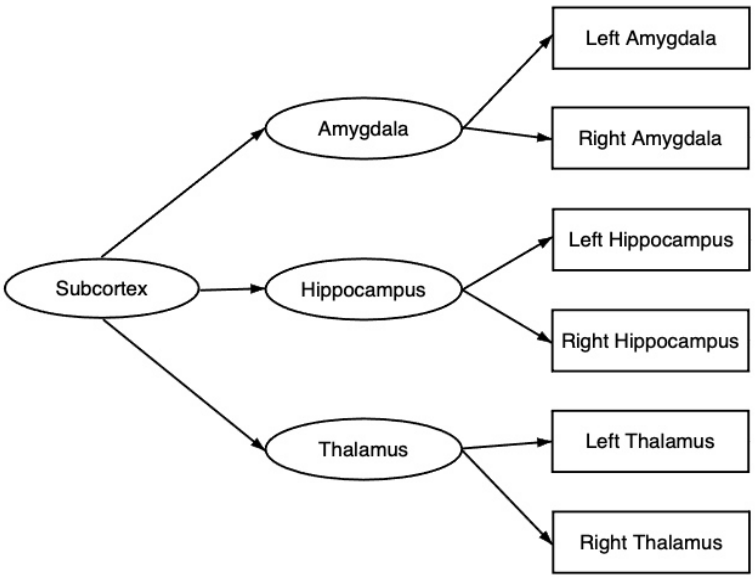
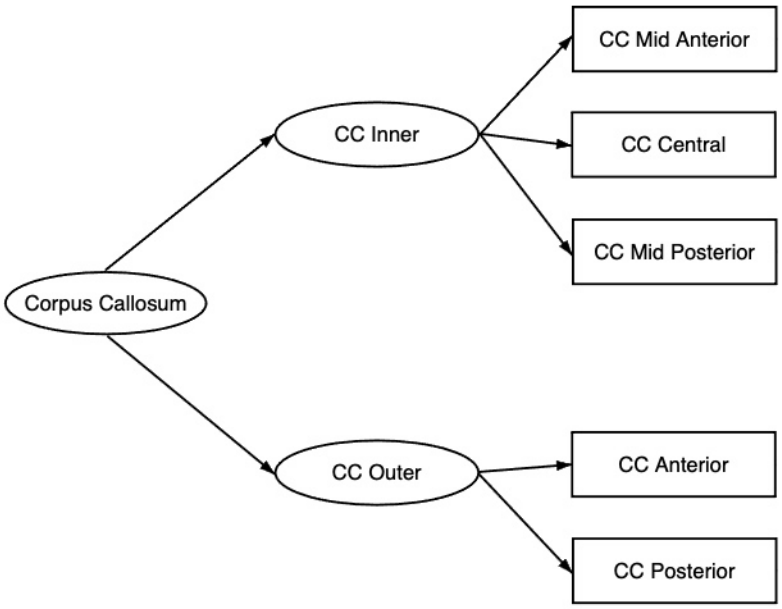


Figure 3.b

Structural Equational Model Illustration of the measurement model of corpus callosum



The HADS scale

Many who experiences a traumatic event that may lead to a trauma disorder will eventually also receive a diagnosis of anxiety and/or depression (Hafstad & Augusti, 2019). Therefore, we wanted to add this variable to our structural equational model as a mediation effect to see whether any trauma-related changes are due directly to the traumatic events or are mediated by anxiety or depression. A mediation effect refers to the situation where a relationship between two variables (trauma and brain volume) may be explained by a third, mediating variable, (anxiety and depression; Gelman & Hill, 2009). In the Tromsø study wave 7, anxiety and depression are measured by the Hospital Anxiety and depression scale (HADS (See Appendix C for full questionnaire)), (Bjelland et al., 2002).

The HADS diagnostic instrument was developed in 1983 by Zigmond and Snaith to diagnose anxiety and depressive disorders more effectively with a short questionnaire of a limited set of symptoms (Bjelland et al., 2002). The questionnaire is quite short and takes only 2-5 minutes to complete. Anxiety and depression were assumed to be the underlying

latent factors where seven questions reflecting anxiety and seven questions reflecting depression where reflexively modeled. Each question has a four point range from 0-3, which gives each category a range of 0-21 score. If the participant scores between 0-7, its regarded as a normal score, 8-11 is regarded as a possible presence of a mood disorder, and a score above 11 or higher is regarded as an indicator for the presence of a mood disorder (Snaith, 2003).

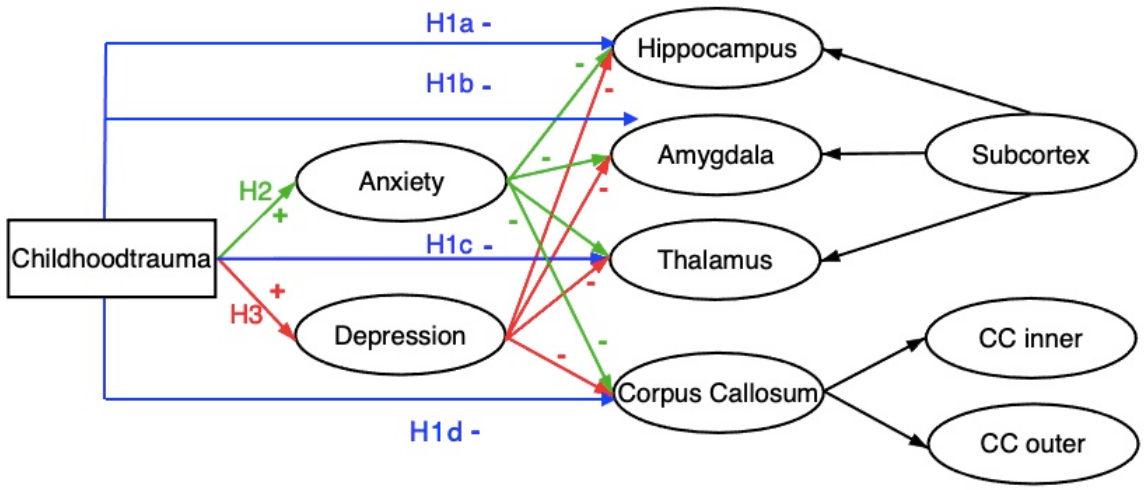
Conceptual framework and research hypothesis

In this study we use Structural Equational Model (SEM) to analyze the connection between brain structure an PTEs with the HADS factors Anxiety and Depression as a mediating factor. This model build is theory-driven and has structural connection between the latent variables and report their loadings on the respecting factor in addition to the measurement model (see Figure 4). We chose to use this method because we believe that this is the best way to report the loadings of each item variable and empirically ground the latent variables.

