Socioeconomic and cognitive roots of trait anxiety in young adults

Running title: Roots of trait anxiety

Pavla Cermakova¹,², Adam Chlapečka³,⁴, Lenka Andrýsková⁵, Milan Brázdil⁶, Klára Marečková¹,⁶

1. Second Faculty of Medicine, Charles University Prague, Czech Republic
2. National Institute of Mental Health, Klecany, Czech Republic
3. Third Faculty of Medicine, Charles University Prague, Czech Republic
4. Centre of Clinical Neuroscience, Department of Neurology, First Faculty of Medicine, General University Hospital, Charles University in Prague, Czech Republic
5. RECETOX, Faculty of Science, MU, Brno, Czech Republic
6. Brain and Mind Research, Central European Institute of Technology, Masaryk University, Brno, Czech Republic

Correspondence to:

Pavla Cermakova, MD, PhD, associate professor
National Institute of Mental Health
Topolová 748
250 67 Klecany
Czech Republic
Pavla.Cermakova@nudz.cz
ABSTRACT

In 54 participants (41% women) from the Czech arm of the European Longitudinal Study of Pregnancy and Childhood, a national birth cohort with prospectively collected data from their birth until young adulthood, we aimed to study the association between early-life socioeconomic deprivation, cognitive ability in adolescence, trait anxiety and resting state functional connectivity of the lateral prefrontal cortex in young adulthood. We found that early-life socioeconomic deprivation was associated with lower cognitive ability in adolescence (at age 13) as well as higher trait anxiety in young adulthood (at age 23/24). Higher cognitive ability in adolescence predicted lower trait anxiety in young adulthood. Resting state functional connectivity between the right lateral prefrontal cortex and a cluster of voxels including left precentral gyrus, left postcentral gyrus and superior frontal gyrus mediated the relationship between lower cognitive ability in adolescence and higher trait anxiety in young adulthood. These findings indicate that lower cognitive ability and higher trait anxiety may be both consequences of socioeconomic deprivation in early life. The recruitment of the right lateral prefrontal cortex may be the underlying mechanism, through which higher cognitive ability may ameliorate trait anxiety.

Key words: trait anxiety; cognition; epidemiology; birth cohort
INTRODUCTION

Trait anxiety predisposes people to the development of anxiety and affective disorders (Chambers et al., 2004; Sandi and Richter-Levin, 2009), the most common mental disorders in the population. It is a personality feature characterized by a tendency to respond with troubles, concerns and worries to various situations (Spielberger and Gorsuch, 1983). Trait anxiety is associated with a range of changes in cognitive functioning; studies show that individuals high in trait anxiety have deficient cognitive control (Bishop, 2009) and apply cognitive biases in the processing of threat-related stimuli (Eysenck, 2000). There is also evidence that higher trait anxiety impairs efficient functioning of the attentional system (Eysenck et al., 2007), is linked to lower academic achievements (Alfonso and Lonigan, 2021) and lower general cognitive ability (Moutafi et al., 2006; Bartels et al., 2012). Even though the association to cognitive ability may be explained by trait anxiety leading to nervousness, which affects performance in cognitive tests (Humphreys and Revelle, 1984), it is also plausible that high cognitive ability may help ameliorate anxiety by enabling reasoning over causes of distress, coping with concerns and promoting the ability to adjust in pursuing emotional needs.

Previously, we have demonstrated that young adults who grew up in poorer households had a higher trait anxiety (Čermaková et al., 2020). A particularly strong risk factor is growing up in a household that cannot secure the family with basic things, such as food, clothes, heating, rent and necessities for the child (Čermaková et al., 2020). As such early-life socioeconomic deprivation (ELSD) of a household is tied with lower cognitive ability of the children, in particular in combination with lower education of parents (Tong et al., 2007), the association of ELSD with
trait anxiety may be due to the fact that low socioeconomic resources do not allow children to
cognitively develop towards their full potential, which deprives them from efficiently pursuing
their mental health.

There is a large body of literature on neural correlates of human cognitive ability (Rypma et al.,
2006), with a growing number of studies concerning disruptions of functional connectivity. It has
been proposed that cognitive ability is the result of large-scale brain networks in frontal, parietal,
temporal and cingulate cortices (Jung and Haier, 2007; Bressler and Menon, 2010; Brancucci,
2012). In particular, the lateral prefrontal cortex (LPFC) has been found to be a key brain region
involved in cognitive ability (Gray and Thompson, 2004; Song et al., 2008). Neuroimaging
studies revealed a co-occurrence of cognitive distortions, ineffective emotion regulation and
alterations in the function of LPFC related to anxiety (Goldin et al., 2009), possibly reflecting
functional impairment of the central executive network in the cognitive control of anxiety (Qiu et
al., 2011).

By using event-related functional magnetic resonance imaging (fMRI) and a behavioural
measure of attention to angry faces, Monk et al. demonstrated that patients with generalized
anxiety disorder manifested greater activation of the right ventral LPFC to trials containing angry
faces (Monk et al., 2006). Moreover, several previous studies, using both event-related fMRI
(Telzer et al., 2008; Monk et al., 2006) and near-infrared spectroscopy scanning while
performing a verbal fluency task (Yokoyama et al., 2015) proposed that LPFC may play a role in
the pathogenesis of trait anxiety (Telzer et al., 2008), generalized anxiety disorder (Monk et al.,
2006) and social anxiety disorder (Yokoyama et al., 2015).
There is also literature on alterations in the function of LPFC related to anxiety using resting-state fMRI techniques. Qiu et al. showed that individuals with social anxiety disorders have decreased coherence in spontaneous neural fluctuations in the blood oxygen level dependent (BOLD) signals of the right dorsal LPFC and inferior parietal gyrus, possibly reflecting the deficit of cognitive control of anxiety (Qiu et al., 2011). Moreover, increased perfusion at rest was found in the ventral LPFC, right anterior frontal and right lateral frontal cortex and right cerebellum in individuals with social anxiety disorder (Warwick et al., 2008). Liao et al found that higher score on the Liebowitz Social Anxiety Scale was associated with greater functional connectivity of ventral LPFC with the rest of the dorsal attention network, possibly contributing to the higher state of vigilance and worse emotional regulation, which are characteristic for patients with social anxiety disorder (Liao et al., 2010). Given that LPFC may play a role in cognitive control of emotional regulation of anxiety, this raises a question whether the functional connectivity between the LPFC and other regions of the brain underlie the association of cognitive ability with trait anxiety.

