Received: 13 December 2021 | Revised: 1 March 2022 | Accepted: 1 March 2022

DOI: 10.1002/npr2.12246

NEUROPSYCHOPHARMACOLOGY REPORTS

WILEY

ORIGINAL ARTICLE

Development of attentional networks during childhood and adolescence: A functional MRI study

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Funding information

JSPS KAKENHI, Grant/Award Number: 18K02480, 19K02611 and 20H04995

Abstract

Attention ability is one of the most important cognitive functions. It develops mainly during school age. However, the neural basis for the typical development of attentional functions has not been fully investigated. To clarify the development of the aforementioned function and its neural basis, this study examined brain function in children and adolescents during the performance of an attention network test (ANT) using functional magnetic resonance imaging. One hundred and sixty-three volunteers (8-23 years, 80 female) participated in this study. Using a modified version of ANT, we assessed the efficiency of two attentional functions—orienting and executive attention—by measuring how reaction time is affected by spatial cue location and flanker congruency and examined the functional brain areas—attentional networks—associated with two attentional functions. Consistent with the findings of previous studies, the superior parietal lobule, visual association cortex, left precentral gyrus, and supplementary motor area were activated during the orienting attention, while the anterior cingulate cortex, visual association cortex, lateral prefrontal cortex, thalamus, and caudate were activated during the executive attention. Moreover, negative correlations with age were found for activations in the inferior frontal gyrus, dorsomedial prefrontal cortex, and caudate nucleus in the orienting attention, while no correlations with age related to executive attention were found. In conclusion, this study revealed common and distinct features in the neural basis of the attentional functions in children and adolescents compared with that of adults and their developmental changes with age.

KEYWORDS

attention, attentional networks, development, executive, fMRI, orienting

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1 | INTRODUCTION

Attention is among the most important cognitive functions in humans, and it develops primarily during school age.[1] Attentional dysfunctions are often associated with brain injury and various psychiatric disorders, and systematic efforts to understand the neural basis of attention are required to improve these attentional difficulties.[2] Previous reports have suggested that human attention consists of three functional subcomponents, each underlain by separable neural networks.[3-5] Alerting attention is the most basic function and refers to the capacity to maintain a state of alert arousal. Orienting attention refers to the capacity to focus on a specific aspect of stimulus and enhance the process by shifting focus. Executive attention refers to the capacity to cope with interference when sensory inputs are inconsistent with the current goal-directed behavior.[6] These findings have transformed our understanding of attentional function related to psychopathological issues, such as attention deficit hyperactivity disorder (ADHD) and anxiety disorders, suggesting that more than one network is ordinarily implicated in the development of disorders, and that the networks often change during the development of the disorder.[2,7]

Fan et al have shown that it is possible to separate and assess these three types of attention using a single integrated behavioral task referred to as the Attentional Network Test (ANT).[4,5] ANT measures the efficiency of each of the three components of the attention network from the reaction time to the direction of an arrow presented on the screen along with other cues and distractors. Alerting attention, orienting attention, and executive attention can be assessed by subtracting RTs for the presence or absence of cues, differences in the spatial arrangement of cues, and congruent and incongruent arrow directions, respectively. Behavioral measurements using ANT have shown no significant correlations between the efficiency of alerting, orienting, and executive attention.[4] Based on these ANT characteristics, it has been widely used to assess the attentional functioning of healthy adults and children as well as individuals with psychiatric disorders with attention difficulties such as ADHD,[8,9] autism spectrum disorder,[10,11] anxiety disorder,[8] and schizophrenia.[12] Similarly, functional imaging results suggest that the functional contrasts while engaged in ANT differentially activate three separable anatomical networks related to the components of attention.[5] The alerting effect showed strong thalamic involvement and activation of anterior and posterior cortical sites, whereas the orienting effect activated parietal sites and frontal eye fields. The executing effect showed the activation of the anterior cingulate cortex, bilateral frontal area, and fusiform gyrus.[5] Although the findings of the development of attentional networks are limited, a functional imaging study on school-age children using ANT showed an increased activation in the putamen and superior frontal gyrus for orienting attention and in the superior temporal gyrus for executive attention in children compared with those in adults, yet no significant activations for alerting attention were noted.[13] However, the typical developmental trajectory of attentional networks from childhood through adolescence to adulthood remains unclear.

