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Master thesis

Mapping normative trajectories of cortical development to internalizing and externalizing problems in youth

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Summary

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Title of thesis: Mapping normative trajectories of cortical development to internalizing and externalizing problems in youth

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My role in the project: The research question for the present thesis was designed by me in collaboration with supervisors. Supervisor PB trained the normative models based on previous work. All handling of outcome data was performed by me, and all statistical models were designed and implemented by me. Supervisor AD helped create the figures on page 20-22. All writing was conducted by me in full. In the manuscript, use of the pronoun “we” indicates that the decision or action was made as a collaborative effort with my supervisors. Use of the pronoun “I” indicates that it was done by me alone.

Abstract

Background: Adolescence is considered one of the most important developmental periods in life, characterized by profound behavioral and neurodevelopmental changes from childhood to full maturity. The heightened neuroplasticity during adolescence, on one hand, facilitates intellectual and emotional development, but on the other hand, may reflect a period of vulnerability. Internalizing and externalizing problems often appear within this developmental window and may predict the later onset of a psychiatric disorder. The internalizing-externalizing spectrum has previously been linked to abnormalities in the development of the cortex. However, studies have typically been limited by small samples and cross-sectional designs. Robust large-scale studies are needed as early detection of the neurobiological signatures of internalizing and externalizing problems may ultimately inform early intervention.

Methods: This longitudinal study utilized a large sample of 6459 participants from the US Adolescence Brain Cognitive Development (ABCD) study. All participants underwent magnetic resonance imaging (MRI) at two time points with a two-year interval between scans (ages ~10 and ~12). Internalizing and externalizing problems were assessed at both timepoints using the Child Behavioral Checklist ages 6-18 (CBCL/6-18). We utilized normative modeling to analyze the range of variation in cortical thickness. Linear mixed-effect regression was employed to examine changes in internalizing and externalizing across time, changes in cortical thickness across time, and the associations between internalizing and externalizing problems and normative trajectories of cortical thickness.

Results: Both internalizing and externalizing problems decreased over time, although the decrease of externalizing problems was not statistically significant. Cortical thickness showed relative stability across time. Negative associations were found between normative trajectories of cortical thickness and externalizing problems in posterior regions, as well as an interaction between the normative trajectory of cortical thickness in right middle frontal sulcus, externalizing problems, and age.

Conclusion: Findings highlight that links between internalizing and externalizing problems

and normative trajectories of cortical development are relatively weak across a two-year timespan. Future studies should seek to include a wider set of imaging measures in order to identify reliable brain biomarkers for internalizing and externalizing problems.

Keywords: adolescence; longitudinal; MRI; cortical thickness; internalizing problems; externalizing problems.

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Introduction

Adolescence is one of the most important developmental windows of life, signified by a behavioral and neurodevelopmental transition from childhood to full maturity. During this period of time, a number of physical, cognitive, and social changes take place, such as hormonal changes (Bordini & Rosenfield, 2011), changes in cognitive capacity (Yurgelun-Todd, 2007), and increased number of social interactions (Kilford et al., 2016). A key aspect of these changes is a rapid reorganization of the brain during this period, particularly in neocortical regions related to executive function, emotion regulation, and social cognition (Steinberg, 2005). This reorganization is characterized by synaptic pruning, where presumably unneeded synaptic connections are discarded, leading to a loss of global brain volume and a reduction in cortical thickness (Bethlehem et al., 2022). This temporary neuroplasticity, on one hand, allows greater adaptability to the environment and improved cognitive functions (Larsen & Luna, 2018). However, on the other hand, it can also bring about the risk of developing mental disorders, such as substance use disorder, mood disorders and anxiety disorders (Paus et al., 2008). The similar age of onset and the high co-occurrence of most common mental disorders have prompted researchers to consider multiple different disorders as a product of the same underlying latent structure (Pasion & Barbosa, 2019). One such suggested structure is the internalizing-externalizing spectrum (Achenbach et al., 2016). Internalizing and externalizing problems are two broad categories of psychological issues. Internalizing problems refer to emotional and behavioral difficulties which are directed inward, such as depression and somatic complaints, whereas externalizing problems always occur in interaction with others, for example aggressive behavior (Achenbach & Rescorla, 2001). Although previous studies have linked brain morphology to externalizing and internalizing problems (Romer et al., 2021), studies have typically been limited by smaller samples and cross-sectional designs. In this thesis, I will firstly summarize brain development and brain vulnerability during adolescence, before moving on to internalizing and externalizing problems. Next, I will review the possible relations between internalizing and externalizing problems and cortical thickness and point out possible limitations of previous

studies. Finally, I will propose a novel way of linking the internalizing-externalizing spectrum to brain morphology and put forward the hypotheses of the present study.

Healthy brain development during adolescence

During adolescence, great changes in human brain anatomy occur. In general, the volume of grey matter (GM) peaks at the year of six in childhood and then follows a near-liner decline throughout adolescence, while the volume of white matter (WM) maintains growth from mid-gestion, peaking at 28.7 years old (Bethlehem et al., 2022). Decrease of WM volume is often interpreted as an indication of synaptic pruning, where many synapses developed during childhood are eliminated during adolescence (Konrad et al., 2013; Paus et al., 2008). Specifically, synaptic pruning is thought to reflect an adaptation process, during which weaker or unnecessary synapses are eliminated. Generally, this process is more pronounced in prefrontal cortex and other frontal regions that contribute to advanced cognitive functions (Spear, 2013). The onset of GM volume decrease varies with different regions. GM loss starts first in primary sensorimotor areas, and then spreads rostrally over frontal cortex and caudally over parietal, occipital, and temporal cortex, and the dorsolateral prefrontal cortex is involved in the process eventually (Gogtay et al., 2004). GM volume decrease is accompanied by WM volume increase, with a WM linear increase in frontal, parietal, occipital, and temporal lobes, steeper in boys than in girls (Giedd et al., 1999). In the process of WM maturation, myelination plays a central role, increasing axonal transmission efficiency between brain regions (Kirby et al., 2022; Paus, 2005).

The structural and functional maturation of adolescent brain are thought to aid the development of more sophisticated cognitive and emotional processing (Larsen & Luna, 2018). During adolescence, executive functions (e.g., working memory, mental flexibility, attentional control, decision-making) continue to develop (Blakemore & Choudhury, 2006). Specifically, Anderson et al. (2001) found stable progress in attentional control, cognitive flexibility, and goal setting skills. Non-human animal, lesion, and human studies suggest that the development of the prefrontal cortex (PFC) is essential to preform executive functions (Kesner & Churchwell, 2011; Løvstad et al., 2012; Yuan & Raz, 2014). In addition, PFC is also involved in social cognition; In a functional magnetic resonance imaging (fMRI) study

about face recognition, Yurgelun-Todd and Killgore (2006) observed a positive correlation between age and functional activity within PFC. At the same time as executive functions and face recognition skills are developed, there are also changes in emotion regulation (Ahmed et al., 2015). Emotion regulation is greatly relied on limbic areas and PFC which show continuous development across adolescence (Schumann et al., 2004). In a reward-seeking behavior study, authors indicated that there were increases in the blood-oxygenation-level-dependent (BOLD) signal in limbic areas during adolescence compared to childhood and adulthood (Galvan et al., 2006). Supporting this, Tyborowska et al. (2016) reported that during adolescence, neural regulation of emotional actions was shifted from limbic areas to PFC. Briefly, brain development occurring during adolescence is a complex and dynamic process, characterized by profound changes in both brain structure and functions.

Vulnerability and risk during adolescence

It is thought that increased plasticity during late childhood and adolescence facilitates intellectual and emotional development, but it may also reflect a period of vulnerability (Konrad et al., 2013). Thus, adolescents have a higher possibility to be negatively affected by external factors, such as family issues, and may develop psychiatric symptoms during this window of development (Brown et al., 1999; Schaan et al., 2019; Steinberg, 2005). Adolescence is marked as a high-risk age range, given that approximately 50% of lifetime DSM-IV disorders have an onset by age 14 (Jaworska & MacQueen, 2015; Kessler et al., 2005). According to the results provided by the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019), mental disorders have been noticeable contributors of disease burden worldwide between 1990 to 2019, accounting for approximately 5% of global disease burden in 2019. The overall number of disable-adjusted life-years (DALYs) raised 55.1% and this trend is expected to continue (Arias et al., 2022; GBD 2019 Mental Disorders Collaborators, 2022). Importantly, the results showed that the number of DALYs kept increasing steadily during childhood and adolescence between 1990 and 2019 (GBD 2019 Mental Disorders Collaborators, 2022). In addition, it is reported that 14% of adolescents aged 10 to 19 are estimated to experience mental disorders (World Health Organization,

2021). The results emphasize the vulnerability of children and adolescents for developing psychiatric symptoms.

The influence of mental disorders is not limited to one domain and is generally long-lasting, impairing individuals' school and/or working performance, relationships between family members and friends, and social functioning, leading to an increased burden on caretakers and an economic burden worldwide. Poor health and low productivity caused by mental disorders cost the world economy 2.5 trillion US dollars per year with expected 6 trillion US dollars cost by 2030 (The Lancet Global Health, 2020). Despite the extreme individual efforts and financial costs, the treatment rates of mental disorders are low (Wang et al., 2007). Therefore, it is of great importance to identify early signs of disorders and implement early interventions.

Internalizing and externalizing problems

Internalizing and externalizing problems often appear when children are of young age and they have been suggested to be trans-diagnostic common markers of many psychiatric disorders and an explanation for their frequent co-occurrence (Fanti & Henrich, 2010; Lancefield et al., 2016). Internalizing and externalizing are two global groupings of behavioral and emotional problems. There are other names referring to the same groups of problems: Personality problems versus Conduct problems (Peterson, 1961), Inhibition versus Aggression (Miller, 1967), and Overcontrolled versus Undercontrolled (Achenbach & Edelbrock, 1978). In this study we used the terminology Internalizing and Externalizing problems which are consistent with the initial naming of the two factors (Achenbach, 1966). Internalizing is defined by the feature of inwardness, which means that the problems are maintained and developed within the individual (Achenbach & Rescorla, 2001). Children with internalizing issues display withdrawal and have fewer social contacts with others (Achenbach & Rescorla, 2001). Externalizing problems, conversely, are outward projections, reflecting conflicts with others, and are generally more noticeable to others (Achenbach & Rescorla, 2001). Symptoms, such as depression, anxiety, and withdrawal, are included in internalizing problems, while externalizing problems include rule-breaking behavior, aggressive behavior, etc. Assessment systems, such as Achenbach System of Empirically

Based Assessment (ASEBA; Achenbach, 2009), the Behavior Assessment System for Children (BASC; Reynolds, 2010), Infant Toddler Social Emotional Assessment (ITSEA; Carter, 2013), and Personality Inventory for Children (PIC; Lachar, 2011), are commonly used to assess internalizing and externalizing problems.

Development of internalizing and externalizing problems

Although internalizing and externalizing groupings reflect distinct problems, they are not mutually exclusive (Achenbach & Rescorla, 2001). They can occur both independently or concurrently in an individual's early childhood (Mesman et al., 2001). After onset, they show high levels of stability in longitudinal studies (Mesman et al., 2001; Willner et al., 2016). In a 16-year longitudinal study, Arslan et al. (2021) showed that the presence of externalizing problems in early childhood had indicated long-term continuity up to early adulthood, and had wide range of influence in physical, social, and pathological personality domains, such as lower satisfaction of general health, social problems, and psychoticism, whereas internalizing problems were not associated with any problems in adulthood. However, it was shown that the stability of internalizing problem may only be seen from adolescence onward (Copeland et al., 2013). In general, externalizing problems in childhood are significantly associated with externalizing problems in adolescence and adulthood, independent of gender (Mesman et al., 2001; Shin et al., 2012). An increase of externalizing problems can be seen as children grow older, and early externalizing problems may also increase the risk of later internalizing problems, which shows that externalizing problems may play an important role for co-occurrence across time (Mesman et al., 2001; Shin et al., 2012; van der Ende et al., 2020). Internalizing problems also increase gradually with age (Gilliom & Shaw, 2004). However, they follow a different pathway. Gender differences are more pronounced, with higher levels of internalizing problems in girls compared to boys, and greater age-related increases in girls than boys (Bongers et al., 2003; Leve et al., 2005; Mesman et al., 2001; Shin et al., 2012). As opposed to externalizing problems, internalizing problems are negatively associated with externalizing problems in later life, and they may serve as 'protective' factors of externalizing problems (Fanti & Henrich, 2010; Mesman et al., 2001; Shin et al., 2012). In other words,

children with internalizing problems are less likely to develop co-occurrent problems as compared to children first developing externalizing problems.

Consequences of internalizing and externalizing problems

Symptoms of internalizing and externalizing problems may predict later internalizing and externalizing problems, but they can also lead to adverse outcomes in other domains, including poor academic achievement, peer difficulties, substance dependence, and suicidal behaviors (Arslan et al., 2021; Fanti & Henrich, 2010a; Fergusson et al., 2005).

Poor academic performance

Both externalizing and internalizing problems impair academic performance. Academic attainment, including lower school GPA and non-completion of school, may in the long run impact an individual's quality of life, and is associated with poor physical health (Mirowsky & Ross, 2003). Studies have firmly shown that children with externalizing problems have greater academic difficulties (Van der Ende et al., 2016). Negative associations were also found between internalizing problems and school functioning, with children with higher levels of internalizing symptoms managing lower grade averages and receiving more fail grades (Pedersen et al., 2019; Riglin et al., 2014).

Peer and social problems

Children exhibiting internalizing and externalizing problems also face problems related to peer and social domains, including peer rejection, asocial behaviors, deviant behaviors, and being associated with deviant peers (Fanti & Henrich, 2010). Having fewer positive activities with peers can be stressful. In general, internalizing or externalizing problems alone is associated with negative outcomes in social domains, but children exhibiting co-occurring problems show greater issues with social and behavioral adjustment (Fanti & Henrich, 2010; Oland & Shaw, 2005). In terms of being asocial with peers, internalizing alone, externalizing alone, and their co-occurrence are linked to asocial behaviors. Internalizing problems are characterized by social avoidance and withdrawal. Accordingly, children showing avoidant and isolating behaviors may be seen by peers as less

social, invoking negative responses from peers (Oland & Shaw, 2005). Children with externalizing problems are hyperactive and show uncontrolled and impulsive behaviors, which might lead to exclusion by peers (Calkins et al., 1999). However, children with co-occurring problems were more excluded by peers and displayed significantly more asocial behaviors with peers, compared with children existing internalizing or externalizing alone, indicating an additive effect of having co-occurring problems (Fanti & Henrich, 2010). Children with externalizing problems alone or co-occurring problems also have a higher risk of showing risky deviant behaviors and associating with deviant peers, while children showing internalizing problems are less likely to engage in risky behaviors, given their lessened social involvement (Fanti & Henrich, 2010; Oland & Shaw, 2005).