The aim of this study was to investigate cognitive mechanisms and biomarkers related to functional connectivity underlying the association of ELSD with trait anxiety in young adulthood. We tested the following hypotheses: 1) Worse ELSD is associated with lower cognitive ability in adolescence, but higher education of parents may reduce the negative impact of ELSD on cognitive ability of their children. 2) Higher cognitive ability in adolescence is associated with lower trait anxiety in young adulthood and this association depends on the level
of ELSD. 3) The functional connectivity between LPFC and other regions of the brain underlies the association of cognitive ability with trait anxiety.

**METHODS**

*Participants*

We studied participants of the Czech arm of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ) (Piler et al., 2017). ELSPAC-CZ is a prenatal cohort (n=5151) whose members were born in 1991/1992. Their mothers were enrolled into the study between the ultrasound examination at 20\textsuperscript{th} week of pregnancy and the birth of the child. They filled in several sets of questionnaires concerning their socioeconomic circumstances, such as experience of ELSD, their education and other markers of socioeconomic position (SEP). Sub-samples of the ELSPAC-CZ cohort were examined within different sub-studies.

At the age of 13, 617 individuals participated in a psychological sub-study, during which their cognitive ability was assessed. Details about the psychological sub-study are provided elsewhere (Ježek et al., 2008). At the age of 23/24 years, 131 members of the ELSPAC-CZ took part in a neuroimaging sub-study “Biomarkers and Underlying Mechanisms of Vulnerability to Depression” (VULDE) (Mareckova et al., 2018; Mareckova et al., 2019a; Mareckova et al., 2019b; Mareckova et al., 2020b), during which functional magnetic resonance imaging (fMRI) and assessment of trait anxiety were conducted. All participants provided written informed consent and ethical approval was obtained from ELSPAC Ethics Committee. All methods were performed in accordance with Declaration of Helsinki. Data from this study is available to
researchers upon request, after approval from the scientific committee. Code can be shared to researchers by the corresponding author of this study upon request.

Measures

ELSD

The main exposure was ELSD, which is a subjective assessment of one's SEP and has been shown to best predict trait anxiety in young adulthood out of a number of early-life SEP including indicators of objective SEP (Čermaková et al., 2020). ELSD was assessed by questionnaires administered to mothers at 6 and 18 months of the offspring. They had a 4-point Likert scale to answer how difficult it is to secure the family with the following five things: food, clothes, heating, rent/other fees, and things necessary for the child. The four possible answers ranged from “very difficult” (coded as 3) to “not difficult at all” (coded as 0). Scores on these five items were summed-up, creating an ELSD score reaching from 0 to 15, with higher values indicating more severe deprivation. The score showed a good internal consistency (Cronbach’s alpha 0.81 at 6 months and 0.82 at 18 months). To reduce measurement error, the final ELSD score was calculated as the mean of the scores for 6 and 18 months.

Covariates

We used information on mother’s and father’s education as we hypothesized that education of parents can modify the association of ELSD with cognitive ability in adolescence. Education was coded in eight categories: 1) primary, 2) vocational without high school graduation, 3) vocational with high school graduation, 4) specialized high school with graduation, 5) general high school
with graduation, 6) post-high school graduation study, 7) university education and 8) postgraduate education. We re-coded both measures so that higher values correspond to lower education.

As ELSD is a subjective assessment of one’s SEP, we also controlled for a measure of objective early-life SEP composed of five indicators: father’s occupation, household income, number of basic utilities, number of household items and crowding ratio, as previously described in detail (Čermaková et al., 2020). There were no signs of deviation from normal distribution, therefore, we created a composite score on objective early-life SEP, as follows: First, we recoded each of the five indicators of early-life SEP so that higher values indicate a more adverse SEP. Second, we created z-scores from each of the five indicators. Third, we averaged the five z-scores, which results in the composite “objective early-life SEP”, with higher values indicating a worse SEP. As the covariates correlate with ELSD, we tested for collinearity in our models, using variance inflation factor (VIF). The VIF reached below 4 in all analyses.

Cognitive ability in adolescence

Cognitive ability was measured within the psychological sub-study in adolescence at the age of 13 years with the Wiener Matrizen-Test (WMT) (Formann and Piswanger, 1979). The WMT is a timed one-dimension intelligence test measuring the ability to logically reason over abstract symbols, which is regarded as a non-verbal estimate of fluid intelligence. It is derived from the Raven’s Progressive Matrices that is designed to measure the eductive component of general intelligence (Raven, 2000). The construct of general intelligence reflects the fact that one’s performance on one type of cognitive task tends to be comparable to that person’s performance
on other cognitive tasks (Spearman, 1961). In WMT, there are 24 multiple choice items, listed in order of difficulty. The total score is the number of correctly answered items, which is a measure used in this study. It will be further referred to as “cognitive ability in adolescence”.

**Trait anxiety in young adulthood**

Trait anxiety was assessed as part of VULDE in young adulthood at the age of 23/24 years with the Spielberger State-Trait Anxiety Inventory (STAI-T) (Spielberger and Gorsuch, 1983) by 20 questions rated on a 4-point Likert scale, with higher scores indicating greater anxiety.