In this study, we measured brain functions engaging in ANT using functional magnetic resonance imaging (fMRI) to clarify the neural basis of attentional networks in children and adolescents and investigated the similarities and differences in their functions compared with adults in previous studies. Moreover, we examined the developmental trajectory of the attentional network throughout childhood and adolescence by considering children and adolescents as a single group and correlating these brain functions with age. This study focused on two of the three attentional networks, particularly those that have been observed to differ between children and adults in previous studies—the orienting and executing networks.

2 | METHODS

2.1 | Participants

One hundred and seventy-two children and adolescents (mean age, 15.1 years; SD, 4.3 years, 8-23 years, and 80 females) were recruited from the local community to participate in this study. The brain activity of participants during ANT was measured using an MR scanner. The race/ethnicity of all participants was Japanese. The exclusion criteria for participation were a previous diagnosis of any psychiatric or neurodevelopmental disorder, head trauma with loss of consciousness, and any history of epilepsy affecting development or growth. All participants had normal or corrected visual acuity and hearing. Seven of all participants were left-handed, and 4 were ambidextrous, based on the Edinburgh Handedness Inventory.[14]

2.2 | Stimuli and procedure

In this study, we used a simplified version optimized for fMRI studies by the authors[5] who developed the original version of the task.[4] The stimuli consisted of five white horizontal arrows pointing to the right or left on a black background (Figure 1). There were two types of target stimuli: congruent targets, in which the central arrow pointed in the same direction as the other arrows (flankers), and incongruent targets, in which the central arrow pointed in the opposite direction. The number of trials and direction of arrows were balanced between the congruent and incongruent conditions. The participant's task was to use the response pad held in his/her right hand to press the button with the index finger when the center arrow was pointing left and the middle finger when pointing right. The target was presented either above or below the fixation crossbar in the center of the screen display, and this fixation is always present during the task. The "asterisk" cue was also presented before the target was presented. The cue was not always presented, and it was either in the center of the screen or above or below the fixation crossbar under cue presentation conditions. The efficiencies of the different attentional networks (orienting and executive control) were assessed by measuring how response times (RTs) were influenced by the presence or absence of spatial cues and congruent or incongruent