Substance use

Internalizing and externalizing problems are also associated with substance use. Externalizing problems are a strong predictor of substance use. Longitudinal studies showed consistent results that early externalizing problems significantly correlated with substance use (e.g., Dodge et al., 2009; Fite et al., 2006; Scalco et al., 2014). However, the relation between internalizing problems and substance use is controversial, and relevant scientific research has reported inconsistent results. Sihvola et al. (2008) found that internalizing problems predicted later substance involvement, whereas some studies interpreted internalizing problems as a protective factor (e.g., Colder et al., 2013). On the one hand, researchers suggested two mechanisms to explain the unique effects of internalizing problems. Self-medication mechanism refers to how adolescents are motivated to engage in substance use in order to reduce their negative feelings, which in turn worsens the consequences of using substance (Hussong et al., 2011). Therefore, internalizing problems play a dangerous role which increases the risk of substance use. On the other hand, internalizing problems may be a protective factor, because adolescents may be afraid of the negative experience or effects of using drugs and/or alcohol, they withdraw from interacting with peers who have behavioral problems, and thus they are less likely to engage in substance usage (Colder et al., 2018). However, for some adolescents with internalizing problems, their environment may increase their likelihood of using substances. They may actively interact with peers who also use

substances, which in turn can provide them opportunities and connections with delinquent peer groups that engage in substance use (Hussong et al., 2011). In these situations, adolescents may rationalize their substance using behavior, and consequently internalizing problems become a risk factor. Furthermore, the effect of internalizing problems is not constant over time: in childhood and early adolescence they may protect youths from using harmful substances, but later on increase the risk in late adolescence and adulthood (Fite et al., 2006; Sung et al., 2004). Besides, the role of internalizing problems needs to be considered in the context of externalizing problems (i.e., co-occurrence). The effect of internalizing problems varies with different levels of externalizing problems. When adolescents have internalizing problems with co-occurrent high levels of externalizing problems, internalizing problems seems to decrease the risk, but they are positively correlated with substance use when externalizing problems are less severe (Scalco et al., 2014).

Suicidal behaviors

Internalizing and externalizing problems existing either alone or concurrently during childhood or adolescence may be linked to a fatal outcome later in life. There are significant associations between internalizing or externalizing problems and attempted suicide or completed suicide. Hence, they can be used to predict suicide behavior in young adults (Soto-Sanz et al., 2019). Furthermore, Commisso et al. (2021) reported people presenting with a co-occurrence of internalizing and externalizing problems had a much higher odds (two or three times higher) of attempting suicide. Notably, females with co-occurring problems had the highest chance compared to other groups (i.e., females with only one of the two groups of problems, males exhibiting internalizing problems with or without externalizing problems).

The associations between internalizing and externalizing problems and cortical thickness

Recent advancements in magnetic resonance imaging (MRI) technology have enabled researchers to investigate the potential associations between structural brain measures and internalizing and externalizing problems. One such measure is cortical thickness, which has been found to be an important biomarker of neurodevelopment, brain aging and is linked to

mental disorders (Ducharme et al., 2016; Hanford et al., 2016; Thambisetty et al., 2010; Zielinski et al., 2014). Cortical thickness may represent a promising avenue for the investigation of the neural substrates of internalizing and externalizing problems. Studies have found evidence of diverging developmental trajectories of cortical thickness in adolescents with internalizing or externalizing problems compared to normal developmental trajectories (e.g., Ameis et al., 2014; Whittle et al., 2020). However, the findings are inconsistent. Regarding internalizing problems, some studies found abnormalities of cortical thickness in the frontal lobe, although the direction of the association varied depending on location. Some studies have indicated that internalizing problems were associated with decreased thickness in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and precentral regions (Bos et al., 2018; Ducharme et al., 2014; Merz et al., 2018; Whittle et al., 2020). In addition, a longitudinal study reported an interaction between internalizing problems and age, which increased internalizing problems were associated with reduced cortical thickness of the ventromedial prefrontal cortex (vmPFC) until middle adolescence, while the association shifted to positive while adolescents were getting older (Ducharme et al., 2014). Global cortical thinning across childhood and adolescence was also observed in relation to internalizing problems, with no specific region related to the association (Luby et al., 2016; Newman et al., 2016). However, there are also studies which found no significant associations between internalizing problems and cortical thickness (e.g., Schmaal et al., 2017). In terms of externalizing problems, findings overlapped partially with those of internalizing problems. Cortical thinning was found in vmPFC, including ACC and OFC, related to externalizing problems (Ameis et al., 2014; Boes et al., 2011; Ducharme et al., 2011). In addition, externalizing problems were also associated with structural abnormalities in postcentral gyrus, inferior frontal gyrus (IFG), middle frontal gyrus, and medial temporal cortex (Ameis et al., 2014; Merz et al., 2018; Shaw et al., 2011; Whittle et al., 2020).

The inconsistencies may be due to the following reasons: 1) participants were in different age ranges; 2) some studies are cross-sectional, whereas others are longitudinal. In the present study, I will address these issues by using a large population-based sample recruited at the same age (age ~10) from the US Adolescent Brain Cognitive Development (ABCD) study. The aim of the present study is to explore the associations between

internalizing and externalizing problems and changes in cortical thickness, potentially gaining a deeper understanding of the underlying mechanism of these problems and their change across time in young individuals. In addition, the present study may also provide insight into whether the neurobiology of externalizing and internalizing problems is shared or unique to each problem.

First, we built normative models which were used to inform the normative ranges of gray matter developmental trajectories. Normative modeling has been introduced as a novel analysis method which can be used to understand heterogeneity at the level of a single subject (Marquand et al., 2016). Similar to how growth charts predict children's development in terms of height and weight relative to their age, normative models map variations within the cohort and define deviations from a normal growth trajectory as outliers within the normative range at each age (Marquand et al., 2016). In addition, a major advantage of normative modeling is that it can detect and map the variation without requiring a consistent neurobiological signature (Marquand et al., 2019).

Second, we performed a three-step analysis using linear mixed-effect models. This first consisted of investigating changes in externalizing and internalizing problems across time. Then, we assessed changes in cortical thickness across time. Lastly, we associated externalizing and internalizing problems with normative trajectories of cortical thickness.

Based on previous research, I expect to see the following: 1a) increased scores on both internalizing and externalizing problems across time, 1b) gender differences in internalizing and externalizing problems, and 2) cortical thinning across time. Given the inconsistent findings in previous studies, I do not have a specific hypothesis regarding 3), the relationship between internalizing and externalizing problems and normative trajectories of cortical thickness.

Materials and Methods

Participants

All participants included in the present study were recruited through the Adolescence

Brain Cognitive Development (ABCD) study. The ABCD study is a longitudinal multi-center study that was launched in the United States in 2016. The ABCD study plans to assess ~12 000 adolescents for multiple times over a period of at least ten years to better understand human developmental trajectories from childhood to young adulthood. By assessing substance use, genetic factors, cultural background, environmental factors, brain structure and functions, the datasets could be used to study the influence of a wide range of factors on human brain development, in turn furthering our understanding of adolescent physical- and mental health. The study is funded by the National Institutes of Health (NIH). A central Institutional Review Board (IRB) at the University of California, San Diego approved the study, and research centers obtained approval from their local IRBs. My access to the ABCD data material was granted through Request #7474 (PI: Westlye). Local approval for handling of data is registered as REK 2019/943. All data handling was performed on TSD (Tjeneste for Sensitive Data), a secure server environment.

The core aim of the ABCD study is to collect a large sample that reflects the diversity of the US population based on variables such as age, gender, race and ethnicity, socio-economic status, and urbanicity. The recruitment procedures were mainly based on school systems, including public and private primary schools, nested within larger catchment areas. Both children and their parents were recruited at the same time. All participants undergo MRI scans, neurocognitive assessments, substance use assessment, demographic, physical, and mental health assessments, culture and environment assessments, and biological testing. The full study design and selection and recruitment procedures have been described previously in Garavan et al. (2018).

With regards to the present study, the data was obtained from Annual Data Release 4.0 which includes structural MRI and behavioral data collected at baseline (age ~10) and two-year follow-up (age ~12). We first applied quality control procedures suggested by the ABCD research groups (Hagler et al., 2019). After applying quality control procedures, 855 scans were excluded due to poor quality of the MR images. Then we removed 110 scans from research sites with less than 100 samples, and 21 scans that included missing values. 5683 scans were used to adapt the normative models. For the final analyses, we included 12918 scans from participants who completed assessments and MR scanning sessions at both time

points. Demographic characteristics of the study sample were reported separately for each time point (Table 2). At baseline, a total of 6459 participants were included, with 53.72% male participants. The mean age of the participants was 9.90 years (SD = 0.62; range: 8.92-11.08 years). At two-year follow-up, 6459 participants were included, comprising 53.72% male participants. The mean age of the participants was 11.94 years (SD = 0.65; range: 10.58-13.75 years).

Behavioral measures

Internalizing and externalizing problems were assessed using the Child Behavioral Checklist ages 6-18 (CBCL/6-18; Achenbach, 2009). CBCL/6-18 is one of the Achenbach System of Empirically Based Assessment (ASEBA) instruments created by Thomas M. Achenbach in 1960s, used to assess behavioral or emotional problems of preschool children, school-age adolescents, adults, and elderly people (Achenbach, 2009). The ASEBA instruments have been shown to be reliable and valid across multiple cultural backgrounds and social settings (Ang et al., 2012; Helstelä et al., 2001; Leung et al., 2006; Schmeck et al., 2001). The core aim of ASEBA is to be a flexible system which can be employed to assess behavioral and emotional problems in a variety of contexts and for diverse target groups.

The present study used CBCL-scores as rated by one parent. The CBCL/6-18 utilizes a three-point Likert scale for scoring. The points reflect the frequency or intensity of the behaviors being measured (0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often True). Higher scores on the syndrome scales reflect increased levels of the problems being measured. Specifically, according to the classification system employed by the CBCL/6-18, higher scores on the anxious/depressed, withdrawn/depressed, and somatic complains scales indicate higher levels of internalizing problems, while higher scores on the rule-breaking behavior and aggressive behavior scales indicate higher levels of externalizing problems. These scores are obtained by summing the scores on the individual items from each syndrome scale. Internalizing and externalizing scores are calculated by summing the scores on the scales in each of the groups. Table 2 shows mean internalizing and externalizing scores at baseline and 2-year follow-up. For ease of comparison and interpretability, scores can be converted to T-scores. This makes it possible to see which ranges participants fall into, i.e. T

score below 60 indicates the normal range, T score 60-63 is the borderline range, meaning that individuals are at risk of developing the certain problem(s), and T score above 63 implies the clinically significant level (Achenbach & Rescorla, 2001). However, as suggested by Achenbach and Rescorla (2001), unstandardized scores of internalizing and externalizing problems were used in any statistical model described later.

MRI data acquisition

All collection of MRI-data was handled by the ABCD consortium. In order to minimize head movement, participants underwent training in a mock scanner, and foam padding was used to stabilize the head (Epstein et al., 2007). In addition, real-time motion detection and correction was applied during the scanning session using different techniques. These include prospective motion correction (PROMO) on GE platform, Volumetric Navigators (vNav) on Siemens, and on Philips if it was available (Tisdall et al., 2012; White et al., 2010). Each experimental session includes T1-weighted and T2-weighted structural MRI, diffusion MRI (dMRI), resting state functional MRI (rs-fMRI), task-fMRI sequences. The order of all sequences were standardized across all research sites (Casey et al., 2018). The whole session took approximately 2 hours to complete.

Since there are 21 data acquisition sites across the US responsible for data collection, models of the scanners vary from site to site. However, only 3T scanners from Siemens Prisma, General Electric (GE) 750, and Philips with standard adult-size head coils (32-channel head coil) are used across all the research sites with a standardized protocol. The parameters used during structural MRI scanning were summarized in Table 1. Participants were instructed to relax and keep their eyes open during the structural sequences.

Table 1. *Scanning parameters*

Model	Siemens (Prisma VE11B-C)	Philips (Acheieva dStream, Ingenia)	GE (MR750, DV25-26)
Matrix	256 x 256	256 x 256	256 x 256
Slices	176	225	208
FOV	256 x 256	256 x 256	256 x 256
Resolution (mm)	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0	1.0 x 1.0 x 1.0
TR (ms)	2500	6.31	2500
TE (ms)	2.88	2.9	2
TI (ms)	1060	1060	1060
FA	8	8	8
Acquisition Time (s)	432	338	369

MRI data analysis

All steps of image pre-processing is described in detail in Hagler et al. (2019). Briefly, the ABCD study employed a standardized set of processing steps, including distortion and motion correction and cross-modality registration. The preprocessed data was then processed to obtain cortical thickness measures using FreeSurfer v5.3.0 (Fischl, 2012). The standard FreeSurfer pipeline was used for cortical surface reconstruction and subcortical segmentation. Subcortical structures were labeled using an automated, atlas-based, volumetric segmentation approach (Fischl et al., 2002), whereas cortical gray matter and underlying white matter voxels were labeled using surface-based nonlinear registration to the atlas, based on cortical

folding patterns (Fischl et al., 1999) and Bayesian classification rules (Desikan et al., 2006; Destrieux et al., 2010; Fischl et al., 2004). To calculate the average cortical thickness for each parcel, fuzzy-cluster parcellations based on genetic correlation of surface area were utilized (Chen et al., 2012). For the present thesis, I used the Destrieux atlas which parcellates the cortex into 148 regions (Destrieux et al., 2010)

Normative modeling

Normative modeling is an emerging statistical analysis tool that can effectively address heterogeneity within research subjects by predicting variance at an individual level (Marquand et al., 2016). In this study, we utilized normative modeling to analyze the range of variation in cortical thickness and identify sources of variance, conducting individual-level statistical inference in the process. Specifically, we estimated normative models using Hierarchical Bayesian Regression (Kia et al., 2021) to estimate the relationship between cortical thickness and age, while controlling for gender and site effects. Hierarchical Bayesian Regression has been recommended as a proper way to address the challenges when research samples are collected from multiple scanning sites. Unlike other methods, Hierarchical Bayesian Regression can estimate site effects and site-related variance during the modeling stage without requiring full access to the raw data and does not remove any clinic-relevant variance (Rutherford et al., 2022). Additionally, the approach provides the possibility to account for more than one source of variance. As mentioned above, both gender and sites were controlled for in the present study (Kia et al., 2021).

The estimation of the normative models was based on a reference cohort that collected 30837 samples, over 43 sites (n of females = 16440, n of males = 14397, mean age for females = 56.4, SD for females = 16.8, mean age for males = 57.1, SD for males = 17.8). Several open datasets were pooled, including the Cambridge Center for Aging and Neuroscience (CAMCAN), the Philadelphia Neurodevelopmental Cohort (PNC), the Human Connectome Project (HCP), the IXI Brain Development dataset, the Open Access Series of Imaging Studies (OASIS), the Human Connectome Project for Early Psychosis (HCPEP), the Enhanced Nathan Kline Institute-Rockland Sample (NKI-RS), the Child Mind Institute Healthy Brain Network (CMI-HBN), the 1000 Functional Connectomes Project (FCON),

OpenNeuro (OPN), and UK Biobank. After estimating the normative models, we used 5683 scans from the ABCD study to adapt the models to the unseen sites of that study. The models could then predict deviation scores (i.e. Z scores) for the test samples of the ABCD cohort (n of samples = 6459) and all brain regions (Kia et al., 2021). The deviation scores indicate the deviations of the samples from the reference cohort. A positive deviation score indicates above-average cortical thickness, whereas a negative deviation score indicates below-average cortical thickness. The deviation scores were then employed in Equation 4, 5, and 6 for linear mixed-effect modeling.

