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Altered strategy in short-term memory for pictures in children with attention-deficit/hyperactivity disorder: A near-infrared spectroscopy study

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ABSTRACT

Strategy in short-term memory for serially presented pictures shifts gradually from a non-phonological to a phonological method as memory ability increases during typical childhood development. However, little is known about the development of this strategic change in children with attention-deficit/hyperactivity disorder (ADHD). To understand the neural basis of ADHD, we investigated short-term memory strategies using near-infrared spectroscopy. ADHD children aged from 6 to 12 years and age- and sex-matched control children were assessed in this study. Regional activity was monitored in the left ventrolateral prefrontal cortex to assess strategies used during short-term memory for visual or phonological objects. We examined the hypothesis that the strategic methods used would be correlated with memory ability. Higher memory ability and the phonological strategy were significantly correlated in the control group but not in the ADHD group. Intriguingly, ADHD children receiving methylphenidate treatment exhibited increased use of phonological strategy compared with those without. In conclusion, we found evidence of an altered strategy in short-term memory in ADHD children. The modulatory effect of methylphenidate indicates its therapeutic efficacy.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent developmental disorders in childhood. Meta-analytic studies suggest that deficits in working memory are key neuropsychological features in children with ADHD (Martinussen et al., 2005; Willcutt et al., 2005). Functional neuroimaging studies on working memory suggest that adults with ADHD tend to use visual strategies, while healthy control participants rely on verbal strategies (Schweitzer et al., 2000, 2004). However, little is known about the developmental strategic profiles for school-aged children with ADHD.

Working memory refers to the maintenance and manipulation of information, and comprises the central executive and two subsidiary systems (Baddeley, 1986). The central executive system is in overall control, and provides oversight and coordination of the subsidiary systems: a visuospatial sketchpad for visual images and a phonological loop for speech-based information. The phonological loop consists of a phonological store and an articulatory control process. The phonological store holds information in a phonological form, while the articulatory control process serves to rehearse the decaying information in the store. The articulatory control process is also implicated in recoding verbalizable pictures into a phonological form (Baddeley, 1986). Functional neuroimaging studies have demonstrated distinct roles of different brain regions in working memory. For example, the left ventrolateral prefrontal cortex (VLPFC) including Broca's area is associated with the articulatory control process (Paulesu et al., 1993; Awh et al., 1996; Henson et al., 2000; Baddeley, 2003; Koelsch et al., 2009), the posterior parietal cortex is implicated in the phonological store (Paulesu et al., 1993; Awh et al., 1996), while the dorsolateral prefrontal cortex (DLPFC) is involved in various processes including encoding (Rypma and D'Esposito, 1999) and active maintenance of information (Cohen et al., 1997).

The maintenance component of working memory, or short-term memory, shows developmental changes in strategy as well as efficiency from preschool years through early adolescence (Gathercole, 1999). The concept of "strategy change" has been

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well illustrated in earlier studies on short-term memory using serially presented pictures of familiar objects (Hitch and Halliday, 1983; Hitch et al., 1989; Halliday et al., 1990; Gathercole and Hitch, 1993). Typically developing children below 7 years of age are likely to rely on a visuospatial sketchpad, while children beyond this age tend to use the phonological loop by recoding pictures into a phonological form. However, this strategy change actually seems to form a continuum from visual to phonological methods and be correlated with children's memory ability rather than with age (Palmer, 2000). Although these findings emerged from behavioral studies, we recently provided the first functional evidence that phonological strategy for a picture is associated with higher ability in verbal short-term memory by monitoring the VLPFC activation with near-infrared spectroscopy (NIRS) (Sanefuji et al., 2011).

NIRS is a noninvasive neuroimaging method for monitoring cerebral changes in oxy-, deoxy-, and total-Hb concentrations by measuring changes in the attenuation of near-infrared light passing through tissue. Increases of oxy- and total-Hb with a concomitant decrease of deoxy-Hb are usually observed in activated cortical areas. NIRS exhibits some advantages over functional magnetic resonance imaging or positron emission tomography in that it is noiseless and is less restrictive to body movements, allowing even preschool children to perform tasks under natural conditions both with auditory and visual presentation (Sanefuji et al., 2011). As NIRS has a sufficient temporal resolution and a good signal-to-noise ratio, it is suitable for event-related task paradigms with relatively few experimental trials (Schroeter et al., 2002). However, limited regions of interest need to be determined before experimentation as each NIRS channel monitors only a small area in the lateral cortical surface with relatively low spatial resolution (Villringer et al., 1993).

To gain better insight into the altered status of short-term memory in ADHD children, we investigated the relationship between the strategies in short-term memory for pictures and memory ability. To estimate which strategy is used by ADHD children, we monitored the left VLPFC activation during free recall of familiar objects with visual and auditory presentation using event-related NIRS, as validated in our previous study (Sanefuji et al., 2011). The activation difference for visual material compared with auditory material in the left VLPFC represented the tendency to use a phonological strategy. We then used correlation analyses to examine the relationship between the activation difference that could represent strategy and memory ability. We predicted that ADHD children would not exhibit the typical pattern of a positive correlation between phonological strategy and higher memory ability as previously observed in healthy children ($n=19$) (Sanefuji et al., 2011), likely owing to their reduced preference for verbal strategies. We also examined the modulatory effect of methylphenidate, the most frequently prescribed medicine for ADHD, on the choice of strategy in ADHD children. Several functional neuroimaging studies have demonstrated that methylphenidate may normalize prefrontal activation patterns in children with ADHD (Shafritz et al., 2004; Epstein et al., 2007; Bush et al., 2008; Rubia et al., 2009). We hypothesized that methylphenidate would have a comparable normalizing effect as determined by NIRS.