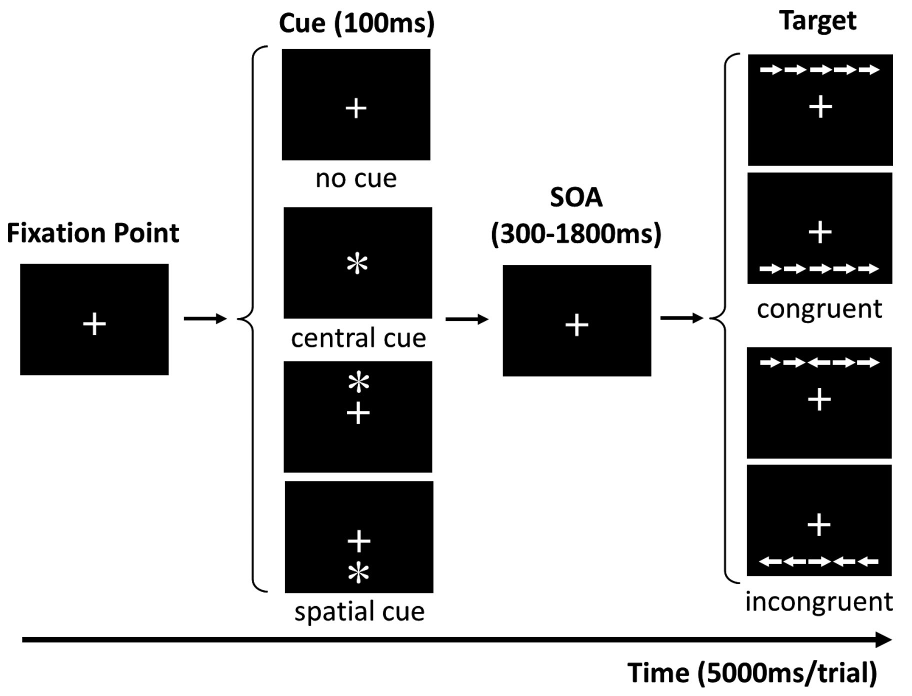

FIGURE 1 Overview of the attention network test. After the fixation point was presented, one of four cues with different spatial patterns was presented for 200 ms After the stimulus onset asynchrony (SOA) of 300-1800 ms, one of two types of arrows with different orientations was presented as target stimuli

flankers.[4,5,13] The orienting effect was determined by differences in RTs between the presence and absence of spatial cues, while the executive control effect was determined by differences between the congruency and incongruency of flankers.[4,5,13]

While performing fMRI using ANT on children, some modifications were also made to the original version regarding the duration of stimuli and interstimuli intervals, average duration per trial, and number of sessions (Figure 1).[4,5] For each trial, the cue was presented first for 200 ms, and there was a variable interval from 300-1800 ms until the target was presented. The duration per trial from the onset of the cue stimuli to the start of the next trial was fixed at 5 seconds. The experiment was conducted in two blocks of 288 trials, that is, 144 trials in each block, with each block divided into four sessions. Trials with error responses were not included in the behavioral and fMRI analyses. All participants were instructed to respond as promptly and accurately as possible.

2.3 | Brain-image acquisition and preprocessing

Image acquisition was performed using a 3-Tesla MRI scanner (Signa Excite, General Electric Medical Systems) with a standard head coil (8-channel HD Brain, GE Healthcare). Functional images were acquired with a T2*-weighted gradient-echo echo-planar imaging sequence. Each volume consisted of 37 slices, with a thickness of 3.5-mm and a 0.5-mm gap, to cover the entire brain. The time interval between the two successive acquisitions of the same slice (repetition time) was 2500 ms, with an echo time of 30 ms and a flip angle of 80°. The field of view was 192 × 192 mm, and the matrix size was 64 × 64, with yielding volume dimensions of 3 × 3 mm. Four fMRI sessions were performed for each participant to acquire 112 volumes. Head movement was minimized by placing memory-foam pillows around the head. A T1-weighted anatomical dataset was obtained from each participant using a magnetization-prepared rapid acquisition gradient-echo sequence (repetition time, 11.316 ms; echo time, 15.26 ms; flip angle, 10°; matrix size, 256 × 256 pixels; slice thickness, 1.0 mm; and a total of 112 transaxial images).

Functional imaging data were analyzed using Statistical Parametric Mapping (SPM) 8 (Wellcome Trust Centre for Neuroimaging) with MATLAB R2016b (MathWorks). First, the initial 5 volumes were discarded, and slice-timing correction was not applied, followed by the spatial realignment of 112 volumes to the mean volume. To control for motion confounding in our data, we investigated the effects of head motion by computing the mean frame-to-frame root mean square motion and the framewise displacement obtained during the realignment process. Subsequently, high-resolution T1 images were co-registered to functional images via a nonlinear image registration approach. Afterward, the functional images were spatially normalized into the Montreal Neurological Institute template and spatially smoothened with an 8-mm full width at half-maximum Gaussian kernel.