We did an Exploratory Factor Analysis (EFA) to investigate why there has been found changes in corpus callosum. Then we used a Confirmatory Factor Analysis (CFA) on the measurement part of our model to determine how well our model fits the data, using Raykov´s reliability coefficient (RRC) to examine the reliability of the different scales (Mehmetoglu & Mittner, 2021). Finally, we ran the full structural equational model (Figure 4) and evaluated the structural model coefficients.

Figure 4

Structural Equational Model Illustration of H1, H2 and H3



[a] The blue line represents the direct effect of childhood trauma on hippocampus, amygdala, thalamus and corpus callosum. We expect that increases in the number of childhood PTEs will have a negative effect on the volume of each of the measured regions of the subcortex and corpus callosum.

[b] The green line represents the indirect effect of anxiety after exposure to PTEs on the measured regions of the subcortex and corpus callosum. We expect that childhood trauma would increase the chance of developing anxiety which again will lead to a negative effect on the volume of the measured regions of the subcortex and corpus callosum.

[c] The red line represents the indirect effect of depression after childhood trauma on the volume of hippocampus, amygdala, thalamus and corpus callosum. Also here, we expect that childhood trauma would increase the chance of developing depression which again will lead to a negative effect on the volume of hippocampus, amygdala, thalamus, and corpus callosum.

Results

Exploratory Factor Analysis of Corpus Callosum

When we established the measurement model for the corpus callosum, we found that the variation in the different parts of the corpus callosum is not well described by the assumption of single underlying factor. Therefore, we chose to run an Exploratory Factor Analysis (EFA) to find out how many factors were is necessary.

We use the eigenvalue rule where we determine the number of factors that have eigenvalues over 1. We use varimax rotation to examine the structure of the loadings. Based on that analysis, we found that two factors had associated eigenvalues larger than one (see Appendix D). When considering the factor loadings of the variables, we chose to remove the corpus callosum mid posterior region because it loaded on both of the factors.

As we can see in Table 3a there is a high correlation between the central and mid-anterior corpus callosum. We also found a high correlation between the anterior and posterior corpus callosum. In Table 3b we examined whether the four regions of the corpus callosum loads on either factor 1 or factor 2. The table shows that the corpus callosum posterior (0.69) and corpus callosum anterior (0.80) both loads strongly on factor 1 and only weakly on factor 2. Corpus callosum central (0.96) and corpus callosum mid anterior (0.80) on the other hand load strongly on factor 2 but not factor 1. Finally, the communality, which explain the proportion of each variable´s variance that can be explained by the factors, where all above .4 which is considered satisfactory. The corpus callosum anterior has a communality of 0.64, the corpus callosum posterior has a communality of 0.49, the corpus callosum mid-anterior has a communality of 0.57 and the corpus callosum central which has a communality of .92.

Therefore, we chose to label the two factors of the corpus callosum into “inner CC” which includes the central and mid-anterior region, and “outer CC”, which include the posterior and anterior region.

Table 3a

Correlation matrix of the variables of the Corpus Callosum

	posterior	mid-posterior	central	mid-anterior	anterior
posterior	1.00				
mid-posterior	0.54	1.00			
central	0.21	0.54	1.00		
mid-anterior	0.21	0.39	0.72	1.00	
anterior	0.56	0.35	0.16	0.18	1.00

Table 3b

Factor loadings and communality of Corpus Callosum from the EFA

	Factor 1	Factor 2	Communality
CC anterior	0.09	**0.80**	0.64
CC posterior	0.15	**0.69**	0.49
CC central	**0.96**	0.09	**0.92**
CC mid-anterior	**0.74**	0.15	0.57

Evaluation of the measurement model

As the first step, we used a confirmatory factor analysis (CFA) to evaluate our measurement model. In this model, we removed all structural connections between the latent factors (while allowing the constructs to be correlated) besides their hierarchical structure (Subcortex was a second-level construct composed of the first-level latent variables Hippocampus, Amygdala and Thalamus: Corpus Callosum was a second-level construct composed of the two first-level latent variables CC inner and CC outer). The resulting table of factor loadings is shown in Table 4.

To test the model fit of our CFA we use a Chi-square test and other common fit criteria that all show a reasonable fit ($\chi 2$=1580.900, p <.00, CFI=.919, TLI=.903, RMSEA=.053 p=.014, AIC= 85762.285, SRMR=.063).

The factor loadings in Table 4 show a non-significant loading on left (β=0.137, z=1.022, p=.307) and right hippocampus (β=0.135, z=1.022, p=.307). There was significant factor loading on left (β=0.558, z=38.127, p<.001) and right thalamus (β=0.551, z=38.154, p<.001). There were also significant factor loading on left (β=0.441, z=16.786, p<.001) and right amygdala (β=0.440, z=16.786, p<.001). On the second-level factor loading on subcortex we see that there is non-significant factor loading on hippocampus (β=4.800, z=0.980, p=.327) and significant factor loading on thalamus (β=0.432, z=11.176, p<.001) and amygdala (β=1.090, z=9.683, p<.001). In the inner CC there is significant factor loading on central CC (β=0.744, z=23.136, p<.001) and CC mid anterior (β=0.812, z=15.584, p<.001). In the outer CC there is significant factor loadings on CC posterior (β=0.497, z=17.139, p<.001) and CC anterior (β=0.669, z=15.584, p<.001). On the second-level factor loading of CC there is significant factor loading on inner CC (β=0.278, z=6.250, p<.001) an outer CC (β=0.506, z=5.284, p<.001). All of the factor loadings on the anxiety subscale of the HADS were significant, “I feel tense or wound up” (β=0.641, z=25.309, p<.001), “I get a feeling as if something awful is about to happen” (β=0.585, z=22.694, p<.001), ”Worrying thoughts go through my mind” (β=0.598, z=23.117, p<.001), “I can sit at ease and feel relaxed” (β=0.562, z=21.694, p<.001), “I get a sort of frightening feeling like `butterflies´ in the stomach” (β=0.552, z=21.136, p<.001), “I feel restless” (β=0.363, z=13.426, p<.001) and “ I get sudden feelings of panic (β=0.439, z=16.208, p<.001). All of the factor loadings on the depression subscale of the HADS were also significant, “I still enjoy the things I used to enjoy” (β=0.634, z=23.389, p<.001), “I can laugh and see the funny side of things” (β=0.571,

z=20.710, p<.001), “I feel cheerful” (β=0.546, z=19.509, p<.001), 2I look forward with enjoyment to things” (β=0.687, z=25.335, p<.001), “I can enjoy a good book or radio or TV program” (β=0.355, z=12.145, p<.001), “I feel as if I am slowed down” (β=0.334, z=11.497, p<.001) and “I have lost interest in my appearance” (β=0.383, z=13.160, p<.001). In anxiety there is significant factor loading on depression (β=0.630, z=24.652, p<.001).

