Empirical Article

Clinical Psychological Science
2016, Vol. 4(6) 1094–1103

DOI: 10.1177/2167702616637820
cpx.sagepub.com

Delay Aversion, Temporal Processing, and N-3 Fatty Acids Intake in Children With Attention-Deficit/Hyperactivity Disorder (ADHD)

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Abstract

This study investigates the association between polyunsaturated fatty acid (PUFA) intake and neurocognitive functions in children with attention-deficit/hyperactivity disorder (ADHD). We recruited 21 drug-naïve children diagnosed with ADHD according to the *Diagnostic and Statistical Manual of Mental Disorders* and 21 non-ADHD controls. The n-3 intake and essential fatty acid (EFA) deficiency severity were recorded while the children were assessed for inhibitory control, delay aversion, and temporal processing with the Go/No Go Task, Delayed Reaction Time Task, and Finger Tapping Task, respectively. The ADHD group had more EFA deficiency symptoms ($p = .02$) and poorer performance in delay aversion ($p = .02$) and temporal processing ($p < .001$). Moreover, ADHD symptoms correlated negatively with n-3 intake and positively with EFA deficiency. In addition, EFA deficiency was associated with higher delay aversion ($p < .001$). Children with ADHD had a higher deficiency of EFA, and EFA deficiency had a positive association with ADHD severity and delay aversion.

Keywords

attention-deficit/hyperactivity disorder, ADHD, n-3, polyunsaturated fatty acids, PUFAs

Received 10/31/15; Revision accepted 2/9/16

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood disorder; its prevalence ranges from 7% to 8% (Gau, Chong, Chen, & Cheng, 2005) in Taiwan and from 5% to 10% in Western countries (Biederman & Faraone, 2005). The core symptoms of ADHD include inattention, hyperactivity, and impulsivity (Feldman & Reiff, 2014). Children with ADHD tend to have impairments in daily activities, social interactions, and academic performances, which may be mediated by their impairments in inhibitory control, delay aversion, and temporal processing (Sonuga-Barke, 2002; Sonuga-Barke, Bitsakou, & Thompson, 2010).

Inhibitory control deficits had been proposed as the core symptoms of ADHD (Nigg, 2001). Children with ADHD, due to impairments in inhibition control, tend to have a slower reaction time and a wider variation of reaction time while performing the task (Winstanley, Eagle, & Robbins, 2006). Moreover, ADHD symptoms are often associated with motivational style (Sonuga-Barke & Taylor, 1992), where children with ADHD tend to prefer choices with immediate reward, and when they are instructed to wait without choice, they become more inattentive and hyperactive during the wait, which then contributes to the development of delay aversion behavior (Sonuga-Barke, 2002; Sonuga-Barke & Taylor, 1992; Sonuga-Barke, Williams, Hall, & Saxton, 1996). In addition to the delay aversion behaviors, the social

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expectation of waiting may further contribute to the development of ADHD manifestation during situations that require waiting (Sonuga-Barke, 2002, 2003, 2005). Studies have also shown that intertemporal variation will affect the performance of children with ADHD, where children with ADHD have impairments not only with time reaction response (Sonuga-Barke et al., 2010) but also with time prediction (Toplak, Dockstader, & Tannock, 2006). The current biological treatments for ADHD include medication such as stimulants (methylphenidate, methylphenidate sustained-release; Feldman & Reiff, 2014) and nonstimulants (atomoxetine; Feldman & Reiff, 2014), which have been reported to improve inattention, hyperactivity, and impulsivity symptoms and also to improve neurocognitive performance (Coghill et al., 2014; Wietecha et al., 2013). On the other hand, other nonbiological treatments have also been practiced to improve ADHD symptoms, including diet restriction, nutritional supplements, and behavior therapy (Sonuga-Barke et al., 2013).