Statistical analyses

Statistical analyses were conducted using R 4.0.0 (R Core Team, 2020). The ultimate aim was to investigate the relationship between normative trajectories of cortical thickness and internalizing and externalizing problems (hypothesis 3), as well as to examine longitudinal changes in internalizing and externalizing problems and cortical thickness (hypothesis 1 and 2). To achieve these, I performed linear mixed-effect analyses using the lme4 package in R (Bates et al., 2015). Multilevel regression was chosen because the data involved two waves of observations. This method is suitable for analyzing longitudinal data with repeated measures, as it accounts for the dependency of observations. The inclusion of random effect terms for each participant accounts for potential differences between individuals that cannot be explained by independent variables. Furthermore, linear mixed-effect regression provides flexibility in handling missing data appropriately. To assess if normative models capture developmental trajectories that are different from a simple linear function, I modelled both the cortical thickness for each site (n=148) and the normative trajectory of each ROI as a function of time. Lastly, internalizing and externalizing was modelled as a function of the normative trajectory of each ROI, as well as a function of an interaction between normative trajectory and time. This results in the following six models:

Equation 1: *CBCL internalizing raw scores ~ intercept +* $\boldsymbol{b_1}$*gender +* $\boldsymbol{b_2}$*age +* $\boldsymbol{b_3}$*years + random(subject_ID) + error*

Equation 2: *CBCL externalizing raw scores ~ intercept + **b**$_1$gender + **b**$_2$age + **b**$_3$years + random(subject_ID) + error*

Equation 3*: ROI-based cortical thickness (n=148) ~ intercept + **b**$_1$gender + **b**$_2$age + **b**$_3$years + random(subject_ID) + random(site_ID) + error*

Equation 4: *deviation scores of cortical thickness (n=148) ~ intercept + **b**$_1$age + **b**$_2$years + random(subject_ID) + error*

Equation 5: *CBCL internalizing raw scores ~ intercept + **b**$_1$deviation scores of cortical thickness (n=148) + **b**$_2$age + **b**$_3$years + **b**$_4$ deviation scores of cortical thickness*years + random(subject_ID) + error*

Equation 6: *CBCL externalizing raw scores ~ intercept + **b**$_1$deviation scores of cortical thickness (n=148) + **b**$_2$age + **b**$_3$years + **b**$_4$ deviation scores of cortical thickness*years + random(subject_ID) + error*

Here, the *intercept* and *b* terms are fixed effects, random terms indicated a random intercept for each subject, and error represents the residual error. Note: gender and site ID were removed from the models which include deviation scores since the effects of gender and site were already accounted for during normative modeling. All resulting p-values were corrected for multiple comparisons using false discovery rate (FDR)-correction (Benjamini & Hochberg, 1995).

Results

Internalizing and externalizing problems

For internalizing problems, the mean score at baseline was 4.99 (SD = 5.37), while the mean score at two-year follow-up was 4.91 (SD = 5.64), and the ranges of internalizing scores were 0-51 and 0-50 at baseline and two-year follow-up, respectively. For externalizing problems, the mean scores were 4.38 (SD = 5.76) and 3.99 (SD = 5.60) at baseline and two-year follow-up, respectively. The range of externalizing scores was 0-49 at baseline, while at two-year follow-up the range was 0-46 (see table 2). In the baseline assessment, 603

participants had clinically significant scores on the internalizing scales, indicating higher levels of internalizing problems (T score > 63). 465 participants were at risk of developing internalizing problems, as their T scores fell within the borderline range (T score 60 – 63). Similarly, 369 participants had clinically significant T scores on the externalizing scales (T score > 63), and 271 were at risk of developing externalizing problems (T score 60-63). At two-year follow-up, 489 participants had clinically significant T scores on the internalizing scales, and 289 were at risk of developing internalizing problems. On the externalizing scales, 249 participants had clinically significant T scores, and 202 were at risk.

Table 2. *Sample Characteristics for Each Time Point*

	Baseline	**Two-year follow-up**
Age, M(SD)	9.90(0.62)	11.94(0.65)
Age, range	8.92-11.08	10.58-13.75
Number of participants	6459(53.72% male)	6459(53.72% male)
Internalizing problems, M(SD)	4.99 (5.37)	4.91 (5.64)
Internalizing problems, range	0-51	0-50
Externalizing problems, M(SD)	4.38 (5.76)	3.99 (5.60)
Externalizing problems, range	0-49	0-46

Note. M = Mean, SD = Standard Deviation

Internalizing and externalizing problems across time

We investigated changes in internalizing and externalizing scores across the two assessment waves. Longitudinal linear mixed-effect regression was conducted to examine the effect of time on symptom scores. It showed a significant effect of time on overall

internalizing scores (B = -0.24, SE = 0.10, t = -2.33, P < 0.05), suggesting that youths' scores on internalizing subscales decreased significantly across two waves of assessment, with no significant gender difference. The results showed that there were no significant changes in externalizing scores (B = -0.16, SE = 0.11, t = -1.55, P = 0.12), indicating that youths' externalizing scores increased slightly, but not significantly. However, the results showed significant gender difference on externalizing problems (B = 1.12, SE = 0.13, t = 8.56, P < 0.001), indicating that boys had significantly higher levels of externalizing problems, compared with girls.

Cortical thickness across time

Multilevel regression was conducted to examine the changes in cortical thickness across time using both ROI-based cortical thickness and deviation scores of cortical thickness. Table 1 and 2 in supplementary detail the full analysis findings.

First, we investigated the effect of time on cortical thickness for each ROI. To achieve this, Equation 3 was employed. The outcomes indicated a statistically significant decrease in cortical thickness in left lingual gyrus (B = -0.006, SE = 0.002, t = -2.65, P < 0.01), left vertical ramus of the anterior segment of the lateral sulcus (B = -0.007, SE = 0.004, t = -2.03, P < 0.05), left posterior ramus of the lateral sulcus (B = -0.006, SE = 0.002, t = -2.48, P < 0.05), occipital pole (left: B = -0.006, SE = 0.003, t = -2.49, P < 0.05; right: B = -0.007, SE = 0.002, t = -2.78, P < 0.01), left superior temporal sulcus (B = -0.005, SE = 0.002, t = -2.88, P < 0.01), right inferior occipital gyrus and sulcus (B = -0.007, SE = 0.003, t = -2.23, P < 0.05), right orbital sulci (B = -0.006, SE = 0.003, t = 0.03, P < 0.05), and a significant increase in cortical thickness in right anterior segment of the circular sulcus of the insula (B = 0.008, SE = 0.003, t = 2.32, P < 0.05). However, none of these effects remained significant after applying FDR correction for multiple comparisons.

Next, deviation scores were used to explore the effect of time on cortical thickness. Here, we used Equation 4. Figure 1 shows the results, which were converted to Cohen's D effect sizes. Note that all the Cohen's D values were nearly zero. Our analysis revealed significant changes in several brain regions, with a significant decline in the left lingual gyrus

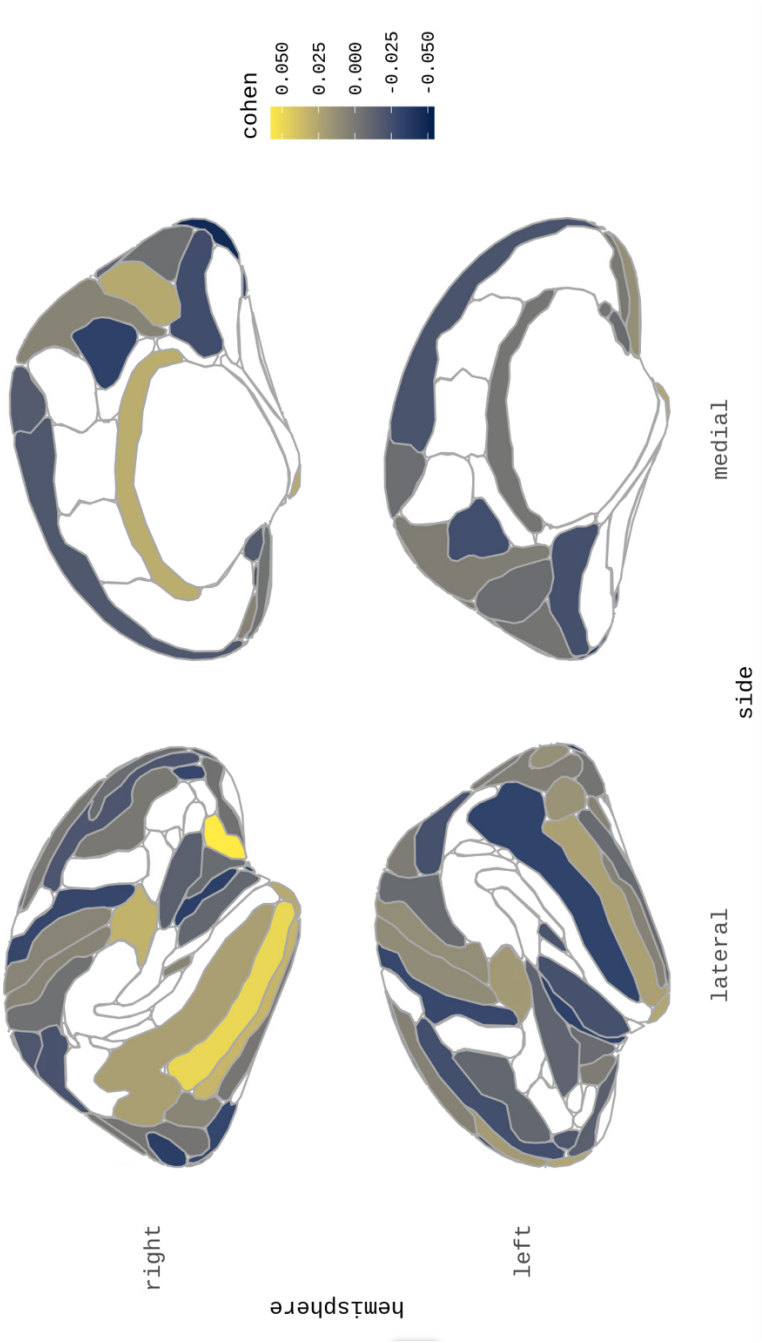

Figure 1. Brain plot showing changes in cortical thickness in different regions across time, modeled using linear mixed-effect regression. The plot was generated using deviation scores of cortical thickness. Cohen's d values were computed based on the results from the models and color-coded in each corresponding region, where lighter colors indicate positive Cohen's d values, darker colors indicate negative Cohen's d values, and transparency indicates that there is missing data.

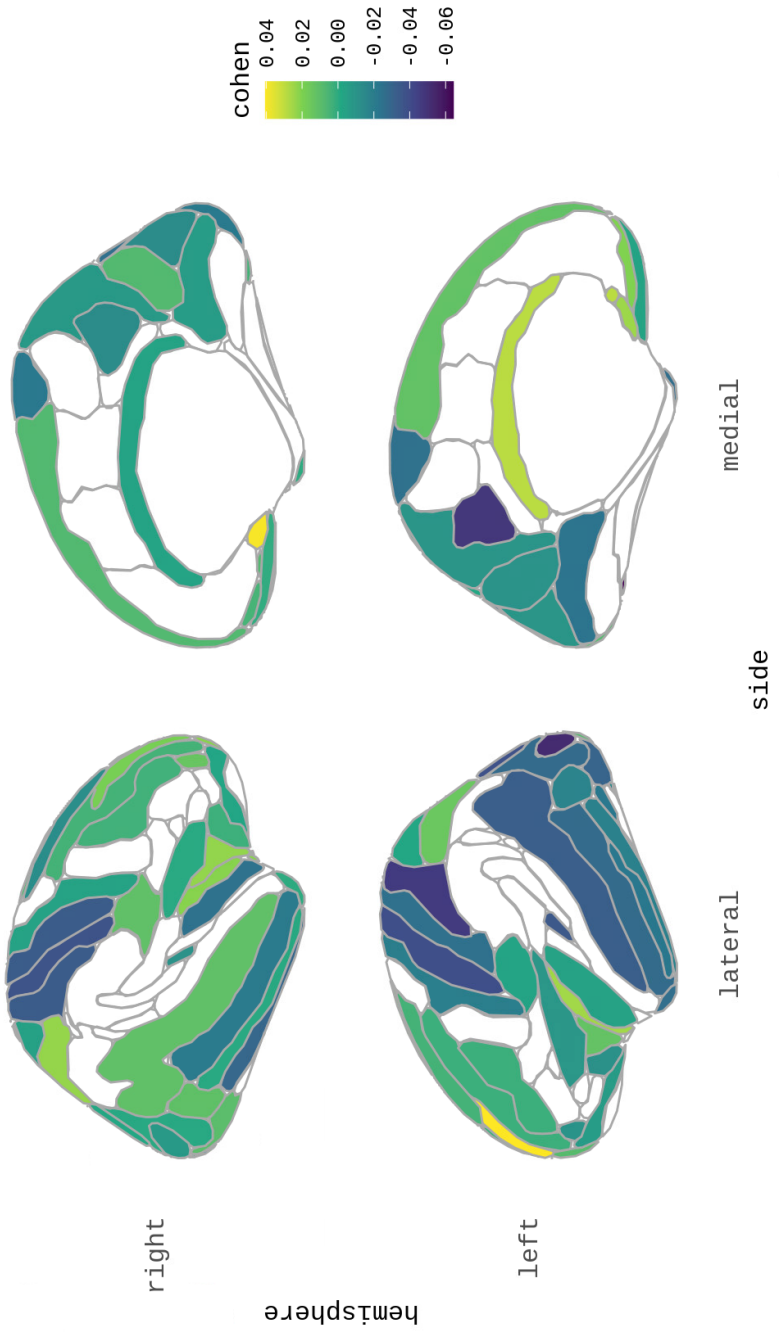

Figure 2. Brain plot showing the association between internalizing problems and cortical thickness in different brain regions, modeled using linear mixed-effect regression. Cohen's d values were computed based on the results from the models and color-coded in each corresponding region, where lighter colors indicate positive Cohen's d values, darker colors indicate negative Cohen's d values, and transparency indicates that there is missing data.

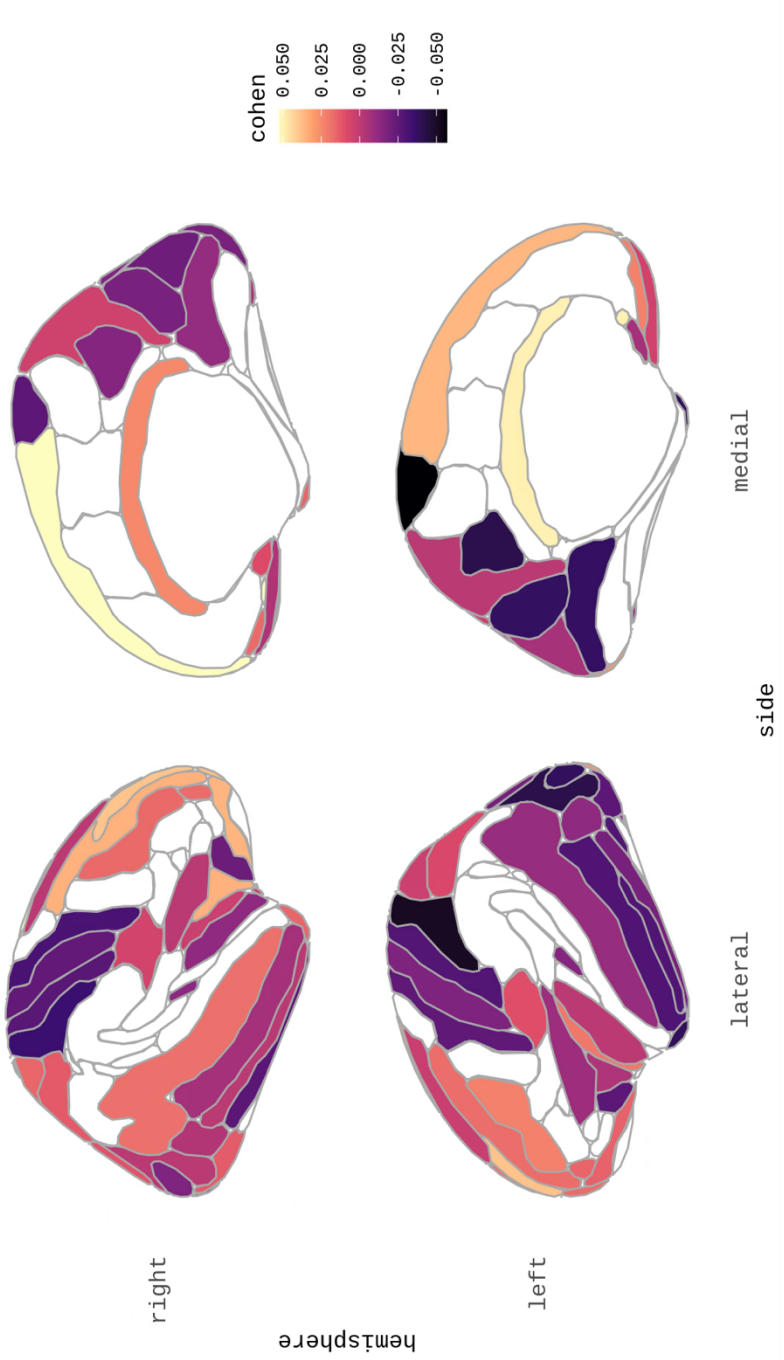

Figure 3. Brain plot showing the association between externalizing problems and cortical thickness in different brain regions, modeled using linear mixed-effect regression. Cohen's d values were computed based on the results from the models and color-coded in each corresponding region, where lighter colors indicate larger Cohen's d values, darker colors indicate smaller Cohen's d values, and transparency indicates that there is missing data.