Furthermore, we used Raykov´s reliability coefficient (RRC) to examine the reliability of the different scales. This coefficient is preferable to the more widely used Cronbach´s alpha because it is more accurate and because it allows to examine how much of the variation formed by our indicators can be attributed to the true score (Mehmetoglu & Mittner, 2021). We see that Thalamus (RRC = 0.852) and inner corpus callosum (RRC = 0.839) have a good reliability, outer corpus callosum (RRC = 0.734), anxiety (RRC = 0.764) and depression (RRC = 0.707) have an acceptable reliability, amygdala (RRC = 0.617) has a questionable reliability and hippocampus (RRC = 0.586) a poor reliability. However, because of the second-level structure, the RRC values may be misleading for the first-level latent variables that converge at a higher level and should be cautiously interpreted.

Table 4

Construct measurement summary: CFA and scale reliability

Item description summary	Estimate	Std. Err	Std. loading	z value
Hippocampus ($\rho_C = 0.585$)				
Left hippocampus	0.137	0.134	0.930	1.022
Right hippocampus	0.135	0.133	0.921	1.022
Thalamus ($\rho_C = 0.852$)				
Left thalamus	0.558	0.015	0.938	38.127*
Right thalamus	0.551	0.014	0.927	38.154*
Amygdala ($\rho_C = 0.617$)				

Left amygdala	0.441	0.026	0.892	16.786*
Right amygdala	0.440	0.026	0.892	16.786*
Subcortex				
Hippocampus	4.800	4.899	0.710	0.980
Thalamus	0.432	0.039	0.256	11.176*
Amygdala	1.090	0.113	0.541	9.683*
Ccinner ($\rho_C = 0.838$)				
Central corpus callosum	0.744	0.032	0.812	23.136*
Mid anterior corpus callosum	0.812	0.036	0.885	22.552*
Ccouter ($\rho_C = 0.733$)				
Corpus callosum posterior	0.497	0.029	0.648	17.139*
Corpus callosum anterior	0.669	0.043	0.870	15.584*
Corpus callosum				
CCinner	0.278	0.044	0.412	6.250*
Ccouter	0.506	0.096	0.636	5.284*
Anxiety ($\rho_C = 0.764$)				
Feeling tense	0.641	0.025	0.670	25.309*
Feeling awful	0.585	0.026	0.611	22.635*
Feeling worried	0.598	0.026	0.621	23.117*
Feeling relaxed	0.562	0.026	0.589	21.694*
Get butterfly feeling	0.552	0.026	0.576	21.136*
Felt panicked	0.363	0.027	0.384	13.426*
Felt restless	0.439	0.027	0.457	16.208*
Depression ($\rho_C = 0.707$)				
Still enjoy things	0.634	0.027	0.639	23.389*
Can laugh	0.571	0.028	0.576	20.710*
Feeling cheerful	0.546	0.028	0.547	19.509*
Look forward with enjoyment	0.687	0.027	0.683	25.335*
Enjoy books or tv	0.355	0.029	0.356	12.145*
Feeling slowed down	0.334	0.029	0.338	11.497*
Loose interest in appearance	0.383	0.029	0.384	0.384*
Anxiety				
Depression	0.630	0.026	0.630	24.652

To establish divergent validity of the various factors, we investigate the square factor correlations. In case we find high correlations between related factors and low correlations between theoretically unrelated ones, we can conclude that divergent validity is present (Holton et al., 2007). In table 5 we see that the related concepts Anxiety and Depression share common variance (R^2=0.34) while correlations with other latent variables are weak. There is a low correlation between inner and outer corpus callosum (R^2=0.07). Between regions of the subcortex we find a high correlation between the amygdala, the thalamus and the hippocampus (R^2=0.79, R^2=0.56, R^2=0.88).

Table 5

Square factor correlation

	Hippocampus	Thalamus	Amygdala	Subcortex	CCinner	CCouter	CC	Anxiety	Depression
Hippocampus	1.000								
Thalamus	0.501	1.000							
Amygdala	0.698	0.451	1.000						
Subcortex	0.881	0.569	0.792	1.000					
CCinner	0.191	0.123	0.172	0.217	1.000				
CCouter	0.062	0.040	0.056	0.071	0.071	1.000			
CC	0.408	0.263	0.366	0.463	0.469	0.152	1.000		
Anxiety	0.001	0.001	0.001	0.001	0.006	0.002	0.013	1.000	
Depression	0.001	0.001	0.001	0.001	0.000	0.001	0.000	0.342	1.000

Evaluation of the structural model

In our structural equational model, the latent variables are brain structure and PTEs with the mediation effect of anxiety and depression. In Figure 4 we see the structural equational model of childhood trauma and the three regions of the subcortex, hippocampus, amygdala, thalamus as well as the corpus callosum mediated by anxiety and depression.

The results of the structural model (see Figure 4) are depicted in Table 6a, and the results are illustrated in Figure 5. The regression coefficients show the number of childhood PTEs had no relation to the volume of the hippocampus (β=-0.048, z=-0.317, p=.752), or the amygdala (β=0.012, z=0.273, p=.785). The relationship between the childhood PTEs and the thalamic volume show a slight decrease (β=-0.054, z=-1.657, p=.097). There is no relationship between anxiety and the volume of hippocampus β=-0.026, z=-0.109, p=.913), or the amygdala β=0.075, z=1.005, p=.315). There is a relationship between anxiety and an increase in the volume of the thalamus (β=0.106, z=1.965, p=.049). There is no relationship between t depression and the volume of the hippocampus (β=0.343, z=0.826, p=.409), the amygdala (β=-0.044, z=-0.582, p=.560), or the thalamus (β=-0.056, z=-1.025, p=.305). There is no relationship between age and hippocampal volume (β=-3.615, z=-1.021, p=.307). There is a relationship between age and decrease in volume of the amygdala (β=-0.995, z=-13.320, p<.001), and the thalamus (β=-0.883, z=-22.201, p<.001). There is no relationship between intracranial volume and hippocampal volume (β=3.109, z=1.020, p=.308). There is relationship between the volume of the amygdala (β=0.819, z=11.017, p<.001), and the thalamus (β=1.004, z=21.009, p<.001). There is no relationship between sex and the volume of hippocampus (β=0.257, z=0.811, p=.417), and the thalamus (β=0.036, z=0.825, p=.409). There is a relationship between sex and the amygdala (β=0.308, z=4.886, p<.001).

