BRAIN DEVELOPMENT AND THE ATTENTION SPECTRUM

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BRAIN DEVELOPMENT AND THE ATTENTION SPECTRUM

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Early-onset and enduring developmental deficits in attention, especially if combined with increased hyperactivity, and impulsivity, may result in constant impairments in multiple domains of personal life. The full spectrum of symptoms is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity, which is maladaptive and inconsistent with a comparable level of developmental age known as Attention Deficit Hyperactivity Disorder (ADHD). ADHD is considered one of the most common neurobehavioral disorders and of childhood, and among the most prevalent chronic health conditions.

Given the wide heterogeneity and complex manifestations of the disorder, there is an importance in a developmental perspective that views ADHD as a multi-factorial disorder with multiple, causal processes, and pathways. The symptoms of ADHD should be cast, not as static or fixed neurobehavioral deficits, but rather in terms of underlying developmental processes.

Even experienced professional might minimize the prevalence of a disorder among certain groups of patients. Therefore, the existence of attention disorders might become "transparent" for both the patient and the professional. This might lead to a non-accurate diagnosis, harm the treatment aspects and has potential non beneficial prognostic aspects.

The developmental approach can provide predictions as to how characteristics associated with attention develop over time and how multiple risk and protective factors transact to impact it's development, as well as the development of a broad range of associated co-morbid features.

Among children with mental retardation, autistic spectrum disorders, children who were born premature, born with low birth weight, as well as among those who suffer from chronic disorders (such as epilepsy, diabetes, chronic kidney disease or asthma), as well as among otherwise healthy preschoolers – the assessment of attention performance might be very challenging.

In this research topic, we explore the latest cutting edge research on the biological and neural pathways as well as on psychosocial and behavioral correlates of brain development and attention spectrum. In doing so we aim to highlight: what is currently known regarding this new conceptualization of attention as a spectrum; the mechanisms underlying this spectrum; and where this field is headed in terms of developing our understanding of the link between brain development and attention performance.

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Brain development and the attention spectrum

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Keywords: spectrum, attention, ADHD, brain, child development

Decreased attention span, hyperactivity, distractibility, and impulsivity are sensitive but non-specific brain functions and behavioral patterns. These expressions of altered functioning should be acknowledged as non-specific, rather than trying to fit them into existing diagnoses.

These abnormalities should be viewed in terms of underlying developmental processes and not as components of discrete non-overlapping disorders. The tendency to squeeze a group of symptoms into a diagnostic entity has the potential to lead to a non-accurate diagnosis, a less than successful treatment plan, and has the potential to be of little prognostic value (Berger and Nevo, 2011).

The developmental approach can provide predictions as to how characteristics associated with attention change over time, and how multiple risk and protective factors influence these temporal changes. It also has the potential to more readily anticipate associated co-morbid features and disorders (Berger and Nevo, 2011; Visser et al., 2014).

Attention Deficit Hyperactivity Disorder (ADHD) seems to be considerably more common than other diagnoses among "double-diagnoses" given to children with developmental dysfunctions. Yet the exact prevalence, neurobiological mechanisms, genetic and epigenetic modifications, diagnostic difficulties and treatment methods have not been clearly identified or quantified.

During the last years, the number of publications in this field has grown substantially, but, in part, due to the wide range of interested professionals, these studies have been published in a wide range of journals, sometimes missing some of their "target" populations.

In this research topic, we have focused on the latest research on the biological and neural pathways, as well as on psychosocial and behavioral correlates of brain development and attention spectrum. Thirty-Eight contributors representing the broad spectrum of professions involved in clinical and research aspects of attention in 11 articles, including original research, review, mini-review, and opinion articles, provided a broad scope of state-of-the art research in order to enhance our knowledge regarding this new conceptualization of attention as a complicated spectrum.

This research topic challenges the reader to view attention in new conceptual ways, including: focusing on brain maturation delay among otherwise healthy children diagnosed with ADHD compared to their age group (Berger et al., 2013); the effects of age and task load on attention success (Remington et al., 2014); the attentional function among children with fetal alcohol spectrum disorder (Lane et al., 2014); the differential diagnosis of sensory modulation disorder and ADHD (Yochman et al., 2013); the effects of environmental distractors on attentional performance (Cassuto et al., 2013); and the much debated effect of alpha-linolenic acid supplementation on ADHD symptoms (Dubnov-Raz et al., 2014).

This research topic also addresses innovative aspects of attention which are discussed in relation to extreme prematurity (O'Shea et al., 2013), the co-occurrence of ADHD and autism (Leitner, 2014), the limited visual orientation ability of children with autism (Landry and Parker, 2013), the possible effects of sex hormones on attentional abilities (Haimov-Kochman and Berger, 2014), and the possibility of elevating hope among ADHD children through virtual reality (Shiri et al., 2014).

We hope that this topic will provide the reader with exciting and thought provoking aspects about the mechanisms underlying attention, and pointing where this field is headed in terms of developing our understanding of the link between brain development and attention performance.

As such, this research topic seeks to serve as a useful tool for a wide range of professionals with special interest in the unusual aspects of attention in order to increase their knowledge, sensitivity and treatment methods among our patients.

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Maturational delay in ADHD: evidence from CPT

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While data from behavioral, neuropsychological, and brain studies suggested that Attention-Deficit/Hyperactivity Disorder (ADHD) is related to a developmental lag that reduces with age, other studies have proposed that ADHD represents a deviant brain function. The present study used a cross-sectional approach to examine whether ADHD children show a developmental delay in cognitive performance measured by continuous performance test (CPT). We thus, compared six age groups of ADHD children ($N = 559$) and their unaffected peers ($N = 365$), aged 6–11, in four parameters of MOXO-CPT performance: Attention, Timing, Hyperactivity and Impulsivity. Results have shown that despite improvement in CPT performance with age, ADHD children continued to demonstrate impaired performance as compared to controls. In most parameters, CPT performance of ADHD children matched that of 1–3 years younger normal controls, with a delay most prominent in older children. However, in the Hyperactivity parameter, ADHD children's performance resembled that of much younger healthy children, with almost no evidence for a developmental catch up. This study suggests that while some cognitive functions develop slower but normally, other functions (e.g., inhibitory control) show a different trajectory.

Keywords: ADHD, CPT, symptoms, maturation, delay, diagnosis

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorders of childhood, characterized by inattention, impulsivity and hyperactivity. Using the DSM-IV criteria [American Psychiatric Association (APA), 2000], prevalence rates in the United States range from 7.4 to 9.9% (Barkley, 2006). There is growing evidence that ADHD has important developmental aspects and its symptoms change considerably over time (Greenberg and Waldman, 1993; Hart et al., 1995; Faraone et al., 2006). Leading researchers (Barkley, 1990, 1997; Gillberg, 2010; Sonuga-Barke and Halperin, 2010) have long argued that ADHD is a "developmental disorder" with early onset and that deficits in inhibition appear in early childhood leading to a cascade of other problems in self-regulation, encompassed under the rubric of executive functioning.

Many children with ADHD have been described as having co-morbid developmental problems in motor coordination, language, behavior, sleep, and mood (Hartsough and Lambert, 1985; Gillberg and Kadesjo, 2003; Kalff et al., 2003; Gillberg, 2010)

Although ADHD symptoms often persist over time (Greydanus et al., 2007), maturation has a significant positive effect on ADHD symptoms in many children (Faraone et al., 2000). These observations have given rise to the hypothesis that ADHD is related to a delay rather than a deviance of normal brain development (Kinsbourne, 1973; Steffensson et al., 1999; El-Sayed, 2002).

According to the "maturational lag" model, ADHD children have neurodevelopment profiles representative of healthy children at younger ages (Kinsbourne, 1973). As a child with ADHD gets older and "catches up" the developmental lag, the symptoms of ADHD might lessen. This model was initially based on the behavioral observation that children with ADHD often behave as younger children, who naturally have lesser ability to sustain attention, display impulse control, and sit still for a long time period.

In support of this model, two longitude studies using computational neuroanatomic techniques demonstrated that children with ADHD follow a similar sequential pattern of cortical development, yet were delayed by as much as 2–3 years, depending upon the specific cortical region (Shaw et al., 2007, 2012). Shaw et al. (2007) used the peak of cortical thickness as delineating a phase of childhood increase followed by adolescent decrease in cortical thickness. Results showed that while the peak in cortical thickness was attained in the cerebrum around 7 years in typically developing children, in children with ADHD, peak cortical thickness was reached around 10 years, with the delay most prominent in lateral prefrontal cortex. In the second longitudinal study, delayed brain maturation (of ∼2 years) in ADHD children was reported in the cortical surface area (Shaw et al., 2012). The authors concluded the congruent delay in both cortical thickness and surface area in ADHD represents a global perturbation in the mechanisms that guide cortical maturation.

