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Research Article

The Effect of Low-Level Indoor Exposure Toluene on Orienting Network

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Objective. The aim is to explore the effect and mechanism of indoor toluene exposure on orienting network. *Methods*. Twenty-two healthy adults were exposed to 0 ppb, 17.5 ppb, 35 ppb, and 70 ppb toluene for 4 hours, respectively. All subjects underwent attention network behavioral test, and their electroencephalographic activity was recorded simultaneously. The causal connection strengths of orienting network were calculated through direct transform function (DTF) methods. The DTF values of orienting networks among four groups were compared. *Results*. (1) The DTF values of parietal outflow ($DTF_{-outflow}$) in 70 ppb toluene condition were higher than those of the 0 ppb, 17.5 ppb, and 35 ppb conditions, respectively. (2) The $DTF_{CZ\text{-}FZ}$ and $DTF_{CZ\text{-}FP2}$ values of 70 ppb toluene condition were found to be lower as compared to 0 ppb condition. The $DTF_{CZ\text{-}FP2}$ values of 70 ppb condition were lower as compared to those of the 17.5 ppb condition. Furthermore, $DTF_{P3\text{-}FP2}$, $DTF_{P4\text{-}FP1}$, and $DTF_{P4\text{-}FZ}$ values of 70 ppb condition were higher as compared to those of the 0 ppb condition. The $DTF_{P3\text{-}FP2}$ values of 70 ppb condition were higher as compared to those of the 17.5 ppb condition. The $DTF_{P4\text{-}FP1}$ values of the 70 ppb condition were higher as compared to those of the 17.5 and 35 ppb conditions. *Conclusion*. Even short-term exposure to indoor toluene at low concentrations significantly impacts orienting network.

1. Introduction

Air pollution is one of the most prevalent causes of disease and premature death worldwide [1, 2]. Air pollution contributes significantly to cognitive decline, and it causes about 2.1 million people worldwide to develop dementia each year, with about 550,000 people in China, accounting for 25% of the world [3, 4]. In previous studies, air pollution from outdoor sources has been linked to cognitive decline, but very few have examined air pollution from indoor sources [5–8].

Humans spend 87% of their time indoors. Indoor air pollution causes two times more cognitive impairment than in the general population [9]. Pollutants in indoor air include particulate matter, gaseous chemical pollutants, and microbial aerosols [10–12]. Indoor air pollution in residential and public buildings is mainly caused by volatile organic compounds (VOCs) [11, 13]. Toluene is the most common indoor VOC detected in several cities around the world, with a detection rate of up to 90% [14–16]. The indoor toluene concentration is usually at the ppb level

[14, 17], with a concentration that ranges from 60 to 70 ppb in the heating house in winter [13], up to 120 ppb in the newly renovated house [18], 390 ppb in the indoor printer shop [19], and 540 ppb in the household coal-fired kitchen [20]. Toluene is a neurotoxic indoor VOC. It has been confirmed by toxicological and pathological methods that PPM levels (50 ppm to 30,00 ppm) of toluene significantly impair cognitive function and key brain regions in occupational exposure, poisoning, and inhalation abuse populations and laboratory animals [21–23]. Current research on the neurotoxicity of toluene has expanded from functional toxicology at ppm level to the influence of indoor toluene exposure at ppb level on human cognitive function. Even exposure to low-concentration indoor toluene for a short period of time affects brain oscillations, according to our previous studies [24]. Furthermore, low levels of toluene exposure affected the functional connectivity of executive control networks [25]. Orientation is the ability to select useful information from external stimuli and shift attention and is the basis for higher cognitive function [26–28]. It is unknown, however, how low concentrations of toluene affect orientation function. The study is aimed at investigating whether low-concentration indoor toluene exposure affects functional connectivity of orienting networks.

Orientation is the cornerstone of all behavior and cognition and can be measured by the attention network test (ANT) [27, 29, 30]. Various studies have demonstrated that brain functional connectivity is critical for normal brain cognition and that it changes during early stage disease processes [31–33]. For the detection of these changes in functional connectivity, electroencephalography (EEG) has been proven useful [34, 35]. A method for assessing neural EEG signals' functional connectivity (FC) is the directional transfer function (DTF), which is highly flexible and easy to implement [36]. DTF values and cognitive behavior performance were significantly weakened by neurological diseases such as epilepsy and depression, as we reported in our previous research. Furthermore, DTF values correlated positively with cognitive behaviors [37, 38]. In previous studies [25], it has been demonstrated that exposure to indoor toluene affects the functional connectivity of the executive control network, but the impact on the orienting network remains unknown.