**Functional connectivity of the brain**

The participants of VULDE underwent a 7-minute closed-eyes resting state fMRI exam, with the following acquisition parameters: voxel size 3 x 3 x 3 mm, repetition time (TR) 2080 ms, echo time (TE) 30 ms, flip angles 90 degrees, 39 slices, matrix 64x64, 200 measurements. Functional connectivity analysis was performed using CONN Functional Connectivity Toolbox version 18.b. and its default pre-processing pipeline (Whitfield-Gabrieli and Nieto-Castanon, 2012). First, functional images were realigned, un-warped, and slice-timing corrected. Next, the images were co-registered with structural data and spatially normalized to the Montreal Neurological Institute (MNI) space. Acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations were flagged as potential outliers. No participant exceeded this threshold. Finally, the images were smoothed using a Gaussian kernel of 8 mm full width at half maximum and de-noised. Confounding effects of subjects’ movement were addressed using CompCor method, which is implemented within CONN (Behzadi et al., 2007). White matter, cerebral spinal fluid and realignment parameters were entered as confounds in the
first-level analysis (Behzadi et al., 2007), and the data were band-pass filtered to .008 Hz–.09 Hz. Details about how head motion was addressed and quality assurance steps are described in detail in the Supplement.

**Statistical analysis**

Derivation of the analytical sample is shown on Figure 1. From 131 participants in the VULDE study, 2 did not undergo resting state fMRI assessment and 7 had missing data on ELSD. From the remaining 122 individuals, 54 had available data on cognitive ability in adolescence, which is the analytical sample used in this study (41% women). When compared to the original ELSPAC-CZ cohort, the analytical sample had a greater proportion of individuals with university educated mothers and a smaller proportion of those whose mothers were younger than 20 at birth. The analytical sample had lower trait anxiety relative to the whole VULDE cohort (Supplementary Table 1).

We conducted the analysis in 3 steps: 1) Association of ELSD with cognitive ability in adolescence; 2) association of cognitive ability in adolescence with trait anxiety in young adulthood and 3) biomarkers related to functional connectivity underlying the association of cognitive ability in adolescence with trait anxiety in young adulthood. Descriptive data is presented as means ± standard deviation (SD), median and interquartile range (IQR) or frequency (n, %), where appropriate. We first assessed the relationships between the main measures with correlations and significant associations were further studied with linear regression. Next, we tested for effect modification of the associations. Effect modification describes the situation where the magnitude of the effect of an exposure variable on
an outcome differs depending on the level of a third variable. To assess effect modification, we tested statistical interaction by including a two-way interaction term between the tested exposure and the potential effect modifier.

In all analyses, we tested for sex as a potential effect modifier. Next, we tested whether mother’s education and father’s education are effect modifiers in the association of ELSD with cognitive ability in adolescence. Finally, we tested whether ELSD is an effect modifier in the association of cognitive ability in adolescence with trait anxiety in young adulthood. For the ease of interpretability, if the interaction was significant, we re-coded the continuous measures into binary variables corresponding to high vs. low level and conducted stratified analyses, adjusting for sex and the remaining covariates. In case of mother’s and father’s education, the binary variable was university and higher education vs. no university education; in case of ELSD, the binary variable was higher than median vs. lower than median ELSD. Data on cognitive ability in adolescence was normally distributed and was used in the analyses in its original form. Data on trait anxiety was skewed and was therefore log-transformed.

To study the underlying biomarkers related to functional connectivity, we conducted a seed-to-voxel analysis to evaluate correlations between the two seeds of our a priori interest (left LPFC and right LPFC) and all other voxels in the brain. These seeds were defined as 10 mm spheres centered at coordinates (MNI): left LPFC -43, 33, 28; and right LPFC: 41, 38, 30. They were defined from Fox et al (Fox et al., 2005). Functional connectivity maps were produced by averaging the BOLD time series in the seed, and then computing the Pearson's correlation coefficient between the seed average time series and those from each voxel in the brain. The
resulting correlations were transformed to normal distribution using Fisher's z transformation. This yielded a map representing the strength of the functional connectivity to the seed region in terms of the z values for each subject. Next, correlations between cognitive ability in adolescence and the strength of the functional connectivity between the left / right LPFC and other voxels were calculated. Seed-to-voxel results are reported when significant at a voxel-wise threshold of level of \( p < 0.05 \) uncorrected and a cluster-level threshold of \( p < 0.05 \) corrected for false discovery rate (FDR).

We then extracted the correlation coefficients for clusters of voxels showing a significant association with cognitive ability in adolescence for each subject from CONN into STATA. Next, we evaluated whether they are associated with trait anxiety, correcting for FDR using Benjamini Hochberg method. In the end, we performed a mediation analysis. We hypothesized that connectivity between the right/left LPFC and the identified cluster of voxels mediates the association of cognitive ability in adolescence with trait anxiety in young adulthood. This mediation hypothesis was tested with a bootstrap procedure to determine the significance of the indirect effect (Preacher and Hayes, 2004). A total of 5000 bootstrap resamples were used to provide stable estimates of the direct, indirect, and total effects. We determined 95% confidence intervals (CIs) from the bootstrap resamples and any interval that did not include 0 was considered to be significantly different from 0. The correlation and regression analyses were performed using STATA version 15, mediation analyses were performed using SPSS version 27. P<0.05 was considered as a threshold for statistical significance.

RESULTS
Characteristics of participants

We studied 54 individuals (41% women, Table 1), whose ELSD score was distributed around the mean of 3 (SD=2). Cognitive ability in adolescence, as measured by the number of correctly answered items from WMT, reached the average of 14 (SD 4). Trait anxiety in young adulthood, as measured by STAI-T, reached the median of 25 (IQR 11). As in our previous study (Čermaková et al., 2020), worse ELSD correlated with greater trait anxiety (Spearman’s rho 0.275; p=0.044).

Association of ELSD with cognitive ability in adolescence

Worse ELSD correlated with lower cognitive ability in adolescence (Spearman’s rho -0.362, p=0.007). There was no effect modification by sex (p for interaction = 0.232) or father’s education (p for interaction = 0.842), but there was a borderline statistically significant interaction with mother’s education (p for interaction = 0.058; see also Supplementary Figure 1). When stratified, worse ELSD was associated with lower cognitive ability in adolescence only in individuals, whose mothers had university or higher education (B=-1.104; 95% CI -1.675 to -0.533; p=0.001; Table 2 and Supplementary Figure 2). This association persisted when adjusted for sex, father’s education and objective early-life SEP (B=-1.178; 95% CI -1.806 to -0.549; p=0.001).