N-3 polyunsaturated fatty acid (PUFA) is one of the supplements being proposed to treat ADHD (Bloch & Qawasmi, 2011; Forbes & Parsons, 2012; Transler, Mitchell, & Eilander, 2013; Yehuda, 2012). N-3 PUFAs have been associated with brain function, cognitive function, and emotional control. N-3 PUFAs are categorized as essential fatty acids (EFAs), which cannot be synthesized within humans and need to be obtained from the diet (Chang, Chen, & Su, 2009; Su, 2009). N-3 PUFAs have been reported to have anti-inflammatory effects on the neurons (Lin, Huang, & Su, 2010; Lu, Tsao, Leung, & Su, 2010; Su et al., 2014) and have immunomodulation effects via neurotransmitter and receptor regulation (Chang et al., 2009). In addition, studies also reported that children with ADHD were more likely to have more parent-reported EFA deficiency symptoms or signs (polydipsia, polyuria, thirst, dry hair, skin problems, etc.; Antalis et al., 2006; Mitchell, Aman, Turbott, & Manku, 1987; Stevens et al., 1995). Moreover, clinical studies have also shown that n-3 PUFA supplements have therapeutic effects on psychiatric disorders including mood disorders (Chang et al., 2015; Lin et al., 2010; Lin et al., 2012; Su, Wang, & Pae, 2013), schizophrenia (Smesny et al., 2014), Alzheimer's disease (Chiu et al., 2008), and ADHD (Isaacs et al., 2011; Transler et al., 2013; Yehuda, 2012).

N-3 PUFAs have been reported to improve only executive functions such as Stroop and spatial working memory, where EPA-rich supplementation demonstrated that participants' brains worked "less hard" and achieved a better cognitive performance than prior to supplementation (Bauer et al., 2014). Moreover, long-chain n-3 PUFAs have been shown to improve scores on verbal fluency, trail making, Stroop color-word, auditory verbal learning, and forward and backward digit span tasks in the elderly (Witte et al., 2014), but no studies have been done in children. In addition, to our knowledge, there has been no study on the association of n-3 PUFA intake and neurocognitive tasks testing inhibitory control, delay aversion, or temporal processing.

Epidemiological studies (Hibbeln et al., 2007; Ng, Meyer, Reece, & Sinn, 2009) and clinical studies (Bloch & Qawasmi, 2011) have shown a positive correlation between n-3 PUFA intake and improvement in ADHD symptoms. However, there have been only a few studies investigating the role of n-3 in neurocognitive function in children (Karr, Alexander, & Winningham, 2011), mainly reporting the effect of docosahexaenoic acid (DHA) on literacy and reading in typically developing (TD) youth (Richardson, Burton, Sewell, Spreckelsen, & Montgomery, 2012) and an ADHD group (Milte et al., 2012).

This study aimed to investigate the association between n-3 PUFAs and neurocognitive function in children with ADHD. Our hypotheses are that (a) children with ADHD will have lower n-3 PUFA intake, more EFA deficiency symptoms, and poorer neurocognitive task performances and (b) n-3 PUFA intake will be positively correlated with neurocognitive task performance.

Method

Subjects

A total of 21 drug-naïve ADHD children diagnosed according to the criteria in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 2000) were recruited from a local rehabilitation clinic and from the Department of Psychiatry of China Medical University Hospital in Taiwan. The inclusion criteria were (a) ADHD diagnosis (current) made by a board-certified child and adolescent psychiatrist, (b) age between 6 and 12 years, and (c) informed consent from the subject and legal guardians. Exclusion criteria included (a) intelligence quotient less than 70, (b) comorbid other *DSM-IV* diagnoses, such as autism spectrum disorder, generalized anxiety disorder, conduct disorder, psychotic disorders, or mood disorders, (c) medical comorbidities including thyroid dysfunction or cerebral palsy, and (d) currently using any PUFA supplement. The informed consent was approved by the China Medical University Hospital Research Ethics Committee.

We also recruited 21 non-ADHD controls (TD group) from the same residential area of the ADHD group. Inclusion criteria included (a) no current or past psychiatric diagnosis, including ADHD, intellectual disability, autism spectrum disorder, generalized anxiety disorder, conduct disorder, psychotic disorder, and mood disorders, or other medical comorbidities, including thyroid dysfunction and cerebral palsy, (b) Peabody Picture Vocabulary Test–Revised

(PPVT-R) percentile scores greater than 5% (scores less than 5% may indicate speech delay or intellectual disability), and (c) informed consent of the children and their legal guardians.

