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Correlations between sleep disturbance and brain cortical morphometry in healthy children

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Abstract

Background: While the importance of adequate sleep duration to normal brain development is well known, more studies are needed to characterize how undiagnosed sleep disturbance other than suboptimal sleep duration may impact brain development. In this study we aim to understand the relationships between sleep disturbance measures and cortical morphometry in typically-developing children without previous diagnoses of sleep pathology.

Methods: Healthy 8-year-old children (30 boys, 37 girls) without clinical diagnosis of sleep disorders were prospectively recruited for brain MRI and their parents completed the Children's Sleep Habits Questionnaire (CSHQ). Total sleep disturbance score, as well as 8 subscales including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing, and daytime sleepiness were calculated, and their relationships with cortical morphometry features including cortical gray matter volume, cortical thickness, and surface area were investigated, controlled for total cortical volume and sex.

Results: The CSHQ total sleep disturbance score significantly correlated with cortical surface area in a cluster in the left middle temporal gyrus ($P < 0.001$, $R = -0.54$). In addition, the bedtime resistance subscale negatively correlated with cortical surface area in a cluster in the right fusiform gyrus ($P < 0.001$, $R = -0.50$). No other clusters showed significant relationships between CSHQ total score or subscales and cortical features for this cohort.

Conclusion: Significant relationships between sleep disturbance scores in typically-developing children without clinical diagnosis of sleep pathology and their brain cortical surface area in two temporal lobe regions were identified, suggesting that undiagnosed sleep disturbance may potentially impact brain development even in healthy children.

Keywords: Sleep disturbance, Children's Sleep Habits Questionnaire, Gray matter volume, Cortical surface area, Cortical thickness

Introduction

The importance of adequate sleep to normal brain development in children is well known (Bell-McGinty et al. 2004). Sleep is considered essential for learning and school performance in children (Cheng 2020; Collins et al. 1994), however current data indicates that most school-age children receive less than the recommended amount of sleep per night (Collins et al. 1994). Sleep changes significantly over development in infants, children and adolescents (Dale et al. 1999). Infant sleep is highly fragmented, occurring in short bouts through the day and night, a rhythm that gradually consolidates to longer bouts of nighttime sleep with a reduction in total sleep time from 12–15 h in infants to 9–11 h for school-aged children (Desikan et al. 2006; Ducharme et al. 2016; Dutil et al. 2018). The developmental changes of sleep occur in concert with brain structural and functional

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development (Bell-McGinty et al. 2004; Fischl et al. 1999; Fjell et al. 2015; Gogtay et al. 2010), and are associated with important neural behavioral factors including language (Hirshkowitz et al. 2015), memory (Cheng 2020; James et al. 2017), and executive function (Knickmeyer et al. 2008; Kocevska 2017).

During normal brain development, cortical gyrification starts in the first trimester of gestation and continues in the fetal and postnatal period, while synapse formation develops dynamically in utero and in early life, followed by gradual pruning throughout childhood. The brain cortical developmental trajectory can be reflected in imaging measures of cortical features, as gray matter volume and cortical surface area increase rapidly during the first year of life and continue to grow gradually through young childhood until preadolescence (Konen et al. 2015; Li et al. 2007; Lucas-de la Cruz et al. 2016), while cortical thickness reaches peak between age 1–2 years (Macey et al. 2018)and starts to decrease thereafter (Macey et al. 2018). Like many other family environmental and lifestyle factors that may potentially impact children's brain development, sleep quality is also important for brain development in children, as studies have demonstrated significant relationships between sleep duration and cortical gray matter volume in children with impacts on cognitive performance (Gogtay et al. 2010), and reduction of cortical gray matter volume (Mindell et al. 2016) and changes of cortical thickness (Okada et al. 2017) in children with obstructive sleep apnea. Nevertheless, more studies are needed to characterize the relationships between sleep quality and children's brain structural development in terms of cortical morphometry such as gray matter volume, cortical thickness, and surface area. In addition, most sleep and brain development studies have focused on sleep duration only and pathologies such as obstructive sleep apnea, with few examining the relationships between brain development and other common types of sleep disturbance, especially in healthy, typically-developing children (Owens et al. 2000).