Association of cognitive ability in adolescence with trait anxiety in young adulthood

Higher cognitive ability in adolescence correlated with lower trait anxiety (Spearman’s rho -0.293; p=0.031). There was no effect modification by sex (p for interaction = 0.925), but there was a significant interaction with ELSD (p for interaction = 0.033; see also Supplementary
Figure 3). When stratified, the association of higher cognitive ability in adolescence with lower trait anxiety was present only in individuals with high ELSD (B=-0.049; 95% CI -0.078 to -0.020; p=0.002; Supplementary Figure 4). This association persisted when adjusted for sex, mother’s education, father’s education and objective early-life SEP (B -0.063; 95% CI -0.105 to -0.021; p=0.005).

**Biomarkers related to functional connectivity**

We present results with the voxelwise threshold of p<0.05 corrected for multiple comparisons as we did not observe significant results at the level of <0.001, which is not consistent with the current standard of thresholding. Cognitive ability in adolescence was associated with functional connectivity between the seeds of interest and 6 clusters of voxels (Table 3). Specifically, it showed a negative relationship between the left LPFC and 3 clusters: First, a cluster including, among other regions, precuneus, cingulate gyrus and supramarginal gyrus (MNI coordinates +10, -26, +38; 4945 voxels, p-FDR < 0.001); second, a cluster including, among other regions, right frontal pole, cingulate gyrus and right paracingulate gyrus (MNI coordinates +28, +40, +18; 4699 voxels, p-FDR < 0.001); and third, a cluster including, among other regions, lateral occipital cortex, supramarginal gyrus and parietal operculum cortex (MNI coordinates -52, -28, +26; 2116 voxels, p-FDR=0.04).

Furthermore, cognitive ability in adolescence showed a negative relationship between the right LPFC and 1 cluster of voxels including, among other regions, precuneus, cingulate gyrus and left middle frontal gyrus (MNI coordinates +18, -32, +26, 4772 voxels, p-FDR<0.001). Finally, cognitive ability in adolescence showed a positive relationship between the right LPFC and 2
clusters: First, a cluster including several parts of cerebellum (MNI coordinates +18, -58, -24; 3148 voxels, p-FDR=0.01; and second, a cluster including left precentral and postcentral gyrus and left superior frontal gyrus (MNI coordinates -62, -08, +18; 2360 voxels, p-FDR=0.03).

Greater positive functional connectivity between the right LPFC and a cluster that included left precentral gyrus, left postcentral gyrus and superior frontal gyrus correlated with lower trait anxiety (Spearman’s rho -0.407; p=0.001/p-FDR=0.012). There was no interaction with sex (p for interaction = 0.670) and the association persisted when adjusted for sex (B=-0.819; 95% CI -1.501 to -0.137; p=0.019; Figure 2). While the total effect of cognitive ability in adolescence on trait anxiety in young adulthood reached borderline statistical significance ($R^2=0.07$, $B=-0.02$, $p=0.053$), a mediation analysis revealed that functional connectivity between the right LPFC and this cluster mediated the relationship between lower cognitive ability in adolescence and higher trait anxiety in young adulthood (ab=-0.012, SE= 0.005, 95% CI [-0.022; -0.002]; Figure 3). Functional connectivity between LPFC and any of the five remaining clusters did not correlate with trait anxiety (p-FDR > 0.05), therefore no further mediation analysis was performed.

DISCUSSION

We aimed to study cognitive and neural mechanisms underlying the association of ELSD with trait anxiety in a cohort of young adults from the Czech Republic, who have been followed since their prenatal period. We found that worse ELSD was associated with lower cognitive ability in adolescence and that this association was strongest in individuals whose mothers reached university education. Further, higher cognitive ability in adolescence predicted lower trait anxiety in young adulthood, particularly among those who experienced high ELSD. The
relationship between higher cognitive ability in adolescence and lower trait anxiety in young adulthood was mediated by functional connectivity between the right LPFC and a large cluster including left precentral, postcentral gyrus and superior frontal gyri.

Our results are in line with a number of studies suggesting that early-life stressors associated with lack of socioeconomic resources negatively influence cognitive functions (Hart et al., 2007; von Stumm and Plomin, 2015; Alves et al., 2016; Cermakova et al., 2018; Flensborg-Madsen et al., 2020; Zhang et al., 2020). Previous studies also indicated that mother’s education has a greater impact on brain health of the offspring than father’s education (Cermakova et al., 2020). Surprisingly, here we show that the combination of mother’s high education and ELSD is the most detrimental to cognitive ability in adolescence. It has been described that a mis-match between the achieved level of education and corresponding socioeconomic status negatively affect one’s mental health (Bracke et al., 2013; Wolbers, 2013) and that poor mental health of mothers is linked to worse mental health and accelerated brain ageing of their offspring (Mareckova et al., 2020a). Our study shows that this may hold for cognitive ability of the offspring as well. Possibly, the stress associated with ELSD may deprive the well-educated mothers from being available for cognitively stimulating activities with their children.

Furthermore, this study is in accord with evidence that low cognitive ability is associated with higher morbidity (Starr et al., 2004; Deary et al., 2009; Sorberg Wallin et al., 2019). Previous studies also indicated that the way adults use their cognitive ability in pursuing their mental health depends on the socioeconomic resources they had at their disposal when they were children (Huisman et al., 2010). Here we show that the association of cognitive ability with trait
anxiety is present particularly among those who experienced high ELSD. High cognitive ability may armour people with resilience. Possibly, these individuals could be more successful in finding solutions for stressful situations or learn more quickly how to avoid them. It is documented that children with a higher cognitive ability regain functioning in the face of adversity easier than children with lower cognitive ability (Garmezy, 1993). Higher cognitive ability may thus indicate a higher cognitive reserve in overcoming disadvantages caused by ELSD and buffer against the odds of developing trait anxiety.