(B = -0.04, SE = 0.02, t = -2.11, P < 0.05), occipital pole (left: B = -0.04, SE = 0.02, t = -2.18, P < 0.05; right: B = -0.04, SE = 0.02, t = -2.42, P < 0.05), and left anterior collateral sulcus (B = -0.05, SE = 0.02, t = -2.73, P < 0.01), as well as a significant increase in left parahippocampal gyrus(B = 0.04, SE = 0.02, t = 2.27, P < 0.05), right middle temporal gyrus (B = 0.04, SE = 0.02, t = 2.47, P < 0.05), and right anterior segment of the circular sulcus of the insula (B = 0.05, SE = 0.02, t = 2.83, P < 0.01). Nonetheless, none of them survived FDR correction.

Internalizing Problems and normative trajectories of cortical thickness

We examined the associations between normative trajectories of cortical thickness (deviation scores) and internalizing problems using Equation 5. Figure 2 describes the overall association between normative trajectories and internalizing scores averaged across time, converted to Cohen's D effect sizes. Note that all Cohen's D values were near-zero. There were both negative and positive associations between cortical thickness and internalizing problems, but none of them survived FDR correction. Similarly, no trajectory*time interactions were found to be significant.

Externalizing Problems and normative trajectories of cortical thickness

We examined the associations between normative trajectories of cortical thickness (deviation scores) and externalizing problems using Equation 6. Results are shown in Figure 3, quantified as the overall association between normative trajectories and externalizing scores averaged across time, converted to Cohen's D effect sizes. Note that all Cohen's D values were near-zero. Medial occipito-temporal sulcus and lingual sulcus on both hemisphere were negatively associated with externalizing problems (left: B = -0.26, SE = 0.06, t = -4.06, P < 0.01; right: B = -0.24, SE = 0.07, t = -3.56, P < 0.05), suggesting that increased thickness in these regions was associated with a decrease in externalizing problems. A significant interaction between cortical thickness in right middle frontal sulcus and time (B = -0.13, SE = 0.03, t = -3.90, P < 0.05) was found, such that the effect of cortical thickness on externalizing problems decreased as age increased.

Discussion

This study aimed to examine the association between internalizing and externalizing problems and normative trajectories of cortical thickness across time. Our approach was to employ a large US sample of children aged ~10 at baseline and ~12 at follow-up. The study yielded three major findings. First, we found that both internalizing and externalizing problems decreased over time, although the decline of externalizing problems was not statistically significant. Second, we observed a relative stability in cortical thickness across time, with no significant mean changes in thickness for any region. Third, we observed a subset of negative associations between normative deviation of cortical thickness and externalizing problems and an interaction between cortical thickness in right middle frontal sulcus, externalizing problems, and age. Analyses of the relationship between normative deviation in cortical thickness and internalizing problems did not yield any significant finding.

The results of the current study indicated that both internalizing and externalizing problems decreased over time, although the decrease in externalizing problems was not significant. However, there were significant gender differences, with boys having higher levels of externalizing problems, compared with girls, although externalizing problems decreased over time for both boys and girls. Findings regarding externalizing problems were in line with previous research including the same age range of participants, where externalizing problems decreased over time (Bongers et al., 2003; Fanti & Henrich, 2010; Leve et al., 2005). Besides, Bongers et al. (2003) also reported a similar gender difference in relation to externalizing problems as observed in the present study. Leve et al. (2005) suggested that the decrease in externalizing problems might be a result of a transition in externalizing problems. As adolescents grow older, they may engage in more convert externalizing behaviors, such as theft, instead of physical conflicts (Lacourse et al., 2002; Tremblay, 2000). Moreover, adolescents spend more time at school, making it difficult for parents to observe the full range of adolescents' externalizing behaviors, which in turn may lead to the decrease in externalizing problems from parents' rating (Kandel, 1986). In contrast

to previous studies reporting continuity in internalizing problems over time, the trajectory of internalizing problems observed in the present study was the opposite (e.g., Bongers et al., 2003; Willner et al., 2016), although a study which used a wider but similar age range also found decreased internalizing problems from ages 9 to 10 and from ages 11 to 12 (Fanti & Henrich, 2010). Copeland et al. (2013) suggested that stability of internalizing problems may be only seen when adolescents are over age 13. It is also worth noting that the present study is based on parental report. It is possible that parents might not be able to access the full range of internalizing problems as adolescents age. Adolescents generally spend less time with parents than with teachers and peers (Kandel, 1986), and internalizing behaviors might therefore be less evident to parents, resulting in an apparent decrease in internalizing symptoms.

In terms of the developmental trajectory of cortical thickness, the results showed a decline in cortical thickness across the temporal and occipital lobes, while several regions in the temporal lobe showed a significant increase, although none of these effects survived correction for multiple comparisons. It has been showed in previous neuroimaging studies that cortical thinning is widespread in all lobes during later adolescence (Thambisetty et al., 2010; Vijayakumar et al., 2016), but this was not apparent in the present sample, potentially due to younger age of the sample. Another possible reason for why our findings differ from previous studies might be due to differences in modeling approaches. Specifically, previous research showed that the developmental trajectories of cortical thickness with normal aging vary in different brain regions showing not only linear, but also non-linear (e.g., quadratic and cubic) and s-shaped trajectories (Ducharme et al., 2016; Fuhrmann et al., 2022; Tamnes et al., 2017). Fuhrmann et al. (2022) suggested that an alternative non-linear mixed-effect approach has great performance in modeling non-linear relationships in cortical developmental trajectories, and it can be used for prediction. However, these findings were based on data material covering the entirety of adolescence, as compared to our highly age-restricted sample.

Additionally, adolescence is a sensitive period of time in human lifespan with rapid structural and functional changes as adolescents mature physically and mentally. Some factors, such as early drug exposure, pubertal development and socioeconomic status may

potentially impact the normal development of the cortex during adolescence, and were not accounted for in the present study. Lopez-Larson et al. (2011) reported that an increase in cortical thickness in the precentral cortex, precuneus, middle frontal cortex, inferior temporal and middle temporal cortices was observed in adolescent marijuana users. Another study found that increased pubertal development was associated with decreased cortical thinning in the superior frontal cortex, and it showed significant gender differences, as only girls showed reduced thinning in the right superior temporal area (Herting et al., 2015). Additionally, specifically for girls, higher levels of estradiol were associated with increased thinning in the middle temporal lobe. Moreover, previous research indicated that the associations between age and cortical thickness are affected by different levels socioeconomic status (Piccolo et al., 2016). The developmental trajectories of cortical thickness were curvilinear at lower levels of socioeconomic status, whereas at higher levels of socioeconomic status, the trajectories were linear. These findings highlight the importance of considering various factors that can influence cortical development during adolescence when interpreting neuroimaging results. However, in the current study, we only modeled relationships controlling for gender and age. Future studies should seek to also include measures of sociodemographic stratification.

We examined the longitudinal changes in cortical thickness using longitudinal linear mixed effect regression employing two sources of data: the ROI-based cortical thickness and deviation scores from normative modeling. Deviation scores were generated based on the ROI-based cortical thickness, but the use of deviation scores provides advantages in analyses. As suggested by Rutherford et al. (2023), some sources of variance and covariates which are not clinically meaningful, such as site effects and gender difference, can be controlled for during normative modeling, which can help to simplify models and in turn contribute to direct comparisons both between and within samples. We employed the same logic in the current study, accounting for gender effects and site effects during the estimation of the normative models based on the reference cohort and adapting the models using material from the ABCD study, simplifying Equation 4-6 by removing the fixed effect of gender and the random effect of research sites. Since all the participants were scanned at different scanning sites, there might be systematic error from multi-site data collection. Similarly, as reported by previous research, there is pronounced gender difference in the development of cortical thickness, and

some differences in developmental trajectories of cortical thickness development can be explained by gender (Ducharme et al., 2016; Im et al., 2006; Sowell et al., 2007). However, analyses did not reveal diverging effects of time for normative trajectories and ROI-based cortical thickness in the present sample.

The current study revealed that there was a negative association between normative trajectories of bilateral medial occipito-temporal sulcus and lingual sulcus and externalizing problems. Although we found significant association between several other trajectories and internalizing problems, they did not survive multiple comparison correction (see supplementary Table 2). Previous fMRI studies have shown that occipital-temporal regions are involved in face recognition and affective interaction (Fehr et al., 2014; Jonas et al., 2016). Specifically, increased activity was observed in these regions when participants were in unpleasant situations compared to neutral situations (Geday et al., 2003). Therefore, the negative association we found between normative trajectories of cortical thickness in medial occipito-temporal sulcus and lingual sulcus and externalizing problems might reflect the difficulties that young people experience when they are in an 'emotional environment' and when they need to interpret others' facial expression accurately, which can contribute to engagement in, for example, physical conflicts (Bongers et al., 2004).

In contrast to previous research, none of the associations between developmental trajectory of cortical thickness and internalizing problems remained significant in the present study after applying FDR correction for multiple comparisons. This might be due to the sample characteristics. The current study employed a large sample which included participants from the ABCD study recruited to reflect demographic diversity of the current population in the US, but not selected as a target sample to reflect specific clinical characteristics. Therefore, as reported in previous research, strong links might not be expected. Owens et al. (2021) analyzed the ABCD data selected from baseline using a linear modeling approach among variables from all questionnaires and cognitive tasks used in the ABCD study. The results indicated that most effects found within the ABCD study were relatively small. Another reason for the lack of significant findings between internalizing problems and developmental trajectories of cortical thickness, both at a single point in time and across time, is that the participants included in the current study were relatively young

and were only followed for two years. In previous studies, strong links have only been found in samples with a much wider age range (over a decade; e.g., Bos et al., 2018; Ducharme et al., 2014; Merz et al., 2018). Furthermore, when exploring the relationship between internalizing and externalizing problems and brain measures, instead of using cortical thickness, another measure to reflect the development of brain should be considered. Although previous research showed that cortical thickness is a reliable biomarker when studying mental problems (Hanford et al., 2016; Whittle et al., 2020; Zielinski et al., 2014), the current study showed that the links between internalizing problems and trajectories of cortical thickness were not strong. Moreover, a large-scale study showed that it is generally difficult to associate internalizing problems with brain biomarkers (Winter et al., 2023). Thus, we might not expect strong links when we use cortical thickness as a predictor of internalizing problems. Previous studies show that both brain volume and cortical thickness are significantly related to externalizing problems (Jarvers et al., 2022; Whittle et al., 2020). Vijayakumar et al. (2016) clearly reflected that cortical volume is the product of cortical thickness and surface area, and each of them is driven by unique underlying mechanisms. Therefore, future studies should explore the potential mechanisms and provide further evidence of which brain measure can be seen as a valid biomarker of problem behaviors. This, in turn, could contribute to early diagnosis, intervention and treatments of internalizing and externalizing problems.

Strengths, limitations, and future considerations

There are two key strengths of the current study. Firstly, this study included a large heterogenous sample of developing children instead of recruiting a clinical or an at-risk sample to access internalizing and externalizing problems. Thus, the results of the current study can provide a better understanding of how internalizing and externalizing problems are linked to cortical morphology across the general population. Secondly, we employed longitudinal design rather than cross-sectional, and used normative modelling rather than group means, which helps to minimize the impact of group-level differences and strengthen the validity of the findings.

However, the current study has a few key limitations. First, the present study does not contain a direct comparison of the performance of models based on regional thickness versus models based on deviation scores from normative cortical thickness. Future studies should seek to directly probe whether the links between observable traits and the development of the cortex are better captured by using normative models, in accordance with Rutherford (2023).

Another limitation is that the assessment of internalizing and externalizing problems relied solely on parent reports. This means that the observation of adolescents' internalizing and externalizing behaviors was limited to the parents' perspective and did not consider the adolescents' behavior in various social environments. As adolescents grow older, they become more independent and spend less time with parents, so parent reports may not provide a comprehensive understanding of the full range of problematic behaviors (Christie & Viner, 2005). Previous studies have compared the validity of different informants regarding rating adolescents' problem behaviors and the consistency and specificity of their reports (De Los Reyes et al., 2015; Martel et al., 2017). It has been found that teachers, parents, and adolescents have their unique views of the problem behaviors, and they also face difficulties while rating the problems behaviors (Dirks et al., 2012). For instance, youths are in rapid cognitive development during adolescence and have limited experience in evaluating behavior, whereas parent reports rely heavily on the closeness between parents and their children (van der Ende et al., 2020). Assessment systems, such as ASEBA, provide assessment forms to access problem behavior in school-age youths from different perspectives and in various environmental settings, i.e. youth self-report, parent report, and forms completed by teachers or other school staff (Achenbach & Rescorla, 2001). An ideal way to improve accuracy of the assessment of internalizing and externalizing problems would be to incorporate multiple sources of information. Van der Ende et al. (2020) suggests that a combination of teacher report and youth self-report is accurate in accessing internalizing problems, but in terms of externalizing problems, parent report with added adolescent self-report is more informative. Thus, using multiple informants and assessment procedures is necessary for a more accurate evaluation.

Another limitation is the lack of control for other factors that may potentially influence the development of internalizing and externalizing problems. A study indicated that a healthy

family environment which youth can receive more support led to a decrease in externalizing problems (Fanti & Henrich, 2010). Parental factors such, as abuse, inter-parental conflict, and over-involvement, have also been associated with problems behaviors (Yap & Jorm, 2015). Other studies have revealed the effects of screen time, family psychopathology, and family income on the development of internalizing and externalizing problems (Ashford et al., 2008; Dearing et al., 2006; Eirich et al., 2022). Therefore, controlling for these factors may help to gain a better understanding of internalizing and externalizing problems.

The present study contained material collected at only two points in time. It is plausible that links between cortical thickness and internalizing or externalizing problems only become apparent when viewed across a longer timespan (as is planned in the ABCD protocol; Bos et al., 2018; Ducharme et al., 2014; Merz et al., 2018). The ABCD study is currently ongoing and will eventually span from baseline to age 20. It could be worth re-examining the present associations as future waves of data are released, including more data points, covering a longer period. Future studies using the sample from the ABCD study should also take different sources of variance into account. The ABCD study employs a variety of assessment instruments and methods, including substance use, genetic factors, cultural background, environment, brain structure and functions, which provides an excellent opportunity to identify potential factors that may influence mental and physical development during adolescence.

Overall, the results of the present study showed that associations between cortical development and internalization and externalization issues were weak to non-existent in a large sample of mostly healthy individuals. Traditionally, studies of behavioral problems and brain development have relied on a case-control approach. However, this method can be problematic due to the high heterogeneity observed in these fields. Patients with similar diagnoses may have different underlying causes, but the case-control approach assumes a symmetrical distribution of cases and controls (Marquand et al., 2016). To address this issue, future studies should also consider using an alternative method, such as normative modeling, that allows for individual-level identification and prediction, across longer periods of time.