2.4 | Statistical analysis

Statistical analysis was performed using SPM8 to examine the relationship between age and functional imaging. Event-related EPI signals were assessed to identify patterns of brain activation for each participant at the first level. Four regressors were modeled at the onset of each trial event (fixation with a central cue or spatial cue and targets with congruent or incongruent flankers), which were convolved with a canonical hemodynamic response function to obtain an event-related signal change. Therefore, contrast images were derived based on the weighted sum of the parameters estimated at the first level of individual analysis. The contrast images (spatial cue—center cue for orienting attention and incongruent flanker—congruent flanker for executive attention) for each participant at the second level and a random-effects model were used for group analysis to obtain population inferences.[15] Thus, the functional regions involved in orienting attention were depicted as the orienting network, and the functional regions involved in executive attention were depicted as the executive network. A one-sample t test was also used to analyze the age-related brain functional areas. The correct response rate, reaction time, and attentional effects of interest were included as covariates to exclude individual differences in attentional processes and the effects of other factors, motor function, on functional activation. Significant signal changes for each contrast were assessed by voxel-wise t-statistics. We determined a height threshold of $P = .001$ without correction for multiple comparisons and an extent threshold of a cluster size of $k > 30$ voxels because the risk of type II errors must be minimized while the risk of type I errors must also be reduced.[16,17]

For the statistical analysis of behavioral response data, we used IBM SPSS 22 software package (SPSS) to perform comparisons of conditions with an analysis of variance (ANOVA).

3 | RESULTS

3.1 | Task performance

The average reaction time (RT) and accuracy for each condition are shown in Table 1. A two-way ANOVA was performed to analyze the effects of the cue condition (orienting effect) and target flanker condition (executive control effect) on RT. A two-way ANOVA revealed that there was a statistically significant interaction between the effects of the cue and target flanker conditions ($F[1, 170] = 21.31$; $P < .001$; $f = 0.14$). A simple main effects analysis showed that spatial cues significantly shortened RTs for both congruent and incongruent target flankers ($F[1, 340] = 23.33$, $P < .001$; and $F[1, 340] = 128.68$, $P < .001$, respectively) and that the congruent target flanker significantly shortened RTs for both center and spatial cues ($F[1, 340] = 89.22$, $P < .001$; and $F[1, 340] = 20.60$, $P < .001$, respectively). A two-way ANOVA was also performed to analyze the effect of the cue and target flanker conditions on accuracy. There was a statistically significant interaction between the effects of the cue and target conditions ($F[1, 170] = 5.065$, $P = .026$, $f = 0.14$). A simple main effect analysis showed that the congruent target flanker significantly increased accuracy for both central and spatial cues ($F[1, 340] = 30.92$, $P < .001$; $F[1, 340] = 5.43$, $P = .02$, respectively), while the spatial cue did not ($F[1, 340] = 2.45$, $P = .12$; $F[1, 340] = 3.14$, $P = .08$, respectively).

Moreover, RTs were negatively correlated with age ($\rho = -0.61$, $P < .001$), while accuracy was not ($\rho = 0.13$, $P = .08$). Moreover, orienting effects were negatively correlated ($\rho = -0.18$, $P < .001$), and executive control effects were positively correlated ($\rho = 0.16$, $P = .036$).

TABLE 1 Mean RT (and SD) and accuracy (and SD) for each condition

	Center cue	Spatial cue	Mean
Congruent			
RT (ms)	592.5 (172.7)	516.5 (155.4)	554.5 (164.1)
Accuracy (%)	95.5 (2.4)	95.1 (2.4)	95.3 (2.4)
Incongruent			
RT (ms)	798.7 (362.3)	611.2 (375.3)	705.0 (368.8)
Accuracy (%)	94.0 (3.3)	94.5 (2.8)	94.3 (3.1)
Mean			
RT (ms)	695.6 (267.5)	563.9 (265.4)	629.7 (266.5)
Accuracy (%)	94.8 (2.9)	94.8 (2.6)	94.8 (2.8)

Note: Orienting effect and executive control effect are calculated by the following equations, respectively. Orienting effect = RT (center cue)—RT (spatial cue) and executive control effect = RT (incongruent)—RT (congruent).

3.2 | Functional regions of attentional networks

We successfully replicated the previous findings related to the neural basis of attention networks (Figure 2). Consistent with a previous study involving adults,[5] the orienting network revealed activations in the superior parietal lobule (SPL), the visual association cortex (VAC), and the left precentral gyrus. The executive network involved the thalamus, anterior cingulate cortex (ACC), right middle frontal gyrus, and left superior and inferior frontal gyri in addition to VAC. In contrast to previous studies involving adults, the present study involving children showed additional activation in the supplementary motor area (SMA) in the orientation network and the caudate nucleus in the executive network.