Measures

Chinese version of the Swanson, Nolan, and Pelham, Version IV Scale–Parent Form (SNAP-IV) questionnaires. The Chinese version of the SNAP-IV (Gau et al., 2008) was used to assess the ADHD symptom severity. The Chinese SNAP-IV has been validated elsewhere (Gau et al., 2008). SNAP-IV consists of 18 *DSM-IV* symptoms of ADHD, including inattention (Items 1–9), hyperactivity (Items 10–15), impulsivity (Items 16–18), and symptoms of the criteria for oppositional defiant disorder (Items 19–26). The symptom severity of each symptom item was rated on a 4-point rating scale (0 = *not at all*, 1 = *just a little*, 2 = *quite a bit*, and 3 = *very much*). A higher total score on Items 1–18 indicated a higher severity of ADHD symptoms.

Food Frequency Questionnaire (FFQ) for children. The FFQ is the most common dietary assessment tool used in large epidemiologic studies of diet and health (Burrows, Berthon, Garg, & Collins, 2012). The FFQ includes 13 categories of nutritional food (e.g., vegetables, fruits, dairy, meat, seafood, internal organs, eggs, soybean products) and 9 categories of low-quality food (e.g., fried food, noodle cups, cakes and pastries, chips, cookies, ice cream, sweetened drinks). Similar foods were listed close to each other to prevent redundant recollection. Consumption was measured over a defined period of time (i.e., the past 3 months). The Chinese FFQ has been validated elsewhere (Chen, Hsu, Hsu, Hwang, & Yang, 2004). The questionnaire uses an 8-point scale from 0 (*no intake of this food during the week*) to 7 (*eating this type of food on an everyday basis for 1 week*); parents were asked to recall the frequency of different types of food intake of their child. FFQ scores have been positively correlated with current nutritional status (Burrows et al., 2012). The n-3 PUFA intake index was calculated by adding up the scores of FFQ Items 11 to 13 regarding consumption of fish, deep-sea fish, shrimp, oyster, crabs, and any type of seafood to account for n-3 PUFA intake. The high-quality (HQ) score was the sum of intake of the 13 nutritional food types of the FFQ. The low-quality (LQ) score was the sum of intake of 9 low nutritional value food types.

Fatty acid deficiency symptoms (FADS) questionnaire. Parents were required to complete a health questionnaire about their child, which included questions about the existence and severity of each of the FADS items: excessive thirst, frequent urination, dry hair, dry skin, dandruff, brittle nails, and small bumps on the skin (Richardson et al., 2000). Parents were required to rate the degree of each of the seven possible FAD symptoms on a scale of 0 to 3 (0 = *not at all*, 1 = *just a little*, 2 = *somewhat*, 3 = *very much*). A significant negative association between FADS score and n-3 PUFAs status has been shown in a previous study (Stevens et al., 1995).

Cognitive function assessments

PPVT-R. Receptive vocabulary knowledge was measured with the PPVT-R (Dunn & Hottel, 1961; Wu et al., 2011). For this task, children were shown sets of four pictures and asked to point to the picture representing the word spoken by the examiner. The PPVT-R manual provides normative data that were collected from a sample of 886 TD children with normal hearing from 3 to 12 years of age. The standard scores for this test were derived from the raw scores using a scale provided by the test developers. The standard scores were based on a mean of 100 and a standard deviation (*SD*) of 15. Some examples of this test material were provided in the appendix to another article (Wu et al., 2011).