In this study, we recruited healthy 8-year-old children without clinical diagnosis of sleep disorders for an MRI study of the brain cortical structure and an assessment of sleep disturbance using the parent-reported Children's Sleep Habits Questionnaire (CSHQ). Cortical gray mater volume, cortical thickness, and surface area in different brain regions were measured, and total sleep disturbance score as well as 8 subscales representing different aspects of sleep disturbance were calculated. The relationships between these brain cortical morphometry features and sleep disturbance scores in children were then evaluated. We hypothesized that increased sleep disturbance reflected by higher CSHQ total score or specific subscale scores would be associated with changes in cortical morphometry parameters such as decreased cortical surface area.

Methods

Subjects

All experimental procedures were approved by the Institutional Review Board of the University of Arkansas for Medical Sciences. All parents provided written informed consent, and all children provided assents. Potential subjects were recruited through print advertisements placed in local newspapers, magazines, and circulars; digital advertisements on local and institutional websites and social media; study flyer/postcards posted in physicians' offices, pharmacies, schools, churches, kid-targeted recreation centers and retail stores; displays at health fairs; and television/radio commercials. Eligibility screening was completed by a clinical research promoter using a standard telephone-administered recruitment/screening script. Inclusion criteria for the participants included: healthy, age 7.5–8.5 years; right-handed; parental report of full-term gestation at birth; parental report of birth weight between 5-95th percentile-for-age; and current body mass index between 5-95th percentile-for-age. Exclusion criteria for the participants included: maternal use of alcohol, tobacco, drug, or psychotropic medications during pregnancy; illnesses and chronic diseases which may affect children's growth or development; psychological/psychiatric diagnoses; neurological impairment or injury; history or current use of anticonvulsant, stimulant, or mood stabilizing medications; and history or current use of remedial special education services. Eighty-one children were initially enrolled, and 71 of them had valid MRI. Among these, 3 did not complete the sleep questionnaire, and 1 had a total sleep disturbance score more than 2 standard deviations higher than the average score and was therefore excluded as an outlier. In total, 67 children had both completed parent-reported sleep disturbance data and valid MRI data and were included in this study. The demographic information of the participants as well as their sleep test scores are listed in Table 1.

MRI data acquisition

All children had a brain MRI examination done at the Radiology Department of the Arkansas Children's Hospital on a 1.5 T Achieva scanner (Philips Healthcare, Best, the Netherlands) with 60-cm bore size, 33-mT/m gradient amplitude, and 100-mT/m/ms maximum slew rate. The built-in body coil was used as a transmitter, and a standard 8-channel sensitivity encoding head coil was used as a receiver. The imaging protocol included a T1-weighted 3D turbo field echo pulse sequence for structural imaging with the following parameters: 7.3 ms

Table 1 Demographic information of the participants and their CSHQ sleep disturbance scores

	Mean ± Standard Deviation	Range [min, max]
Sex	30 boys and 37 girls	
Age at MRI (years)	7.9 ± 0.3	[7.5, 8.5]
Total Sleep Disturbance Score	40.1 ± 4.0	[33, 51]
Bedtime Resistance	7.0 ± 1.4	[5, 12]
Sleep Onset Delay	1.4 ± 0.6	[1, 3]
Sleep Duration	3.3 ± 0.6	[3, 6]
Sleep Anxiety	4.8 ± 1.0	[4, 7]
Night Waking	3.4 ± 0.8	[3, 7]
Parasomnias	8.1 ± 1.2	[7, 11]
Sleep Disordered Breathing	3.1 ± 0.4	[1, 4]
Daytime Sleepiness	11.6 ± 2.4	[8, 19]

TR; 3.4 ms TE; 8° flip angle; 1 × 1x1 mm acquisition voxel size; 256 × 232x150 matrix size; 2 averages; and 7 min of scan time. All T1 Images were reviewed on the scanner at the time of scanning, and scans with substantial motion artifacts were repeated. Children unable to complete the scan with valid data were excluded.