3.3 | Correlation with age in attention networks

Functional activations of the orienting network associated with age are shown in Table 2. Activations in the bilateral inferior frontal gyrus (IFG)/insular (Figure 3A), dorsomedial prefrontal cortex (DMPFC)/ACC (Figure 3B), anterior prefrontal cortex, motor cortex, caudate nucleus (Figure 3C), and ventral tegmental area showed significant negative correlations with age, while no functional activations were found to correlate positively with age. There were no functional activations that correlated significantly with age in the executive network.

4 | DISCUSSION

In this study, we measured brain functions during ANT using fMRI to clarify the neural basis of attentional networks in children and adolescents. We compared the neural basis of the aforementioned

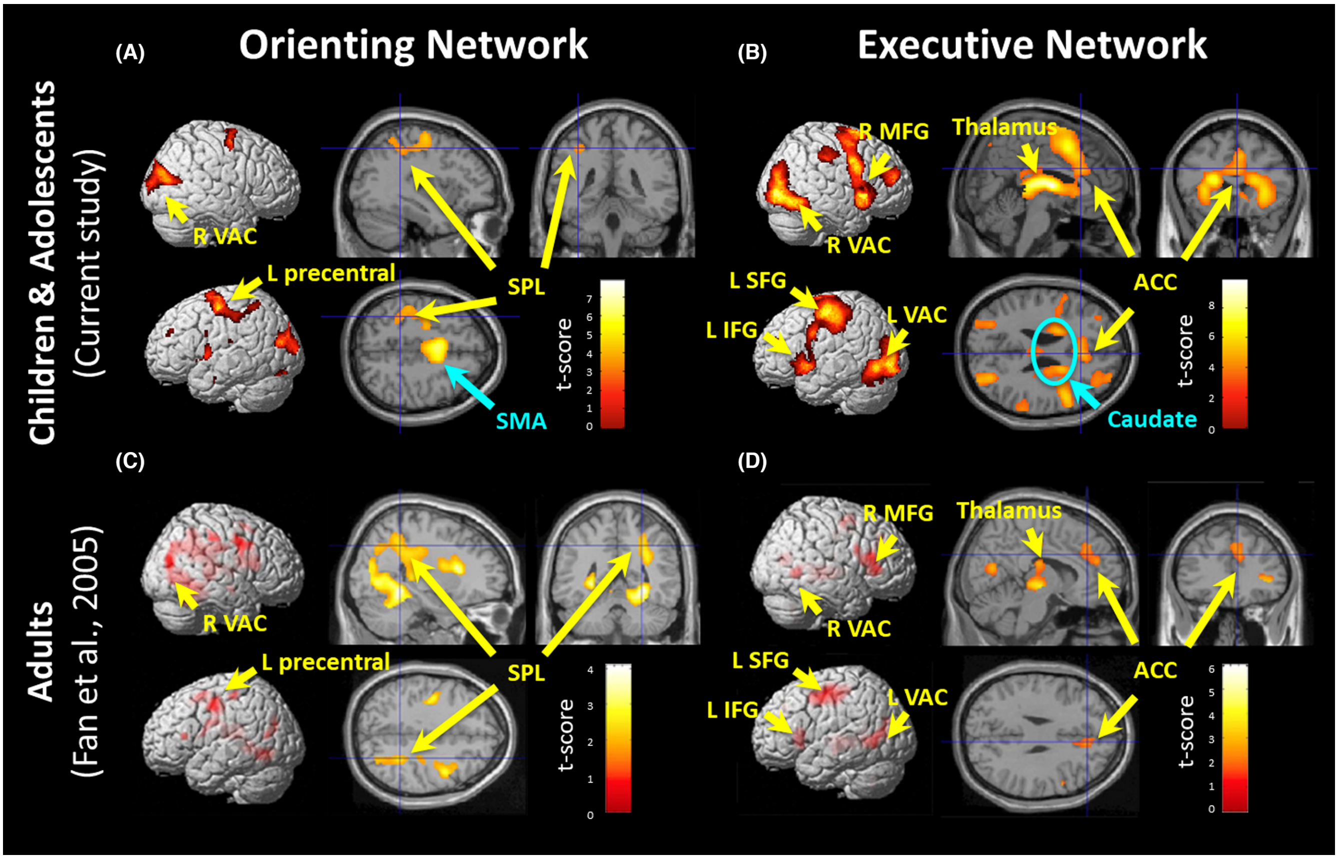

FIGURE 2 Comparison of brain activities during childhood and adulthood using the ANT task. Brain activities of orienting (A) and executive (B) attention in children and adolescents and orienting (C) and executive (D) attention in adults

TABLE 2 Functional activations correlated with age in the orienting process of attention

Brain region	BA	Side	MNI coordinates (mm)			Statistics (peak-level)	
			x	*y*	*z*	*t*-score	*P*-value
Positive							
None							