Go/No Go Task (GNG). GNG is a computer-based task specifically developed for this study. It was based on previously developed GNG tasks (e.g., Sonuga-Barke et al., 2010). In this task, a motor response has to be selectively executed or inhibited depending on whether a go (yellow arrow) or no-go (purple arrow) stimulus appears on the computer screen in 75% or 25% of the trials, respectively. The interstimulus interval for all stimuli was 2,000 ms, including prestimulus duration of 250 ms and stimulus duration of 750 ms, followed by response duration (blank screen) of 1,000 ms. The task was administered in one block of 100 experimental trials. However, participants were provided with 10 practice trials before the experimental trials. Children were instructed to respond as fast and as accurately as they could to the go stimuli by pressing the "0" (left) or "." (right) of the number keypad indicating the direction of the yellow left- or right-pointing arrow, respectively, but not to respond to no-go stimuli. The probability of a correctly inhibited response to the no-go stimulus was regarded as the main index of the GNG task.

Delayed Reaction Time task (DRT). DRT is a modified version of the DRT task used in previous studies (Sonuga-Barke & Taylor, 1992) and was developed to measure the impact of event rate on delay aversion as indicated by an increased reaction time (RT) to a delayed stimulus. During the task, a stimulus (an airplane facing either left or right) appears in the center of the computer

screen for either a 3-s or 20-s period of delay. The subject was required to respond as quickly and accurately as possible to the disappearance of the stimulus, by pressing either the "0" or "." on the keypad in response to the direction the airplane is heading, respectively. Each trial was started with a fixation tone of 500 ms. The participants had 2 practice trials (1 trial for each delay condition) and then 12 experimental trials (6 trials for each delay condition). The presentation of the heading direction of the airplane was counterbalanced. The interval between each trial was 1,000 ms. A control task containing 20 trials was also used; it has the same structure and visual components as the DRT and essentially had no delay (the stimulus were presented for 100 ms) prior to the response being required. This is a useful control against which to judge sensitivity to delay.

The Delayed Reaction Time Index (DRTi) represents the RT difference between the delay task (either 20 s or 3 s) and the nondelay task (0 s); a larger index indicates a stronger delay aversion. This index can be separately calculated for the 3-s delay task ($RT_{3s\ mean} - RT_{0s\ mean}$) and the 20-s delay task ($RT_{20s\ mean} - RT_{0s\ mean}$). The DRT Delayed Sensitivity Index (DRT DSI; ms) = ($RT_{20s\ mean} - RT_{0s\ mean}$) – ($RT_{3s\ mean} - RT_{0s\ mean}$). A larger DRT DSI indicates increased deficits in delay aversion.

Finger Tapping Task (FTT). FTT was the task used to investigate temporal process in ADHD (Sonuga-Barke et al., 2010). Each trial started with a tone of 100 ms, and the tone appeared every 1,200 ms. The subject was asked to press "0" on the left side of the keypad with the right index finger in response to the tone. The tone occurred rhythmically 15 times (hint task). When the tone disappeared, the subject was asked to continue to press "0" intermittently, keeping the same rhythm, 41 times (nonhint task). The temporal processing ability (synchronization time) was being calculated as the mean nonhint task reaction time divided by the mean hint task reaction time, multiplied by 100 (Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003). Moreover, the variability of the FTT index was calculated as the hint task reaction time standard deviation divided by the nonhint task reaction time standard deviation, multiplied by 100 (Toplak & Tannock, 2005). The higher the index, the greater the variability in synchronizing ability.

Statistical analyses

All statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS) Version 18.0 for Windows. Demographic and clinical characteristics of the ADHD and TD groups were compared using *t* tests or chi-square tests where appropriate. Pearson correlation was used to evaluate the association among ADHD scores, EFA deficiency scores, and neurocognitive performance measures. A *p* value less than .05 indicates statistical significance.

Results

Demographic data

The mean age of the ADHD group was 8.02 (*SD* = 1.41) years old, and the mean age of the control group was 8.43 (*SD* = 1.57) years old. There were no differences in terms of age ($p = .39$), sex ($p = .34$), socioeconomic status ($p = .66$), n-3 intake ($p = .16$), LQ food intake ($p = .38$), or HQ food intake ($p = .38$; Table 1). The ADHD group had higher SNAP-IV total scores, inattention subscale scores, and hyperactivity subscale scores ($p < .001$) than the control group. The ADHD group also had more EFA deficiency symptoms than the TD group ($p < .02$; Table 1).