In Table 6a the regression coefficients show that there is a relationship between childhood PTEs and a decrease in the volume of the corpus callosum (β=-0.128, z=-1.987, p=.047). There is a relationship between anxiety and an increase in the volume of the corpus callosum (β=0.299, z=2.639, p=.008). There is no relationship between depression and the volume of the corpus callosum (β=0.131, z=-1.236, p=.217). There is a relationship between age and a decrease in the volume of the corpus callosum (β-0.535, z=-5.380, p<.001). There is a relationship between intracranial volume and an increase in the volume of the corpus callosum (β=1.421, z=6.511, p<.001). There is a relationship between age and a decrease in the volume of the corpus callosum (β=-0.481, z=-4.481, p<.001).

In Table 6a we also see the effects childhood PTEs, age and sex have on anxiety. There is a relationship between childhood PTEs and anxiety (β=0.078, z=2.497, p=.013). There is a relationship between age and anxiety (β=-0.168, z=-5.400, p<.001). There is also a relationship between sex and anxiety (β=-0.222, z=-7.114, p<.001).

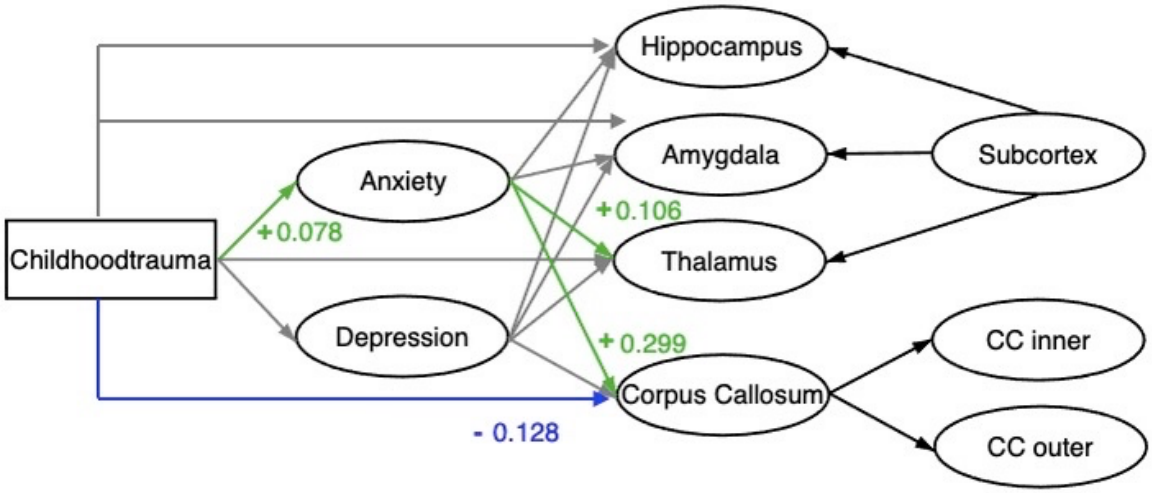
In Table 6a we also see the effects childhood trauma, age and sex have on depression. There is no relationship between childhood PTEs and depression (β=0.057, z=1.805, p=.071). There is no relationship between age and depression (β=0.035, z=1.124, p=.261). There is also no relationship between sex and depression (β=0.058, z=1.873, p=.061).

In Table 6a we see the effect sex have on childhood PTEs. There is no relationship between sex and childhood PTEs (β=0.046, z=-1.763, p=.078).

In table 6a, we see that none of the indirect effects from childhood PTEs to any of the investigated local brain regions mediated through anxiety or depression were significant.

Figure 5

Illustration of the results of the Structural Equational Model



[a] Our results of the CFA show that there is an indirect effect between decrease in corpus callosum after the experience of childhood PTEs.

[b] Our results also show that there is an indirect effect in the development of anxiety after the experience of childhood PTEs. The increase in development of anxiety after childhood PTEs which again lead to an increase of local brain volume in the thalamus and the corpus callosum.

Table 6a

Integrated regression model for Hippocampus, Amygdala, Thalamus and Corpus Callosum

Item description summary	Estimate	Std. Err	Std. loading	z value
Hippocampus				
Childhood trauma	-0.048	0.151	-0.007	-0.317
Anxiety	-0.026	0.240	-0.004	-0.109
Depression	0.343	0.415	0.051	0.826
Age	-3.615	3.542	-0.531	-1.021

Intracranial volume	3.109	3.048	0.461	1.020
Sex	0.257	0.317	0.038	0.811
Amygdala				
Childhood trauma	0.012	0.045	0.006	0.273
Anxiety	0.075	0.075	0.039	1.005
Depression	-0.044	0.075	-0.022	-0.582
Age	-0.995	0.075	-0.490	-13.320*
Intracranial volume	0.819	0.074	0.407	11.017*
Sex	0.308	0.063	0.153	4.886*
Thalamus				
Childhood trauma	-0.054	0.032	-0.031	-1.657
Anxiety	0.106	0.054	0.065	1.965*
Depression	-0.056	0.054	-0.033	-1.025
Age	-0.883	0.040	-0.518	-22.201*
Intracranial volume	1.004	0.048	0.594	21.009*
Sex	0.036	0.043	0.021	0.825
Corpus Callosum				
Childhood trauma	-0.128	0.065	-0.078	-1.987*
Anxiety	0.299	0.113	0.192	2.639*
Depression	-0.131	0.106	-0.081	-1.236
Age	-0.535	0.100	-0.326	-5.380*
Intracranial volume	1.421	0.218	0.873	6.511*
Sex	-0.481	0.107	-0.295	-4.481*
Anxiety				
Childhood trauma	0.078	0.031	0.073	2.497*
Age	-0.168	0.031	-0.160	-5.400*
Sex	-0.221	0.031	-0.212	-7.114*
Depression				
Childhood trauma	0.057	0.031	0.056	1.805
Age	0.035	0.031	0.035	1.124
Sex	0.058	0.031	0.058	1.873
Childhood trauma				
Sex	-0.046	0.026	-0.047	-1.763

Indirect effects				
Trauma → Anxiety → Hippocampus	-0.002	0.019	-0.000	-0.109
Trauma → Depression → Hippocampus	0.019	0.026	0.003	0.751
Trauma → Anxiety → Amygdala	0.006	0.006	0.003	0.932
Trauma → Depression → Amygdala	-0.002	0.004	-0.001	-0.554
Trauma → Anxiety → Thalamus	0.008	0.005	0.005	1.545
Trauma → Depression → Thalamus	-0.003	0.004	-0.002	-0.892
Trauma → Anxiety → CC	0.023	0.013	0.014	1.815
Trauma → Depression → CC	-0.007	0.007	-0.004	-1.020