Negative							
Insula/inferior frontal gyrus	13/47	R	28	18	−16	4.02	.0001
Inferior frontal gyrus/insula	47/13	L	−32	22	−12	3.80	.0002
Dorsomedial prefrontal cortex/anterior cingulate cortex	8/24	L	−2	31	39	3.85	.0002
Anterior prefrontal cortex	10	R	30	58	−2	3.85	.0002
Caudate	–	R	9	7	3	3.78	.0002
Ventral tegmental area	–	L	−2	−20	−6	3.65	.0004
Motor cortex	6	R	45	−14	44	3.62	.0004

group with that of adults. We also examined the developmental trajectory of the attentional network throughout childhood and adolescence by correlating these brain functions with age. Results have shown that SPL, VAC, and left precentral gyrus were activated in orienting attention as in adulthood, whereas SMA was specifically activated in adolescents. For executive attention, the ACC, VAC, lateral prefrontal cortex (superior, middle, and inferior gyri), and thalamus were activated as in adulthood, while the caudate nucleus was specifically activated in adolescents. Moreover, negative correlations with age were found in activations in the IFG/insular, DMPFC/ACC, and caudate nucleus in orienting attention, while no correlations with age were found in executive attention. These results suggest that different functional areas are involved in the attention networks in children and adolescents than in adults, and