Indirect neurobiological support to the maturation-lag model comes from cross-sectional structural imaging studies which yielded reduced size in cortico-striatal brain regions that are known to develop late in adolescence (Krain and Castellanos, 2006). Additionally, research of brain activity demonstrated

underactivation in those regions where function develops linearly with age between childhood and adulthood (Krain and Castellanos, 2006; Rubia et al., 2006; Smith et al., 2006). Electroencephalography (EEG) studies have documented increased slow wave activity (mostly theta) (Lazzaro et al., 2001; Clarke et al., 2002; El-Sayed et al., 2002; Yordanova et al., 2009) in preadolescent and adolescents with ADHD compared with normal controls. This finding has been interpreted as different arousal level in children with ADHD, which could be due to a delay in functional cortical maturation (Mann et al., 1992).

Further evidence for the maturational lag model was found in neuropsychological functioning of ADHD children. ADHD children showed later development of executive functions, such as inhibitory self-control, attention, and temporal foresight, which are mainly dependent on circuits in the frontal lobes (Barkley, 1997; Kalff et al., 2003; Rubia et al., 2007). For example, Shue and Douglas (1992) have demonstrated that on tests sensitive to frontal lobe functions (but not temporal lobe) ADHD children lagged 3–4 years behind their healthy peers. However, ADHD deficits in neuropsychological performance were not necessarily related to brain developmental delay. In order to test whether ADHD is related to a maturational lag in brain development, Doehnert et al. (2010) examined CPT performance and ERP (event related potentials) markers of attention and inhibitory control deficits in ADHD and non-ADHD children in three time points. Although CPT performance was consistent with the developmental lag model, ERP data did not support the developmental lag hypothesis for attentional dysfunction in ADHD. Results showed that ADHD effects may mimic age effects at the level of behavior or performance but these effects were unrelated to patterns of neural activation. Additional studies using ERP (Johnstone et al., 2001; Smith et al., 2004), Magnetic Resonance Imaging (MRI) (Castellanos et al., 2000) and functional Magnetic Resonance Imaging (fMRI) (Mostofsky et al., 2006; Zhu et al., 2008) indicated that ADHD deficits shared little in common with the pattern of brain activity seen in younger control children, which suggests that ADHD children may have a deviant brain function rather than a maturation delay.

While ADHD symptoms and neuropsychological dysfunction are correlated (Nigg, 2005; Seidman, 2006) it is still unclear to which degree neuropsychological functioning parallels the attenuation of ADHD symptoms over time. Evidence suggests that children with ADHD continued to exhibit impaired neuropsychological functioning despite clinical improvement of ADHD symptoms (Fischer et al., 2005; Halperin et al., 2008; Hinshaw et al., 2007). For example, Hinshaw et al. (2007) found that commission errors in the Conners' CPT were not related to ADHD diagnostic status over a 5 year period (persisters and remitters did not differ on this outcome at follow up). In contrast, other studies (Fischer et al., 2005; Halperin et al., 2008) reported that persisters, but not remitters were significantly differentiated from controls on commission errors on an identical pairs CPT task. To explain the association between behavioral and neuropsychological functioning of ADHD across the life-span, Halperin and Schulz (2006) argued that ADHD is caused by non-cortical neural dysfunction that is present early in ontogeny, remains relatively static throughout life, and is not associated with the reduction of symptoms typically seen over development. Age- related symptom reduction is attributed to prefrontally-mediated executive functions compensating for more primary and enduring subcortical deficits. According to this model, neuropsychological deficits on task measuring effortful controlled processing (e.g., commission errors on a go/no-go task) should decrease with maturation paralleling the reduction of ADHD symptomatology. On the other hand, neuropsychological deficits on tasks measuring automatic and less conscious control (e.g., reaction time variability) tend to persist over time remaining unrelated to ADHD symptom presentation.

Most of the longitudinal studies addressing ADHD manifestations over time examined ADHD symptoms dichotomously (i.e., either the patient meets ADHD criteria or not) (Vaughn et al., 2011). Because the use of diagnostic stability is related to the definition of remission, it changes significantly between studies (Biederman et al., 2000; Spencer et al., 2002; Faraone et al., 2006). For instance, when ADHD samples included only those who met full diagnostic criteria for ADHD the rate of persistence was ∼15% at age of 25 years. However, when partial remission was also included, almost two thirds of ADHD cases suffered from significant clinical impairments in adulthood (Faraone et al., 2006). Another problem with many longitudinal studies is that they use long follow up that may be insensitive to smaller changes in performance. Thus, Vaughn et al. (2011) highlightened the need to include more frequent assessments over a longer period of time, to fully map the likely non-linear developmental trajectories.

The present study used a cross-sectional approach in order to examine whether ADHD children show a developmental delay in CPT performance that mirrors the delayed maturation documented in brain development studies. We hypothesized that ADHD children will perform worse than normal controls in CPT and that their performance would consistently match that of younger typically developed children. We thus, compared six age groups of ADHD children and their unaffected peers (6–11 years) in four parameters of CPT performance to determine whether the disorder is characterized by a delay in cognitive development.

MATERIALS AND METHODS

PARTICIPANTS

Participants in this study were 924 children aged 6–11 years, of them 539 boys and 385 girls. The ADHD group included 559 children diagnosed with ADHD and the control group included 365 children without ADHD. The children were divided into six age categories (6–11 years). For example, the category of "8 years" included children who were equal or older than 8 years old, but younger than 9 years old. Background variables are presented in **Table 1**. In the majority of age groups, the ADHD and control groups did not differ in age or gender distributions. In the group of 10 years, the control group were slightly older than the ADHD group (mean age of 10.60 vs., 10.45 years, respectively). The ADHD group included more boys relatively to the control group at ages 6 and 7.

Participants in the ADHD group were recruited from children referred to the out-patient paediatric clinics of a Neuro-Cognitive Center, based in a tertiary care university hospital. The children were referred through their paediatrician, general practitioner, teacher, psychologist, or directly by the parents.

Table 1 | participants' background variables.

Age category		ADHD ($N = 559$)		Control ($N = 365$)		Difference
6	N	107		53		
	Male	76 (71.03%)		27 (50.94%)		$\chi^2_{(1,N=160)} = 6.23$*
	female	31 (28.97%)		26 (49.06%)		
	Age M (*SD*)	6.53	(0.30)	6.57	(0.27)	$t_{(158)} = -0.88$
7	N	111		94		
	Male	73 (65.77%)		39 (41.49%)		$\chi^2_{(1,N=205)} = 12.20$***
	female	38 (34.23%)		55 (58.51%)		
	Age M (*SD*)	7.45	0.02	7.46	0.03	$t_{(203)} = -0.22$
8		112		70		
	Male	66 (58.93%)		33 (47.14%)		$\chi^2_{(1,N=182)} = 2.41$
	female	46 (41.07%)		37 (52.86%)		
	Age M (*SD*)	8.51	0.28	8.45	0.32	$t_{(180)} = 1.30$
9	N	93		57		
	Male	56 (60.22%)		33 (57.89%)		$\chi^2_{(1,N=150)} = 0.08$
	female	37 (39.78%)		24 (42.11%)		
	Age M (*SD*)	9.51	0.27	9.53	0.28	$t_{(148)} = -0.31$
10	N	77		59		
	Male	47 (61.04%)		32 (54.24%)		$\chi^2_{(1,N=136)} = -0.63$
	female	30 (38.96%)		27 (45.76%)		
	Age M (*SD*)	10.46	0.31	10.60	0.28	$t_{(134)} = -2.67$**
11	N	59		32		
	Male	39 (66.10%)		18 (56.25%)		$\chi^2_{(1,N=91)} = 0.86$
	female	20 (33.90%)		14 (43.75%)		
	Age M (*SD*)	11.50	0.33	11.39	0.28	$t_{(89)} = 1.47$

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Inclusion criteria for participants in the ADHD group were:

(1) Each child met the criteria for ADHD according to DSM-IV-TR criteria (APA, 2000), as assessed by a certified paediatric neurologist. The diagnostic procedure included an interview with the child and parents, fulfilment of questionnaires, and medical/neurological examination that confirmed ADHD diagnosis.
(2) Each child scored above the standard clinical cut off values for ADHD symptoms on ADHD/DSM-IV Scales (APA, 2000).
(3) All children were drug naïve.