By creating an indoor environment with multigradient toluene concentrations within the environment chamber, the present study was performed to investigate how low levels of indoor toluene affect orienting network. With EEG, the physiological electrical activity of the brain was detected during the ANT. In order to determine the mechanism behind the negative effects of toluene on cognitive function, we calculated the functional connectivity of the orienting network based on EEG signal and DTF method.

2. Materials and Methods

2.1. Participants. In total, 22 healthy students from Tianjin University participated in this study. All subjects' neural electrical activity was collected during the orienting task state using the attention network behavioral test and electroencephalogram [24, 25, 39]. A total of five criteria were required for inclusion: (1) age 18-26 years, (2) nationality Han, (3) right-handedness, (4) a body mass index (BMI) of 20-24 kg/m^2, and (5) good physical and mental health without a history of chronic disease. For exclusion, the criteria are as follows: (1) asthma, allergic rhinitis, bronchitis, and disorders of olfaction; (2) smoking, drinking, or using illicit drugs; (3) brain damage, cognitive impairment, or other neurological disorders; (4) mental illnesses such as depression and anxiety; and (5) being exposed to air pollution for a long period of time. The subjects were required to wash their hair and take a bath the night before the test, to get plenty of sleep, to avoid staying up late, to eat a normal diet on the test day to avoid an empty stomach, and not to use alcohol, coffee, tea, and functional stimulant beverages and drugs. Both participants and investigators were blinded to the concentration of toluene in the present study. During the study, each subject had to complete four different exposure concentrations of toluene. The subjects wore uniformly issued long sleeves and pants and entered the environmental chamber to sit quietly for 4 hours. The neurologists instructed the subjects to complete an attention network test training during this time. This was to ensure that the subjects were familiar with the test process. After sitting still for 4 hours, the subjects formally took the attention network behavioral test, while EEG data were recorded.

According to our previous study [14] and studies from other countries [40, 41], indoor toluene concentrations are mostly within the range of ppb in real life. Due to this, ppb levels of toluene were simulated in this study. Based on the recommended safe exposure concentrations set by the OEHHA, approximately 70 ppb of toluene is the maximum safe concentration. Therefore, the maximum toluene concentration is set at 70 ppb in this study. Two concentration gradients are set below 35 ppb, 17.5 ppb, and 0 ppb for the control group.

We assessed the participants' mental states by using the Montreal Cognitive Assessment (MoCA), Hamilton Anxiety Scale (HAMA), and Pittsburgh Sleep Quality Index (PSQI) which are all clinically validated instruments. Study participants' demographic data are presented in Table 1. This study is approved by Tianjin Medical University General Hospital ethics committee.

In the experiment, participants were assessed on their subjective perceptions of environmental parameters. As described in our previous studies [24, 42], a questionnaire for indoor air quality (IAQ) was administered to assess various aspects of indoor air quality, such as comfort temperature, moisture, illumination, freshness of air, unpleasant odors, background sounds, air quality, and discomfort. In a multichoice question regarding discomfort, there was a choice of no discomfort, tiredness, nausea, anxiety, head pain, eye dryness, and breathlessness, as well as a blank space for adding new symptoms. This study was controlled before and after the study, in which 0 ppb toluene exposure was the control group. The perceived quality of the air in the chamber and the discomfort questionnaire did not differ statistically significantly between the toluene exposure group and the control group.

Table 1: Subject demographics and clinical details.

Items	Values (mean ± standard deviation)
Male/female	11/11
Age (year)	21.68 ± 1.25
Education (year)	15.09 ± 0.87
BMI (kg/m^2)	21.36 ± 1.05
Montreal Cognitive Assessment (MoCA)	29.00 ± 0.76
Hamilton Anxiety Scale (HAMA)	1.55 ± 0.67
Pittsburgh Sleep Quality Index (PSQI)	2.64 ± 1.36

2.2. Environment Control and Exposure to Toluene. Our previous study detailed the process of exposure to toluene and the measures taken to control the environment [25]. Briefly, two subjects were positioned simultaneously in a closed chamber equipped with a system for circulating fresh air into the room (Figure 1) in a within-subject experiment. Fresh air was supplied at a rate of 199.5 L/s per person. This was a double-blind, randomized study in which both subjects and investigators did not know the extent of exposure to toluene. Based on the OEHHA's recommended safe exposure concentration, four toluene concentrations were considered: a concentration of 0 ppb (toluene_0 group) corresponded to no toluene exposure; a concentration of 17.5 ppb (toluene_1 group), 35 ppb (toluene_2 group), and 70 ppb (toluene_3 group) corresponded to exposure to toluene at those respective concentrations. ANT tasks and simultaneous EEG recordings were performed on all participants. During the experiments, each subject was exposed to four toluene concentration gradients in a random order. The experiments were conducted at intervals of more than 12 h to ensure that the body had time to clear toluene. Our previous studies [24, 25] provided details of the design of the experiment and how to control the toluene concentration and other environmental parameters in the environmental chamber.