Inattention, hyperactivity, diet, and EFA deficiency

ADHD symptom total scores had a positive correlation with EFA deficiency score (FADS score, parental reports of physical manifestation of fatty acid deficiency of their child) severity ($p = .02$), but no significant correlation was found with the type of food intake reported in the diet in the ADHD group. In addition, ADHD inattention subscale scores have a positive correlation with EFA deficiency score severity ($p < .01$). Meanwhile, no correlation was found between the proportion of n-3 intake and EFA deficiency symptom severity in both the ADHD and TD groups (data not shown).

Neurocognitive function

The ADHD group had a lower PPVT-R mean ($p = .01$), higher DRT DSI ($p = .02$), longer RT on nonhint FTT ($p < .001$), and more difficulty in maintaining the same speed on FTT ($p < .001$; Table 2). On the other hand, no differences were found on the GNG task between the ADHD and TD groups.

EFA deficiency, diet, and cognitive function

EFA deficiency and cognitive function. DRT DSI was positively associated with EFA deficiency in the TD group ($p < .001$; see the table in the Supplemental Material available online) but not in the ADHD group. No significant correlation was found between GNG and FTT task performance and EFA deficiency in both the ADHD and TD groups.

Table 1. Demographic Data

	ADHD (n = 21)		TD (n = 21)			
Demographic	*M*	*SD*	*M*	*SD*	*t*	*p*
Age (years)	8.02	1.41	8.43	1.57	−0.90	.39
SNAP-IV	45.00	14.24	13.90	7.27	8.90	<.001**
SNAP-IA	17.24	4.98	5.00	2.81	9.80	<.001**
SNAP-IH	16.24	6.24	4.00	3.27	8.00	<.001**
SES index	37.38	10.94	38.86	10.34	0.80	.66
N-3PUFA	7.86	4.54	10.73	2.60	−1.43	.16
HQ	67.68	9.08	70.91	13.78	−0.89	.38
LQ	32.35	9.08	29.09	13.78	0.89	.38
EFA Def	7.24	4.56	4.43	2.98	2.37	.02*

Note: ADHD = attention-deficit/hyperactivity disorder; EFA Def = essential fatty acid deficiency; HQ = high-quality food; LQ = low-quality food; N-3PUFA = omega-3 polyunsaturated fatty acids; SES = socioeconomic status; SNAP-IA = inattention score of SNAP-IV; SNAP-IH = hyperactivity score of SNAP-IV; SNAP-IV = Swanson, Nolan, and Pelham Scale for ADHD Severity total score; *t* = independent sample *t* test; TD = typically developing youths.
*p < .05. **p < .001.

Diet and cognitive function. FTT hint RT correlated positively with HQ food intake and negatively with LQ food intake in the TD group (p < .05), but not in the ADHD group (Table 3). Moreover, FTT hint variability correlated negatively with HQ food intake and positively with LQ food intake (p < .05; Table 3). In addition, FTT hint variability also correlated negatively with n-3 food intake in the groups as a whole (p < .05; Table 3). Yet, after we

Table 2. Neurocognitive Tasks

		ADHD (n = 21)		TD (n = 21)			
Task		*M*	*SD*	*M*	*SD*	*t*	*p*
PPVT-R							
Verbal (%)		71.86	24.75	88.48	13.61	−2.70	.01*
Go/No Go Task							
RT (ms)		530.11	65.24	519.11	60.60	0.56	.58
Reaction accuracy (%)		87.45	9.70	89.87	10.74	−0.76	.45
Inhibition accuracy (%)		86.99	6.93	86.25	11.07	0.26	.80
DRT Task							
Non-DRT (ms)		361.00	79.99	350.84	60.06	0.466	.64
3-s DRT (ms)		926.65	512.29	706.30	358.70	1.615	.12
20-s DRT (ms)		748.77	352.14	731.87	305.74	0.166	.87
DRTi (ms)		477.79	388.25	368.25	300.92	1.022	.31
DRT DSI (ms)		−177.88	280.40	25.57	264.46	−2.419	.02*
Finger Tapping Task							
Hint	RT (ms)	1172.33	15.29	1155.81	39.32	1.794	.08
	Var (ms)	117.05	51.29	116.48	69.21	0.030	.98
No hint	RT (ms)	1000.29	128.36	1135.20	162.65	−2.984	<.01*
	Var (ms)	141.20	62.85	172.79	175.01	−0.779	.44
Speed (%)		85.34	10.96	98.29	14.11	−3.323	<.001**
Var index		14.29	6.49	14.74	14.37	−0.132	.90