Discussion

This study investigated the effect of potentially traumatic events experienced during childhood on the local volume of the brain regions hippocampus, amygdala, thalamus and corpus callosum and whether any such effect was mediated by anxiety or depression, respectively. The structural equational model shows that childhood PTEs had a direct effect on the volume of corpus callosum and high score on anxiety measured by the anxiety subscale of the HADS. On the other hand, we did not find, as hypothesized, significant structural changes of the hippocampus, amygdala or thalamus based on the number of experienced childhood PTEs as found in earlier studies (Badura-Brack et al., 2020; Bromis et al., 2018; van der Kolk, 2002). We also did not find a direct effect of childhood PTEs on the depression subscale of the HADS. However, we did find an increase in the volume of the thalamus and the corpus callosum for those who scored high on the anxiety scale. One of the thalamus tasks is to convey information to the amygdala during fear expression, which can explain why we observed structural brain changes in thalamus on the participants that score high on anxiety.

Since the subcortex is a big part of the activated system for those who experience trauma, this is a surprising find. The amygdala is also one of the main brain regions who is

activated in patients who is diagnosed with an anxiety disorder. Studies also show that the subcortex is well preserved during the aging of the brain, which doesn´t suggest that there should be an implication of aging that effect the result of the measurements of the hippocampus, amygdala and thalamus. Many studies have investigated how trauma effects the participants in both childhood and adulthood (Felitti et al, 1998; Nemeroff, 2004; Thimm et al, 2021). There are also many studies that have investigated how trauma in adulthood effect older participants, i.e., veterans (Cardenas et al, 2011). But, to our knowledge, there is no study that have investigated how childhood trauma effect brain regions in older participants. Therefore, since we haven´t other studies with a sample of older participants to compare this data to, this may be the reason why we haven´t found any structural changes in brain structure on the hippocampus, amygdala or thalamus.

Our results show that participants who have experienced PTEs show a decrease in the volume of CC. Previous research on structural brain changes on corpus callosum on participants diagnosed with PTSD have also shown decreases in the volume of the CC (Teicher & Samson, 2016). However, there is still no good answer for why there should be this effect on the corpus callosum. As far as we know the corpus callosum is not a part of relevant activated brain regions in PTSD patients or on people who are diagnosed with an anxiety disorder. Therefore, it is difficult to determine a cause behind these structural changes in the CC and forms a basis for further research. However, the reason why we may see this structural change in CC on participants who have experienced childhood PTEs can be because the limbic system course through the splenium, and fewer axons may lead to less response inhibition. This again may lead to more PTSD related symptoms, for example flashbacks (De Bellis et al., 1999). Another role of the corpus callosum is problem solving. Reduction in the volume of the CC may lead to difficulties in problem-solving difficulties for people who have experienced PTEs (Teicher et al., 2016).

We did not find any indirect effect between childhood PTEs on any of the investigated local brain regions mediated through anxiety or depression. Therefore, we found no evidence for hypothesis 2, “Are those who experience PTEs more likely to get anxiety disorders, which in turn lead to changes in a) hippocampus, b) amygdala, c) thalamus or d) corpus callosum (mediation effect)?” or hypothesis 3, “Are those who experience PTEs more likely to get depressive disorders, which in turn lead to changes in a) hippocampus, b) amygdala, c) thalamus or d) corpus callosum (mediation effect)?”

In contrast to studies on healthy aging of the brain, our findings suggest that there is a strong correlation between age and decrease in brain volume even when controlling for intracranial volume on all investigated brain regions except for the hippocampus. Hippocampus is also the only brain region in this study that we did not find any significant changes in either childhood trauma, anxiety, depression, age, intracranial volume or gender. Previous studies have shown that there seems to be a linear decline in hippocampal volume in men over the age of thirty while this effect was not found in women (Pruessner et al., 2001). Since all of our participants are over the age of forty, it is quite surprising that we did not find any significant decline of male hippocampal volume.

When it comes to gender, we found that males had larger volume of amygdala and thalamus, and smaller volume of corpus callosum compares to females. In previous studies there was no evidence for gender differences in the size of the amygdala (Kim et al., 2012). On the other hand, previous research shows that males tend to have a larger volume of both thalamus and corpus callosum (Ahsan et al., 2007; Bishop & Wahlsten, 1997), but our findings suggests that there may be more behind the myth that women have larger volumes of corpus callosum that have been rejected by Bishop & Wahlsten (1997) based on previous studies having too low a sample size. A study conducted by Ardekani et al. (2013) where

they investigated a sample size of 316 participants, provided strong evidence that the volume of the corpus callosum is larger in the female participants.

Limitations

Since we don´t have information if the participants from the Tromsø Study wave 7 have a diagnosis of PTSD or a different trauma disorder and the studies we have compared this data to investigate participants already diagnosed with PTSD, we cannot conclude whether the structural brain changes observed for the corpus callosum, and the absence of an effect on the hippocampus, amygdala and thalamus are due to the potentially traumatic event or the diagnosis of PTSD. However, this can also be seen as a strength of our design since this can be an indicator for further research on structural brain changes in participants who have experienced PTEs to further imply if the structural brain changes in hippocampus, amygdala and thalamus is a result of the diagnosis of PTSD or the traumatic event itself.

The research questions regarding mental trauma used in the Tromsø Study wave 7 are based on the participants own interpretation of the event. For example, the question regarding witnessing violence, “Have you witnessed someone close to you being exposed to violence or sexual abuse (for example, hit, kicked, beaten, robbed, or threatened with a firearm)” may be interpreted in various ways. If someone has seen their close friend or sibling get in a fight after the influence of alcohol in a bar, this may be less traumatizing than if someone has seen a parent being violently abused by their other parent. Since the participants have answered that they have experienced this under the age of 18, the chance of experiencing this as a result of a barfight is smaller than if we had looked on the participants that have experienced this for of traumatic event after the age of 18.

Since our sample size comprises exclusively older participants (forty years and older), this can be influential to the relevant changes in brain structure. The reason why we find decrease in corpus callosum on the participants who have experienced PTEs may be a result

of the natural aging of the prefrontal regions of the corpus callosum such as rostrum and genu. But since this is a large sample size, there is a smaller chance that the natural aging of the brain is the only contributing factor to this effect. Also, our findings show that there is already a strong aging effect on the CC in addition to the effect of the experience of PTEs.