MRI data analysis

All MRI data were exported to a Macintosh workstation with the FreeSurfer software (version 7.1.0, developed by the Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging) installed for cortical analysis. Standard preprocessing steps including motion correction, non-brain tissue removal, and transformation to the Talairach space were applied (Papeo et al. 2019). Image was segmented to gray matter, white matter, and cerebrospinal fluid (CSF), followed by intensity normalization, tessellation of cortical gray/white matter boundaries, automated topology correction, and surface deformation (Philby et al. 2017; Remer et al. 2017). Cortical surface models were generated, inflated, and based on the computation of the local curvature, surface area and surface normal, registered to a spherical atlas for cortical parcellation (Ronan 2019). Moreover, a full-width/half-max Gaussian blurring kernel of 10 mm was applied to smooth the parameter maps after resampling the data onto the average subject. All processed or intermediate images were visually inspected to ensure quality. Cortical thickness was estimated as the shortest distances between gray/white to gray/CSF boundaries; surface area was measured by assigning an area to each vertex equal to the average of its surrounding triangles; and cortical gray matter volume was measured by the volume in between the gray/white and gray/CSF boundaries. These parameter maps were then fed to a General Linear Model (GLM) in FreeSurfer to evaluate relationships with sleep disturbance scores.

Sleep disturbance evaluation

All parents completed a Children's Sleep Habits Questionnaire (CSHQ) onsite for their children. Detailed instructions were given and any questions they had regarding completing the CSHQ questionnaire were answered by trained research staff. The CSHQ includes 33 sleep items for scoring and assesses 8 subscales of sleep disturbance including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing, and daytime sleepiness. Thirty-one items were answered as "usually" (if it occurs 5 or more times a week) which translated to a numerical score of 3 for the item, "sometimes" (if it occurs 2–4 times a week) which translated to a numerical score of 2 for the item, or "rarely" (if it occurs 1 time a week or never occurs) which translated to a numerical score of 1 for the item. Two items were answered as "falls asleep" which translated to a numerical score of 3, "very sleepy" which translated to a numerical score of 2, or "not sleepy" which translated to a numerical score of 1. The CSHQ subscales as well as the total CSHQ sleep disturbance score were calculated using the provided formulas based on the 33 individual item scores. The validity of CSHQ in screening for children with sleep disorders has been verified (Sadeh et al. 2014; Schlarb et al. 2010; Seehagen et al. 2015). The internal consistency between overall score and subscales, the inter-rater consistency, and the test–retest reliability all appeared to be good (Short et al. 2018). In addition, correlations between CSHQ assessments and actigraphy measured sleep quality indicators such as sleep latency and awakenings have been reported (Taveras et al. 2017).

Statistics

Relationships between sleep disturbance total score and subscales and brain cortical features such as cortical gray matter volume, surface area, and cortical thickness were tested using GLM with the DODS (different offset, different slope) method in FreeSurfer. Specifically, to test the relationships between sleep disturbance scores and cortical morphometry, GLMs with DODS were used to fit for each vertex for cortical thickness, cortical surface area, or gray matter volume, which were defined as dependent variables. Sex was included as a covariate, because of reported sex differences in brain cortical development in children. Total cortical volume was also included as a covariate in the analysis to account for variations in individual brain cortical size. All analyses were applied to each hemisphere separately. The operations in the FreeSurfer GLM were performed at each voxel or vortex separately. The input were the cortical gray matter volume, surface area, and cortical thickness feature maps smoothed with a Gaussian kernel with a 10 mm full-width/half-maximum. The global design matrix with a FreeSurfer group descriptor file of DODS were fed into the GLM, with the rows representing all subjects, and columns representing the covariates and the corresponding sleep scores in each evaluation. To correct for multiple comparisons, large number of simulations were performed under the null hypothesis to see how often the value of a statistic from the true analysis is exceeded. This simulator is based on FSL's permuation simulator (randomise) and AFNI's null-z simulator (AlphaSim) and this approach works well for surface-based data as traditional random field theory is harder to implement. In our study, $P \leq 0.0001$ threshold was used for cluster forming for the vertex-wise analyses. Clusters were obtained after regressing out the effects of all covariates. To identify clusters with significant relationships (between sleep disturbance scores and cortical morphometry features) after appropriate multiple comparison correction, the cluster-wise precomputed Z Monte Carlo simulation with 10,000 iterations was applied to every cluster. A corrected cluster-wise P of ≤ 0.05 was regarded as significant.