We identified several brain regions, specifically left precentral and postcentral gyrus and superior frontal gyri, whose strength of the functional connectivity with the right LPFC underlies the association between higher cognitive ability in adolescence and lower trait anxiety in young adulthood. These results are in line with the growing evidence that altered somatic brain network, including precentral gyrus (somatic motor cortex) and postcentral gyrus (somatosensory cortex) plays a major role in trait anxiety (Li et al., 2019). Another study of adolescents with anxiety disorders (generalized anxiety disorder, social phobia, separation anxiety disorder) demonstrated that the difference in grey-matter volume in these regions is an essential factor in the pathogenesis of trait anxiety (Strawn et al., 2015). Our results are in accord with these findings, reveal the importance of somatic brain regions in trait anxiety and provide a new perspective on anxiety, which could be followed-up by further research. We speculate that higher cognitive ability and the associated increase in functional connectivity between both somatic and prefrontal brain regions during rest could inhibit the activity of right LPFC and protect against development of trait anxiety. Previous studies showed that anxious people require greater activity of the postcentral gyrus to cope with anxiety (Li et al., 2019). We suggest that the
synchronous activation of the LPFC and the somatic brain network may indicate the involvement of cognitive control, mitigating anxiety.

Superior frontal gyrus, part of the prefrontal cortex, is generally considered to be the vital brain region for the cognitive control system (Niendam et al., 2012) and emotion-regulation processes (Frank et al., 2014). Superior frontal gyrus is also involved in both acute psychosocial stress (Pruessner et al., 2008) and chronic life stress (Li et al., 2016). As cognitive control is a fundamental part of cognitive ability and psychosocial stress is undoubtedly linked to trait anxiety, these studies provide a solid basis for the interpretation of our findings. To the best of our knowledge, the present study is the first to suggest simultaneous involvement of both somatic and prefrontal brain regions in the association between cognitive ability and trait anxiety.

This study is limited by its low sample size and selective dropout. As expected in longitudinal studies with a long follow-up (Young et al., 2006), the participants in the analytical sample are not representative towards the general population. In our case, the analytical sample had better socioeconomic conditions than the whole ELSPAC cohort at baseline and they also seemed to have better mental health as compared to the complete VULDE cohort. This biases our results due to selection. However, we repeated some analyses on a larger sample of participants from the whole ELSPAC cohort and found consistent associations (Supplementary Table 2). As in the smaller analytical sample, we found an association of worse ELSD with lower cognitive ability in adolescence and we also found no effect modification by sex and father’s education, but significant effect modification by mother’s education.
In addition, we found the association using a voxelwise threshold of p<0.05, but not using the threshold of p<0.001, which is the current standard. That may increase the chance of false positive results. Given this, the results need to be replicated in the future. Finally, we acknowledge that this study is observational in design and causality cannot be established as there may be residual confounding factors. We conclude that growing up in households that face socioeconomic difficulties may have long-term negative consequences on one’s cognitive ability and mental health. Higher cognitive ability and the related increase in the recruitment of the right LPFC may, however, ameliorate the experience of anxiety.

**FUNDING**

This work was supported by Ministry of Health of the Czech Republic (grant NU20J-04-00022), grant PRIMUS (247066) conducted at Charles University, the European Union (Marie Curie Intra-European Fellowship for Career Development, FP7-PEOPLE-IEF-2013, grant #6485124) and the Ministry of Education, Youth and Sports of the Czech Republic/MEYS (CEITEC 2020, LQ1601, LM2018121, LO1611). We also acknowledge the core facility MAFIL of CEITEC MU supported by the Czech-BioImaging large RI projects (LM2015062, LM2018129 funded by MEYS CR) for their support with obtaining scientific data presented in this paper.

**CONFLICT OF INTEREST**

None.
REFERENCES

Alfonso, S. V. & Lonigan, C. J. (2021) 'Trait anxiety and adolescent's academic achievement: The role of executive function', Learning and Individual Differences, 85, p. 101941.

Alves, A. F., Martins, A. & Almeida, L. S. (2016) 'Interactions between Sex, Socioeconomic Level, and Children's Cognitive Performance', Psychol Rep, 118(2), pp. 471-486.

Bartels, M., van Weegen, F. I., van Beijsterveldt, C. E. M., Carlier, M., Polderman, T. J. C., Hoekstra, R. A. & Boomsma, D. I. (2012) 'The five factor model of personality and intelligence: A twin study on the relationship between the two constructs', Personality and Individual Differences, 53(4), pp. 368-373.

Behzadi, Y., Restom, K., Liau, J. & Liu, T. T. (2007) 'A component based noise correction method (CompCor) for BOLD and perfusion based fMRI', Neuroimage, 37(1), pp. 90-101.

Bishop, S. J. (2009) 'Trait anxiety and impoverished prefrontal control of attention', Nature neuroscience, 12(1), pp. 92-98.

Bracke, P., Pattyn, E. & von dem Knesebeck, O. (2013) 'Overeducation and depressive symptoms: diminishing mental health returns to education', Sociol Health Illn, 35(8), pp. 1242-1259.

Brancucci, A. (2012) 'Neural correlates of cognitive ability', Journal of neuroscience research, 90(7), pp. 1299-1309.

Bressler, S. L. & Menon, V. (2010) 'Large-scale brain networks in cognition: emerging methods and principles', Trends in cognitive sciences, 14(6), pp. 277-290.

Cermakova, P., Formanek, T., Kagstrom, A. & Winkler, P. (2018) 'Socioeconomic position in childhood and cognitive aging in Europe', Neurology, 91(17), pp. e1602-e1610.

Cermakova, P., Pikhart, H., Ruiz, M., Kubinova, R. & Bobak, M. (2020) 'Socioeconomic position in childhood and depressive symptoms in later adulthood in the Czech Republic', Journal of affective disorders.