Limitation factors to having a sample size that consist of older people may also include that the measure of PTEs may be clouded by memory such that many people who have had PTEs did not report them (or they got re-interpreted) which is a common problem with post-hoc self-reports that reach far into the past. The participants who were negatively inflicted by PTEs may also already "worked-through" their symptoms of for example depression at the age of 40 or higher, so they are no longer present. What was previously seen as good parenting may also be strongly changed, which may influence how some of the participants chose to answer the questions related to childhood abuse.

Typically, depression is a highly co-morbid condition associated with the experience of traumatic events. Our study did not find a significant increase of depression as measured by the HADS scale in the participants that had experienced more PTEs as measured in this sample. Since this sample size is collected from a population-based study in the north of Norway there may be other contributing factors to this. The north of Norway is located above the Arctic circle which consist of a weather pattern that changes drastically from season to season. For example, during the winter season, the sun does not rise at all during two of the darkest months, and during the summer season, the sun does not go down at all during the lightest months. Friborg et al. (2014) have done studies at the phenomenon Seasonal Depressive disorder (SAD) where they studied participants living north of the arctic circle and how lighting conditions, among other things, affected their sleep patterns and mood during the seasonal changes. They found that insomnia, fatigue and depressive mood was present in the participants who suffer from SAD. They also found that the seasonality was a

big moderator for depressive mood (Friborg et al., 2014). These factors may contribute to a higher depressive state on the participants populated in the north of Norway, which again can influence the prevalence of depressive disorders in the participants that have not experienced a PTE.

To measure differently the effect of childhood trauma, we could have focused more on how they measured childhood experiences in the Adverse Childhood Experience study (ACE). This may had given us another perspective than the one that we have after only focusing on how they chose to portray the potentially traumatic events in the questionnaire in the Tromsø Study wave 7. The ACE study emphasizes more on the relationship of health and disease to the exposure to childhood emotional, physical, and sexual abuse as well as the number of categories related to child maltreatment (Felitti et al., 1998). This may be a factor to consider in further research on this field.

Summary and basis for further research

Our study did not show structural brain changes in hippocampus, amygdala and thalamus due to PTEs. We did, however, find structural brain changes on the corpus callosum. We are unsure whether this finding is a result of the fact that we investigated participants who have experienced potentially traumatic events rather than relying on a PTSD diagnosis as done by previous studies. It is also possible that this finding reflects our inclusion of older participants who have experienced childhood trauma. Both of these questions could be investigated further in future research.

It would also be interesting to investigate further the impact these structural differences in brain structure have on the development of mental illness (or whether they are the consequence of one). There is a lot of evidence for the development of other mental illnesses after the experience of a potentially traumatic event, but we don´t know if the structural changes in brain structure a part of the development of these mental illnesses is.

Research on this can help with the identification and prevention of risk factors that again can contribute to better healthcare for those who are unfortunate enough to experience potentially traumatic events. It would also be interesting to examine this further by coupling the Tromsø study with for example the HUNT study, which is a similar population study in Trondheim, to help answer these questions.

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Appendix A

The ACE score

Prior to your 18th birthday:

1. Did a parent or other adult in the household often or very often… Swear at you, insult you, put you down, or humiliate you? or Act in a way that made you afraid that you might be physically hurt?

   No___If Yes, enter 1 __

2. Did a parent or other adult in the household often or very often… Push, grab, slap, or throw something at you? or Ever hit you so hard that you had marks or were injured?

   No___If Yes, enter 1 __

3. Did an adult or person at least 5 years older than you ever… Touch or fondle you or have you touch their body in a sexual way? or Attempt or actually have oral, anal, or vaginal intercourse with you?

   No___If Yes, enter 1 __

4. Did you often or very often feel that … No one in your family loved you or thought you were important or special? or Your family didn't look out for each other, feel close to each other, or support each other?

   No___If Yes, enter 1 __

5. Did you often or very often feel that … You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you? or Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?

   No___If Yes, enter 1 __

6. Were your parents ever separated or divorced?

   No___If Yes, enter 1 __

7. Was your mother or stepmother:

   Often or very often pushed, grabbed, slapped, or had something thrown at her? or Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard? or Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?

   No___If Yes, enter 1 __

8. Did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?

   No___If Yes, enter 1 __

9. Was a household member depressed or mentally ill, or did a household member attempt suicide? No___If Yes, enter 1 __

10. Did a household member go to prison?

    No___If Yes, enter 1 __

Now add up your "Yes" answers: _ This is your ACE Score

Appendix B

The MMS Scale used in Tromsø wave 7

COGNITIVE - **COGNITIVE**

ATTENDED_WORD_TEST_PART_1_T72 - Attended word test part one
1 : Attended
ATTENDED_TAPPING_TEST_T72 - Attended finger tapping test
1 : Attended
ATTENDED_MMS_T72 - Attended MMS
1 : Attended
MMSDATE_T72 - Current date
TAP_NO_HANDS_T72 - Number of hands
ORDER_REM_BARN_T72 - Order of rememberance of the word - BARN
MMSWEEKDAY_T72 - Current weekday
ORDER_REM_FLASKE_T72 - Order of rememberance of the word - FLASKE
TAP_BEST_HAND_T72 - If one hand, which hand? (RIGHT, LEFT)
MMSMONTH_T72 - Current month
ORDER_REM_PENN_T72 - Order of rememberance of the word - PENN
TAP_DOMINANT_HAND_T72 - Dominant hand
TAP_PRACTICE_DOMINANT_T72 - Finger tapping test (10 sec), Practice, Dominant hand, Number of taps
MMSSEASON_T72 - Current season
ORDER_REM_STORM_T72 - Order of rememberance of the word - STORM
ORDER_REM_NESE_T72 - Order of rememberance of the word - NESE
MMSYEAR_T72 - Current year
TAPPING_1_DOMINANT_T72 - Finger tapping test (10 sec), Trial 1, Dominant hand, Number of taps
ORDER_REM_FJELL_T72 - Order of rememberance of the word - FJELL
TAPPING_2_DOMINANT_T72 - Finger tapping test (10 sec), Trial 2, Dominant hand, Number of taps
MMSADDRESS_T72 - Patients current address
ORDER_REM_FLESK_T72 - Order of rememberance of the word - FLESK
TAPPING_3_DOMINANT_T72 - Finger tapping test (10 sec), Trial 3, Dominant hand, Number of taps
MMSZIPCODE_T72 - Patients current zip-code
TAPPING_MEAN_DOMINANT_T72 - Finger tapping test (10 sec), Dominant hand, Mean number of taps
MMSTOWN_T72 - Town/village of current address
ORDER_REM_STUBBE_T72 - Order of rememberance of the word - STUBBE
TAP_PRACTICE_NONDOMINANT_T72 - Finger tapping test (10 sec), Practice, Non-dominant hand, Number of taps
MMSCOUNTY_T72 - County of current address
ORDER_REM_ELV_T72 - Order of rememberance of the word - ELV
ORDER_REM_HEST_T72 - Order of rememberance of the word - HEST
TAPPING_1_NONDOMINANT_T72 - Finger tapping test (10 sec), Trial 1, Non-dominant hand, Number of taps
MMSCOUNTRY_T72 - Country of current address
ORDER_REM_OLJE_T72 - Order of rememberance of the word - OLJE