Concluding remarks

In summary, the findings suggest that both internalizing and externalizing problems decreased as adolescents aged, and cortical thickness remained relatively stable with no significant changes in cortical thickness for any brain region. Negative associations were found between normative trajectories of cortical thickness in posterior regions and externalizing problems, as well as an interaction between normative trajectory of cortical thickness in right middle frontal sulcus, time, and externalizing problems. However, no significant association was found between normative trajectory of cortical thickness and internalizing problems, which emphasizes the need for further research to identify valid brain biomarkers for examining internalizing problems. Overall, these findings deepen the understanding of internalizing and externalizing problems in the general adolescent population and highlight the potential utility of normative modeling in future studies.

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Supplementary

Table 1. *Results of linear mixed-effect models showing the association between externalizing problems and cortical thickness*

Variable	Estimate	SE	t	P
LH_G_and_S_frontomargin	0.06	0.06	0.93	0.62
Time	-0.20	0.11	-1.85	0.07
LH_G_and_S_frontomargin *time	0.01	0.03	0.22	0.92
LH_G_and_S_occipital_inf	-0.09	0.06	-1.42	0.45
Time	-0.20	0.11	-1.85	0.07
LH_G_and_S_occipital_inf *time	-0.01	0.03	-0.20	0.94
LH_G_and_S_paracentral	-0.19	0.06	-3.11	0.08
Time	-0.20	0.11	-1.85	0.07
LH_G_and_S_paracentral *time	0.01	0.03	0.37	0.87
LH_G_and_S_subcentral	0.03	0.06	0.52	0.79
Time	-0.20	0.11	-1.87	0.07
LH_G_and_S_subcentral *time	-0.07	0.03	-2.31	0.19
LH_G_and_S_transv_frontopol	0.13	0.06	2.20	0.24
Time	-0.19	0.11	-1.84	0.07
LH_G_and_S_transv_frontopol *time	-0.02	0.03	-0.76	0.77
LH_G_and_S_cingul_Ant	0.14	0.06	2.29	0.23
Time	-0.02	0.11	-1.89	0.07
LH_G_and_S_cingul_Ant *time	-0.09	0.03	-2.74	0.12
LH_G_and_S_cingul_Mid_Ant	-0.03	0.06	-0.50	0.80
Time	-0.20	0.11	-1.85	0.07
LH_G_and_S_cingul_Mid_Ant *time	-0.03	0.03	-0.96	0.66
LH_G_and_S_cingul_Mid_Post	-0.01	0.06	-0.13	0.95
Time	-0.19	0.11	-1.84	0.07
LH_G_and_S_cingul_Mid_Post *time	-0.001	0.03	-0.03	0.98
LH_G_cingul_Post_dorsal	-0.08	0.06	-1.33	0.48

Time	-0.19	0.01	-1.83	0.07
LH_G_cingul_Post_dorsal *time	0.01	0.03	0.46	0.87
LH_G_cingul_Post_ventral	0.07	0.06	1.03	0.59
Time	-0.20	0.11	-1.86	0.07
LH_G_cingul_Post_ventral *time	-0.04	0.03	-1.15	0.60
LH_G_cuneus	-0.02	0.06	-0.36	0.85
Time	-0.19	0.11	-1.81	0.07
LH_G_cuneus *time	0.03	0.03	0.91	0.66
LH_G_front_inf_Opercular	0.13	0.06	2.08	0.24
Time	-0.19	0.11	-1.83	0.07
LH_G_front_inf_Opercular *time	-0.06	0.03	-1.88	0.33
LH_G_front_inf_Orbital	0.12	0.06	1.93	0.26
Time	-0.19	0.11	-1.84	0.07
LH_G_front_inf_Orbital *time	-0.04	0.03	-1.34	0.58
LH_G_front_inf_Triangul	0.12	0.06	1.91	0.26
Time	-0.19	0.11	-1.84	0.07
LH_G_front_inf_Triangul *time	-0.06	0.03	-1.88	0.33
LH_G_front_middle	0.06	0.06	0.94	0.62
Time	-0.20	0.11	-1.86	0.07
LH_G_front_middle *time	-0.07	0.03	-2.35	0.19
LH_G_front_sup	0.12	0.06	1.97	0.26
Time	-0.20	0.11	-1.85	0.07
LH_G_front_sup *time	-0.08	0.03	-2.47	0.17
LH_G_Ins_lg_and_S_cent_ins	0.06	0.06	1.03	0.59
Time	-0.20	0.11	-1.86	0.07
LH_G_Ins_lg_and_S_cent_ins *time	-0.04	0.03	-1.23	0.60
LH_G_insular_short	-0.01	0.06	-0.24	0.91
Time	-0.20	0.11	-1.87	0.07
LH_G_insular_short *time	-0.04	0.03	-1.31	0.58

LH_G_occipital_middle	-0.15	0.06	-2.31	0.23
Time	-0.19	0.11	-1.83	0.07
LH_G_occipital_middle *time	0.01	0.03	0.43	0.87
LH_G_occipital_sup	-0.004	0.06	-0.06	0.96
Time	-0.20	0.11	-1.86	0.07
LH_G_occipital_sup *time	-0.20	0.03	-0.67	0.79
LH_G_oc_temp_lat_fusifor	-0.04	0.07	-0.65	0.72
Time	-0.20	0.11	-1.86	0.07
LH_G_oc_temp_lat_fusifor *time	-0.02	0.03	-0.61	0.80
LH_G_oc_temp_med_Lingual	-0.13	0.06	-1.96	0.26
Time	-0.20	0.11	-1.87	0.07
LH_G_oc_temp_med_Lingual *time	0.02	0.03	0.67	0.79
LH_G_oc_temp_med_Parahip	-0.15	0.06	-2.39	0.23
Time	-0.19	0.11	-1.80	0.07
LH_G_oc_temp_med_Parahip *time	0.03	0.03	0.94	0.66
LH_G_orbital	0.05	0.06	0.78	0.68
Time	-0.20	0.11	-1.89	0.07
LH_G_orbital *time	-0.06	0.03	-2.05	0.28
LH_G_pariet_inf_Angular	0.01	0.06	0.24	0.91
Time	-0.20	0.11	-1.86	0.07
LH_G_pariet_inf_Angular *time	-0.04	0.03	-1.21	0.60
LH_G_pariet_inf_Supramar	0.05	0.06	0.75	0.70
Time	-0.20	0.11	-1.86	0.07
LH_G_pariet_inf_Supramar *time	-0.05	0.03	-1.60	0.47
LH_G_parietal_sup	0.01	0.06	0.18	0.93
Time	-0.20	0.11	-1.88	0.07
LH_G_parietal_sup *time	-0.06	0.03	-1.73	0.43
LH_G_postcentral	-0.10	0.06	-1.59	0.41
Time	-0.19	0.11	-1.84	0.07

LH_G_postcentral *time	0.002	0.03	0.06	0.98
LH_G_precentral	-0.08	0.06	-1.40	0.46
Time	-0.20	0.11	-1.86	0.07
LH_G_precentral *time	-0.01	0.03	-0.29	0.89
LH_G_precuneus	-0.004	0.06	-0.07	0.96
Time	-0.20	0.11	-1.86	0.07
LH_G_precuneus *time	-0.03	0.03	-1.06	0.63
LH_G_rectus	0.02	0.06	0.27	0.90
Time	-0.20	0.11	-1.89	0.07
LH_G_rectus *time	-0.05	0.03	-1.46	0.53
LH_G_subcallosal	-0.02	0.06	-0.36	0.85
Time	-0.19	0.11	-1.84	0.07
LH_G_subcallosal *time	-0.004	0.03	-0.11	0.97
LH_G_temp_sup_G_T_transv	0.03	0.06	0.44	0.81
Time	-0.20	0.11	-1.85	0.07
LH_G_temp_sup_G_T_transv *time	-0.04	0.03	-1.17	0.60
LH_G_temp_sup_Lateral	0.10	0.06	1.54	0.42
Time	-0.20	0.11	-1.85	0.07
LH_G_temp_sup_Lateral *time	-0.04	0.03	-1.35	0.58
LH_G_temp_sup_Plan_polar	0.01	0.06	0.16	0.94
Time	-0.19	0.11	-1.83	0.07
LH_G_temp_sup_Plan_polar *time	-0.04	0.03	-1.14	0.60
LH_G_temp_sup_Plan_tempo	-0.06	0.06	-0.94	0.62
Time	-0.20	0.11	-1.85	0.07
LH_G_temp_sup_Plan_tempo *time	-0.02	0.03	-0.64	0.79
LH_G_temporal_inf	-0.07	0.06	-1.05	0.59
Time	-0.20	0.11	-1.85	0.07
LH_G_temporal_inf *time	-0.01	0.03	-0.46	0.87
LH_G_temporal_middle	-0.10	0.06	-1.66	0.38

Time	-0.19	0.11	-1.83	0.07
LH_G_temporal_middle *time	0.03	0.03	1.02	0.63
LH_Lat_Fis_ant_Horizont	0.19	0.06	3.01	0.08
Time	-0.20	0.11	-1.86	0.07
LH_Lat_Fis_ant_Horizont *time	-0.04	0.03	-1.39	0.55
LH_Lat_Fis_ant_Vertical	-0.04	0.06	-0.60	0.74
Time	-0.20	0.11	-1.85	0.07
LH_Lat_Fis_ant_Vertical *time	-0.002	0.03	-0.05	0.98
LH_Lat_Fis_post	-0.04	0.07	-0.65	0.72
Time	-0.20	0.11	-1.91	0.07
LH_Lat_Fis_post *time	-0.07	0.03	-2.07	0.28
LH_Pole_occipital	0.10	0.06	1.54	0.42
Time	-0.20	0.11	-1.87	0.07
LH_Pole_occipital *time	-0.06	0.03	-1.84	0.35
LH_Pole_temporal	-0.12	0.06	-2.06	0.24
Time	-0.19	0.11	-1.81	0.07
LH_Pole_temporal *time	-0.001	0.03	-0.04	0.98
LH_S_calcarine	-0.13	0.07	-2.05	0.24
Time	-0.20	0.11	-1.88	0.07
LH_S_calcarine *time	0.03	0.03	1.01	0.63
LH_S_central	-0.06	0.06	-0.93	0.62
Time	-0.20	0.11	-1.85	0.07
LH_S_central *time	-0.01	0.03	-0.43	0.87
LH_S_cingul_Marginalis	-0.08	0.06	-1.23	0.51
Time	-0.20	0.11	-1.86	0.07
LH_S_cingul_Marginalis *time	-0.04	0.03	-1.16	0.60
LH_S_circular_insula_ant	-0.09	0.06	-1.44	0.45
Time	-0.20	0.11	-1.85	0.07
LH_S_circular_insula_ant *time	-0.03	0.03	-0.95	0.66

LH_S_circular_insula_inf	-0.003	0.06	-0.04	0.97
Time	-0.20	0.11	-1.88	0.07
LH_S_circular_insula_inf *time	-0.07	0.03	-2.16	0.25
LH_S_circular_insula_sup	-0.03	0.06	-0.50	0.80
Time	-0.20	0.11	-1.89	0.07
LH_S_circular_insula_sup *time	-0.08	0.03	-2.64	0.12
LH_S_collat_transv_ant	-0.10	0.06	-1.60	0.41
Time	-0.20	0.11	-1.87	0.07
LH_S_collat_transv_ant *time	0.02	0.03	0.70	0.79
LH_S_collat_transv_post	-0.04	0.06	-0.70	0.71
Time	-0.20	0.11	-1.85	0.07
LH_S_collat_transv_post *time	0.003	0.03	0.12	0.97
LH_S_front_inf	0.07	0.06	1.22	0.51
Time	-0.20	0.11	-1.88	0.07
LH_S_front_inf *time	-0.09	0.03	-2.82	0.10
LH_S_front_middle	0.12	0.06	2.08	0.24
Time	-0.20	0.11	-1.88	0.07
LH_S_front_middle *time	-0.09	0.03	-2.88	0.10
LH_S_front_sup	0.01	0.06	0.13	0.95
Time	-0.19	0.11	-1.85	0.07
LH_S_front_sup *time	-0.08	0.03	-2.61	0.12
LH_S_interm_prim_Jensen	-0.14	0.06	-2.34	0.23
Time	-0.19	0.11	-1.83	0.07
LH_S_interm_prim_Jensen *time	0.03	0.03	1.09	0.61
LH_S_intrapariet_and_P_trans	0.02	0.06	0.40	0.84
Time	-0.20	0.11	-1.86	0.07
LH_S_intrapariet_and_P_trans *time	-0.04	0.03	-1.19	0.60
LH_S_oc_middle_and_Lunatus	-0.14	0.06	-2.11	0.24
Time	-0.19	0.11	-1.84	0.07

LH_S_oc_middle_and_Lunatus *time	-0.03	0.03	-0.90	0.66
LH_S_oc_sup_and_transversal	-0.07	0.06	-1.08	0.58
Time	-0.20	0.11	-1.85	0.07
LH_S_oc_sup_and_transversal *time	-0.01	0.03	-0.46	0.87
LH_S_occipital_ant	-0.04	0.06	-0.69	0.71
Time	-0.19	0.11	-1.84	0.07
LH_S_occipital_ant *time	-0.04	0.03	-1.12	0.60
LH_S_oc_temp_lat	-0.10	0.07	-1.52	0.42
Time	-0.20	0.11	-1.87	0.07
LH_S_oc_temp_lat *time	-0.01	0.03	-0.42	0.87
LH_S_oc_temp_med_and_Lingual	-0.26	0.06	-4.06	0.01**
Time	-0.19	0.11	-1.80	0.07
LH_S_oc_temp_med_and_Lingual *time	-0.01	0.03	-0.29	0.89
LH_S_orbital_lateral	0.05	0.06	0.82	0.66
Time	-0.20	0.11	-1.86	0.07
LH_S_orbital_lateral *time	-0.04	0.03	-1.14	0.60
LH_S_orbital_med_olfact	-0.11	0.06	-1.89	0.26
Time	-0.20	0.11	-1.85	0.07
LH_S_orbital_med_olfact *time	-0.002	0.03	-0.07	0.98
LH_S_orbital_H_Shaped	0.12	0.06	2.05	0.24
Time	-0.20	0.11	-1.86	0.07
LH_S_orbital_H_Shaped *time	-0.02	0.03	-0.52	0.84
LH_S_parieto_occipital	-0.14	0.07	-2.06	0.24
Time	-0.20	0.11	-1.90	0.07
LH_S_parieto_occipital *time	-0.03	0.03	-1.02	0.63
LH_S_pericallosal	0.18	0.07	2.64	0.15
Time	-0.19	0.11	-1.83	0.07
LH_S_pericallosal *time	0.004	0.03	0.13	0.97
LH_S_postcentral	-0.18	0.06	-2.79	0.11

Time	-0.20	0.11	-1.87	0.07
LH_S_postcentral *time	-0.01	0.03	-0.41	0.87
LH_S_precentral_inf_part	-0.10	0.06	-1.55	0.42
Time	-0.19	0.11	-1.84	0.07
LH_S_precentral_inf_part *time	-0.02	0.03	-0.68	0.79
LH_S_precentral_sup_part	-0.10	0.06	-1.68	0.38
Time	-0.20	0.11	-1.85	0.07
LH_S_precentral_sup_part *time	-0.02	0.03	-0.64	0.79
LH_S_suborbital	0.08	0.06	1.22	0.51
Time	-0.20	0.11	-1.85	0.07
LH_S_suborbital *time	-0.02	0.03	-0.55	0.83
LH_S_subparietal	-0.14	0.06	-2.89	0.23
Time	-0.20	0.11	-1.88	0.07
LH_S_subparietal *time	-0.01	0.03	-0.23	0.92
LH_S_temporal_inf	-0.10	0.06	-1.62	0.40
Time	-0.20	0.11	-1.85	0.07
LH_S_temporal_inf *time	-0.02	0.03	-0.75	0.77
LH_S_temporal_sup	-0.04	0.06	-0.56	0.77
Time	-0.20	0.11	-1.88	0.07
LH_S_temporal_sup *time	-0.05	0.03	-1.55	0.49
LH_S_temporal_transverse	-0.05	0.07	-0.80	0.66
Time	-0.19	0.11	-1.85	0.07
LH_S_temporal_transverse *time	-0.002	0.03	-0.08	0.98
RH_G_and_S_frontomargin	0.12	0.06	2.07	0.24
Time	-0.20	0.11	-1.85	0.07
RH_G_and_S_frontomargin *time	-0.05	0.03	-1.46	0.53
RH_G_and_S_occipital_inf	0.05	0.07	0.68	0.71
Time	-0.20	0.11	-1.87	0.07
RH_G_and_S_occipital_inf *time	-0.05	0.03	-1.66	0.45