Participants in the control group were randomly recruited from pupils in regular classes at primary schools. Inclusion criteria for participants in the control group were:

(1) Each child scored below the clinical cut off point for ADHD symptoms on ADHD/DSM-IV Scales (APA, 2000).
(2) Absence of academic or behavioral problems, as reported by parents and teachers.

Exclusion criteria were intellectual disability, other chronic condition, chronic use of medications, and other primary psychiatric diagnosis (e.g., depression, anxiety, and psychosis). All participants agreed to participate in the study and their parents gave written informed consent to the study, approved by the Helsinki committee (IRB) of Hadassah-Hebrew University Medical Center (Jerusalem, Israel).

MEASURES

Measurement of child behavior

The parent and teacher forms of the Conner's ADHD/DSM-IV Scales were used to assess the level of children's ADHD behaviors (Conners, 1997a,b; APA, 2000).

The MOXO continuous performance test

This study employed the MOXO-CPT version[1] (Berger and Goldzweig, 2010), which is a standardized computerized test designed to diagnose ADHD related symptoms. The test included visual and auditory stimuli that serve as distractors.

The total duration of the test was 15.2 min, and it is composed of eight levels (114.15 s, 53 trials each). In each trial a stimulus

[1]The term "MOXO" derives from the world of Japanese martial arts and means a "moment of lucidity." It refers to the moments preceding the fight, when the warrior clears his mind from distracting, unwanted thoughts, and feelings.

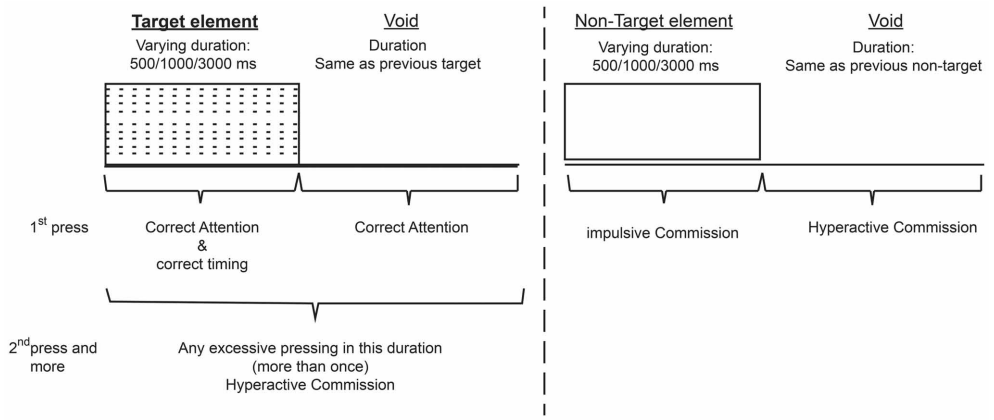

FIGURE 1 | Definition of the time line (Target and non-target stimuli were presented for 500, 1000, or 3000 ms. Each stimulus was followed by a void period of the same duration. The stimulus remained on the screen for the full duration regardless the response. Distracting stimuli were not synchronized with target/non-target's onset and could be generated during target/non-target stimulus or during the void period).

(target/non-target) was presented for 500, 1000, or 3000 ms and then followed by a "void" period of the same duration (**Figure 1**). The stimulus remained on the screen for the full duration no matter if a response was produced. This practice allowed the measuring response timing (whether the response occurred during stimulus presentation or the void period) as well as the accuracy of the response.

In each level 33 target and 20 non-target stimuli were presented. Both target and non-target stimuli were cartoon pictures that do not include any letters. The absence of letters is important given the fact that ADHD patients tend to have learning difficulties e.g., dyslexia, dyscalculia) that may be confound with CPT performance (Seidman et al., 2001). The stimuli were presented sequentially in the middle of a computer screen and the participant was instructed to respond as quickly as possible to target stimuli by pressing the space bar once, and only once. The participant was also instructed not to respond to any other stimuli except the target, and not to press any other key but the space bar.

Test level and distracting stimuli—In order to simulate everyday environment of children, the MOXO-CPT contained distracting stimuli. This feature is unique to this specific CPT. Distractors were short animated video clips containing visual and auditory features which can appear separately or together. This enabled to present three types of distractions that characterize everyday environment: (a) visual distractors (e.g., animated flying bird); (b) auditory distractors (e.g., bird singing); and (c) combination of both visual and auditory distractors (e.g., animated flying bird with the sound of a bird singing).

Overall, six different distractors were included, each of them could appear as pure visual, pure auditory or as a combination of them. Each distractor was presented for a different duration ranging from 3.5–14.8 s, with a fixed interval of 0.5 s between two distractors. Distractors' onset was not synchronized with target/non-target's onset and could be generated during target/non-target stimulus or during the void period. Visual distractors appeared at one of four spatial locations on the sides of the screen: down, up, left or right. Different levels of the MOXO-CPT were characterized by a different set of distractors: levels 1 and 8 did not include any distractors but only target and non-target stimuli, levels 2 and 3 contained pure visual stimuli, levels 4 and 5 contained pure auditory stimuli, and levels 6 and 7 contained a combination of visual and auditory stimuli. The sequence of distracters and their exact position on the display were constant for each level. The burden of the distracting stimuli increased at the odd number levels; in the 2nd, 4th, and 6th level only one distractor was presented at a time, while in the 3rd, 5th, and 7th level two distractors were presented simultaneously.

Performance indices. The MOXO-CPT included four performance indices: attention, Timing, Impulsivity, and Hyperactivity. For detailed description of performance indices see Supplementary A.

Attention. This index corresponded to the number of correct responses (a space bar keystroke in response to a target stimulus) performed during the stimulus presentation or the void period that followed it. This index was considered as a pure measure of sustained attention because it measured correct responses independently of the response time.

Timing. The timing index was the number of correct responses given only during the time in which the target stimulus was present on the screen.

Impulsivity. The impulsivity index was the number of commission responses performed only during the time in which a non-target stimulus was present on the screen.

Hyperactivity. The hyperactivity index was the total number of commission responses that were not coded as impulsive responses (e.g., multiple keystrokes in response to a target stimulus, responses performed in the void period after a non-target stimulus, random key pressing).

DATA ANALYSES

All analyses were conducted with SAS software for Windows version 9.2. First, *T*-tests for independent samples and chi-square tests were used for examining group differences across demographic variables. Second, *T*-tests for independent samples were used to measure the effect of group on CPT indices. Then, each age category of ADHD children was matched to a group of typically developing children which had the closest mean value in the same parameter, by using Cohen's d measure (absolute difference in the mean values of the two groups divided by pooled standard deviation for each age.

RESULTS

First, differences in CPT performance parameters (Attention, Timing, Hyperactivity, and Impulsivity) between ADHD children and their age-matched healthy peers were examined by two tailed *t*-test analyses for independent samples.

As can be seen in **Table 2**, in all age groups children with ADHD received significantly lower scores in the Attention and Timing parameters than normal controls. That is, ADHD children were less attended to the stimuli and performed less reactions on accurate time. In age groups 6, 7, and 10 ADHD children produced significantly more hyperactive and impulsive responses as compared to non-ADHD children. Marginally significant differences between the two groups were observed at ages 8 and 11 in hyperactivity responses ($p = 0.07$ and $p = 0.08$, respectively) and at age 9 for impulsivity responses ($p = 0.06$). The rest of the comparisons did not yield significant group differences.

In order to evaluate the developmental trajectories of the attention performance, each age category of ADHD children was matched to a group of typically developing children which had the closest mean value in the same parameter. The matched group was chosen by using Cohen's d measure (absolute difference in the mean values of the two groups divided by pooled

Table 2 | Differences between ADHD children and their typically developed peers in MOXO-CPT performance.