2.3. Behavioral Task Procedures. It is described in previous studies [24] that the ANT program designed by Fan et al. was adopted in this study. Orienting refers to a subject's capacity to select and judge information effectively when confronted with an external stimulus. It is the process of converting an invalid cue into an effective cue. This means that the orienting response effect is the reaction time to the central cue task minus the reaction time to the spatial cue task [24, 27, 30]. As previously described [24], orienting's response effect ($\text{Orienting}_{\text{effect}}$) was calculated using the following formula:

$$\text{Orienting}_{\text{effect}} = \text{RT}_{\text{center}} - \text{RT}_{\text{spatial}}. \quad (1)$$

2.4. Recording of Electroencephalography (EEG). The details of scalp EEG data collection during subjects' rest and ANT tasks have been described in previous studies [24].

2.5. Analyses of Electroencephalograms

2.5.1. Functional Connection Strength Is Calculated Using Directional Transfer Function. The Granger causality analysis, which utilizes multivariate autoregression (MVAR), a tool for analyzing time series, has shown to be highly effective in determining the strength of functional connections. Using the Granger causality analysis method to calculate directional transfer function (DTF) has proved effective in constructing functional brain networks [25]. Quantitative evaluation of functional connections is achieved using the DTF value. On the frequency f, the DTF from channel j to channel i represents the causal relationship between the two channels. The calculation formula is as follows:

$$\gamma_{ij}(f) = \frac{|H(f)|^2}{\sum_{m=1}^{k}|H_{im}(f)|^2}, \quad (2)$$

where $\gamma_{ij}(f)$ represents the ratio of channel j's influence on channel i compared to the influence of all other channels on channel i, k is the number of channels, and H is the transfer matrix.

2.5.2. Functional Connections' Spatial Distribution. Channel i's causal association strength (DTF_i) is frequently used to quantify its activity in the brain network. As described in our previous studies [25, 38], DTF_i is the arithmetic mean of all causal associations associated with channel i. The formula is as follows:

$$\text{DTF}_i = \frac{1}{2(k\text{-}1)}\sum_{j\neq i\in v}\left(\gamma_{ij} + \gamma_{ji}\right). \quad (3)$$

In the DTF matrix, γ_{ij} represents the average value of $\gamma_{ij}(f)$ in the given frequency band, k denotes the number of channels, and v represents other channels. In causal networks, the DTF_i indicator provided valuable information about channel i's activity.

2.5.3. FC among Brain Regions. We mapped key brain regions in the orienting network using 19 electrodes and observed FC strength between these brain regions: the frontal, parietal, occipital, and temporal regions [25, 38]. Functional connectivity from region p to region k can be calculated using the formula below:

$$\text{DTF}_{kp} = \frac{1}{MN}\sum_{i\in K}\sum_{i\in L}\gamma_{ij}, \quad (4)$$

where γ_{ij} is the average value of $\gamma_{ij}(f)$ in the characteristic frequency band, DTF_{kp} represents the functional connection between brain region p and brain region k, M and N are the numbers of channels in brain regions k and p, respectively, and K and L represent the set of channels contained in brain regions k and p, respectively, in accordance with our previous description [25, 38].