RH_G_and_S_paracentral	-0.09	0.06	-1.45	0.45
Time	-0.20	0.11	-1.88	0.07
RH_G_and_S_paracentral *time	-0.04	0.03	-1.15	0.60
RH_G_and_S_subcentral	0.02	0.06	0.30	0.89
Time	-0.19	0.11	-1.85	0.07
RH_G_and_S_subcentral *time	-0.02	0.03	-0.79	0.75
RH_G_and_S_transv_frontopol	0.15	0.06	2.53	0.19
Time	-0.20	0.11	-1.86	0.07
RH_G_and_S_transv_frontopol *time	-0.06	0.03	-1.91	0.33
RH_G_and_S_cingul_Ant	0.08	0.06	1.34	0.48
Time	-0.20	0.11	-1.85	0.07
RH_G_and_S_cingul_Ant *time	-0.05	0.03	-1.45	0.53
RH_G_and_S_cingul_Mid_Ant	0.03	0.06	0.47	0.81
Time	-0.20	0.11	-1.85	0.07
RH_G_and_S_cingul_Mid_Ant *time	-0.03	0.03	-0.79	0.75
RH_G_and_S_cingul_Mid_Post	0.02	0.06	0.29	0.89
Time	-0.19	0.11	-1.84	0.07
RH_G_and_S_cingul_Mid_Post *time	-0.01	0.03	-0.34	0.87
RH_G_cingul_Post_dorsal	0.06	0.06	1.00	0.60
Time	-0.19	0.11	-1.82	0.07
RH_G_cingul_Post_dorsal *time	0.01	0.03	0.32	0.87
RH_G_cingul_Post_ventral	-0.07	0.07	-1.09	0.58
Time	-0.20	0.11	-1.85	0.07
RH_G_cingul_Post_ventral *time	0.05	0.03	1.53	0.51
RH_G_cuneus	-0.08	0.06	-1.19	0.52
Time	-0.20	0.11	-1.85	0.07
RH_G_cuneus *time	-0.001	0.03	-0.04	0.98
RH_G_front_inf_Opercular	0.02	0.06	1.89	0.26
Time	-0.19	0.11	-1.84	0.07

RH_G_front_inf_Opercular *time	-0.09	0.03	-2.96	0.10
RH_G_front_inf_Orbital	-0.02	0.06	-0.26	0.90
Time	-0.20	0.11	-1.85	0.07
RH_G_front_inf_Orbital *time	-0.02	0.03	-1.08	0.62
RH_G_front_inf_Triangul	0.19	0.06	3.04	0.08
Time	-0.19	0.11	-1.81	0.07
RH_G_front_inf_Triangul *time	-0.04	0.03	-1.23	0.60
RH_G_front_middle	0.11	0.06	1.90	0.26
Time	-0.20	0.11	-1.85	0.07
RH_G_front_middle *time	-0.09	0.03	-2.88	0.10
RH_G_front_sup	0.18	0.06	2.87	0.10
Time	-0.20	0.11	-1.85	0.07
RH_G_front_sup *time	-0.10	0.03	-3.33	0.07
RH_G_Ins_lg_and_S_cent_ins	0.01	0.06	0.15	0.94
Time	-0.20	0.11	-1.86	0.07
RH_G_Ins_lg_and_S_cent_ins *time	-0.03	0.03	-0.81	0.74
RH_G_insular_short	0.10	0.06	1.77	0.33
Time	-0.20	0.11	-1.86	0.07
RH_G_insular_short *time	-0.07	0.03	-2.01	0.30
RH_G_occipital_middle	-0.004	0.06	-0.07	0.96
Time	-0.20	0.11	-1.87	0.07
RH_G_occipital_middle *time	-0.04	0.03	-1.32	0.58
RH_G_occipital_sup	-0.06	0.06	-0.89	0.63
Time	-0.20	0.11	-1.87	0.07
RH_G_occipital_sup *time	-0.02	0.03	-0.54	0.83
RH_G_oc_temp_lat_fusifor	-0.08	0.07	-1.25	0.51
Time	-0.20	0.11	-1.87	0.07
RH_G_oc_temp_lat_fusifor *time	-0.02	0.03	-0.70	0.79
RH_G_oc_temp_med_Lingual	-0.08	0.06	-1.24	0.51

Time	-0.19	0.11	-1.84	0.07
RH_G_oc_temp_med_Lingual *time	0.01	0.03	0.41	0.87
RH_G_oc_temp_med_Parahip	-0.14	0.06	-2.20	0.24
Time	-0.19	0.11	-1.81	0.07
RH_G_oc_temp_med_Parahip *time	-0.01	0.03	-0.35	0.87
RH_G_orbital	0.12	0.06	1.93	0.26
Time	-0.20	0.11	-1.91	0.07
RH_G_orbital *time	-0.09	0.03	-2.86	0.10
RH_G_pariet_inf_Angular	0.05	0.06	0.85	0.65
Time	-0.20	0.11	-1.88	0.07
RH_G_pariet_inf_Angular *time	-0.05	0.03	-1.70	0.43
RH_G_pariet_inf_Supramar	0.03	0.06	0.55	0.77
Time	-0.20	0.11	-1.85	0.07
RH_G_pariet_inf_Supramar *time	-0.02	0.03	-0.70	0.79
RH_G_parietal_sup	0.05	0.06	0.84	0.65
Time	-0.20	0.11	-1.90	0.07
RH_G_parietal_sup *time	-0.08	0.03	-2.38	0.19
RH_G_postcentral	-0.10	0.06	-1.51	0.42
Time	-0.19	0.11	-1.83	0.07
RH_G_postcentral *time	0.02	0.03	0.53	0.83
RH_G_precentral	-0.09	0.06	-1.67	0.38
Time	-0.20	0.11	-1.87	0.07
RH_G_precentral *time	-0.01	0.03	-0.35	0.87
RH_G_precuneus	0.01	0.06	0.22	0.91
Time	-0.20	0.11	-1.85	0.07
RH_G_precuneus *time	-0.01	0.03	-0.37	0.87
RH_G_rectus	-0.01	0.06	-0.22	0.91
Time	-0.20	0.11	-1.89	0.07
RH_G_rectus *time	-0.05	0.03	-1.61	0.47

RH_G_subcallosal	0.03	0.06	0.44	0.81
Time	-0.19	0.11	-1.84	0.07
RH_G_subcallosal *time	-0.02	0.03	-0.53	0.83
RH_G_temp_sup_G_T_transv	-0.04	0.06	-0.73	0.71
Time	-0.20	0.11	-1.86	0.07
RH_G_temp_sup_G_T_transv *time	-0.02	0.03	-0.66	0.79
RH_G_temp_sup_Lateral	0.08	0.06	1.34	0.48
Time	-0.19	0.11	-1.84	0.07
RH_G_temp_sup_Lateral *time	-0.02	0.03	-0.74	0.77
RH_G_temp_sup_Plan_polar	0.06	0.06	0.06	0.59
Time	-0.19	0.11	-0.19	0.07
RH_G_temp_sup_Plan_polar *time	-0.03	0.03	-0.03	0.66
RH_G_temp_sup_Plan_tempo	0.03	0.06	0.44	0.81
Time	-0.20	0.11	-1.86	0.07
RH_G_temp_sup_Plan_tempo *time	-0.03	0.03	-1.04	0.63
RH_G_temporal_inf	-0.09	0.06	-1.49	0.43
Time	-0.20	0.11	-1.86	0.07
RH_G_temporal_inf *time	-0.01	0.03	-0.37	0.87
RH_G_temporal_middle	-0.02	0.06	-0.39	0.84
Time	-0.19	0.11	-1.83	0.07
RH_G_temporal_middle *time	0.01	0.03	0.35	0.87
RH_Lat_Fis_ant_Horizont	0.04	0.06	0.68	0.71
Time	-0.19	0.11	-1.83	0.07
RH_Lat_Fis_ant_Horizont *time	-0.01	0.03	-0.32	0.87
RH_Lat_Fis_ant_Vertical	0.07	0.06	1.14	0.56
Time	-0.19	0.11	-1.83	0.07
RH_Lat_Fis_ant_Vertical *time	-0.07	0.03	-2.33	0.19
RH_Lat_Fis_post	0.04	0.06	0.61	0.74
Time	-0.20	0.11	-1.89	0.07

RH_Lat_Fis_post *time	-0.06	0.03	-1.91	0.33
RH_Pole_occipital	-0.07	0.06	-1.03	0.59
Time	-0.20	0.11	-1.89	0.07
RH_Pole_occipital *time	-0.01	0.03	-0.42	0.87
RH_Pole_temporal	0.05	0.06	0.81	0.66
Time	-0.20	0.11	-1.86	0.07
RH_Pole_temporal *time	-0.07	0.03	-2.28	0.20
RH_S_calcarine	-0.04	0.07	-0.61	0.74
Time	-0.20	0.11	-1.85	0.07
RH_S_calcarine *time	0.01	0.03	0.18	0.94
RH_S_central	-0.08	0.06	-1.35	0.48
Time	-0.19	0.11	-1.84	0.07
RH_S_central *time	-0.02	0.03	-0.66	0.79
RH_S_cingul_Marginalis	-0.08	0.06	-1.28	0.50
Time	-0.20	0.11	-1.86	0.07
RH_S_cingul_Marginalis *time	-0.001	0.03	-0.02	0.99
RH_S_circular_insula_ant	-0.08	0.06	-1.23	0.51
Time	-0.19	0.11	-1.80	0.07
RH_S_circular_insula_ant *time	-0.02	0.03	-0.60	0.80
RH_S_circular_insula_inf	-0.04	0.06	-0.68	0.71
Time	-0.20	0.11	-1.86	0.07
RH_S_circular_insula_inf *time	-0.04	0.03	-1.40	0.55
RH_S_circular_insula_sup	-0.004	0.06	-0.06	0.96
Time	-0.19	0.11	-1.84	0.07
RH_S_circular_insula_sup *time	-0.01	0.03	-0.43	0.87
RH_S_collat_transv_ant	-0.01	0.07	-0.10	0.96
Time	-0.19	0.11	-1.84	0.07
RH_S_collat_transv_ant *time	0.005	0.03	0.14	0.96
RH_S_collat_transv_post	-0.02	0.06	-0.30	0.89

Time	-0.20	0.11	-1.88	0.07
RH_S_collat_transv_post *time	-0.04	0.03	-1.17	0.60
RH_S_front_inf	0.05	0.06	0.89	0.63
Time	-0.20	0.11	-1.85	0.07
RH_S_front_inf *time	-0.05	0.03	-1.64	0.45
RH_S_front_middle	0.12	0.06	2.08	0.24
Time	-0.20	0.11	-1.87	0.07
RH_S_front_middle *time	-0.13	0.03	-3.90	0.01*
RH_S_front_sup	-0.002	0.06	-0.04	0.97
Time	-0.20	0.11	-1.86	0.07
RH_S_front_sup *time	-0.06	0.03	-1.95	0.33
RH_S_interm_prim_Jensen	0.03	0.06	0.46	0.81
Time	-0.19	0.11	-1.83	0.07
RH_S_interm_prim_Jensen *time	-0.01	0.03	-0.18	0.94
RH_S_intrapariet_and_P_trans	0.04	0.06	0.68	0.71
Time	-0.20	0.11	-1.89	0.07
RH_S_intrapariet_and_P_trans *time	-0.08	0.03	-2.65	0.12
RH_S_oc_middle_and_Lunatus	-0.06	0.06	-0.93	0.62
Time	-0.20	0.11	-1.88	0.07
RH_S_oc_middle_and_Lunatus *time	-0.04	0.03	-1.18	0.60
RH_S_oc_sup_and_transversal	0.04	0.06	0.59	0.75
Time	-0.20	0.11	-1.86	0.07
RH_S_oc_sup_and_transversal *time	-0.04	0.03	-1.43	0.54
RH_S_occipital_ant	-0.02	0.06	-0.19	0.93
Time	-0.19	0.11	-1.84	0.07
RH_S_occipital_ant *time	-0.07	0.03	-2.09	0.28
RH_S_oc_temp_lat	-0.10	0.06	-1.48	0.43
Time	-0.20	0.11	-1.87	0.07
RH_S_oc_temp_lat *time	-0.03	0.03	-1.05	0.63

RH_S_oc_temp_med_and_Lingual	-0.24	0.07	-3.56	0.03*
Time	-0.20	0.11	-1.85	0.07
RH_S_oc_temp_med_and_Lingual *time	0.01	0.03	0.32	0.87
RH_S_orbital_lateral	0.06	0.06	0.92	0.62
Time	-0.19	0.11	-1.84	0.07
RH_S_orbital_lateral *time	-0.03	0.03	-0.96	0.66
RH_S_orbital_med_olfact	0.08	0.06	1.35	0.48
Time	-0.19	0.11	-1.84	0.07
RH_S_orbital_med_olfact *time	0.01	0.03	0.24	0.92
RH_S_orbital_H_Shaped	0.07	0.06	1.10	0.58
Time	-0.20	0.11	-1.87	0.07
RH_S_orbital_H_Shaped *time	-0.05	0.03	-1.70	0.43
RH_S_parieto_occipital	-0.06	0.06	-1.01	0.60
Time	-0.19	0.11	-1.83	0.07
RH_S_parieto_occipital *time	-0.001	0.03	-0.04	0.98
RH_S_pericallosal	0.09	0.07	1.28	0.50
Time	-0.19	0.11	-1.83	0.07
RH_S_pericallosal *time	0.04	0.03	1.28	0.60
RH_S_postcentral	-0.12	0.06	-1.93	0.26
Time	-0.20	0.11	-1.87	0.07
RH_S_postcentral *time	-0.03	0.03	-0.96	0.66
RH_S_precentral_inf_part	-0.03	0.06	-0.46	0.81
Time	-0.19	0.11	-1.83	0.07
RH_S_precentral_inf_part *time	-0.05	0.03	-1.47	0.53
RH_S_precentral_sup_part	-0.63	0.06	-1.12	0.57
Time	-0.20	0.11	-1.85	0.07
RH_S_precentral_sup_part *time	0.03	0.03	0.90	0.66
RH_S_suborbital	0.06	0.06	0.90	0.63
Time	-0.20	0.11	-1.86	0.07

RH_S_suborbital *time	-0.04	0.03	-1.33	0.58
RH_S_subparietal	-0.05	0.06	-0.85	0.65
Time	-0.20	0.11	-1.88	0.07
RH_S_subparietal *time	-0.04	0.03	-1.21	0.60
RH_S_temporal_inf	-0.005	0.06	-0.07	0.96
Time	-0.19	0.11	-1.83	0.07
RH_S_temporal_inf *time	0.02	0.03	0.61	0.80
RH_S_temporal_sup	0.06	0.07	0.97	0.62
Time	-0.20	0.11	-1.85	0.07
RH_S_temporal_sup *time	-0.03	0.03	-1.11	0.61
RH_S_temporal_transverse	-0.05	0.06	-0.73	0.71
Time	-0.19	0.11	-1.83	0.07
RH_S_temporal_transverse *time	0.02	0.03	0.60	0.80

Note. * indicates P < 0.05. ** indicates P < 0.01.