Age category (Years)	MOXO-CPT parameter	ADHD ($N = 559$)		Control ($N = 365$)		*t*	*df*	*p*(2-tailed)
		Mean	(*SD*)	Mean	(*SD*)			
6	N	107		53				
	Attention	211.1	43.75	234	22.24	−3.59	158	<0.001
	Timing	140.8	37.58	157	33.99	−2.64	158	<0.01
	Hyperactive	97.52	141.5	41.71	33.23	2.83	158	<0.01
	Impulsivity	28.23	33.04	15.70	10.79	2.69	158	<0.01
7		111		94				
	Attention	231.8	25.01	246.7	13.75	−5.18	203	<0.001
	Timing	160.2	33.17	177.1	27.18	−3.94	203	<0.001
	Hyperactive	64.23	63.64	38.21	23.23	3.76	203	<0.001
	Impulsivity	19.38	12.16	15.83	9.31	2.31	203	<0.05
8		112		70				
	Attention	242.8	15.10	249.4	14.02	−2.92	180	<0.01
	Timing	175.6	28.71	190.4	26.53	−3.48	180	<0.001
	Hyperactive	52.14	97.50	30.33	27.81	1.82	180	0.07
	Impulsivity	16.5	12.37	14.94	9.30	0.90	180	0.37
		93		57				
9	Attention	242	35.78	253.4	10.48	−2.33	148	<0.05
	Timing	190.3	41.27	205.2	23.32	−2.48	148	<0.05
	Hyperactive	44.57	50.01	32.26	32.01	1.52	148	0.13
	Impulsivity	18.32	11.74	15.11	6.53	1.89	148	0.06
		77		59				
10	Attention	246.5	25.19	255.3	12.55	−2.47	134	<0.05
	Timing	197.5	35.78	217.7	24.23	−3.72	134	<0.001
	Hyperactive	40.19	40.72	24.98	29.70	2.42	134	<0.05
	Impulsivity	16.36	9.73	13.18	7.51	2.08	134	<0.05
		59		32				
11	Attention	250	15.91	258	8.12	−2.66	89	<0.01
	Timing	205.7	29.48	228.3	19.10	−3.91	89	<0.001
	Hyperactive	30.08	36.08	17.47	23.14	1.79	89	0.08
	Impulsivity	14.23	11.09	13.22	7.07	0.47	89	0.64

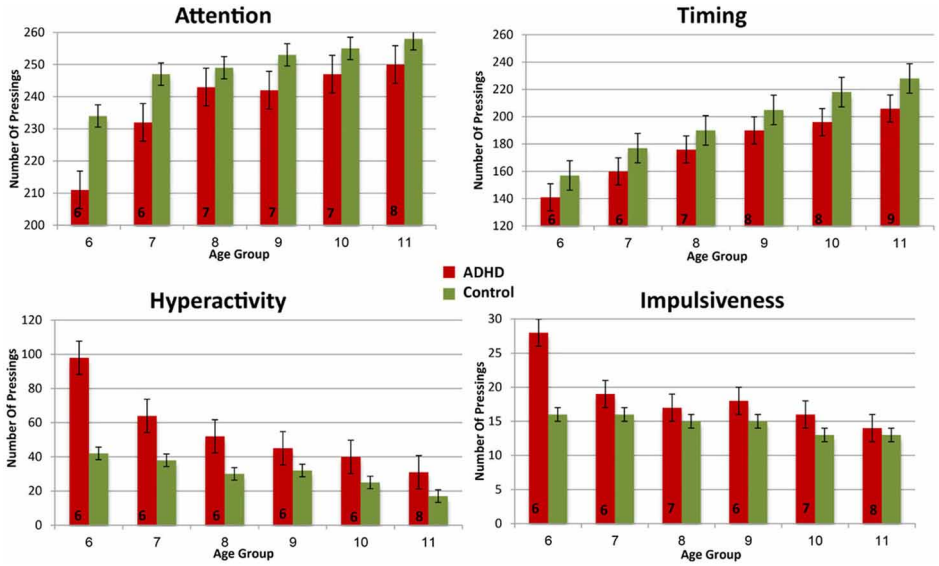

FIGURE 2 | Performance in four CPT parameters among ADHD children and control group.

standard deviation for each age) (**Tables B1–B4**, Appendix B). Results are shown in **Figure 2**. As can be seen in the figures, both ADHD and control groups showed higher scores in Attention and Timing parameters and lower scores in Hyperactivity and Impulsivity with maturation, but the performance of ADHD children matched that of younger healthy controls. In the Attention parameter, the performance of 6–7 years old ADHD children closely resembled the performance of 6 years old typically developing children. Furthermore, the performance of 8–10, and 11 years old ADHD children closely resembled that of a 7 and 8 years old typically developing children, respectively. A very similar pattern was found for the Timing parameter: performance of 6–7 years ADHD children closely resembled the performance of 6 years old typically developing children. The performance of 8, 9–10, and 11 years old ADHD children closely resembled that of 7, 8, and 9 years old typically developing children, respectively. A slightly different, non-linear, pattern was obtained in the Impulsivity parameter, in which 6–7 and 9 years old ADHD children performed as 6 years old non-ADHD children, 8 and 10 ADHD children performed as 7 years old non-ADHD children, and 11 years old ADHD performed as 8 years old non-ADHD. In the Hyperactivity parameter, ADHD children aged 6–10 performed as 6 years old controls, whereas 11 years old ADHD children performed similar to 8 years old children.

In most CPT indices, except Hyperactivity, ADHD children consistently lagged 1–3 years behind their typically developed peers. However, the delay was more prominent in older ages: while at ages 6–8, CPT performance of ADHD children resembled that of 6–7 years old controls, at ages 10-11, ADHD children were more likely to perform as 7–8 years old controls.

DISCUSSION

This paper examined CPT performance of ADHD and non-ADHD children, in order to determine whether the disorder is characterized by a delayed development of attentional functions. Consistent with previous literature (Drechsler et al., 2005; Doehnert et al., 2010; Vaughn et al., 2011), our results have shown that ADHD children of all ages were significantly more inattentive and performed fewer reactions on accurate timing than the control group. In some age groups (6, 7, and 10 years), children with ADHD also produced significantly more hyperactive and impulsive responses than non-ADHD children, whereas in others (8, 9, and 11 years) only marginal or no group effects were found. This finding indicated that despite improvement in CPT performance, ADHD children continue to demonstrate impaired functioning as compared to healthy controls.

In line with findings from longitudinal studies (Shaw et al., 2007, 2012; Vaughn et al., 2011), our results revealed that ADHD and typically developing children showed a similar sequence of development in their attention capacities, but on a different time. In most CPT parameters, performance of ADHD children, delayed and matched that of 1–3 years younger healthy controls.

This pattern of maturation-lag in CPT performance mirrors the 2–3 delayed maturation of the brain in ADHD children (Shaw et al., 2007, 2012). In this context, the current study suggests that at least part of the difficulties of ADHD children could be explained by developmental delay that improves with time. Nevertheless, cautions should be taken when interpreting maturation lag in CPT performance as directly associated with a parallel lag in brain development. As reported previously, the two domains may not be directly linked (Doehnert et al., 2010). More large scale longitudinal studies of brain structure and function are required to address this point (Sonuga-Barke, 2010).

Inconsistent with Halperin and Schulz's (2006) hypothesis and with previous studies indicating that the decline in ADHD symptoms is most apparent for hyperactivity–impulsivity

symptoms than in inattentiveness symptoms (Biederman et al., 2000; Fischer et al., 2005; Vaughn et al., 2011), the current study did not identify different developmental patterns for inattentiveness vs. hyperactivity-impulsivity symptoms. Although hyperactive responses showed a slower pace of change relatively to other CPT indices, they had little in common with the developmental trajectory of impulsive responses. The discrepancy from studies mentioned above may be due to the cross-sectional design of the current study that does not detect within-subjects differences. In addition, our findings may be attributed to the type of neuropsychological task used. In contrast to other CPTs, the present CPT included environmental distracters that may increase the complexity of the task, especially for ADHD children. These higher cognitive demands may explain the lack of developmental catch up which is often observed in hyperactive and impulsive responses (Biederman et al., 2000; Fischer et al., 2005; Vaughn et al., 2011).

Moreover, the majority of the behavioral studies is based on subjective measures of ADHD (e.g., parents rating, parent/children interview) and many of them included only boys (Hart et al., 1995; Biederman et al., 2000). There is evidence to suggest that when including girls in a sample, the proportion of participants with ADHD decreases with age (Cole et al., 2008). Finally, some longitudinal studies (Vaughn et al., 2011) included children who were treated by psychostimulants, whereas our sample included only drug naïve children.

It is still unclear why the difference between ADHD and non-ADHD children was more pronounced in older than in younger children. First, this finding indicates that the test provided sufficient cognitive demands for all ages, especially for older children that often find CPT too easy (Barkley, 1991; Robin, 1998; Uno et al., 2006). Second, it might also suggest that the detection of group differences may be more pronounced before adolescence than in early childhood. This finding is consistent with Drechsler et al. (2005) who found that differences between ADHD and non-ADHD children in reaction time variability and inhibitory tasks were most pronounced just before adolescence (mean age 12) than in younger children and tend to diminish into adolescence. Importantly, the increasing difference between the groups reduces the possibility of a developmental catch up before adolescence.

The findings reported here should be viewed against methodological limitations.