After clusters with significant relationships were identified, the average cortical morphometry parameters in each cluster for each subject were extracted and correlated with sleep disturbance scores to calculate correlation coefficients using Spearman's Partial Correlation test with sex and total cortical volume controlled.

Results

All children had normal MRI on the T1 weighted images without incidental findings requiring medical attention. The CSHQ total sleep disturbance score and the 8 subscales (Table 1) all have mean values and standard deviations comparable to a published cohort on a community sample of school age children with larger sample size (Sadeh et al. 2014). The total sleep disturbance scores for all children were lower than the reported average score (54) of a clinical cohort, other than the single subject that was excluded (who had a total score of 62).

The cortical morphometry analysis revealed two clusters with significant relationships between sleep disturbance scores and cortical features. These clusters were summarized in Table 2. Specifically, the CSHQ total sleep disturbance score significantly correlated with cortical surface area in one cluster in the left middle temporal gyrus (cluster-wise corrected $P < 0.001$, correlation coefficient $R = -0.54$) (Fig. 1). In addition, the bedtime resistance subscale (determined by measures of frequency of: going to bed at the same time; falling asleep in own or other's bed; needing parent in room to sleep, struggling at bedtime, and being afraid of sleeping alone) negatively correlated with cortical surface area in one cluster in the right fusiform gyrus (cluster-wise corrected $P < 0.001$, correlation coefficient $R = -0.50$). (Fig. 2). These negative relationships suggest that the more sleep disturbance, the less cortical surface area development in temporal brain regions.

While cortical gray matter volume and cortical thickness were also calculated and their relationships with sleep disturbance scores were also evaluated in the GLM model, there were no clusters showing significant relationships with corrected $P \leq 0.05$.

Discussion

There is behavioral evidence that sleep is important for cognitive function in children (Tham et al. 2017), and a better understanding of the developmental relationships between sleep, brain regional and network structure and cognitive function in childhood is needed. A recent large scale study in 9–11 year old children identified significant

Table 2 Clusters in brain cortex with significant relationships (cluster-wise corrected $P \leq 0.05$) between sleep disturbance scores and cortical morphometry features. L: left brain hemisphere; R: right brain hemisphere

Location of cluster	Cluster Size (mm^2)	Sleep Disturbance Type	Cortical Feature Type
L: middle temporal gyrus	444	CSHQ total	Surface area
R: fusiform gyrus	339	Bedtime resistance	Surface area