Note: ADHD = attention-deficit/hyperactivity disorder; DRT = Delayed Reaction Time; DRTi = Delayed Reaction Time Index; DSI = Delayed Sensitivity Index; PPVT-R = Peabody Picture Vocabulary Test–Revised; RT = reaction time; TD = typically developing youths; *t* = independent sample *t* test; Var = variability; verbal = verbal intelligence.
*p < .05. **p < .001.

Table 3. Diet and Neurocognitive Function

Variable		ADHD (n = 21)			TD (n = 20)			Total (N = 41)		
		N-3	HQ	LQ	N-3	HQ	LQ	N-3	HQ	LQ
PPVT-R										
Verbal		.22	.38	−.38	.09	.09	−.09	.21	.26	−.26
Go/No Go Task										
RT		.08	.23	−.23	.07	−.06	.06	.05	.05	−.05
RT accuracy		.19	−.09	−.09	−.10	.19	−.19	.05	−.09	−.09
Inhibition accuracy		.02	−.14	.14	.27	.30	−.30	.19	.15	−.15
DRT Task										
Non-DRT		−.13	.14	−.05	−.13	−.22	.22	−.14	−.09	.09
3-s DRT		−.17	−.09	.09	−.00	−.24	.24	−.13	−.09	.09
20-s DRT		−.02	.06	−.06	.32	.05	−.05	.08	.05	−.05
DRTi		−.19	.10	−.10	.18	−.08	.08	−.02	−.01	.02
DRT DSI		.04	−.16	.16	.37	.38	−.38	.29	.19	−.19
Finger Tapping Task										
Hint	RT	.11	−.22	.22	.40	.47*	−.47*	.26	.27	−.27
	Var	−.34	.33	−.33	−.32	−.44*	.44*	−.32*	−.18	.18
No hint	RT	.03	.26	−.26	.20	.19	−.19	.21	.25	−.25
	Var	.08	.03	−.03	.24	.04	−.04	.22	.05	−.05

Note: ADHD = attention-deficit/hyperactivity disorder; DRT = Delayed Reaction Time; DRTi = Delayed Reaction Time Index; DSI = Delayed Sensitivity Index; HQ = high-quality food; LQ = low-quality food; N-3 = omega-3 polyunsaturated fatty acids; PPVT-R = Peabody Picture Vocabulary Test–Revised; RT = reaction time; TD = typically developing youths; Var = variability; verbal; verbal intelligence.
*$p < .05$.

performed Bonferroni correction, these significances disappeared. On the other hand, no correlation was found between DRT, GNG, and FTT task performances and the quality and type of food intake in the ADHD group.

Discussion

The main findings of our study are that (a) the ADHD group had greater EFA deficiency severity than the TD group but no differences in n-3 intake and (b) ADHD symptoms and DRT DSI correlated positively with EFA deficiency. First of all, the ADHD group had greater EFA deficiency severity (parental reports of frequency of occurrence of EFA deficiency associated physical symptoms) than the TD group, despite there being no differences in the food intake proportion of LQ, HQ, or n-3 in their diets. This is compatible with a previous study reporting no differences between n-3 intake in ADHD and TD groups, whereas the ADHD group had lower blood levels of n-3 PUFAs (Chen et al., 2004). Moreover, a positive correlation was found between ADHD symptoms and EFA deficiency (FADS score), but no correlation was found between ADHD symptoms and n-3 diet intake. Our finding is in concordance with the report of Stevens et al. (1995), where ADHD symptoms were positively correlated with FADS score.