The most important shortcomings of this study are its relatively small sample and the imbalance of gender distribution in the younger age groups (6–7). Although CPT performance is often affected by gender (Newcorn et al., 2001; Hasson and Fine, 2012), our results consistently showed that ADHD children performed as younger typically developed children at all ages and at all CPT parameters. Therefore, differences between the two groups could not be solely attributed to differences in gender distributions. In addition, all data in this study was limited to children between 6 and 11 years. We were able to draw a behavioral curve and describe milestones of attention performance but it is yet to be uncovered which pattern characterizes later stages of development. It was also impossible to determine whether the performance of 6 years old children with ADHD resembled that of younger typically developed children.

The fact that we used cross sectional design limits the test's power to detect within-subject changes in cognitive functions. In addition, because only clinically referred children participated in the study, our results may not generalize to ADHD in the community. Furthermore, participation in the study was based on a voluntary agreement of children and their parents. This self-selected sampling strategy tends to be biased toward favoring more cooperative and motivated individuals. Therefore, it is not possible to determine whether this sample also represents other children that were not recruited and whether cooperation is confounded with ADHD variables. This limitation is typical to most clinic-based ADHD studies around the world (Lee and Ousley, 2006; Gau et al., 2010). Another limitation of the study is the exclusion of ADHD children with severe comorbidities. Since ADHD is associated with many psychiatric disorders (Gentile et al., 2006) this exclusion limits the generalization of our results. Finally, more work is needed to determine if the normalization in some ADHD symptoms reflects true remission of ADHD symptoms or is due to the developmental insensitivity of the test.

This study shed light on the age -related CPT changes in both ADHD and non-ADHD children. Our results suggest that despite improvement in CPT across childhood, ADHD continue to demonstrate impaired cognitive functioning as compared to non-ADHD children. Importantly, this study suggests that while some cognitive functions develop slower but normally, other functions (e.g., inhibitory control) do not show a clear developmental trajectory. The cross-sectional approach chosen for this study allowed frequent evaluations of typically ADHD-related behavior, which is independent upon definition of remission and persistence. Thus, it was possible to trace small and non-linear changes in performance. One of the major difficulties in early diagnosis of ADHD is that decisions about the inappropriateness of behavior in young children are based on subjective judgments of the observers (Rousseau et al., 2008; Berger and Nevo, 2011). Hence, our results highlight the importance of the CPT as an objective tool that is not affected by reporter's bias.

Future research is needed to investigate the course of ADHD symptoms in wider spectrum of age, in specific sub-types of ADHD, and in response to psychostimulants. Moreover, it is important to examine the clinical and behavioral implications of improvement in CPT performance.

AUTHOR CONTRIBUTIONS

Itai Berger suggested the study. Itai Berger, Merav Aboud, Julia Melamed, and Hanoch Cassuto collected the data. Itai Berger, Ortal Slobodin, and Hanoch Cassuto designed the study with assistance from Merav Aboud and Julia Melamed. Ortal Slobodin, Itai Berger, and Hanoch Cassuto performed the statistical analysis. Itai Berger, Ortal Slobodin, and Hanoch Cassuto wrote the manuscript. All of the authors contributed to interpret the findings and writing the manuscript, and read and approved the final manuscript.

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APPENDIX A

DESCRIPTION OF PERFORMANCE INDICES

Attention

This parameter included the number of correct responses (pressing the key in response to a target stimulus), which were performed either during the stimulus presentation on the screen or during the void period that followed. Thus, it was possible to evaluate whether the participant responded correctly to the target (was attentive to the target) independently of how fast he was. Knowing how many responses are expected, it was also possible to calculate the number of times the target was presented, but the participant did not respond to it (omission errors).

Timing

This parameter included the number of correct responses (pressing the key in response to a target stimulus) which were performed only while the target stimulus was still presented on the screen. This parameter did not include responses that were performed during the void period (after the stimulus has disappeared).

According to the National institute of mental health (2012), inattention problems in ADHD may be expressed in "difficulties in processing information as quickly and accurately as others." Traditionally, difficulties in timing at a CPT are evaluated by mean response time for correct responses to the target (which is interpreted as a measure of information processing and motor response speed) and by the standard deviation of response time for correct responses to the target (which is interpreted as a measure of variability or consistency) (Greenberg, 1997). In these paradigms the stimulus is presented for short and fixed periods of time and the response occurs after the stimulus has disappeared. Given the short, fixed presentation, accurate but slow participants may be mistakenly diagnosed as inattentive. While a group of patients would respond correctly if allowed more time, inattentive patients would not respond at all because they were not alert to the target. Therefore, the measurement of response time per-se, addresses only the ability to respond quickly, but not the ability to respond accurately. By implanting a void period after each stimulus and using variable presentation durations of the elements, the MOXO-CPT could distinguish accurate responses performed in "good timing" (quick and correct responses to the target performed during stimulus presentation) from accurate but slow responses (correct responses to the target performed after the stimulus presentation; during the void period). These two aspects of timing correspond to the two different problems of ADHD described by the National institute of mental health (2012); responding quickly and responding accurately.

Impulsivity

This parameter included the number of commission errors (responses to a non-target stimulus), performed as responses to the non-target stimuli. Usually, commission errors are coded in any case of inappropriate response to the target (e.g., pressing a random key) (Greenberg, 1997). In contrast, the MOXO-CPT's impulsivity parameter considered as impulsive behavior only the pressings on the keyboard's space–bar in response to non-target stimulus. All other non-inhibited responses (e.g., pressing the keyboard more than once) were not coded as impulsive responses (as will describe in the next paragraph).

Hyperactivity

This parameter included all types of commission responses that are not coded as impulsive responses. Several examples are: (1) Multiple responses- pressing the keyboard's space bar more than once (in response to target/non-target), which is commonly interpreted as a measure of motor hyper-responsivity (Greenberg, 1997). The MOXO-CPT considered as multiple responses only the second press and above (the first response would be considered as correct response with good timing, as correct response with poor timing, or as impulsive response, depends on the type of element appearing on the screen). (2) Random key pressing—pressing any keyboard button other than the space bar. By separating commission errors due to impulsive behavior from commission errors due to motor hyper-responsivity, it was possible to identify the multiple sources of response inhibition problems. Thus, the MOXO- CPT was able to differentiate impulsive responses from hyperactive responses.

APPENDIX B

Table B1 | ADHD and control group with the minimal difference in the attention parameter, using Cohen's D measure.

		Control age- group					
		6	**7**	**8**	**9**	**10**	**11**
ADHD age-group	6	0.60246*	1.07079	1.08913	1.17669	1.23039	1.21309
	7	0.09286*	0.72549	0.82178	1.01614	1.09397	1.17063
	8	0.50006	0.26728*	0.44492	0.76526	0.87376	1.09176
	9	0.25377	0.17423*	0.25822	0.39191	0.45764	0.51231
	10	0.51866	0.01297*	0.14136	0.33912	0.42792	0.53201
	11	0.83389	0.22301	0.04006*	0.24912	0.37256	0.58475

Table B2 | ADHD and control group with the minimal difference in the timing parameter, using Cohen's D measure.

		Control age- group					
		6	**7**	**8**	**9**	**10**	**11**
ADHD age-group	6	0.44365*	1.09475	1.47402	1.93149	2.29619	2.55171
	7	0.09651*	0.55199	0.98194	1.49041	1.89167	2.22267
	8	0.61228	0.05103*	0.52987	1.09457	1.54204	1.95677
	9	0.86170	0.38201	0.00046*	0.41655	0.76452	1.02502
	10	1.15767	0.65330	0.22424*	0.24752	0.64407	0.96688
	11	1.53692	1.01883	0.54672	0.01755*	0.44408	0.85829

Table B3 | ADHD and control groups with the minimal difference in the hyperactivity parameter, using Cohen's D measure.

		Control age- group					
		6	**7**	**8**	**9**	**10**	**11**
ADHD age-group	6	0.47499*	0.56749	0.60247	0.55383	0.62999	0.64051
	7	0.40416*	0.52664	0.64230	0.56272	0.72219	0.81695
	8	0.12620*	0.18925	0.27798	0.23131	0.33574	0.39912
	9	0.06384*	0.16332	0.33940	0.25653	0.45259	0.60512
	10	0.04021*	0.06138	0.28050	0.18594	0.41871	0.62244
	11	0.33463	0.28175	0.00765*	0.09309	0.15460	0.39219

Table B4 | ADHD and control groups with the minimal difference in the impulsivity parameter, using Cohen's D measure.