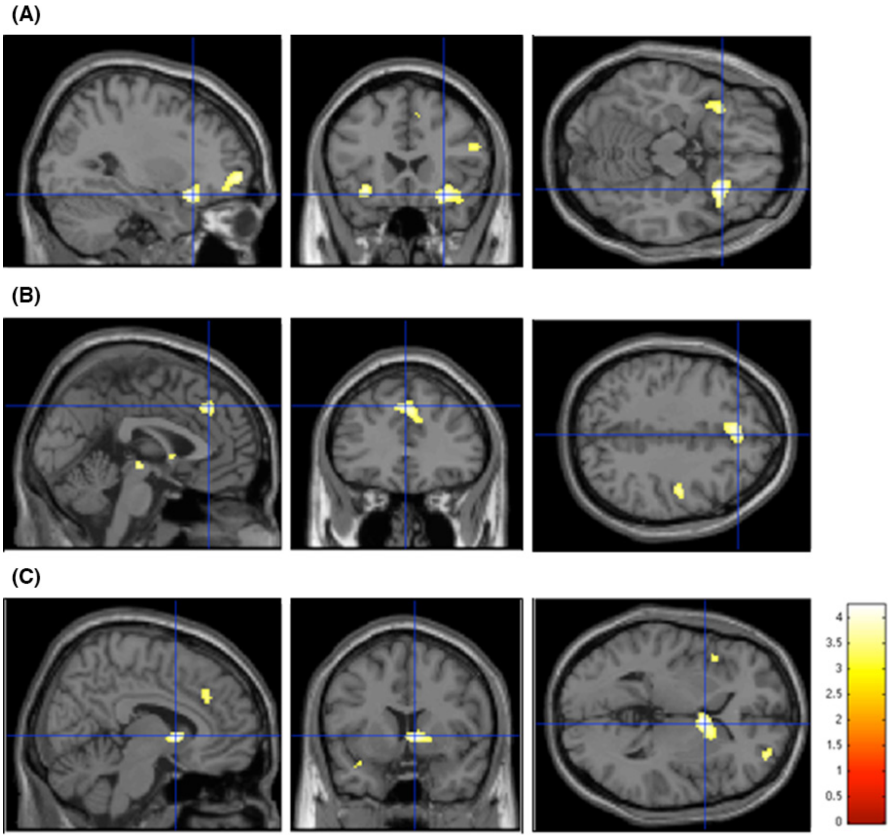

FIGURE 3 Functional activations negatively correlated with age during orienting attention. (A) Inferior frontal gyrus/insular cortex; (B) dorsomedial prefrontal cortex; and (C) caudate nucleus

that the diversity of the recruited functional areas in the orienting network disappears with age.

Compared with previous studies on adulthood, we found that the involvement of SPL, VAC, and left precentral gyrus in orienting attention and the ACC, VAC, lateral prefrontal cortex, and thalamus in executive attention were replicated during childhood and adolescence, while the involvement of SMA in orienting attention and caudate nucleus in executive attention was specific during childhood and adolescence. It has been widely recognized that the superior parietal lobule is involved in orienting to spatial locations of visual signals.[5,13] DMPFC, including ACC, is involved in conflict resolution when a person is asked to respond to a conflicting stimulus array[5,13]; this suggests that the superior parietal lobule and DMPFC play important roles in orienting and executive attention regardless of the developmental stage. Moreover, the activation of bilateral VACs was replicated during childhood and adolescence, as well as adulthood, for both orienting and executive attention,[5] suggesting the involvement of VACs independent of the developmental stage during the processing of attention to visual stimuli. For orienting attention, the specific activation of SMA during childhood and adolescence shown in the current study is consistent with the previous finding of a reduced involvement of SMA with age observed during attention allocation using an oddball task.[18] The detailed mechanisms underlying the specific activation of the caudate nucleus during childhood and adolescence during the executive attention are unclear as recent primate studies on the involvement of the caudate nucleus in the learning of attentional functions have shown.[19] However, motivation may play a greater role during childhood because of the involvement of learning in executive attention. In contrast, previous studies using ANT to directly compare brain function in childhood and adulthood have shown specific activation of the right insula and left superior frontal gyrus in orienting attention and left superior temporal gyrus in executive attention in childhood,[13] but these findings were largely not replicated in this study. Although the reason is unclear, one explanation may be that the population in this study was a large heterogeneous group that included females and adolescents without distinguishing between sex and developmental stage, while the previous study was a small group of 16 male children.

A correlational analysis with age during childhood and adolescence showed no functional areas associated with executive attention, while functional areas such as the insular cortex, medial prefrontal cortex, and caudate nucleus were involved in orienting attention. All of these functional regions are expected to be involved in executive attention in adults. Nevertheless, the finding that these regional activations in orienting attention were negatively correlated with age suggests that these two attentional networks, which were functionally undifferentiated in childhood, may have differentiated during development, thereby decreasing the involvement of executive processes for orienting attention. Although the IFG is involved in attention reallocation triggered by external stimuli,[20] DMPFC is involved in error detection and conflict resolution,[21,22] and the caudate nucleus is involved in motivation and learning,[19,23] all of which are part of the executive attentional processes.[2,5] It is possible that these functional areas are recruited in orienting attention during childhood when the attentional networks is not sufficiently differentiated and that their involvement disappears during later development.