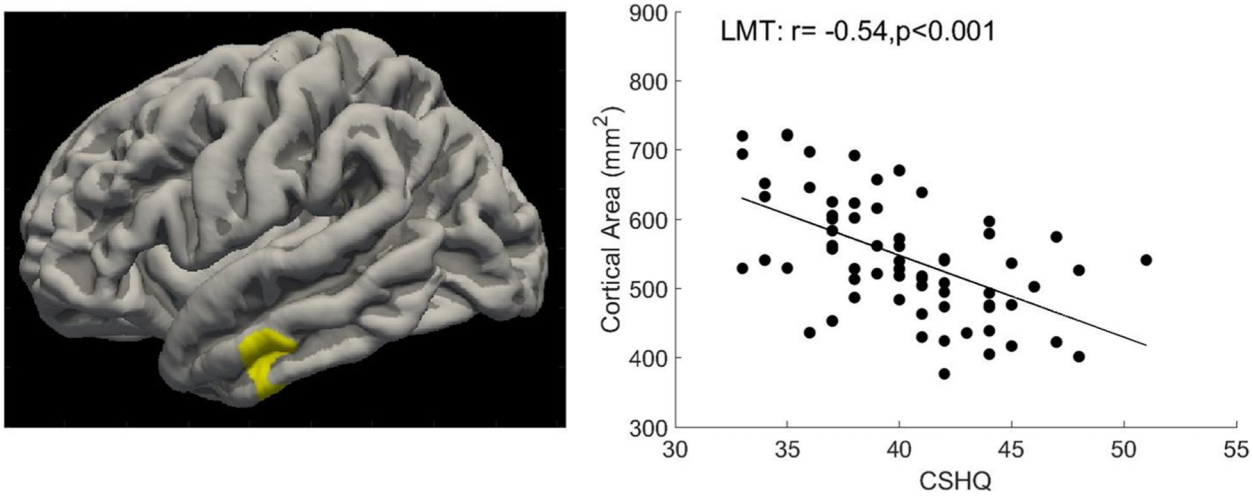

Fig. 1 The image on the left shows a cluster in the left middle temporal (LMT) gyrus with significant relationship (cluster-wise corrected $P \leq 0.05$) between CSHQ total sleep disturbance score and cortical surface area, in standard MNI305 atlas. The scatter plot on the right illustrates the data of CSHQ total score vs. cortical surface area in this cluster for all subjects, and the correlation coefficient calculated by Spearman's Partial Correlation test

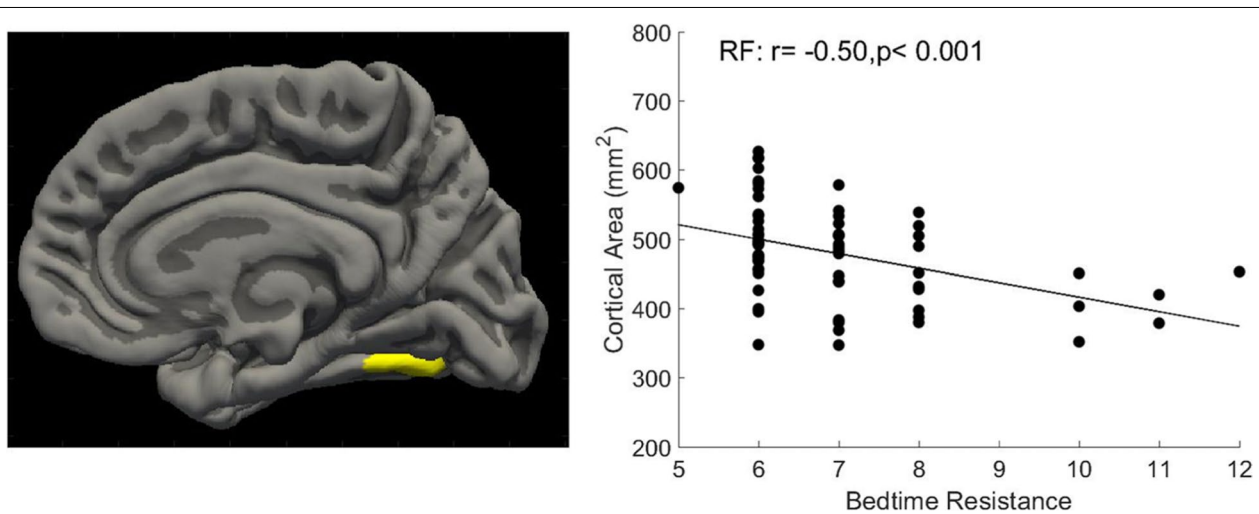

Fig. 2 The image on the left shows a cluster in the right fusiform (RF) gyrus with significant relationship (cluster-wise corrected $P \leq 0.05$) between bedtime resistance and cortical surface area, in standard MNI305 atlas. The scatter plot on the right illustrates the data of CSHQ subscale (bedtime resistance) vs. cortical surface area in this cluster for all subjects, and the correlation coefficient calculated by Spearman's Partial Correlation test

relationships between longer sleep duration and higher brain volume in orbitofrontal cortex, prefrontal and temporal cortex, precuneus, and supramarginal gyrus (Gogtay et al. 2010). Moreover, higher cognitive scores were associated with higher volume in some of these brain regions (Gogtay et al. 2010). Nevertheless, relationships between brain structure and other aspects of sleep quality (such as different types of sleep disturbance) were not investigated in that study, and other cortical features such as surface area and thickness were not investigated. In our study, we report results for the relationship between brain cortical morphometric features (including cortical gray matter volume, cortical surface area, and cortical thickness) and parent-reported sleep disturbance in younger school aged children.