		Control age- group					
		6	**7**	**8**	**9**	**10**	**11**
ADHD age-group	6	0.45153*	0.49734	0.50401	0.48621	0.55861	0.51320
	7	0.31343*	0.32409	0.39786	0.40298	0.57398	0.54783
	8	0.06743	0.06048*	0.13786	0.12947	0.30258	0.28715
	9	0.23001*	0.23538	0.31393	0.31876	0.49788	0.47438
	10	0.06538	0.05617*	0.14905	0.14761	0.35929	0.34771
	11	0.13338	0.15874	0.06945*	0.09495	0.11092	0.10310

** Age of control group with most resembling performance (minimal Cohen's d score).*

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I can see clearly now: the effects of age and perceptual load on inattentional blindness

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Attention and awareness are known to be linked (e.g., see Lavie et al., 2014, for a review). However the extent to which this link changes over development is not fully understood. Most research concerning the development of attention has investigated the effects of attention on distraction, visual search and spatial orienting, typically using reaction time measures which cannot directly support conclusions about conscious awareness. Here we used Lavie's Load Theory of Attention and Cognitive Control to examine the development of attention effects on awareness. According to Load Theory, awareness levels are determined by the availability of attentional capacity. We hypothesized that attentional capacity develops with age, and consequently that awareness rates should increase with development due to the enhanced capacity. Thus we predicted that greater rates of inattentional blindness (IB) would be found at a younger age, and that lower levels of load will be sufficient to exhaust capacity and cause IB in children but not adults. We tested this hypothesis using an IB paradigm with adults and children aged 7–8, 9–10, 11–12 and 13 years old. Participants performed a line-length judgment task (indicating which arm of a cross is longer) and on the last trial were asked to report whether they noticed an unexpected task-irrelevant stimulus (a small square) in the display. Perceptual load was varied by changing the line-length difference (with a smaller difference in the conditions of higher load). The results supported our hypothesis: levels of awareness increased with age, and a moderate increase in the perceptual load of the task led to greater IB for children but not adults. These results extended across both peripheral and central presentations of the task stimuli. Overall, these findings establish the development of capacity for awareness and demonstrate the critical role of the perceptual load in the attended task.

Keywords: perceptual load, inattentional blindness, development, attention, awareness, distractor, conscious perception

INTRODUCTION

Attention and awareness, though two distinct concepts, are intrinsically linked. The way in which they interact has been the subject of fierce debate over the past decades (Lavie et al., 2014). Anecdotally we know all too well that in some situations people appear to be completely unaware of anything outside their focus of attention (try talking to a child engaged in their favorite pursuit, for example playing their newest video game) yet in other situations people are constantly distracted and fail to focus. Even less is known about how the interplay between these processes is affected by development. The bulk of the previous research has assessed the development of attention using reaction time measures to examine age-related changes in susceptibility to distraction, visual search ability and spatial orienting. This research clearly demonstrates that control over selective attention and resistance from distraction develop with age (Plude et al., 1994). However it does not link attention to awareness as we briefly review below.

Studies of spatial attention and orienting demonstrate that while there is some evidence of mature spatial cueing effects from an early age (e.g., Brodeur and Enns, 1997), the reaction time costs associated with invalid cues appear to be far greater for children than adults (e.g., Pearson and Lane, 1990; Brodeur and Boden, 2000). This greater cost is thought to reflect children's inability to disengage attention from the invalidly cued location and then redirect attention to the appropriate location. Moreover, children also fail to modulate their orienting responses in the face of varying cue predictability, suggesting that the control processes that govern orienting develop over childhood (Brodeur and Boden, 2000). However, the reaction time measures used in these studies do not tell us about the extent to which development of control over orienting attention leads to improved visual awareness.

Similarly, differences between adults and children are seen in Garner interference effects. Garner interference refers to the slowing of target responses caused by variation within an irrelevant dimension. For example, when shown cards that differ in color

and value, the time taken to sort them on the basis of a relevant dimension (e.g., color) is greater when the irrelevant dimension (value) also differs from card to card (and *vice versa*) (Garner and Felfoldy, 1970). Such interference effects have been shown to vary developmentally: effects on response latencies were relatively large for younger children aged 4–5, 6–7 and 10–11 years (compared with adults), but gradually decreased with increasing age (e.g., Shepp and Swartz, 1976; Barrett and Shepp, 1988; Shepp and Barrett, 1991). This finding was particularly apparent when target and distractor dimensions were conjoined in one stimulus, and were therefore not easily separable. Together, these studies imply that the efficiency of gating irrelevant information is generally poorer at a young age but improves gradually with maturation. In addition, Stroop studies indicate that younger children are susceptible to greater interference than older children and adults, and this effect has been seen in both visual and auditory modalities (e.g., Hanauer and Brooks, 2003; and see MacLeod, 1991 for a review; Stroop, 1935; Posnansky and Rayner, 1977). Comalli et al. (1962) demonstrated that interference effects from incongruent words on color-naming latencies decreased with age throughout childhood and into adulthood (age range 7–80 years). Response competition studies also demonstrate that children (aged 4, 5 and 7 years) are less able than adults (aged 20 years) to filter out distractors (Enns and Akhtar, 1989) and that developmental trends in this ability are seen across childhood (5–12 years) (Enns and Girgus, 1985; Ridderinkhof et al., 1997).

While the evidence described so far demonstrates the development of attention control processes, it cannot inform us about the development of the capacity for visual awareness, because the aforementioned studies used indirect measures of perception (e.g., effects on target reaction times (RTs)) rather than direct measures (e.g., awareness reports). Effects on reaction times can be attributed to any processing component between the stimulus and response and clearly do not tell us about the extent of intrusions of the irrelevant stimuli into awareness. To the best of our knowledge there is only one study that has assessed relative awareness rates in children and adults. Memmert (2006) showed that, when asked to count ball passes between basketball players, children failed more often than teenagers (aged 13 years) and adults to notice a person dressed in a gorilla suit walking among the players (using the inattentional blindness (IB) video clip as used by Simons and Chabris, 1999). While this study only used one age group of children (8 years), and therefore developmental conclusions are limited, the finding that children had lower awareness reports than adults is potentially encouraging regarding the development of capacity for visual awareness.

Here we used Load Theory of Attention and Cognitive Control (Lavie et al., 2004) to address the development of the effects of attention on awareness within a framework that may able to provide a more comprehensive account for attention development than those just focused on attentional control. We suggest that cognitive maturation involves not only the development of attentional top-down control mechanisms that are responsible for preventing irrelevant distraction, but also the development of attentional capacity. Since according to Load Theory the level of perceptual processing that leads to awareness is determined by the availability of attentional capacity (e.g., Lavie et al., 2014), the developmental increase of this capacity should directly result in increased awareness rates with age. Note that for ease we shall use the contracted term "capacity for awareness" to refer to this linkage in the rest of the article. This has critical predictions for the development of attention and awareness as we outline below.

Load Theory states that focused selective attention (on task relevant rather than irrelevant information) depends not only on goal-directed cognitive control but also on the perceptual load (amount of potentially task-relevant information) of a given task. While full top-down cognitive control ability is necessary for the active maintenance of the current task priorities (including prioritization of relevant over irrelevant stimuli), this alone is insufficient to achieve exclusive focus on relevant items. In tasks of low perceptual load, spare capacity left over from the processing of task-relevant stimuli will "spill over" resulting in the perception of distractor stimuli. It is only when the perceptual load of the task is high enough to exhaust perceptual capacity that distractor perception—and their intrusions into awareness—will be prevented (Cartwright-Finch and Lavie, 2007; Macdonald and Lavie, 2008, 2011; Lavie et al., 2009; Carmel et al., 2011).

What are the implications for development? If attentional capacity for perception and awareness develops with age then we would expect first, that children will have lower levels of awareness than adults overall, and second, that a smaller increase in load will have a greater impact on reducing levels of awareness in children but not adults. These smaller increases in load would be sufficient to exhaust capacity in children, but not for adults who possess a larger capacity. At such levels adults are therefore expected to be more prone to the processing of irrelevant stimuli, whereas the children would be better able to focus and harder to detract from their task. Indeed, the studies showing children are more prone to distraction (Enns and Girgus, 1985; Enns and Akhtar, 1989; Ridderinkhof et al., 1997) involved a small number of stimuli in the display which would be expected to involve only a low level of load and therefore not to tax capacity.