TAPPING_2_NONDOMINANT_T72 - Finger tapping test (10 sec), Trial 2, Non-dominant hand, Number of taps
MMSWORDS_T72 - Number of words correctly repeated
ORDER_REM_SYKKEL_T72 - Order of rememberance of the word - SYKKEL
TAPPING_3_NONDOMINANT_T72 - Finger tapping test (10 sec), Trial 3, Non-dominant hand, Number of taps
MMSTRIALS_T72 - Number of repetitions
NO_IMMEDIATE_RECALL_T72 - Number of words immediately recalled
TAPPING_MEAN_NONDOMINANT_T72 - Finger tapping test (10 sec), Non-dominant hand, Mean number of taps
MMSSPELLING_T72 - Number of letters correctly spelled of the word Sword
CONFABULATION_BARN_T72 - Confabulation - BARN
TAPPING_COMMENTS_T72 - Finger tapping test comments
MMSSUBTRACTIONS_T72 - Number of correct subtractions
CONFABULATION_FLASKE_T72 - Confabulation - FLASKE
DATE_TAPPING_T72 - Date of finger tapping test
MMSABSTRACT_THINKING_T72 - Highest score of number of letters and number of subtractions
CONFABULATION_PENN_T72 - Confabulation - PENN
TIME_TAPPING_T72 - Time of finger tapping test
MMSRECALL_T72 - Number of correctly recalled words
CONFABULATION_STORM_T72 - Confabulation - STORM
MMSPENCIL_T72 - Correctly naming of a pencil
CONFABULATION_NESE_T72 - Confabulation - NESE
CHKIN_TAPPING_T72 - Date and time of regestering in a persons identification number at the finger tapping test
MMSWATCH_T72 - Correctly naming of a watch
CONFABULATION_FJELL_T72 - Confabulation - FJELL
MMSSENTENCE_T72 - Ability to repeat a sentence
CONFABULATION_FLESK_T72 - Confabulation - FLESK
MMS3INSTRUCTIONS_T72 - Ability to comprehend and perform an instruction of 3 consecutive tasks
CONFABULATION_STUBBE_T72 - Confabulation - STUBBE
MMSWRITTEN_INSTRUCTION_T72 - Ability to perform a written instruction
CONFABULATION_ELV_T72 - Confabulation - ELV
MMSWRITING_T72 - Ability to write a full sentence
CONFABULATION_HEST_T72 - Confabulation - HEST
MMSCOPYING_T72 - Ability to copy a double pentagon figure
CONFABULATION_OLJE_T72 - Confabulation - OLJE
MMSTOTAL_SCORE_T72 - Total score of Mini Mental Status Test
CONFABULATION_SYKKEL_T72 - Confabulation - SYKKEL
MMSTIRED_T72 - Missing values due to fatigue
NO_CONFAB_T72 - Number of confabulations
MMSAPHASIA_T72 - Missing values due to aphasia
REASON_1_PART_1_T72 - Reason for not participation - Part 1: Tired
MMSSIGHT_T72 - Missing values due to impaired sight
REASON_2_PART_1_T72 - Reason for not participation - Part 1: Refuse
MMSHEARING_T72 - Missing values due to impaired hearing
REASON_3_PART_1_T72 - Reason for not participation - Part 1: Practical problems
MMSPARESIS_T72 - Missing values due to paresis

REASON_4_PART_1_T72 - Reason for not participation - Part 1: Impaired sight
MMSREFUSE_T72 - Missing values due to refusal
REASON_5_PART_1_T72 - Reason for not participation - Part 1: Impaired hearing
MMSOTHER_T72 - Missing values due to other causes, text
REASON_6_PART_1_T72 - Reason for not participation - Part 1: Aphasia
DATE_MMS_T72 - Date of mms test
REASON_7_PART_1_T72 - Reason for not participation - Part 1: Other
TIME_MMS_T72 - Time of mms test
WORD_PART_1_DATE_T72 - Date of wordtest - Part 1
WORD_PART_1_TIME_T72 - Time of wordtest - Part 1
MMSCOMMENTS_T72 - MMS comments
WORD_PART_1_COMMENTS_T72 - Wordtest comments - Part 1
ATTENDED_WORD_TEST_PART_2_T72 - Attended word test part two
1 : Attended
RECOGNITION_1_PART_2_T72 - Recognition of word - Part 2 - SMØR
1 : Yes
0 : No
RECOGNITION_2_PART_2_T72 - Recognition of word - Part 2 - NESE
1 : Yes
0 : No
RECOGNITION_3_PART_2_T72 - Recognition of word - Part 2 - JENTE
1 : Yes
0 : No
RECOGNITION_4_PART_2_T72 - Recognition of word - Part 2 - TRE
1 : Yes
0 : No
RECOGNITION_5_PART_2_T72 - Recognition of word - Part 2 - PAPIR
1 : Yes
0 : No
RECOGNITION_6_PART_2_T72 - Recognition of word - Part 2 - FLASKE
1 : Yes
0 : No
RECOGNITION_7_PART_2_T72 - Recognition of word - Part 2 - OLJE
1 : Yes
0 : No
RECOGNITION_8_PART_2_T72 - Recognition of word - Part 2 - ELV
1 : Yes
0 : No
RECOGNITION_9_PART_2_T72 - Recognition of word - Part 2 - SAFT
1 : Yes
0 : No
RECOGNITION_10_PART_2_T72 - Recognition of word - Part 2 - VANN
1 : Yes
0 : No
RECOGNITION_11_PART_2_T72 - Recognition of word - Part 2 - FJELL
1 : Yes
0 : No
RECOGNITION_12_PART_2_T72 - Recognition of word - Part 2 - ORKAN
1 : Yes
0 : No