The supply of long-chain n-3 fatty acids EPA and DHA in the general population is often inadequate. In the eating habits prevalent in most countries, food tends to be rich in n-6 fatty acids such as linoleic acid (LA) and arachidonic acid (AA), and low in long-chain n-3 fatty acids such as EPA and DHA. Moreover, a possible explanation for a lack of differences of n-3 intake between two groups but more EFA deficiency symptoms in the ADHD group may be due to the differences in n-3 PUFA metabolism between the two groups. For example, children with ADHD may have either a higher metabolic rate of n-3 or a less efficient n-3 metabolic pathway than TD children, resulting in lower n-3 status and more EFA deficiency symptom presentations, despite the similar intake of n-3 in both groups.

The three factors affecting n-3 PUFAs metabolism include (a) conversion rate from α-Linolenic acid (ALA) to DHA and EPA, (b) genetic influences on converting enzymes, and (c) a gender effect (Schuchardt, Huss, Stauss-Grabo, & Hahn, 2010). First, n-3 PUFAs have the greatest affinity for the corresponding enzyme system, the synthesis of EPA and DHA from ALA is slow and low yielding (Pawlosky, Hibbeln, Novotny, & Salem, 2001), and it is estimated that to obtain 1 g EPA it is necessary to intake 20 g pure ALA (Brenna, 2002). Second, various studies have reported genetically induced differences

in the conversion of precursor substances (Koletzko, Demmelmair, Schaeffer, Illig, & Heinrich, 2008). For example, carriers of single nucleotide polymorphisms (SNPs) of the *FADS1* and *FADS2* (fatty acid desaturase) genes, which code for enzymes (delta-5 desaturase and delta-6 desaturase) that play a major role in the conversion of LA and ALA into PUFAs, have been suggested to have elevated AA, rather than n-3, contents in their serum phospholipids, whereas a significant association has been found between an *FADS2* SNP and ADHD (Brookes, Chen, Xu, Taylor, & Asherson, 2006). Last, the conversion efficiency of n-3 PUFAs also appears to be gender-specific dependent on sex. In vivo metabolization studies have shown that conversion of ALA into EPA and DHA is more efficient in young women than young men (Burdge & Wootton, 2002), which is consistent with the higher prevalence of ADHD among boys as opposed to girls. Animal studies have also shown that male animals are at risk for PUFA deficiencies or imbalances, as testosterone inhibits the synthesis of PUFAs whereas estrogens protect them from breaking down (Marra & de Alaniz, 1989). In summary, a patient with ADHD may require a larger amount of precursors, like ALA, to obtain the optimal level of n-3 PUFAs when compared with TD children. Moreover, those who carry an *FADS2* SNP tend to have a less efficient n-3 metabolism. Last, being male, who account for two-thirds or more of the childhood and teenage ADHD population, may increase the risk of PUFA deficiency.

Our findings may implicate that ADHD individuals require more n-3 supplementation than TD children due to differences in EFA metabolism. The previous study examined 10 ADHD clinical trials with 699 children with ADHD (predominantly males, 60%–87%) and showed that a high dose of EPA (1–2 g) supplementation was required for significant improvement in ADHD clinical symptoms (Bloch & Qawasmi, 2011). Thus, normal daily recommendations of n-3 PUFA supplementation might not be sufficient to help improve EFA deficiency symptoms and inattention, hyperactivity, and impulsivity symptoms in children with ADHD.

The ADHD group had more problems with inhibition control and temporal processing and exhibited more delay aversion behaviors in our study; this is similar to previous study results of neurocognitive function in ADHD (Toplak & Tannock, 2005; Winstanley et al., 2006) and further supports Sonuga-Barke's theory (Sonuga-Barke, 2003). More interesting, our data reveal that some of these deficits, such as delay aversion and temporal processing, are associated with EFA deficiency. The motivational style problem and temporal processing deficit thus may particularly be associated with nutrition factors, such as EPA and DHA, essential for brain development.