Encouraging evidence for the suggestion that the capacity for perception increases with age has been obtained in a few previous studies. Multiple object tracking significantly increases from 7–22 years of age (Dye and Bavelier, 2010). Visual search literature indicates that adults perform visual search significantly better than children (e.g., Thompson and Massaro, 1989; Kaye and Ruskin, 1990; Brodeur et al., 1997) and that children show an increased search rate with age (Donnelly et al., 2007; Woods et al., 2013) and these age-related differences are particularly apparent in the more demanding search tasks—for example, in search for conjunction of features (color and orientation) rather than a single feature (color, orientation or size alone; Donnelly et al., 2007). The age-related improvement in visual search ability has been interpreted by some as evidence that selective attention and resistance to distraction develop with maturation. On closer consideration of the nature of visual search, however, it is clear that the non-target items in a visual search array are not irrelevant distractors, because they are task relevant (i.e., they have to be searched among in order to find

the target, or to conclude that the target is absent from the array). Hence, these findings may indicate increased capacity for perceptual discrimination rather than improved ability to reject distractors. Moreover, as we discussed earlier, the reliance on RT measures in visual search studies falls short of providing direct evidence about perceptual processes related to conscious awareness.

Another line of support for our suggestion that attentional capacity for perception develops with ages comes from an event related potentials (ERP) study (Couperus, 2011) on the impact of perceptual load on neural markers of unattended perception in groups of children (7–18 years) and adults (mean age 24 years). Participants were asked to identify whether a character in the center of the screen was a letter or number, and load was manipulated by changing the stimulus duration (shorter presentation time representing higher load). Neural activity to an irrelevant character (a % sign presented offset from the central task) was recorded. Results demonstrated that for all age groups the amplitude of the P100 to unattended stimuli was lower under high load conditions than under low load conditions. However, for younger age groups the level of load needed to elicit these differences was far lower than for older children and adults.

Thus, overall we propose that development of selective attention involves both maturation of frontal cognitive control processes (as shown by the attention control RT studies) and an increase in perceptual capacity (as hinted by the motion tracking, visual search and recent ERP study). Interestingly, although maturation of the capacity for frontal cognitive control would allow older children to have better control over interference by irrelevant information that had been perceived, the development of perceptual capacity should lead to more cases of perception of irrelevant information, for example when the perceptual load of the task is sufficient to exhaust the smaller capacity of children and prevent awareness of additional stimuli, but leaves spare capacity in older children and adults who, consequently, can continue to process the irrelevant stimulus.

To date, only one study has begun to address this hypothesis. Huang-Pollock et al. (2002) tested children and adults on a visual search task with flanking distractors at varying levels of perceptual load. Their results showed that for all age groups, a distractor interference effect was seen at the lower levels of perceptual load and that this was eliminated at the highest level of load. The decline in interference effect, however, was seen at a lower level of load for the younger age groups. This is indicative of reduced capacity in these groups. As with many of the previous studies, however, the measures used by Huang-Pollock et al. were indirect (RT effects) and thus cannot support conclusions about awareness.

In the present study we therefore set out to test the effects of perceptual load on awareness using an IB paradigm (adapted from that used by Cartwright-Finch and Lavie, 2007) which directly assesses conscious awareness reports. Participants were asked to judge the line lengths of a cross shape with horizontal and vertical arms and an unexpected, irrelevant stimulus (a small gray square) was presented in the display on the final trial of the task. We assessed awareness for this irrelevant stimulus across a number of age groups at different levels of perceptual load. Perceptual load was varied by changing the relative lengths of the cross arms (more similar length in higher load conditions). Three levels of load were used: low and high load length parameters based on previous research (Cartwright-Finch and Lavie, 2007) and an intermediate load level (with length parameters in between those used for low and high based on pilot testing with children). Notice that the irrelevant stimulus used in this paradigm was not a strong competitor for attentional selection (e.g., it was not visually salient nor did it compete with the target response, c.f. Carmel et al., 2012). In this way our task allows us to clearly address perceptual capacity without the potential counter-effects of maturation of cognitive control functions (which are expected to improve distractor rejection). Importantly, any demands on cognitive control involved in the line-length discrimination task, did not vary across perceptual load conditions (since the task remained exactly the same, only the length of the lines varied). Thus effects of cognitive control could not confound or counter act the effects of perceptual load *per se*. If perceptual capacity does indeed increase with development then we expect the level of awareness for the irrelevant distractor to increase with age, and that a moderate increase in load will have a greater impact on the awareness rates at younger ages.

EXPERIMENT 1

METHODS

In Experiment 1, levels of awareness were examined for an unexpected, peripheral square shape (critical stimulus) across various age groups under two different levels of perceptual load. Awareness for this critical stimulus (in this, and all experiments in this study) was assessed on the final trial as is customary in the IB paradigm (e.g., Mack and Rock, 1998). Note that the IB measure is solely based on that single report for each participant because once participants have been asked about their awareness one cannot be sure that on subsequent trials the stimulus will be entirely unattended to, hence the single critical-trial nature of the task.

Participants

Two-hundred and three participants were recruited from the Science Museum, London. After exclusions (see Results section), experimental age groups consisted of the following participants (*N*, mean age; SD): 7–8 year-olds (40, 7 years 11 m; 5.5 m), 9–10 year-olds (44, 9 years 11 m; 6.7 m), 11–12 year-olds (40, 12 years 0 m; 7.4 m), 13–14 year-olds (32, 14 years 0 m; 7.0 m), and adults (32, 30 years; 10 years). All participants reported normal or corrected-to-normal vision.

Stimuli and apparatus

The experiment was presented using E-Prime version 1.1 (Psychology Software Tools Inc.) on a PC connected to a 17″ monitor (1024 × 768 screen resolution; 75% contrast). Viewing distance was fixed at 60 cm with a chinrest. Stimulus displays were bitmap images created in Microsoft Paint and the background remained white throughout. Target displays consisted of a black cross at the center of the screen. One arm of the cross (either vertical

or horizontal) subtended 3.9° whilst the shorter arm subtended either 0.7° (low load condition) or 2.0° (intermediate load condition). By using this intermediate level of perceptual load, the task is sensitive to developmental changes. Previous experiments (Lavie and Cox, 1997) have found no difference in the extent of distractor processing between low and intermediate levels of load (array sizes of 1, 2 and 4) in adults but differences have been seen in children (raising array size from 2 to 4 items; Huang-Pollock et al., 2002). On the seventh trial, a black outline square shape (sides subtending 0.3°) was presented in addition to the cross (see **Figure 1**). This critical stimulus appeared in one of four peripheral locations (counterbalanced between participants) all equidistant from fixation at 3.35° eccentricity, and positioned halfway between two neighboring cross-arms. A mesh pattern consisting of straight black lines of different orientations against the white background was used as a visual mask.

Procedure

Each trial proceeded as follows: small central fixation dot (1400 ms), blank interval (57 ms), fixation dot (97 ms), second blank interval (43 ms), centrally-located target cross (110 ms) and visual mask (496 ms). The repetition of the fixation dot and blank interval was in order that the fixation dot appeared to flicker, providing temporal warning for the onset of the task display. Participants were asked to indicate which arm of the cross was longer (horizontal or vertical) and responses were entered by the experimenter. All trials were initiated by the experimenter pressing the space bar. Participants were instructed to fixate centrally throughout and to guess if they were unsure.

Each participant completed 7 experimental trials: 6 non-critical trials and 1 critical trial. Within both non-critical and critical trials, the horizontal cross-arm was longer on half the trials (the vertical longer on the other half) with order counterbalanced across participants.

On the seventh trial, the critical stimulus was presented and the cross-task response was made and entered by the experimenter as normal. Immediately following response entry, participants were asked whether they noticed anything else appearing on the screen that had not been there before. Participants responded verbally giving details of the object if they could. The critical trial was then repeated in a final control trial. Before this trial, participants were instructed to ignore the cross and instead, look for anything extra that appeared in the display. Awareness for the critical stimulus was measured immediately after trial-termination by direct verbal report as before. Only participants reporting awareness for the critical stimulus on these control trials were included in the analysis.

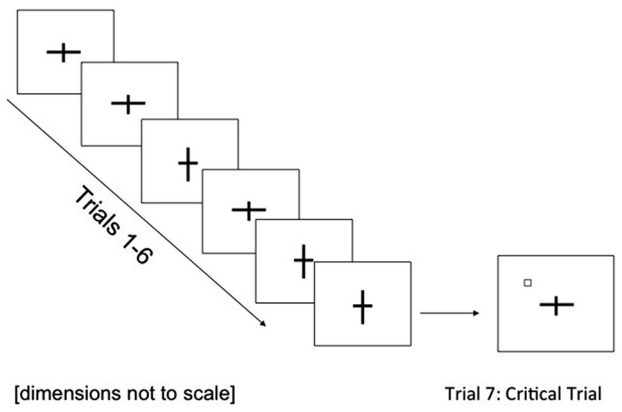

FIGURE 1 | Example of stimulus displays and trial sequence (low load) used in Experiment 1. In the intermediate load condition, the cross arms were more similar in length (a difference of 1.9°).