Čermaková, P., Andrýsková, L., Brázdil, M. & Marečková, K. (2020) 'Socioeconomic deprivation in early life and symptoms of depression and anxiety in young adulthood: mediating role of hippocampal connectivity', Psychol Med, pp. 1-10.

Deary, I. J., Whalley, L. J. & Starr, J. M. (2009) A lifetime of intelligence: Follow-up studies of the Scottish mental surveys of 1932 and 1947, American Psychological Association.

Erikson, R., Goldthorpe, J. H. & Portocarero, L. (1979) 'Intergenerational class mobility in three Western European societies: England, France and Sweden', The British Journal of Sociology, 30(4), pp. 415-441.

Eysenck, M. W. (2000) 'A cognitive approach to trait anxiety', European Journal of Personality, 14(5), pp. 463-476.

Eysenck, M. W., Derakshan, N., Santos, R. & Calvo, M. G. (2007) 'Anxiety and cognitive performance: Attentional control theory', Emotion, 7(2), pp. 336-353.

Flensborg-Madsen, T., Falgreen Eriksen, H. L. & Mortensen, E. L. (2020) 'Early life predictors of intelligence in young adulthood and middle age', PLoS One, 15(1), p. e0228144.

Formanek, T., Kagstrom, A., Winkler, P. & Cermakova, P. (2019) 'Differences in cognitive performance and cognitive decline across European regions: a population-based prospective cohort study', European Psychiatry, 58, pp. 80-86.

Formann, A. K. & Piswanger, K. (1979) Wiener Matrizen-Test (WMT), Beltz Test.
Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C. & Raichle, M. E. (2005) 'The human brain is intrinsically organized into dynamic, anticorrelated functional networks', *Proceedings of the National Academy of Sciences*, 102(27), pp. 9673-9678.

Frank, D., Dewitt, M., Hudgens-Haney, M., Scheffler, D., Ball, B., Schwarz, N., Hussein, A., Smart, L. & Sabatinelli, D. (2014) 'Emotion regulation: quantitative meta-analysis of functional activation and deactivation', *Neuroscience & Biobehavioral Reviews*, 45, pp. 202-211.

Garmezy, N. (1993) 'Children in poverty: Resilience despite risk', *Psychiatry*, 56(1), pp. 127-136.

Goldin, P. R., Manber, T., Hakimi, S., Canli, T. & Gross, J. J. (2009) 'Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat', *Archives of general psychiatry*, 66(2), pp. 170-180.

Gray, J. R. & Thompson, P. M. (2004) 'Neurobiology of intelligence: science and ethics', *Nature Reviews Neuroscience*, 5(6), pp. 471-482.

Hart, S. A., Petrill, S. A., Deckard, K. D. & Thompson, L. A. (2007) 'SES and CHAOS as environmental mediators of cognitive ability: A longitudinal genetic analysis', *Intelligence*, 35(3), pp. 233-242.

Huisman, M., Araya, R., Lawlor, D. A., Ormel, J., Verhulst, F. C. & Oldehinkel, A. J. (2010) 'Cognitive ability, parental socioeconomic position and internalising and externalising problems in adolescence: findings from two European cohort studies', *European journal of epidemiology*, 25(8), pp. 569-580.

Humphreys, M. S. & Revelle, W. (1984) 'Personality, motivation, and performance: a theory of the relationship between individual differences and information processing', *Psychological review*, 91(2), p. 153.

Chambers, J. A., Power, K. G. & Durham, R. C. (2004) 'The relationship between trait vulnerability and anxiety and depressive diagnoses at long-term follow-up of Generalized Anxiety Disorder', *Journal of Anxiety Disorders*, 18(5), pp. 587-607.

Ježek, S., Lacinová, L., Širůček, J. & Michalčáková, R. (2008) 'The psychological branch of the ELSPAC study: A survey of 15-year-old respondents'.

Jung, R. E. & Haier, R. J. (2007) 'The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence', *Behavioral and Brain Sciences*, 30(2), p. 135.

Kagstrom, A., Alexova, A., Tuskova, E., Csajbok, Z., Schomerus, G., Formanek, T., Mladá, K., Winkler, P. & Cermakova, P. (2020) 'The treatment gap for mental disorders and associated factors in the Czech Republic', *European Psychiatry*, 59, pp. 37-43.

Kucera, M., Wolková, K. & Cermakova, P. (2020) 'Changes in depressive symptoms of older adults in the Czech Republic', *Journal of affective disorders*, 261, pp. 139-144.

Li, G., Ma, X., Bian, H., Sun, X., Zhai, N., Yao, M., Qu, H., Ji, S., Tian, H. & Zhuo, C. (2016) 'A pilot fMRI study of the effect of stressful factors on the onset of depression in female patients', *Brain Imaging and Behavior*, 10(1), pp. 195-202.

Li, X., Zhang, M., Li, K., Zou, F., Wang, Y., Wu, X. & Zhang, H. (2019) 'The Altered Somatic Brain Network in State Anxiety', *Frontiers in Psychiatry*, 10.

Liao, W., Chen, H., Feng, Y., Mantini, D., Gentili, C., Pan, Z., Ding, J., Duan, X., Qiu, C. & Lui, S. (2010) 'Selective aberrant functional connectivity of resting state networks in social anxiety disorder', *Neuroimage*, 52(4), pp. 1549-1558.

Mareckova, K., Klasnja, A., Andryskova, L., Brazdil, M. & Paus, T. (2019a) 'Developmental origins of depression-related white matter properties: Findings from a prenatal birth cohort', *Hum Brain Mapp*, 40(4), pp. 1155-1163.
Mareckova, K., Klasnja, A., Bencurova, P., Andryskova, L., Brazdil, M. & Paus, T. (2019b) 'Prenatal Stress, Mood, and Gray Matter Volume in Young Adulthood', *Cereb Cortex, 29*(3), pp. 1244-1250.