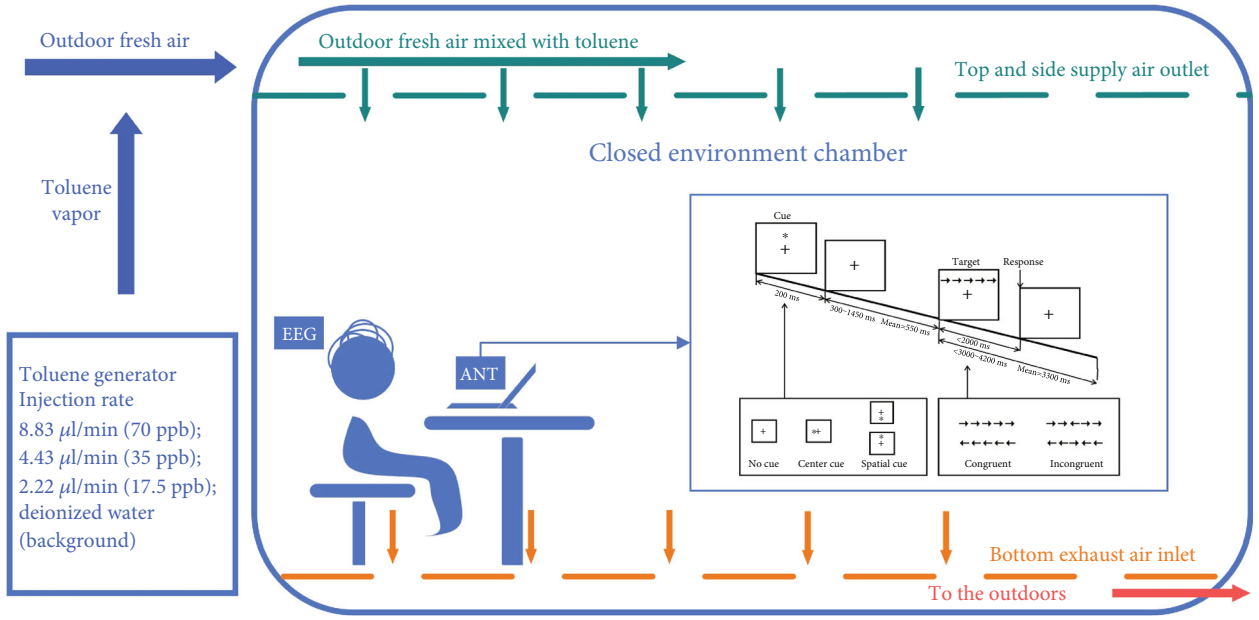

Figure 1: The experimental design and the behavioral ANT of the participants.

In order to evaluate the causal network efficiency of the orienting network, the following criteria were used:

$$\mathrm{DTF}_{\_\mathrm{Orienting}} = \mathrm{DTF}_{\_\mathrm{spatial}} - \mathrm{DTF}_{\_\mathrm{center}}, \quad (5)$$

where $\mathrm{DTF}_{\_\mathrm{Orienting}}$ represents the average DTF value in orienting network, $\mathrm{DTF}_{\_\mathrm{spatial}}$ represents the average DTF value for spatial tasks, and the DTF values in center tasks are represented by $\mathrm{DTF}_{\_\mathrm{center}}$.

2.6. Statistical Analysis. The analyses used SPSS 25.0 (SPSS Inc.). Data were expressed as mean ± standard error. More than three groups were compared using analysis of variance (ANOVA), while post hoc analyses were performed using least significant difference (LSD). The Spearman rank analysis was performed to evaluate the relationship between $\mathrm{DTF}_{\_\mathrm{outflow}}$ from the parietal region and toluene exposure concentrations. The following P values are considered statistically significant: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

3. Result

3.1. Behavior Performance. The results of this study were analyzed by 22 subjects who participated in all experiments. According to our previously described research [24], no significant differences were found between the four groups in $\mathrm{Orienting}_{\mathrm{effect}}$.

3.2. FC of Orienting Network after Exposure to Toluene. In Figures 2(a)–2(c), the topographic map of theta band DTFs in orienting network is shown. As shown by the topography, theta activity was clearly present along the midline of the parietal region. Theta DTFs appear to increase gradually with toluene concentration in orienting network. In order to determine whether theta DTFs of various brain regions differed between four different toluene groups, functional connectivity of theta band was compared between them. Parietal region DTF values were found to be significantly greater than those of other regions (Figure 2(d)). Intergroup comparisons revealed significant differences in DTFs between the four groups in four brain regions. Based on statistical analysis, the toluene_3 group had higher functional connection strength in the parietal region than the toluene_0 group in orienting network (LSD, $P = 0.0058$, Figure 2(e)).

3.3. The Characteristics of the $\mathrm{DTF}_{\_outflow}$ and $\mathrm{DTF}_{\_inflow}$ in Parietal Regions after Exposure to Toluene. As shown in Figures 3(a)–3(d), the functional connectivity between brain regions in orienting network was mapped using a matrix diagram. $\mathrm{DTF}_{\_\mathrm{outflow}}$ from the parietal region to other brain areas increases gradually as toluene concentrations rise in the orienting network (ANOVA, $F = 7.602$, $P = 0.003$), and the $\mathrm{DTF}_{\_\mathrm{outflow}}$ in toluene_3 was significantly higher than that in toluene_0 (LSD, $P = 0.028$, Figure 3(e)), toluene_1 (LSD, $P = 0.019$, Figure 3(e)), and toluene_2 (LSD, $P = 0.047$, Figure 3(e)). $\mathrm{DTF}_{\_\mathrm{inflow}}$ from other brain regions to the parietal region, however, was not statistically significant (ANOVA, $F = 0.062$, $P = 0.971$, Figure 3(f)). To determine the relationship between toluene exposure concentrations and $\mathrm{DTF}_{\_\mathrm{outflow}}$ from the parietal region, the Spearman rank analysis was applied. As shown in Figure 3(g), the $\mathrm{DTF}_{\_\mathrm{outflow}}$ value from the parietal region was positively correlated with toluene exposure concentrations ($R = 0.8$, $P < 0.001$).