EFA deficiency severity in the TD group had a positive correlation with DRT DSI, and a higher DRT DSI implicated increased deficits in delay aversion. Previous animal studies have shown a significant association between hyperactivity in rats and a low level of n-3 PUFAs in the frontal cortex (Vancassel et al., 2007). Moreover, fish oil supplementation of 3,600 mg DHA + 840 mg EPA per week, when compared with placebo, in schoolchildren aged 9 to 12 years showed a significant decrease in impulsivity ($p = .008$), especially in girls (Itomura et al., 2005). Thus, EFA may play an important role in hyperactivity or impulsivity, and EFA deficiency may further contribute to ADHD symptom manifestation.

The correlation analysis showed that food intake had a correlation with measures of FTT but not with GNG or DRT task in our study. N-3 intake had a negative correlation with hint variability in FTT, which indicates that n-3 may be essential for temporal processing in healthy children. N-3, such as EPA, has been suggested to help reduce Stroop Task RT in young adults (Bauer et al., 2014). Moreover, we found LQ food intake to have a negative correlation with hint RT and a positive correlation with hint variability in TD group, whereas HQ food intake had a positive correlation with hint RT and a negative correlation with hint variability in TD group. Shorter hint RT and higher hint variability may both imply higher impulsivity, which may manifest as temper outburst and impulsive behaviors in ADHD. This is compatible with previous reports where LQ food intake has been associated with children's emotional problems (Kim & Chang, 2011) and ADHD severity (Kohlboeck et al., 2012), whereas HQ food intake has been negatively associated with ADHD severity (Kohlboeck et al., 2012).

It is interesting to note that we found a correlation between FTT task and diet intake not in the ADHD group but in the TD group; this may indicate that temporal processing is sensitive to LQ and HQ intake in general. On the other hand, we found EFA deficiency to be sensitive to delay aversion and impulsivity in the TD group but not in the ADHD group, which may indicate that EFA is essential for impulse control in general. Hence, TD children are encouraged to take a balanced diet of HQ and n3 PUFAs to maintain optimal performance on daily activities. A surplus of HQ and n3 PUFAs in diet intake may be recommended and essential for children with ADHD to help improve their temporal processing deficits and impulsivity.

Limitations

This is a cross-sectional study. One of the limitations is small sample size; hence, it is likely to be underpowered for detecting some hypothesized effects. However, our study was able to show that the ADHD group had more EFA deficiency and that different quality of food intake is associated with neurocognitive function performance.

Another limitation to our study is that when we performed Bonferroni correction for multiple comparisons in this study, the significance might have been lost after correction. Thus, to avoid missing potential important markers, we kept the results presentation. Another limitation is that we did not use an objective lab measure of n-3 PUFAs to make the study findings more robust. Future longitudinal studies are needed to support the impact of n-3 on neurocognitive function in children with ADHD.

Conclusion

Children with ADHD had a higher deficiency of EFAs in this study, and EFA deficiency has been shown to have a positive association with ADHD severity and delay aversion. Hence, EFA deficiency may play a role in the clinical manifestation and neurocognitive performance of children with ADHD. Longitudinal studies of n-3 supplementation in children with ADHD focusing on the impact on clinical symptoms and neurocognitive performances will be needed to further support our findings.

Author Contributions

K. P. Su designed the study and wrote the protocol. J. P. Chang managed the literature searches and paper writing. J. P. Chang, Y.-T. Huang, Y.-J. Lu helped with subject enrollment and conducted the study. Y.-T. Huang and L. Jingling undertook the statistical analyses of the study. J. P. Chang and L. Jingling contributed to the design of the study (the behavioral tasks) and interpretation of the results. All authors contributed to and have approved the final manuscript.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Funding

The work was supported by the following grants: MOST104-2314-B-039-022-MY2, 103-2320-B-039-036, 103-2320-B-039-MY3, MOST103-2320-B-038-012-MY3, NSC 103-2923-B-039-002-MY3, NSC-101-2627-B-039-004, and 102-2911-I-039-501 from the Ministry of Science and Technology; and DMR100-IRB0-160, CMU103-S-03, DMR-103-078, 102-068, and CMUH104-S-16-03 from the China Medical University in Taiwan.

Supplemental Material

Additional supporting information may be found at http://cpx.sagepub.com/content/by/supplemental-data.

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