RECOGNITION_13_PART_2_T72 - Recognition of word - Part 2 - BARN
1 : Yes
0 : No
RECOGNITION_14_PART_2_T72 - Recognition of word - Part 2 - STORM
1 : Yes
0 : No
RECOGNITION_15_PART_2_T72 - Recognition of word - Part 2 - MOPED
1 : Yes
0 : No
RECOGNITION_16_PART_2_T72 - Recognition of word - Part 2 - HUND
1 : Yes
0 : No
RECOGNITION_17_PART_2_T72 - Recognition of word - Part 2 - PENN
1 : Yes
0 : No
RECOGNITION_18_PART_2_T72 - Recognition of word - Part 2 - HEST
1 : Yes
0 : No
RECOGNITION_19_PART_2_T72 - Recognition of word - Part 2 - BENSIN
1 : Yes
0 : No
RECOGNITION_20_PART_2_T72 - Recognition of word - Part 2 - BERG
1 : Yes
0 : No
RECOGNITION_21_PART_2_T72 - Recognition of word - Part 2 - SYKKEL
1 : Yes
0 : No
RECOGNITION_22_PART_2_T72 - Recognition of word - Part 2 - FLESK
1 : Yes
0 : No
RECOGNITION_23_PART_2_T72 - Recognition of word - Part 2 - HAKE
1 : Yes
0 : No
RECOGNITION_24_PART_2_T72 - Recognition of word - Part 2 - STUBBE
1 : Yes
0 : No
REASON_1_PART_2_T72 - Reason for not participation - Part 2: Tired
REASON_2_PART_2_T72 - Reason for not participation - Part 2: Refuse
REASON_3_PART_2_T72 - Reason for not participation - Part 2: Practical problems
REASON_4_PART_2_T72 - Reason for not participation - Part 2: Impaired sight
REASON_5_PART_2_T72 - Reason for not participation - Part 2: Impaired hearing
REASON_6_PART_2_T72 - Reason for not participation - Part 2: Aphasia
REASON_7_PART_2_T72 - Reason for not participation - Part 2: Other
WORD_PART_2_DATE_T72 - Date of wordtest - Part 2
WORD_PART_2_TIME_T72 - Time of wordtest - Part 2
WORD_PART_2_COMMENTS_T72 - Wordtest comments - Part 2
SUM_RECOGNITION_T72 - Sum recognition
ATTENDED_CODING_TEST_T72 - Attended digit-symbol coding test
1 : Attended
NO_OF_SYMBOLS_CODING_T72 - Number of symbols given

NO_OF_MISTAKES_CODING_T72 - Number of mistakes
NO_OF_MISSED_CODES_T72 - Number of missed codes
REASON_1_CODING_T72 - Reason for not participation - Coding: Tired
REASON_2_CODING_T72 - Reason for not participation - Coding: Refuse
REASON_3_CODING_T72 - Reason for not participation - Coding: Practical problems
REASON_4_CODING_T72 - Reason for not participation - Coding: Impaired sight
REASON_5_CODING_T72 - Reason for not participation - Coding: Impaired hearing
REASON_6_CODING_T72 - Reason for not participation - Coding: Aphasia
REASON_7_CODING_T72 - Reason for not participation - Coding: Other
REASON_8_CODING_T72 - Reason for not participation - Coding: Impaired hand motor function
CODING_DATE_T72 - Date of codingtest
CODING_TIME_T72 - Time of codingtest
CODING_COMMENTS_T72 - Codingtest comments
NOT_CORRECTED_CODING_T72 - Coding form not available

Appendix C

The HADS Scale used in Tromsø wave 7

ANXIETY AND DEPRESSION - Q2 - **ANXIETY AND DEPRESSION - Q2**

FEAR_T7 - Have you experienced sudden fear without apparent reason during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

WORRIED_T7 - Have you felt afraid or anxious during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

DIZZY_T7 - Have you experienced faintness or dizziness during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

TENSE_T7 - Have you felt tense or upset during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

BLAME_YOURSELF_T7 - Have you easily blamed yourself during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

INSOMNIA_T7 - Have you had sleeping problems during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

DEPRESSED_T7 - Have you felt depressed or sad during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

USELESS_T7 - Have you felt useless, worthless during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

STRUGGLE_T7 - Have you felt that everything is a struggle during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much

4 : Very much

FUTURE_T7 - Have you felt hopelessness with regard to the future during the last week?

1 : No complaint
2 : Little complaint
3 : Pretty much
4 : Very much

HADS_TENSE_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I feel tense or 'wound up'.

3 : Most of the time
2 : A lot of the time
1 : From time to time, occasionally
0 : Not at all

HADS_ENJOY_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I still enjoy the things I used to enjoy.

0 : Definitely as much
1 : Not quite so much
2 : Only a little
3 : Hardly at all

HADS_AWFUL_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I get a sort of frightened feeling as if something awful is about to happen.

3 : Very definitely and quite badly
2 : Yes, but not too badly
1 : A little, but it doesn't worry me
0 : Not at all

HADS_LAUGH_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I can laugh and see the funny side of things.

0 : As much as I always could
1 : Not quite so much now
2 : Definitely not so much now
3 : Not at all

HADS_WORRY_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. Worrying thoughts go through my mind.

3 : A great deal of the time
2 : A lot of the time
1 : From time to time, but not too often
0 : Only occasionally

HADS_CHEERFUL_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I feel cheerful.

3 : Not at all
2 : Not often
1 : Sometimes
0 : Most of the time

HADS_RELAXED_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I can sit at ease and feel relaxed.

0 : Definitely
1 : Usually
2 : Not often
3 : Not at all

HADS_SLOWED_DOWN_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I feel as if I am slowed down.

3 : Nearly all the time
2 : Very often
1 : Sometimes
0 : Not at all

HADS_BUTTERFLIES_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I get a sort of frightened feeling like 'butterflies' in the stomach.

0 : Not at all
1 : Occasionally
2 : Quite often
3 : Very often

HADS_APPERANCE_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I have lost interest in my apperance.

3 : Definitely
2 : I don't take as much care as I should
1 : I may not take as much care
0 : I take just as much care as ever

HADS_RESTLESS_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I feel restless as I have to be on the move.

3 : Very much indeed
2 : Quite a lot
1 : Not very much
0 : Not at all

HADS_LOOK_FORWARD_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I look forward with enjoyment to things.

0 : As much as I ever did
1 : Rather less than I used to
2 : Definitely less than I used to
3 : Hardly at all

HADS_PANIC_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I get sudden feelings of panic.

3 : Very often indeed
2 : Quite often
1 : Not very often
0 : Not at all

HADS_ENJOY_BOOK_TV_T7 - Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't think too long over your replies: your immediate is best. I can enjoy a good book or radio of TV program.

0 : Often
1 : Sometimes
2 : Not often
3 : Very seldom

Appendix D

Eigenvalues from the correlation matrix

Eigenvalues of factors				
[1]	1.49	0.64	-0.19	-0.24
Eigenvalues of components				
[1]	2.03	1.25	0.44	0.28
Eigenvalues of simulated components				
[1]	1.05	1.02	0.98	0.28