3.4. Core Brain Regions' Functional Connectivity after Exposure to Toluene in Orienting Network. Core brain areas' DTF values were compared between the four groups, as shown in Figure 4(a). There was a significant difference in DTF values between groups for CZ to FZ ($\mathrm{DTF}_{\mathrm{CZ\text{-}FZ}}$), CZ to FP2

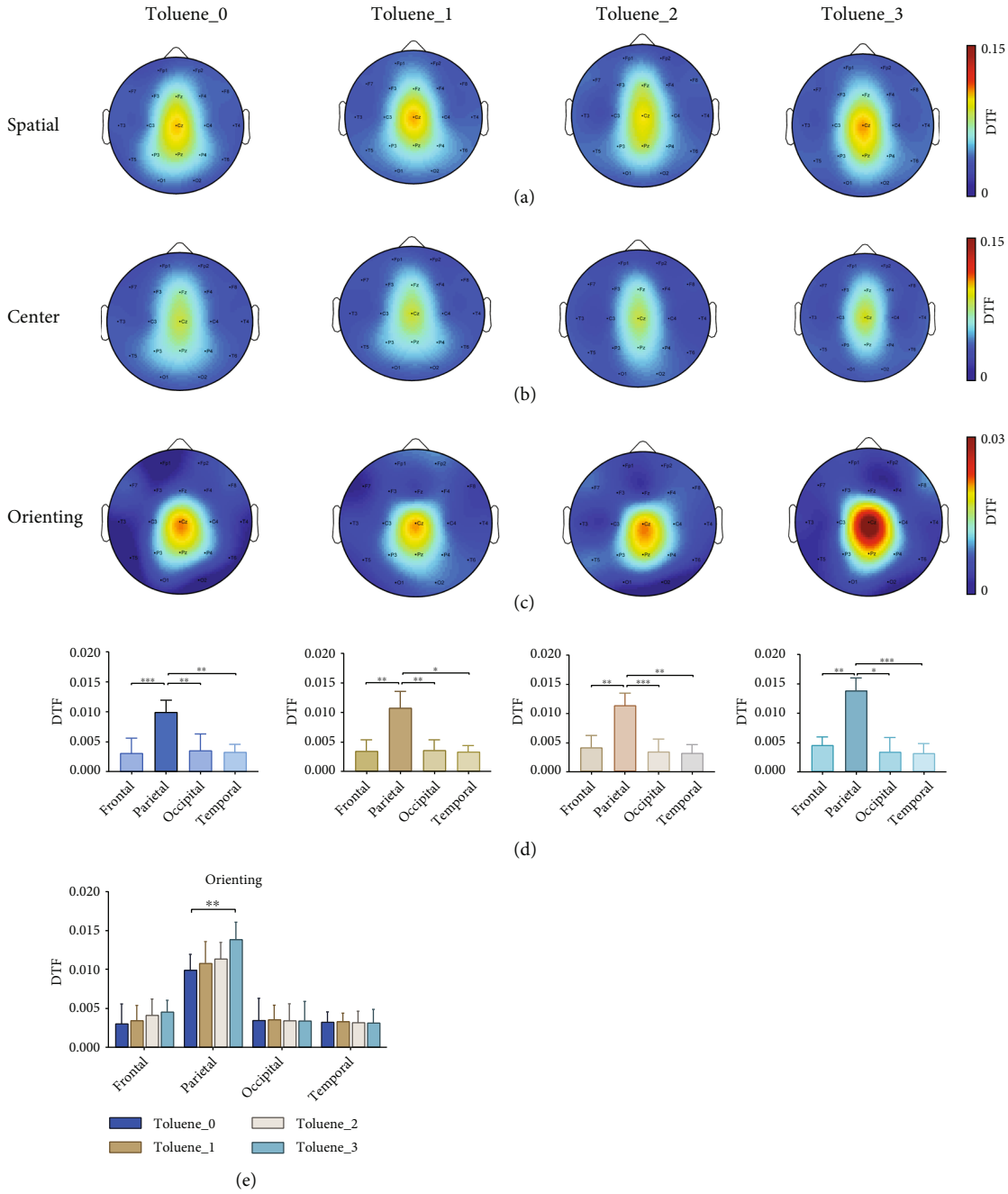

Figure 2: Analyses of topographic maps and DTF power in orienting networks. (a) Theta DTF distributions during spatial tasks. Color indicates strength of the power. (b) Theta DTF distributions during center tasks. (c) Theta DTF distributions in orienting network. (d) The average DTFs of orienting network is compared across four different brain regions in each group. In all groups, the parietal region had the highest average DTFs. (e) Orienting network was compared among four groups based on average DTFs of four brain regions (LSD, $P < 0.05$). $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

($DTF_{CZ\text{-}FP2}$), P3 to FP2 ($DTF_{P3\text{-}FP2}$), P4 to FP1 ($DTF_{P4\text{-}FP1}$), and P4 to FZ ($DTF_{P4\text{-}FZ}$) (Figure 4(b)).