Mareckova, K., Marecek, R., Andryskova, L., Brazdil, M. & Nikolova, Y. S. (2020a) 'Maternal Depressive Symptoms During Pregnancy and Brain Age in Young Adult Offspring: Findings from a Prenatal Birth Cohort', *Cerebral Cortex, 30*(7), pp. 3991-3999.

Mareckova, K., Marecek, R., Andryskova, L., Brazdil, M. & Nikolova, Y. S. (2020b) 'Maternal Depressive Symptoms During Pregnancy and Brain Age in Young Adult Offspring', *Cerebral Cortex*.

Mareckova, K., Marecek, R., Bencurova, P., Klanova, J., Dusek, L. & Brazdil, M. (2018) 'Perinatal stress and human hippocampal volume: Findings from typically developing young adults', *Sci Rep, 8*(1), p. 4696.

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., Blair, R. J. R., Chen, G., Charney, D. S. & Ernst, M. (2006) 'Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder', *American Journal of Psychiatry, 163*(6), pp. 1091-1097.

Moutafi, J., Furnham, A. & Tsaousis, I. (2006) 'Is the relationship between intelligence and trait Neuroticism mediated by test anxiety?', *Personality and Individual Differences, 40*(3), pp. 587-597.

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C. & Carter, C. S. (2012) 'Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions', *Cognitive, Affective, & Behavioral Neuroscience, 12*(2), pp. 241-268.

Piler, P., Kandrnal, V., Kukla, L., Andrásková, L., Švancara, J., Jarkovský, J., Dušek, L., Pikhart, H., Bobák, M. & Klánová, J. (2017) 'Cohort Profile: The European Longitudinal Study of Pregnancy and Childhood (ELSPAC) in the Czech Republic', *International Journal of Epidemiology, 46*(5), pp. 1379-1379f.

Preacher, K. J. & Hayes, A. F. (2004) 'SPSS and SAS procedures for estimating indirect effects in simple mediation models', *Behavior research methods, instruments, & computers, 36*(4), pp. 717-731.

Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., Renwick, R., Dagher, A., Meaney, M. J. & Lupien, S. (2008) 'Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies', *Biological psychiatry, 63*(2), pp. 234-240.

Qiu, C., Liao, W., Ding, J., Feng, Y., Zhu, C., Nie, X., Zhang, W., Chen, H. & Gong, Q. (2011) 'Regional homogeneity changes in social anxiety disorder: a resting-state fMRI study', *Psychiatry Research: Neuroimaging, 194*(1), pp. 47-53.

Raven, J. (2000) 'The Raven's progressive matrices: change and stability over culture and time', *Cognitive psychology, 41*(1), pp. 1-48.

Rypma, B., Berger, J. S., Prabhakaran, V., Bly, B. M., Kimberg, D. Y., Biswal, B. B. & D'Esposito, M. (2006) 'Neural correlates of cognitive efficiency', *Neuroimage, 33*(3), pp. 969-979.

Sandi, C. & Richter-Levin, G. (2009) 'From high anxiety trait to depression: a neurocognitive hypothesis', *Trends in neurosciences, 32*(6), pp. 312-320.

Seblova, D., Brayne, C., Machů, V., Kuklová, M., Kopecek, M. & Cermakova, P. (2019) 'Changes in Cognitive Impairment in the Czech Republic', *Journal of Alzheimer's Disease, 72*, pp. 693-701.
Song, M., Zhou, Y., Li, J., Liu, Y., Tian, L., Yu, C. & Jiang, T. (2008) 'Brain spontaneous functional connectivity and intelligence', *Neuroimage*, 41(3), pp. 1168-1176.

Sorberg Wallin, A., Koupil, I., Gustafsson, J. E., Zammit, S., Allebeck, P. & Falkstedt, D. (2019) 'Academic performance, externalizing disorders and depression: 26,000 adolescents followed into adulthood', *Soc Psychiatry Psychiatr Epidemiol*, 54(8), pp. 977-986.

Spearman, C. (1961) "'General Intelligence' Objectively Determined and Measured'.

Spielberger, C. D. & Gorsuch, R. L. (1983) *State-trait anxiety inventory for adults: Manual and sample: Manual, instrument and scoring guide*, Consulting Psychologists Press.

Starr, J. M., Taylor, M. D., Hart, C. L., Smith, G. D., Whalley, L. J., Hole, D. J., Wilson, V. & Deary, I. J. (2004) 'Childhood mental ability and blood pressure at midlife: linking the Scottish Mental Survey 1932 and the Midspan studies', *Journal of hypertension*, 22(5), pp. 893-897.

Strawn, J. R., Hamm, L., Fitzgerald, D. A., Fitzgerald, K. D., Monk, C. S. & Phan, K. L. (2015) 'Neurostructural abnormalities in pediatric anxiety disorders', *J Anxiety Disorder*, 32, pp. 81-88.

Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Ernst, M., Pine, D. S. & Monk, C. S. (2008) 'Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents', *Biological psychology*, 79(2), pp. 216-222.

Tong, S., Baghurst, P., Vimpani, G. & McMichael, A. (2007) 'Socioeconomic position, maternal IQ, home environment, and cognitive development', *The Journal of pediatrics*, 151(3), pp. 284-288. e281.

von Stumm, S. & Plomin, R. (2015) 'Socioeconomic status and the growth of intelligence from infancy through adolescence', *Intelligence*, 48, pp. 30-36.

Warwick, J., Carey, P., Jordaan, G., Dupont, P. & Stein, D. (2008) 'Resting brain perfusion in social anxiety disorder: a voxel-wise whole brain comparison with healthy control subjects', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 32(5), pp. 1251-1256.

Whitfield-Gabrieli, S. & Nieto-Castanon, A. (2012) 'Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks', *Brain connectivity*, 2(3), pp. 125-141.

Wolfers, M. (2013) 'Job Mismatches and their Labour-Market Effects among School-Leavers in Europe', *European Sociological Review*.