Table 2. *Results of linear mixed-effect models showing the association between internalizing problems and cortical thickness*

Variable	Estimate	SE	t	P
LH_G_and_S_frontomargin	0.03	0.06	0.47	0.92
Time	-0.23	0.10	-2.27	0.03*
LH_G_and_S_frontomargin *time	-0.01	0.03	-0.38	-0.92
LH_G_and_S_occipital_inf	-0.10	0.06	-1.62	0.63
Time	-0.23	0.10	-2.25	0.03*
LH_G_and_S_occipital_inf *time	0.04	0.03	1.20	0.71
LH_G_and_S_paracentral	-0.08	0.06	-1.37	0.66
Time	-0.23	0.10	-2.26	0.03*
LH_G_and_S_paracentral *time	0.03	0.03	0.86	0.81
LH_G_and_S_subcentral	-0.01	0.06	-0.17	0.96
Time	-0.23	0.10	-2.28	0.03*

LH_G_and_S_subcentral *time	-0.03	0.03	-0.83	0.81
LH_G_and_S_transv_frontopol	0.13	0.06	2.12	0.46
Time	-0.23	0.10	-2.29	0.03*
LH_G_and_S_transv_frontopol *time	-0.06	0.03	-1.99	0.65
LH_G_and_S_cingul_Ant	0.06	0.06	0.99	0.76
Time	-0.23	0.10	-2.31	0.03*
LH_G_and_S_cingul_Ant *time	-0.06	0.03	-1.98	0.65
LH_G_and_S_cingul_Mid_Ant	-0.07	0.06	-1.20	0.68
Time	-0.23	0.10	-2.26	0.03*
LH_G_and_S_cingul_Mid_Ant *time	0.004	0.03	0.13	0.95
LH_G_and_S_cingul_Mid_Post	-0.01	0.06	-0.18	0.96
Time	-0.23	0.10	-2.27	0.03*
LH_G_and_S_cingul_Mid_Post *time	-0.01	0.03	-0.29	0.92
LH_G_cingul_Post_dorsal	-0.003	0.06	-0.05	0.99
Time	-0.23	0.10	-2.26	0.03*
LH_G_cingul_Post_dorsal *time	0.01	0.03	0.22	0.93
LH_G_cingul_Post_ventral	0.04	0.06	0.66	0.92
Time	-0.23	0.10	-2.28	0.03*
LH_G_cingul_Post_ventral *time	-0.04	0.03	-1.20	0.71
LH_G_cuneus	-0.03	0.06	-0.51	0.92
Time	-0.23	0.10	-2.23	0.03*
LH_G_cuneus *time	0.04	0.03	1.21	0.71
LH_G_front_inf_Opercular	0.01	0.06	0.14	0.96
Time	-0.23	0.10	-2.28	0.03*
LH_G_front_inf_Opercular *time	-0.06	0.03	-1.71	0.65
LH_G_front_inf_Orbital	0.05	0.06	0.80	0.89
Time	-0.23	0.10	-2.26	0.03*
LH_G_front_inf_Orbital *time	-0.001	0.03	-0.03	0.98
LH_G_front_inf_Triangul	0.09	0.06	1.44	0.66

Time	-0.23	0.10	-2.27	0.03*
LH_G_front_inf_Triangul *time	-0.05	0.03	-1.51	0.71
LH_G_front_middle	0.01	0.06	0.13	0.96
Time	-0.23	0.10	-2.30	0.03*
LH_G_front_middle *time	-0.06	0.03	-1.79	0.65
LH_G_front_sup	0.04	0.06	0.65	0.92
Time	-0.23	0.10	-2.28	0.03*
LH_G_front_sup *time	-0.03	0.03	-1.01	0.76
LH_G_Ins_lg_and_S_cent_ins	0.08	0.06	1.31	0.66
Time	-0.23	0.10	-2.30	0.03*
LH_G_Ins_lg_and_S_cent_ins *time	-0.07	0.03	-2.10	0.65
LH_G_insular_short	0.04	0.06	0.66	0.92
Time	-0.23	0.10	-2.29	0.03*
LH_G_insular_short *time	-0.04	0.03	-1.20	0.71
LH_G_occipital_middle	-0.09	0.06	-1.51	0.63
Time	-0.23	0.10	-2.23	0.03*
LH_G_occipital_middle *time	0.04	0.03	1.11	0.74
LH_G_occipital_sup	-0.10	0.06	-1.64	0.63
Time	-0.24	0.10	-2.31	0.03*
LH_G_occipital_sup *time	-0.01	0.03	-0.42	0.91
LH_G_oc_temp_lat_fusifor	-0.01	0.06	-0.22	0.96
Time	-0.23	0.10	-2.29	0.03*
LH_G_oc_temp_lat_fusifor *time	-0.03	0.03	-1.01	0.76
LH_G_oc_temp_med_Lingual	-0.13	0.06	-2.08	0.46
Time	-0.23	0.10	-2.28	0.03*
LH_G_oc_temp_med_Lingual *time	0.04	0.03	1.36	0.71
LH_G_oc_temp_med_Parahip	-0.09	0.06	-1.43	0.66
Time	-0.23	0.10	-2.27	0.03*
LH_G_oc_temp_med_Parahip *time	0.06	0.03	1.78	0.65

LH_G_orbital	-0.02	0.06	-0.36	0.94
Time	-0.23	0.10	-2.28	0.03*
LH_G_orbital *time	-0.01	0.03	-0.19	0.93
LH_G_pariet_inf_Angular	-0.06	0.06	-1.03	0.74
Time	-0.23	0.10	-2.27	0.03*
LH_G_pariet_inf_Angular *time	-0.01	0.03	-0.37	0.92
LH_G_pariet_inf_Supramar	0.02	0.06	0.29	0.96
Time	-0.23	0.10	-2.29	0.03*
LH_G_pariet_inf_Supramar *time	-0.05	0.03	-1.47	0.71
LH_G_parietal_sup	-0.01	0.06	-0.11	0.96
Time	-0.23	0.10	-2.28	0.03*
LH_G_parietal_sup *time	-0.01	0.03	-0.41	0.91
LH_G_postcentral	-0.09	0.06	-1.38	0.66
Time	-0.23	0.10	-2.26	0.03*
LH_G_postcentral *time	0.03	0.03	0.97	0.76
LH_G_precentral	-0.06	0.06	-1.05	0.74
Time	-0.23	0.10	-2.29	0.03*
LH_G_precentral *time	0.01	0.03	0.43	0.91
LH_G_precuneus	-0.03	0.06	-0.52	0.92
Time	-0.23	0.10	-2.29	0.03*
LH_G_precuneus *time	-0.02	0.03	-0.80	0.82
LH_G_rectus	-0.01	0.06	-0.17	0.96
Time	-0.24	0.10	-2.32	0.03*
LH_G_rectus *time	-0.05	0.03	-1.39	0.71
LH_G_subcallosal	0.07	0.06	1.26	0.67
Time	-0.23	0.10	-2.26	0.03*
LH_G_subcallosal *time	-0.04	0.03	-1.04	0.76
LH_G_temp_sup_G_T_transv	-0.08	0.06	-1.31	0.66
Time	-0.23	0.10	-2.28	0.03*

LH_G_temp_sup_G_T_transv *time	0.01	0.03	0.33	0.92
LH_G_temp_sup_Lateral	-0.01	0.06	-0.14	0.96
Time	-0.23	0.10	-2.26	0.03*
LH_G_temp_sup_Lateral *time	0.01	0.03	0.31	0.92
LH_G_temp_sup_Plan_polar	-0.06	0.06	-0.95	0.80
Time	-0.23	0.10	-2.26	0.03*
LH_G_temp_sup_Plan_polar *time	-0.01	0.03	-0.16	0.94
LH_G_temp_sup_Plan_tempo	-0.02	0.06	-0.34	0.94
Time	-0.23	0.10	-2.26	0.03*
LH_G_temp_sup_Plan_tempo *time	0.01	0.03	0.37	0.92
LH_G_temporal_inf	-0.06	0.06	-1.02	0.75
Time	-0.23	0.10	-2.27	0.03*
LH_G_temporal_inf *time	0.01	0.03	0.26	0.92
LH_G_temporal_middle	-0.09	0.06	-1.50	0.63
Time	-0.23	0.10	-2.26	0.03*
LH_G_temporal_middle *time	0.05	0.03	1.41	0.71
LH_Lat_Fis_ant_Horizont	0.08	0.06	1.33	0.66
Time	-0.23	0.10	-2.28	0.03*
LH_Lat_Fis_ant_Horizont *time	-0.05	0.03	-1.55	0.71
LH_Lat_Fis_ant_Vertical	-0.11	0.06	-1.88	0.53
Time	-0.23	0.10	-2.30	0.03*
LH_Lat_Fis_ant_Vertical *time	-0.004	0.03	-0.13	0.95
LH_Lat_Fis_post	-0.05	0.06	-0.83	0.87
Time	-0.24	0.10	-2.32	0.03*
LH_Lat_Fis_post *time	-0.04	0.03	-1.27	0.71
LH_Pole_occipital	0.03	0.06	0.46	0.92
Time	-0.23	0.10	-2.30	0.03*
LH_Pole_occipital *time	-0.04	0.03	-1.14	0.72
LH_Pole_temporal	-0.08	0.06	-1.39	0.66

Time	-0.23	0.10	-2.25	0.03*
LH_Pole_temporal *time	0.004	0.03	0.12	0.95
LH_S_calcarine	-0.08	0.06	-1.29	0.67
Time	-0.23	0.10	-2.28	0.03*
LH_S_calcarine *time	0.04	0.03	1.21	0.71
LH_S_central	-0.13	0.06	-2.12	0.46
Time	-0.23	0.10	-2.23	0.03*
LH_S_central *time	0.05	0.03	1.53	0.71
LH_S_cingul_Marginalis	-0.10	0.06	-1.62	0.63
Time	-0.23	0.10	-2.28	0.03*
LH_S_cingul_Marginalis *time	-0.02	0.03	-0.59	0.85
LH_S_circular_insula_ant	-0.04	0.06	-0.62	0.92
Time	-0.23	0.10	-2.26	0.03*
LH_S_circular_insula_ant *time	0.03	0.03	1.00	0.76
LH_S_circular_insula_inf	-0.01	0.06	-0.22	0.96
Time	-0.23	0.10	-2.27	0.03*
LH_S_circular_insula_inf *time	-0.01	0.03	-0.22	0.93
LH_S_circular_insula_sup	-0.03	0.06	-0.47	0.92
Time	-0.24	0.10	-2.32	0.03*
LH_S_circular_insula_sup *time	-0.08	0.03	-2.35	0.56
LH_S_collat_transv_ant	-0.02	0.06	-0.34	0.94
Time	-0.23	0.10	-2.28	0.03*
LH_S_collat_transv_ant *time	0.003	0.03	0.09	0.95
LH_S_collat_transv_post	-0.22	0.06	-3.52	0.06
Time	-0.23	0.10	-2.27	0.03*
LH_S_collat_transv_post *time	0.06	0.03	1.74	0.65
LH_S_front_inf	0.01	0.06	0.12	0.96
Time	-0.23	0.10	-2.29	0.03*
LH_S_front_inf *time	-0.04	0.03	-1.24	0.71

LH_S_front_middle	0.13	0.06	2.19	0.46
Time	-0.24	0.10	-2.32	0.03*
LH_S_front_middle *time	-0.11	0.03	-3.50	0.07
LH_S_front_sup	0.01	0.06	0.22	0.96
Time	-0.23	0.10	-2.27	0.03*
LH_S_front_sup *time	-0.05	0.03	-1.45	0.71
LH_S_interm_prim_Jensen	-0.08	0.06	-1.35	0.66
Time	-0.23	0.10	-2.27	0.03*
LH_S_interm_prim_Jensen *time	0.01	0.03	0.27	0.92
LH_S_intrapariet_and_P_trans	0.05	0.06	0.78	0.89
Time	-0.23	0.10	-2.28	0.03*
LH_S_intrapariet_and_P_trans *time	-0.03	0.03	-0.98	0.76
LH_S_oc_middle_and_Lunatus	-0.18	0.06	-2.88	0.29
Time	-0.23	0.10	-2.22	0.03*
LH_S_oc_middle_and_Lunatus *time	0.06	0.03	1.71	0.65
LH_S_oc_sup_and_transversal	-0.13	0.06	-2.07	0.46
Time	-0.23	0.10	-2.25	0.03*
LH_S_oc_sup_and_transversal *time	0.03	0.03	0.97	0.76
LH_S_occipital_ant	-0.06	0.06	-0.93	0.80
Time	-0.23	0.10	-2.26	0.03*
LH_S_occipital_ant *time	0.01	0.03	0.27	0.92
LH_S_oc_temp_lat	-0.14	0.06	-2.15	0.46
Time	-0.23	0.10	-2.30	0.03*
LH_S_oc_temp_lat *time	0.004	0.03	0.13	0.95
LH_S_oc_temp_med_and_Lingual	-0.14	0.06	-2.27	0.46
Time	-0.23	0.10	-2.26	0.03*
LH_S_oc_temp_med_and_Lingual *time	0.05	0.03	1.57	0.71
LH_S_orbital_lateral	-0.03	0.06	-0.57	0.92
Time	-0.23	0.10	-2.29	0.03*

LH_S_orbital_lateral *time	-0.02	0.03	-0.59	0.85
LH_S_orbital_med_olfact	-0.07	0.06	-1.17	0.68
Time	-0.23	0.10	-2.30	0.03*
LH_S_orbital_med_olfact *time	-0.04	0.03	-1.17	0.71
LH_S_orbital_H_Shaped	0.04	0.06	0.74	0.89
Time	-0.23	0.10	-2.26	0.03*
LH_S_orbital_H_Shaped *time	0.02	0.03	0.70	0.83
LH_S_parieto_occipital	-0.04	0.06	-0.58	0.92
Time	-0.23	0.10	-2.27	0.03*
LH_S_parieto_occipital *time	0.01	0.03	0.22	0.93
LH_S_pericallosal	0.10	0.07	1.55	0.63
Time	-0.23	0.10	-2.27	0.03*
LH_S_pericallosal *time	-0.02	0.03	-0.60	0.85
LH_S_postcentral	-0.16	0.06	-2.26	0.39
Time	-0.23	0.10	-2.28	0.03*
LH_S_postcentral *time	0.02	0.03	0.67	0.84
LH_S_precentral_inf_part	-0.05	0.06	-0.82	0.87
Time	-0.23	0.10	-2.28	0.03*
LH_S_precentral_inf_part *time	-0.04	0.03	-1.37	0.71
LH_S_precentral_sup_part	-0.05	0.06	-0.90	0.82
Time	-0.23	0.10	-2.27	0.03*
LH_S_precentral_sup_part *time	-0.02	0.03	-0.46	0.91
LH_S_suborbital	0.07	0.06	1.11	0.69
Time	-0.23	0.10	-2.27	0.03*
LH_S_suborbital *time	-0.01	0.03	-0.31	0.92
LH_S_subparietal	-0.16	0.06	-2.63	0.39
Time	-0.24	0.10	-2.31	0.03*
LH_S_subparietal *time	0.01	0.03	0.21	0.93
LH_S_temporal_inf	-0.08	0.06	-1.24	0.68