The $DTF_{CZ\text{-}FZ}$ values of toluene_3 were significantly lower than those of toluene_0 (LSD, $P = 0.040$; Figure 4(c)). The $DTF_{CZ\text{-}FP2}$ values of toluene_3 were significantly lower than those of toluene_0 and toluene_1 (toluene_3 vs. toluene_0, LSD, $P = 0.005$; toluene_3 vs. toluene_1, LSD, $P = 0.022$; Figure 4(d)). The $DTF_{P3\text{-}FP2}$ values of toluene_3 were significantly higher than those of toluene_0 and toluene_1 (toluene_3 vs. toluene_0, LSD, $P = 0.040$; toluene_3 vs. toluene_1, LSD, $P = 0.035$; Figure 4(e)). The $DTF_{P4\text{-}FP1}$ values of toluene_3 were significantly higher than those of toluene_0, toluene_1, and toluene_2 (toluene_3 vs. toluene_0, LSD, $P < 0.001$; toluene_3 vs. toluene_1, LSD, $P =$

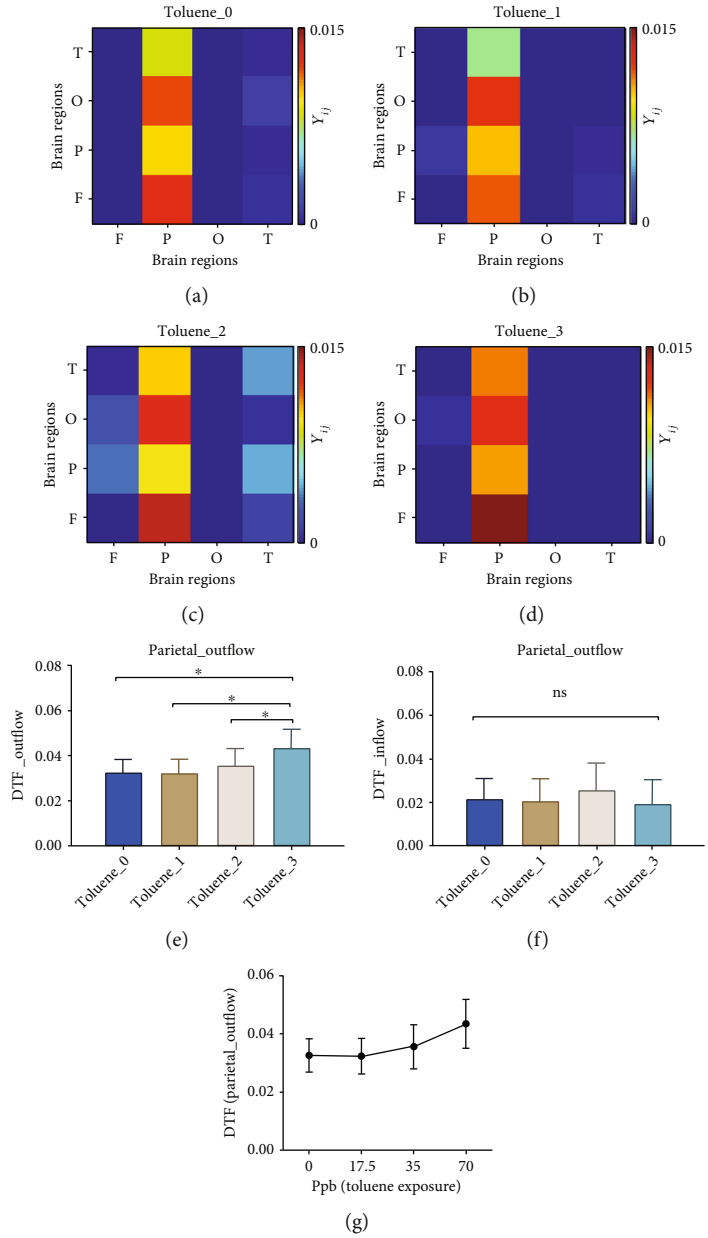

FIGURE 3: Matrix diagram of functional connectivity in orienting network. (a–d) The functional connectivity of the orienting network for four groups, respectively. Use color to illustrate the functional connection. The color darkness increases with increasing strength. (e) The average DTFs of the parietal_outflow in orienting network were compared between four groups. (f) The average DTFs of the parietal_inflow in orienting network were compared between four groups. (g) Correlation between average DTFs of the parietal_outflow in orienting network and toluene exposure concentrations. $^{*}P < 0.05$.