Yokoyama, C., Kaiya, H., Kumanoh, H., Kinou, M., Umekage, T., Yasuda, S., Takei, K., Nishikawa, M., Sasaki, T. & Nishimura, Y. (2015) 'Dysfunction of ventrolateral prefrontal cortex underlying social anxiety disorder: A multi-channel NIRS study', *NeuroImage: Clinical*, 8, pp. 455-461.

Young, A. F., Powers, J. R. & Bell, S. L. (2006) 'Attrition in longitudinal studies: who do you lose?', *Australian and New Zealand journal of public health*, 30(4), pp. 353-361.

Zhang, Z., Liu, H. & Choi, S. W. (2020) 'Early-life socioeconomic status, adolescent cognitive ability, and cognition in late midlife: Evidence from the Wisconsin Longitudinal Study', *Soc Sci Med*, 244, p. 112575.
FIGURE LEGENDS

**Figure 1** Derivation of the study sample

![Diagram showing the derivation of the study sample]

**Figure 2** Functional connectivity between the right lateral prefrontal cortex and a cluster including left precentral gyrus, left postcentral gyrus and left superior frontal gyrus

The left part of the figure shows a cluster of voxels functionally connected with the right lateral prefrontal cortex that is also associated with cognitive ability in adolescence. This cluster includes mainly left precentral gyrus, left postcentral gyrus and left superior frontal gyrus. Coordinates: -62 -08 +18; size of cluster: 2360. The right part of the figure shows an association of greater functional connectivity between this cluster and the right lateral prefrontal cortex with lower trait anxiety, adjusted for sex.
Figure 3 Mediation analysis

Results are $B$ (standard error); *$p<0.05$, **$p<0.001$

CI, confidence interval

![Diagram of mediation analysis]

Parameter estimate of mediation:
$ab = -0.012 (0.005), 95\% \text{ CI } -0.022 ; -0.002$

Table 1 Characteristics of participants

| Characteristic                           | Value             | n   |
|-----------------------------------------|-------------------|-----|
| Early-life socioeconomic deprivation    | mean $3.0 \pm \text{ SD } 2.2$ | 54  |
|                                         | median 2.5 (IQR 3.5) |     |
|                                         | range 0-9.5       |     |
| Cognitive ability in adolescence        | mean $13.6 \pm \text{ SD } 3.8$ | 54  |
|                                         | median 13 (IQR 5)  |     |
|                                         | range 3-22        |     |
Trait anxiety          mean 26.4 ± SD 8.5          54
                        median 24.5 (IQR 11)
                        range 14-51

Mother’s education: university and higher, n (%)   20 (37)          43
Father’s education: university and higher, n (%)   18 (33)          44

Objective early-life socioeconomic position

Father’s occupation: white-collar worker* 32 (59)          53
Household income in CZK, mean ± SD 8 090 ± 3 496          54
Number of basic utilities, mean ± SD 6.5 ± 1.4          54
Number of household items, mean ± SD 5.6 ± 1.5          42
Crowding ratio, mean ± SD 1.7 ± 0.7          54
Composite score, mean ± SD 0.02 ± 0.66          54

*White-collar worker defined as class I, II and III according to Erikson, Goldthorpe and Portocareros (EGP) scheme (Erikson et al., 1979)

SD, standard deviation; IQR, interquartile range

**Table 2 Relationships between the main variables, stratified by effect modifiers**

|                          | B (95% CI) |
|--------------------------|------------|
|                          | Mother’s education |
| Association of ELSD with cognitive ability in adolescence | University or higher | No university education |
| Unadjusted               | -1.104     | 0.164 |
|                          | (-1.675; -0.533)** | (-0.530; 0.858) |
| Adjusted for sex         | -1.169     | 0.165 |
Adjusted for sex, father’s education and objective socioeconomic position

ELSD

Association of cognitive ability in adolescence with trait anxiety in young adulthood

|                | High       | Low       |
|----------------|------------|-----------|
| Unadjusted     | -0.049     | 0.002     |
| Adjusted for sex | -0.044     | 0.000     |
| Adjusted for sex, father’s education, mother’s education and objective socioeconomic position | -0.063 | 0.017 |

-0.095; 0.201
(-0.071; -0.017)**
(-0.078; -0.020)**
(-0.028; 0.031)

***p<0.001; **p<0.01; *p<0.05

ELSD, early-life socioeconomic deprivation; CI, confidence interval

Table 3 Clusters of voxels functionally connected with right and left lateral prefrontal cortex associated with cognitive ability in adolescence

| Seed | Correlation between seed and cluster | MNI coordinates (x, y, z) | Size of cluster | p-FDR | Brain regions included in the cluster |
|------|-------------------------------------|--------------------------|-----------------|-------|--------------------------------------|
| Left LPFC | Negative | +10  -26  +38 | 4945          | 0.0004 | precuneus; cingulate gyrus, posterior division; supramarginal gyrus, posterior division right; supramarginal gyrus, anterior division right; lateral occipital cortex, superior division right; angular gyrus right; parietal operculum cortex right; lateral occipital cortex, inferior division right; middle temporal gyrus, temporooccipital part right |
| Left LPFC | Negative | +28  +40  +18 | 4699          | 0.0004 | frontal pole right; cingulate gyrus, anterior division; paracingulate gyrus |
| Region                        | Direction | MNI Coordinates | Cluster Size | p-value |
|-------------------------------|-----------|-----------------|--------------|---------|
| Left LPFC Negative           |          | -52 -28 +26     | 2116         | 0.0378  |
| Right LPFC Positive          |          | +18 -58 -24     | 3148         | 0.0109  |
| Right LPFC Positive          |          | -62 -08 +18     | 2360         | 0.0269  |
| Right LPFC Negative          |          | +18 -32 +26     | 4772         | 0.0006  |

- **LPFC**, lateral prefrontal cortex; **FDR**, false-discovery rate; **MNI**, Montreal Neurological Institute

Only regions included in the cluster that have min. 100 voxels are reported.