Our results revealed two areas in the temporal lobe which showed decreased cortical surface area that was related to sleep disturbances. A cluster in the left middle temporal gyrus was significantly related to overall sleep disturbances reflected by the CSHQ total scores. This

result is consistent with the recent study reporting reduction in temporal cortical volume to be associated with shorter sleep duration and poorer cognitive function (Gogtay et al. 2010). Together, these data suggest that poorer sleep quality and reduced duration are associated with developmental changes in the temporal lobe that adversely affect cognitive function. The middle temporal gyrus is a temporal association area that is part of several functional brain networks, including a fronto-temporo-parietal executive control network, a social-semantic network and an auditory processing network. Furthermore, the middle temporal gyrus has been associated with the representation of meaning, with studies reporting activations related to observed actions, word processing and semantic memory (Urbain et al. 2016; Vermeulen et al. 2019). Children with obstructive sleep apnea exhibited widespread reductions in cortical thickness and volume, including the temporal cortical regions (Mindell et al. 2016; Wang et al. 2019)that are suggested to be due to disruptions in normal developmental processes rather than the neurodegenerative changes posited for adult patients of obstructive sleep apnea (Wang et al. 2019).

We also found significant correlations between cortical surface area of the right fusiform gyrus and the CSHQ subscale score for bedtime resistance. The fusiform gyrus is functionally a part of the temporal lobe network, where it forms part of the posterior visual processing stream. In its posterior divisions, the region shows functional connections to superior temporal gyrus, parietal and frontal regions with the left fusiform gyrus more tightly coupled to areas responsible for visual-language perception (Wurm et al. 2019). One previous study has shown decreased activation in non-verbal recognition task post sleep deprivation in the right fusiform gyrus (Zhang et al. 2016), and another study has shown decreased response to inhibitary control in the fusiform gyrus after sleep deprivation (Zhao et al. 2019), both suggesting potential functional consequences to this region associated with sleep disturbance.

Our study was not designed to test the causal relationships between sleep disturbance and changes in brain development, or to explore the underlying mechanisms for relationships between them. None of the children in our cohort had a diagnosed sleep disorder and their sleep disturbance scores were all below those of clinical cohorts. Nevertheless, we were still able to demonstrate statistically significant relationships between variations in sleep disturbance scores and changes in brain cortical morphometry features, particularly cortical surface area, in specific brain regions. Our results indicate that quality of sleep (in terms of less sleep disturbance) may be important for the typical developing brain.

There are several limitations for this study. The study was cross-sectional and regions identified with relationships between sleep disturbance and changes in cortical morphometry features were relatively small. A longitudinal cohort with a larger sample size may identify more regions with consistent or transit correlations between cortical morphometry features and sleep disturbance, and may allow control for more potential confounding factors such as family environment and lifestyle. Furthermore, while psychological diagnosis was an exclusion criterion, subclinical depression and anxiety were not screened and measures of depressive and anxiety symptoms were not available, which may be important mediating factors changing the relationships between sleep disturbance and cortical surface area in these children. Finally, while we have demonstrated brain regions showing relationships between cortical structural development and sleep disturbance, we do not have functional outcome measures specifically tied with these brain regions.

Conclusion

Significant relationships between parent-reported sleep disturbance scores (including total scores and subscales such as bedtime resistance) in typically developing children and their brain cortical surface area in two temporal lobe regions were identified, suggesting that undiagnosed sleep disturbance may potentially impact brain development even in healthy children.

Abbreviations

CSHQ: Children's Sleep Habits Questionnaire; MRI: Magnetic resonance imaging; GLM: General linear model.

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Authors' contributions

XN and TL performed data analysis; LJLP drafted part of the manuscript; CEB assisted data analysis; TMB contributed in the design and conduct of the study; XO designed and supervised the study and drafted majority of the manuscript. All authors edited the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The data used in this manuscript will be available upon written request to the corresponding author.

Declarations

Ethics approval and consent to participate
All experimental procedures were approved by the local Institutional Review Board. All parents provided written informed consent, and all children provided assents.

Consent for publication
Not applicable.

Competing interests
None.

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