2. Methods

2.1. Subjects

The present study was approved by the Ethics Committee of the Graduate School of Medical Sciences, Kyushu University. Written informed consent was obtained from parents before the investigation. Thirteen Japanese children with ADHD were recruited from the outpatients treated at the Department of Child Psychiatry, Kyushu University Hospital, Japan. The diagnosis of the ADHD was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and the ADHD Rating Scale-IV (ADHD-RS-IV) (DuPaul et al., 1998) as rated by parents and teachers with diagnostic assessment by pediatric psychologists and pediatric psychiatrists. Inclusion criteria for ADHD children were (1) age of 6–13 years, (2) right-handedness confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971), and (3) IQ above 85 on the Japanese version of the Wechsler Intelligence Scale for Children, third edition (WISC-III-Japanese) (Japanese WISC-III Publication Committee, 1998). Exclusion criteria were the presence of (1) comorbid disorders other than oppositional defiant and conduct disorders, (2) a history of neurological diseases such as epilepsy, cerebral palsy, and brain injury, and (3) psychotropic medication other than methylphenidate. For evaluation of memory ability, each child performed the Digit Span subtest of the WISC-III-Japanese at each NIRS experiment.

Eleven children with their optimal regular use (18 or 27 mg/day) of osmotic-release oral system methylphenidate (Concerta®, Janssen Pharma, Tokyo, Japan) were monitored by NIRS with withdrawal of medication at least 24 h for the first scan (off-medication), and with medication at 2–3 h before experiments for the second scan (on-medication). The data from three children were discarded because of severe motion artifacts in the NIRS signals at the first scan of off-medication. Two drug-naive children were monitored only once. Thus, we analyzed 10 children (eight off-medication and two drug-naive children), nine boys with combined type and one girl with predominantly inattentive type (age range: 6.9–12.3 years; mean [S.D.]: 10.1 [1.8]). Further, for assessment of the effect of methylphenidate, one of the eight off-medication children was excluded because of severe motion artifacts in the NIRS signals at the second (on-medication) scan. Therefore, we analyzed seven children, all boys with combined type, for comparison of off-medication with on-medication conditions (age range: 8.2–12.3 years; mean [S.D.]: 10.4 [1.6] at the first scan). The intervals between the first and second scans for the seven children were 3 weeks to 20 months (median: 3.1 months). There was no significant difference in Digit Span score (paired Student's t-test: $p>0.3$) between off- (mean [S.D.]: 15.7 [3.4]) and on-medication conditions (mean [S.D.]: 16.3 [3.3]).

As a control, we used the data from 19 right-handed healthy children (10 girls, age range: 5.4–11.0 years, Digit Span score: 7–15) that we previously reported (Sanefuji et al., 2011). These subjects have no history of preexisting neurological or developmental disorders. Among these controls, six girls with a Digit Span score of 11 or less were excluded to obtain a control sample matched with the ADHD children for Digit Span score and sex. We then used the data of the 13 remaining control children (nine boys, age range: 5.4–11.0 years; mean [S.D.]: 8.4 [2.0], Digit Span score: 9–15; mean [S.D.]: 11.6 [2.3]). There were no significant differences between the control and ADHD groups in Digit Span score, age (two-tailed Student's t-tests: $p>0.05$), and sex (Fisher's exact test: $p>0.05$).

2.2. Instruments

A multichannel NIRS system (OMM-2001; Shimadzu, Kyoto, Japan) was used to monitor temporal changes in oxy-, deoxy-, and total-Hb concentrations. The absorption of near-infrared light at 780, 805, and 830 nm wavelength was measured at a scanning rate of 70 ms. A visual–auditory stimulus presentation system (IS-703 AV Tachistoscope; Iwatsu, Tokyo, Japan) controlled stimulus presentation with on-line connection to the NIRS system.

2.3. Channel positions

Four channels were set on F3, F4, F7, and F8 according to the international 10–20 system for electroencephalography (Jasper, 1958). These approximate positions correspond to the left and right DLPFC and the left and right VLPFC, respectively, based on an anatomical craniocerebral correlation study (Okamoto et al., 2004). Each channel was constructed by a pair consisting of an emitter probe and a detector probe at a distance of 3 cm from each other. Bolt-combined probes were screwed one by one into four separate head-holders arranged to cover the exact channel positions. To visualize the anatomical positions of the channels on the cerebral cortex, we used the data from VLPFC and DLPFC positions superimposed on the three-dimensionally reconstructed cerebral cortex (Sanefuji et al., 2011). Two additional channels were placed on CP3 and CP4 in accordance with the 10–10 system (Oostenveld and Praamstra, 2001). These approximate positions correspond to the left and right posterior parietal cortex (Koessler et al., 2009). However, NIRS data of these two channels were excluded from analysis owing to severe motion artifacts caused by unstable fixation of the probes on the head.

2.4. Stimulus materials

Stimuli consisted of child-familiar items (e.g., car, rabbit, and grapes). These items have two or three morae (mora is a phonological unit of sound in Japanese, analogous to a syllable in English) when pronounced. In the visual condition, each item was presented as a color picture at the center of a display, and was subtended approximately 3° to visual angle. In the auditory condition, each item was presented as a female voice (Amano and Kondo, 1999) from an audio speaker.