0.002; toluene_3 vs. toluene_2, LSD, $P = 0.001$; Figure 4(f)). The $DTF_{P4\text{-}FZ}$ values of toluene_3 were significantly higher than toluene_0 (LSD, $P = 0.004$; Figure 4(g)).

4. Discussion

In our study, we found that short periods of exposure to low concentrations of indoor toluene did not affect the behavioral performance of the orienting network. However, it changed the functional connectivity of the orienting network. Based on our previous results [24], theta band is the main frequency band for orienting network. In this study, theta functional connectivity of the orienting network under different toluene concentrations was analyzed. In the orienting network, theta band functional connections are mainly found in the parietal region. With the increase of indoor toluene concentration, the theta functional connectivity of the characteristic channel and between the frontal and parietal regions was strengthened. In addition, the $DTF_{\_outflow}$ of the parietal region was increased. By enhancing causality in the frontal-parietal network, short-term exposure to low toluene may have affected the orienting network.

The realization of any cognitive activity requires the interconnection of various brain regions and the coordinated

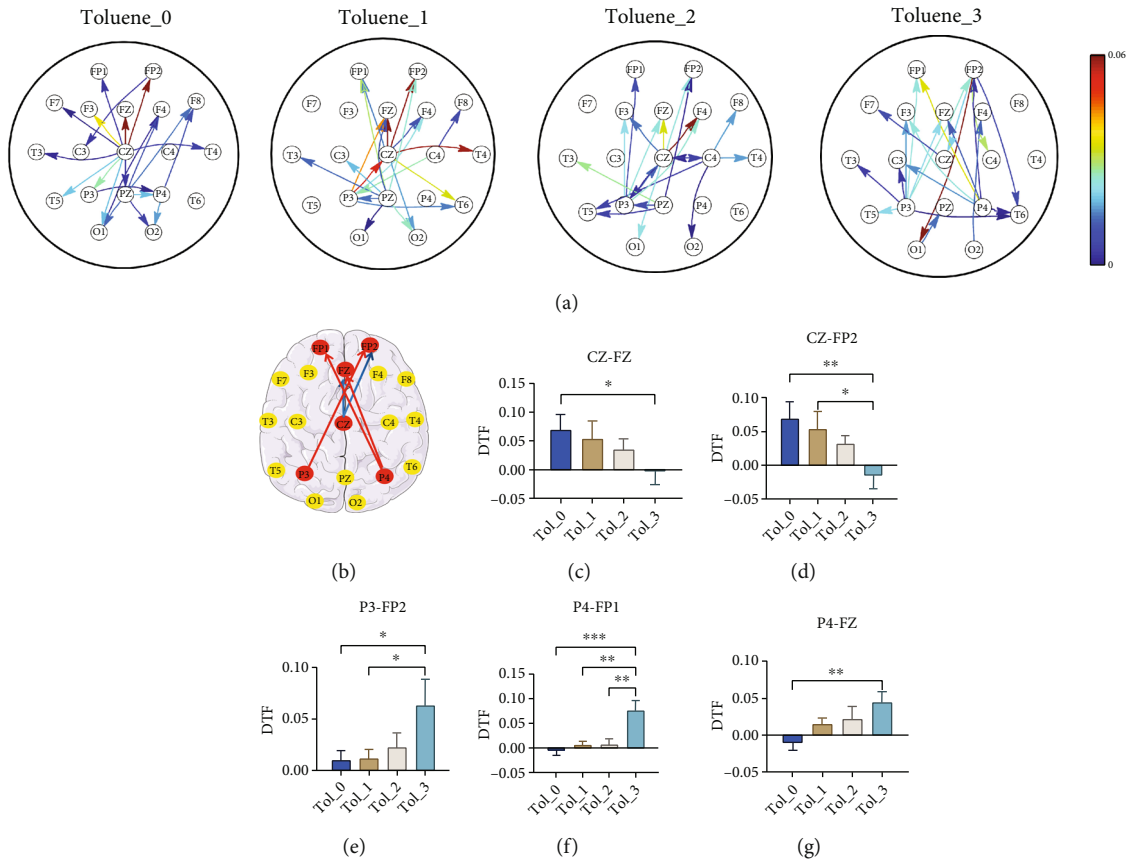

FIGURE 4: Functional connectivity between core brain areas in orienting networks. (a) The topographic map of functional connections between core brain regions in the orienting network. Using arrows to indicate the direction of functional connectivity and color to indicate network strength, we were able to visualize the functional connectivity across core nodes. (b) Network node functional connectivity varied significantly between groups (red solid dots and lines indicated an increase; blue solid dots and lines indicated a decrease). (c–g) Different groups were compared on the values of $DTF_{CZ\text{-}FZ}$ (c), $DTF_{CZ\text{-}FP2}$ (d), $DTF_{P3\text{-}FP2}$ (e), $DTF_{P4\text{-}FP1}$ (f), and DTF $_{P4\text{-}FZ}$ (g). $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

operation and interaction between brain networks [43, 44]. The parietal and frontal cortices were the core regions of the orienting network [45, 46]. The frontal-parietal network was activated during the orienting task [46, 47]. In this study, after 70 ppb toluene exposure for 4 hours, the functional connection strength in the parietal region increased, which means that more efforts are needed to complete the same orienting task.