Time	-0.23	0.10	-2.26	0.03*
LH_S_temporal_inf *time	0.02	0.03	0.72	0.82
LH_S_temporal_sup	-0.11	0.06	-1.78	0.56
Time	-0.24	0.10	-2.32	0.03*
LH_S_temporal_sup *time	-0.003	0.03	-0.11	0.95
LH_S_temporal_transverse	-0.12	0.06	-1.86	0.53
Time	-0.23	0.10	-2.28	0.03*
LH_S_temporal_transverse *time	-0.02	0.03	-0.60	0.85
RH_G_and_S_frontomargin	0.07	0.06	1.18	0.68
Time	-0.23	0.10	-2.27	0.03*
RH_G_and_S_frontomargin *time	-0.02	0.03	-0.77	0.82
RH_G_and_S_occipital_inf	0.03	0.07	0.51	0.92
Time	-0.23	0.10	-2.26	0.03*
RH_G_and_S_occipital_inf *time	-0.01	0.03	-0.29	0.92
RH_G_and_S_paracentral	-0.07	0.06	-1.21	0.68
Time	-0.23	0.10	-2.29	0.03*
RH_G_and_S_paracentral *time	-0.01	0.03	-0.25	0.92
RH_G_and_S_subcentral	0.04	0.06	0.59	0.92
Time	-0.23	0.10	-2.28	0.03*
RH_G_and_S_subcentral *time	-0.02	0.03	-0.49	0.91
RH_G_and_S_transv_frontopol	0.09	0.06	1.54	0.63
Time	-0.23	0.10	-2.29	0.03*
RH_G_and_S_transv_frontopol *time	-0.06	0.03	-1.08	0.65
RH_G_and_S_cingul_Ant	-0.01	0.06	-0.14	0.96
Time	-0.23	0.10	-2.28	0.03*
RH_G_and_S_cingul_Ant *time	-0.01	0.03	-0.35	0.92
RH_G_and_S_cingul_Mid_Ant	-0.06	0.06	-1.04	0.74
Time	-0.23	0.10	-2.28	0.03*
RH_G_and_S_cingul_Mid_Ant *time	-0.01	0.03	-0.22	0.93

RH_G_and_S_cingul_Mid_Post	-0.03	0.06	-0.48	0.92
Time	-0.23	0.10	-2.27	0.03*
RH_G_and_S_cingul_Mid_Post *time	0.01	0.03	0.41	0.91
RH_G_cingul_Post_dorsal	0.04	0.06	0.59	0.92
Time	-0.23	0.10	-2.26	0.03*
RH_G_cingul_Post_dorsal *time	0.01	0.03	0.32	0.92
RH_G_cingul_Post_ventral	0.01	0.06	0.19	0.96
Time	-0.23	0.10	-2.27	0.03*
RH_G_cingul_Post_ventral *time	-0.01	0.03	-0.29	0.92
RH_G_cuneus	-0.05	0.06	-0.73	0.89
Time	-0.23	0.10	-2.24	0.03*
RH_G_cuneus *time	0.03	0.03	0.88	0.81
RH_G_front_inf_Opercular	0.12	0.06	2.02	0.46
Time	-0.23	0.10	-2.27	0.03*
RH_G_front_inf_Opercular *time	-0.09	0.03	-2.77	0.28
RH_G_front_inf_Orbital	0.11	0.06	1.76	0.56
Time	-0.23	0.10	-2.28	0.03*
RH_G_front_inf_Orbital *time	-0.06	0.03	-1.72	0.65
RH_G_front_inf_Triangul	0.08	0.06	1.33	0.66
Time	-0.23	0.10	-2.26	0.03*
RH_G_front_inf_Triangul *time	-0.02	0.03	-0.52	0.90
RH_G_front_middle	0.01	0.06	0.22	0.96
Time	-0.23	0.10	-2.29	0.03*
RH_G_front_middle *time	-0.05	0.03	-1.73	0.65
RH_G_front_sup	0.02	0.06	0.40	0.94
Time	-0.23	0.10	-2.29	0.03*
RH_G_front_sup *time	-0.05	0.03	-1.50	0.71
RH_G_Ins_lg_and_S_cent_ins	0.06	0.06	1.12	0.69
Time	-0.23	0.10	-2.28	0.03*

RH_G_Ins_lg_and_S_cent_ins *time	-0.03	0.03	-0.94	0.76
RH_G_insular_short	0.07	0.06	1.19	0.68
Time	-0.23	0.10	-2.28	0.03*
RH_G_insular_short *time	-0.04	0.03	-1.10	0.74
RH_G_occipital_middle	-0.003	0.06	-0.04	0.99
Time	-0.23	0.10	-2.27	0.03*
RH_G_occipital_middle *time	-0.01	0.03	-0.20	0.93
RH_G_occipital_sup	-0.09	0.06	-1.41	0.66
Time	-0.23	0.10	-2.27	0.03*
RH_G_occipital_sup *time	0.02	0.03	0.61	0.85
RH_G_oc_temp_lat_fusifor	0.04	0.06	0.62	0.92
Time	-0.23	0.10	-2.29	0.03*
RH_G_oc_temp_lat_fusifor *time	-0.02	0.03	-0.78	0.82
RH_G_oc_temp_med_Lingual	-0.10	0.06	-1.55	0.63
Time	-0.23	0.10	-2.22	0.03*
RH_G_oc_temp_med_Lingual *time	0.08	0.03	2.39	0.56
RH_G_oc_temp_med_Parahip	-0.03	0.06	-0.48	0.92
Time	-0.23	0.10	-2.28	0.03*
RH_G_oc_temp_med_Parahip *time	0.03	0.03	0.94	0.76
RH_G_orbital	-0.01	0.06	-0.13	0.96
Time	-0.23	0.10	-2.26	0.03*
RH_G_orbital *time	0.01	0.03	0.42	0.91
RH_G_pariet_inf_Angular	0.03	0.06	0.50	0.92
Time	-0.23	0.10	-2.29	0.03*
RH_G_pariet_inf_Angular *time	-0.04	0.03	-1.08	0.76
RH_G_pariet_inf_Supramar	-0.03	0.06	-0.46	0.92
Time	-0.23	0.10	-2.26	0.03*
RH_G_pariet_inf_Supramar *time	0.03	0.03	0.83	0.81
RH_G_parietal_sup	-0.01	0.06	-0.24	0.96

Time	-0.23	0.10	-2.29	0.03*
RH_G_parietal_sup *time	-0.02	0.03	-0.47	0.91
RH_G_postcentral	-0.13	0.06	-2.03	0.46
Time	-0.23	0.10	-2.25	0.03*
RH_G_postcentral *time	0.03	0.03	0.92	0.76
RH_G_precentral	-0.01	0.06	-0.22	0.96
Time	-0.23	0.10	-2.27	0.03*
RH_G_precentral *time	0.01	0.03	0.26	0.92
RH_G_precuneus	-0.03	0.06	-0.41	0.94
Time	-0.23	0.10	-2.28	0.03*
RH_G_precuneus *time	-0.02	0.03	-0.70	0.83
RH_G_rectus	0.002	0.06	0.03	0.99
Time	-0.24	0.10	-2.32	0.03*
RH_G_rectus *time	-0.05	0.03	-1.52	0.71
RH_G_subcallosal	0.12	0.06	2.05	0.46
Time	-0.23	0.10	-2.25	0.03*
RH_G_subcallosal *time	-0.03	0.03	-0.94	0.76
RH_G_temp_sup_G_T_transv	-0.03	0.06	-0.55	0.92
Time	-0.23	0.10	-2.52	0.03*
RH_G_temp_sup_G_T_transv *time	0.06	0.03	1.78	0.65
RH_G_temp_sup_Lateral	0.03	0.06	0.52	0.92
Time	-0.23	0.10	-2.26	0.03*
RH_G_temp_sup_Lateral *time	-0.003	0.03	-0.08	0.96
RH_G_temp_sup_Plan_polar	-0.03	0.06	-0.57	0.92
Time	-0.23	0.10	-2.27	0.03*
RH_G_temp_sup_Plan_polar *time	0.05	0.03	1.44	0.71
RH_G_temp_sup_Plan_tempo	-0.05	0.06	-0.87	0.84
Time	-0.23	0.10	-2.29	0.03*
RH_G_temp_sup_Plan_tempo *time	-0.03	0.03	-1.04	0.76

RH_G_temporal_inf	-0.10	0.06	-1.60	0.63
Time	-0.23	0.10	-2.28	0.03*
RH_G_temporal_inf *time	0.01	0.03	0.18	0.93
RH_G_temporal_middle	-0.07	0.06	-1.15	0.68
Time	-0.23	0.10	-2.24	0.03*
RH_G_temporal_middle *time	0.04	0.03	1.37	0.71
RH_Lat_Fis_ant_Horizont	0.02	0.06	0.36	0.94
Time	-0.23	0.10	-2.27	0.03*
RH_Lat_Fis_ant_Horizont *time	-0.04	0.03	-1.33	0.71
RH_Lat_Fis_ant_Vertical	-0.02	0.06	-0.35	0.94
Time	-0.23	0.10	-2.27	0.03*
RH_Lat_Fis_ant_Vertical *time	-0.02	0.03	-0.61	0.85
RH_Lat_Fis_post	0.01	0.06	0.23	0.96
Time	-0.23	0.10	-2.30	0.03*
RH_Lat_Fis_post *time	-0.04	0.03	-1.18	0.71
RH_Pole_occipital	-0.07	0.06	-1.16	0.68
Time	-0.23	0.10	-2.28	0.03*
RH_Pole_occipital *time	0.02	0.03	0.53	0.89
RH_Pole_temporal	0.001	0.06	0.01	0.99
Time	-0.23	0.10	-2.27	0.03*
RH_Pole_temporal *time	-0.04	0.03	-1.28	0.71
RH_S_calcarine	-0.02	0.06	-0.36	0.94
Time	-0.23	0.10	-2.26	0.03*
RH_S_calcarine *time	0.02	0.03	0.73	0.82
RH_S_central	-0.11	0.06	-1.86	0.53
Time	-0.23	0.10	-2.25	0.03*
RH_S_central *time	0.02	0.03	0.63	0.85
RH_S_cingul_Marginalis	-0.10	0.06	-1.62	0.63
Time	-0.23	0.10	-2.26	0.03*

RH_S_cingul_Marginalis *time	0.06	0.03	2.06	0.65
RH_S_circular_insula_ant	0.01	0.06	0.14	0.96
Time	-0.23	0.10	-2.27	0.03*
RH_S_circular_insula_ant *time	-0.001	0.03	-0.04	0.98
RH_S_circular_insula_inf	-0.08	0.06	-1.36	0.66
Time	-0.23	0.10	-2.26	0.03*
RH_S_circular_insula_inf *time	0.03	0.03	1.02	0.76
RH_S_circular_insula_sup	-0.002	0.06	-0.03	0.99
Time	-0.23	0.10	-2.28	0.03*
RH_S_circular_insula_sup *time	-0.03	0.03	-0.83	0.81
RH_S_collat_transv_ant	0.06	0.06	0.86	0.84
Time	-0.23	0.10	-2.27	0.03*
RH_S_collat_transv_ant *time	-0.02	0.03	-0.51	0.90
RH_S_collat_transv_post	0.01	0.06	0.22	0.96
Time	-0.23	0.10	-2.21	0.03*
RH_S_collat_transv_post *time	0.05	0.03	1.53	0.71
RH_S_front_inf	0.01	0.06	0.19	0.96
Time	-0.23	0.10	-2.28	0.03*
RH_S_front_inf *time	-0.02	0.03	-0.73	0.82
RH_S_front_middle	0.06	0.06	0.99	0.76
Time	-0.23	0.10	-2.29	0.03*
RH_S_front_middle *time	-0.09	0.03	-2.76	0.28
RH_S_front_sup	-0.04	0.06	-0.68	0.92
Time	-0.23	0.10	-2.28	0.03*
RH_S_front_sup *time	-0.03	0.03	-0.79	0.82
RH_S_interm_prim_Jensen	0.002	0.06	0.03	0.99
Time	-0.23	0.10	-2.24	0.03*
RH_S_interm_prim_Jensen *time	0.06	0.03	1.83	0.65
RH_S_intrapariet_and_P_trans	0.08	0.06	1.27	0.67

Time	-0.23	0.10	-2.29	0.03*
RH_S_intrapariet_and_P_trans *time	-0.05	0.03	-1.45	0.71
RH_S_oc_middle_and_Lunatus	-0.03	0.06	-0.43	0.94
Time	-0.23	0.10	-2.25	0.03*
RH_S_oc_middle_and_Lunatus *time	0.81	0.03	0.81	0.82
RH_S_oc_sup_and_transversal	-0.01	0.06	-0.10	0.96
Time	-0.23	0.10	-2.28	0.03*
RH_S_oc_sup_and_transversal *time	-0.01	0.03	-0.45	0.91
RH_S_occipital_ant	0.04	0.06	0.59	0.92
Time	-0.23	0.10	-2.27	0.03*
RH_S_occipital_ant *time	-0.01	0.03	-0.26	0.92
RH_S_oc_temp_lat	-0.05	0.06	-0.72	0.89
Time	-0.23	0.10	-2.27	0.03*
RH_S_oc_temp_lat *time	0.003	0.03	0.11	0.95
RH_S_oc_temp_med_and_Lingual	-0.12	0.07	-1.77	0.56
Time	-0.23	0.10	-2.25	0.03*
RH_S_oc_temp_med_and_Lingual *time	0.06	0.03	1.72	0.65
RH_S_orbital_lateral	0.04	0.06	0.72	0.89
Time	-0.23	0.10	-2.28	0.03*
RH_S_orbital_lateral *time	-0.04	0.03	-1.15	0.72
RH_S_orbital_med_olfact	0.07	0.06	1.14	0.68
Time	-0.23	0.10	-2.25	0.03*
RH_S_orbital_med_olfact *time	0.03	0.03	0.97	0.76
RH_S_orbital_H_Shaped	0.05	0.06	0.77	0.89
Time	-0.23	0.10	-2.28	0.03*
RH_S_orbital_H_Shaped *time	-0.02	0.03	-0.74	0.82
RH_S_parieto_occipital	0.03	0.06	0.41	0.94
Time	-0.23	0.10	-2.24	0.03*
RH_S_parieto_occipital *time	0.04	0.03	1.30	0.71

RH_S_pericallosal	-0.01	0.06	-0.18	0.96
Time	-0.23	0.10	-2.27	0.03*
RH_S_pericallosal *time	-0.02	0.03	-0.73	0.82
RH_S_postcentral	-0.12	0.06	-1.85	0.53
Time	-0.23	0.10	-2.25	0.03*
RH_S_postcentral *time	0.04	0.03	1.32	0.71
RH_S_precentral_inf_part	0.02	0.06	0.36	0.94
Time	-0.23	0.10	-2.27	0.03*
RH_S_precentral_inf_part *time	-0.04	0.03	-1.30	0.71
RH_S_precentral_sup_part	0.02	0.06	0.36	0.94
Time	-0.23	0.10	-2.27	0.03*
RH_S_precentral_sup_part *time	0.02	0.03	0.59	0.85
RH_S_suborbital	0.02	0.06	0.26	0.96
Time	-0.23	0.10	-2.27	0.03*
RH_S_suborbital *time	0.0003	0.03	0.01	0.99
RH_S_subparietal	-0.05	0.06	-0.74	0.89
Time	-0.23	0.10	-2.30	0.03*
RH_S_subparietal *time	-0.02	0.03	-0.50	0.90
RH_S_temporal_inf	-0.003	0.06	-0.04	0.99
Time	-0.23	0.10	-2.27	0.03*
RH_S_temporal_inf *time	-0.02	0.03	-0.61	0.85
RH_S_temporal_sup	0.04	0.06	0.60	0.92
Time	-0.23	0.10	-2.27	0.03*
RH_S_temporal_sup *time	0.01	0.03	0.41	0.91
RH_S_temporal_transverse	-0.04	0.06	-0.60	0.92
Time	-0.23	0.10	-2.27	0.03*
RH_S_temporal_transverse *time	-0.02	0.03	-0.74	0.82

Note. * indicates $P < 0.05$.