It is interesting to determine the relationship between these suggested age-related transformations in brain function and the development of brain structure in childhood and adolescence. Although it is well known that gray matter volume gradually decreases from childhood through adolescence and into adulthood,[24,25] no clear findings have been made on whether task-induced regional brain function correlates with gray matter volume. A previous study in adults using an executive function task found a negative association between task performance and regional cortical thickness in a wide range of areas,[26] including the insular cortex, medial prefrontal cortex, and caudate nucleus, which were negatively associated with age in this study. Furthermore, in a previous study examining the interaction between age and regional cortical thickness on attentional function in children and adolescents similar to this study, a negative interaction between orienting and age resulted in significant clusters in the insula, while cortical thickness showed no significant age interaction with executive attention, consistent with this study.[27] However, since the regional areas of function and cortical thickness in the association between attentional function and age were not always consistent, an analysis of the association between both modalities in the same sample would be fruitful.

This study has several limitations that should be accounted for in the future. First, this study utilized a cross-sectional design that precluded the identification of causal links between age, the development of attention, and brain functions as their neural basis. Therefore, their interpretability is limited by possible reverse causality and the influence of other variables. Longitudinal studies are required to more fully elucidate the association between attentional functions and brain development. Second, we did not examine the alerting attention in this study. The development of the neural basis of alerting attention should also be clarified, although it was not possible to examine the alerting effect in this study due to the limitations of the experimental design because the participants were children. Third, we did not examine the effects of both global and regional brain structures (gray matter volume and cortical thickness) on the relationship between attentional networks and age. As already discussed, to clarify this point, the interaction of age with the correlation between image modalities acquired from the same sample must also be examined. We did not also assess gonadal hormones in adolescents, although they are sexually mature during this period. Since it is already widely known that gonadal hormones influence brain development, it is important to clarify how they affect the brain development of attentional functions. Fourth, although we compared the results of this study with those of previous studies on adult brain function to clarify the characteristics of brain function in children and adolescents, we only confirmed the replication of activation patterns and their differences by visual inspection. It should be noted that the results were not derived from quantitative assessment. Finally, due to the limitations of the experimental setup, the task performance under the same conditions as in the previous study was not replicated. Specifically, this study used only the right hand in contrast to previous studies that used both hands during ANT, and the sample size was also significantly different from previous studies, which may have resulted in a different activation pattern from previous studies.

In conclusion, this study reveals the relationships between brain activation and the developmental aspects of attention. We observed significant developmental differences in brain activation patterns related to key aspects of attention. Specifically, we clarified the similarities and differences of functional regions during childhood and adolescence by comparing them with those during adulthood in previous studies. Moreover, we attempted to identify the functional regions related to the development of orienting and executive process in attentional function during childhood and adolescence by a correlation analysis with age. These results suggest that some brain regions may change their function related to attentional processing during development, and that, in turn, the neural networks for attentional functions may be not innately independent of each other, but rather, the functional areas develop in an interdependent manner.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Numbers JP19K02611 (to DNS and TXF), 18K02480, and 20H04995 (to TXF).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

DNS and HO contributed to the conception and design of the study and performed the experiments. DNS and TXF contributed to statistical data analysis. TXF wrote the first draft of the manuscript. TK contributed to the conception and design of the study. HTY, TF, KM, and AT performed the experiments, collected the data, revised the manuscript critically for intellectual content, and approved the submitted version.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEW BOARD

The study protocol was approved by the Research Ethics Committee of the University of Fukui, Japan, and all procedures adhered to the Declaration of Helsinki and the Ethical Guidelines for the Clinical Studies of the Ministry of Health, Labour, and Welfare of Japan.

INFORMED CONSENT

All participants or parents of the participants provided written informed consent for participation in this study.

REGISTRY AND THE REGISTRATION NUMBER OF THE STUDY/TRIAL

n/a.

ANIMAL STUDIES

n/a.

DATA AVAILABILITY STATEMENT

The data cannot be made publicly available as data sharing was not included in the consent form.

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How to cite this article: Saito DN, Fujisawa TX, Yanaka HT, Fujii T, Kochiyama T, Makita K, et al. Development of attentional networks during childhood and adolescence: A functional MRI study. Neuropsychopharmacol Rep. 2022;42:191–198. https://doi.org/10.1002/npr2.12246