The orienting network, which is one of the subnetworks of attention and is responsible for directing attention to a cued location, mainly involves the dorsal attention network (DAN) and ventral attention network (VAN) [45]. DAN refers to endogenous spatial attention, which is a top-down selective processing guided by the subject's goals and internal values [48]. The core areas of DAN are the PFC and posterior parietal region, which are responsible for controlling visual spatial attention, also known as the dorsal frontal-parietal network [49]. VAN refers to the bottom-up orientation mediated by external stimuli. The core areas include the temporoparietal junction (TPJ), the ventral frontal cortex, and the insula [50, 51]. In the current study, the key nodes of the orienting network included the dorsal anterior cingulate gyrus (corresponding to CZ), dorsomedial prefrontal area (corresponding to FZ), left anterior prefrontal cortex (corresponding to FP1), right anterior prefrontal cortex (corresponding to FP2), left posterior parietal area (corresponding to P3), and right posterior parietal area (corresponding to P4) based on 10-20 cortical standard projection points [52]. After indoor toluene exposure at low concentrations (ppb levels), the DTFs from CZ to FZ ($DTF_{CZ\text{-}FZ}$) and to FP2 ($DTF_{CZ\text{-}FP2}$) were weakened, while the DTFs from P4 to FZ ($DTF_{P4\text{-}FZ}$) and to FP1 ($DTF_{P4\text{-}FP1}$) and from P3 to FP2 ($DTF_{P3\text{-}FP2}$) were enhanced after the 70 ppb toluene exposure, which indicated that the endogenous attention network was compromised and VAN was enhanced to compensate for the impairment.

The cholinergic system promotes top-down sensory information processing in the cortex and plays a significant role in spatial orientation [53]. Previous studies have confirmed that acute toluene exposure increased the release of dopamine from the medial prefrontal cortex (mPFC) and the dorsal and ventral striatum [54, 55]. The orienting network is regulated by the choline system, which indirectly supports the influence of toluene on spatial positioning function from the perspective of neurotransmitters.

It was still possible for this study to have some limitations. As a first point, the sample size was small, but the research was completely randomized and self-controlled,

which mitigated the negative effects of a small sample size. Secondly, it is possible to become tired or bored after sitting in an environmental chamber for four hours. This may have potential impact on orienting network. In this study, toluene exposure tests were conducted on the same subjects in four groups at different concentrations, while the toluene_0 (0 ppb) group was established as a control group. During each test, discomfort questionnaire was also assessed, reducing interference with the results. Finally, EEG has a low spatial resolution, so it cannot pinpoint the exact location of a brain area. To validate our findings in the future, we would like to conduct a multimodal EEG-MRI study with a larger sample size.

5. Conclusions

Low-concentration indoor toluene exposure increased brain theta band functional connectivity without evident behavioral changes. Endogenous attention networks were compromised, and VAN was enhanced to compensate for the impairment. The neural network mechanism by which toluene affects orientation may be this one. It helps us better understand how indoor air pollutants affect cognition and the brain network. The findings of this study can be used to develop safer methods of measuring indoor air quality in the future.

Data Availability

The data used to support the findings of this study are included within the article.

Ethical Approval

Tianjin Medical University General Hospital's ethics committee approved this study. Institutional research committee ethical standards were followed for all procedures involving human participants. Those ethical standards are based on the 1964 Helsinki Declaration and subsequent amendments.

Consent

All participants provided written informed consent.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Contributions to the design and concept of this study have been made by all authors. Yijun Song and Junjie Liu designed the study; Changqing Zhan, Jie Liu, Liping Pan, Jiajing Wang, Peiran Yu, Xin Zhang, Zukun Wang, and Lei Zhao collected data; Changqing Zhan, Jiajing Wang, and Mingrui Cui analyzed the data under the supervision of Yijun Song and Junjie Liu; Changqing Zhan, Liping Pan, Jiajing Wang, and Mingrui Cui drafted the paper under the supervision of Yijun Song. The manuscript was critically revised by all authors. The final manuscript was read and approved by all authors. Changqing Zhan, Liping Pan, Jiajing Wang, and Mingrui Cui contributed equally to this work.

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