RESULTS

Participants who failed the control trial (11), the critical trial target response (1), or to perform the task at all (1); and participants who gave uninterpretable responses (3) were excluded from the analyses. Remaining participants were divided among the experimental groups as follows: 7–8 years, low load (20) and intermediate load (20); 9–10 years, low load (24) and intermediate load (20); 11–12 years, low load (20) and intermediate load (20); 13–14 years, low load (16) and intermediate load (16); and adults, low load (16) and intermediate load (16). All participants included in the analyses performed the task adequately, with four or more correct line-length judgments entered. All of the participants who reported awareness of the critical stimulus (i.e., made a "Yes" response to the critical question) were able to describe correctly its location and at least two of its major features (shape, size or color). **Figure 2** presents the percentage of reported awareness as a function of age (7–8 years, 9–10 years, 11–12 years, 13–14 years, adults) and perceptual load (low load, intermediate load). χ^2-tests were performed on the data.

Overall rate of awareness

The analysis revealed a significant increase in overall rate of awareness reports with age, χ^2 (4, N = 188) = 41.88, $p < 0.001$ (see **Figure 2**).

Post-hoc χ^2 comparisons (with Bonferroni-Holm corrected α-levels for multiple comparisons) revealed similar levels of awareness at the two youngest age groups (7/40 reports in 7–8 year-olds vs. 10/44 reports in 9–10 year-olds, χ^2 (1, N = 84) = 0.36, p = 0.55). However, children aged 9–10 years gave significantly lower proportions of aware reports than children aged 11–12 years (20/40 reports, χ^2 (1, N = 84) = 6.79, p = 0.009). Children aged 11–12 years showed the same rates of awareness as children aged 13–14 years (16/32 reports, χ^2 (1, N = 72) = 0, p = 1.00). However, children of 13–14 years gave significantly fewer reports of awareness than adults (27/32, χ^2 (1, N = 64) = 8.58, p = 0.003). It seems, therefore, that capacity for awareness develops with age from 7 years old to adulthood.

This pattern was also seen at each load level: there was a significant increase in awareness reports with age under low load (χ^2 (4, N = 96) = 26.42, $p < 0.001$) and intermediate load (χ^2 (4, N = 92) = 22.16, $p < 0.001$). Under low load, specific comparisons showed significant increases from 9–10 to 11–12 year-olds (6/24 reports vs. 14/20 reports, χ^2 (1, N = 44) = 8.91, p = 0.003) but no other significant differences between age groups ($p > 0.60$). Under intermediate load, a significant increase was seen between 13–14 year-olds and adults (5/16 reports vs. 12/16

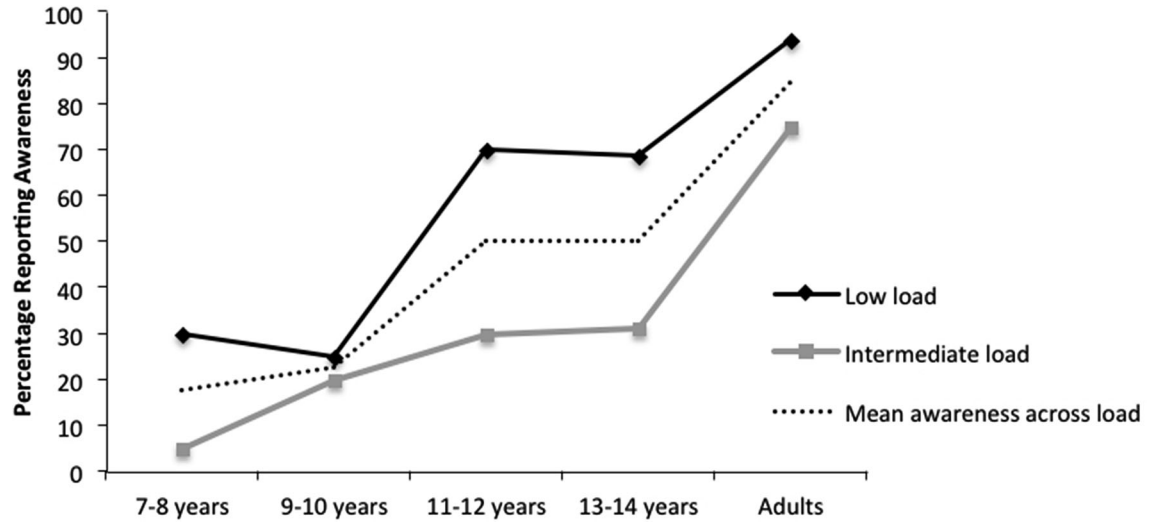

FIGURE 2 | Percentage of reported awareness of a peripheral critical stimulus (central target) as a function of perceptual load (low vs. intermediate) and age group, *N* = 188, in Experiment 1.

reports, χ^2 (1, $N = 32$) = 6.15, $p = 0.013$) with no other significant developmental changes ($p > 0.10$ in all other comparisons).

While this pattern of increase in awareness with age groups was expected with a moderate increase in level of load, it was somewhat unexpected that it was also found in the low load condition. However, note that despite the fairly evident difference in line length (difference of 3.2°) the low load task did take up some capacity. Moreover, recall that for the younger children we hypothesized that they have a smaller capacity. Therefore at a younger age, even low capacity consumption is likely to engage a larger proportion of their smaller total capacity, therefore having a larger effect on awareness for the unattended stimulus.

Impact of perceptual load

Significantly fewer participants reported awareness for the critical stimulus when performing a task of intermediate load (28/92) compared with a task of low load (52/96), χ^2 (1, $N = 188$) = 10.82, $p < 0.01$. Importantly, comparing the effects of load for each age group revealed that increasing the perceptual load from low to intermediate level reduced awareness in all groups of children other than 9–10 year-olds: 7–8 years (6/20 vs. 1 /20 in low and intermediate load groups respectively, χ^2 (1, $N = 40$) = 4.33, $p = 0.037$); 9–10 years (6 of 24 vs. 4 of 20, χ^2 (1, $N = 44$) = 0.02, $p = 0.69$); 11–12 years (14/20 vs. 6 /20, χ^2 (1, $N = 40$) = 6.40, $p = 0.01$); 13–14 years (11 of 16 vs. 5 of 16, χ^2 (1, $N = 32$) = 4.5, $p = 0.034$). The lack of a significant load effect for participants aged 9–10 years is likely to be due to the low level of awareness under low load, producing a floor effect which limited any further reduction. As predicted, in the adult group, a moderate increase in the level of load did not affect awareness (15/16 vs. 12/16, χ^2 (1, $N = 32$) = 2.1, $p = 0.14$) (see **Figure 2**).

A 2 × 5 multi-way frequency analysis of load (low, intermediate) by age (7–8, 9–10, 11–12, 13–14, adult) did not reveal a significant interaction, χ^2 (4, $N = 188$) = 3.08, $p = 0.54$. However, inspection of **Figure 2** suggests that this may be due to the restricted load effect caused by the low baseline level of awareness in the younger age groups. Indeed, when the two older age groups of children were combined (11–12 and 13–14) and compared with adults, the interaction of load (low, intermediate) by age (11–14, adults) reached significance, χ^2 (1, $N = 104$) = 4.57, $p = 0.027$.

EXPERIMENT 2

Experiment 1 demonstrates that awareness for stimuli outside the focus of attention develops with age, and moreover this is impacted by a small increase in the level of perceptual load suggesting decreased capacity for awareness in all children compared to adults. However, as the target was always presented in the center and the critical stimulus in the periphery, it is possible that there was a contribution to the overall effect of age on awareness from development of the ability to disengage from the focus on fixation (e.g., Pearson and Lane, 1990; Brodeur and Boden, 2000). To investigate this, in Experiment 2 we presented targets in the same range of peripheral positions as the critical stimulus in Experiment 1, to prevent engagement of a spatial focus that centered on fixation and excluded the periphery.

METHODS

Participants

Two-hundred and ten visitors to the Science Museum, London took part in this experiment. After exclusions (see Results section), participants (*N*, mean age; SD) were divided between the following age groups: 7–8 year-olds (40, 8 years 0 m; 6.7 m), 9–10 year-olds (44, 9 years 11 m; 7.0 m), 11–12 year-olds (40, 11 years 11 m; 7.1 m), 13–14 year-olds (36, 14 years 0 m; 7.0 m), and adults (32, 36 years; 11 years). All participants reported normal or corrected-to-normal vision.

Apparatus and procedure

Apparatus and procedure were as in Experiment 1.

Stimuli

Figure 3 presents an example of the stimuli used in this experiment. A fixation square subtending 1.4° was presented at the screen's center. The size of the fixation square was chosen in order to eliminate the possibility of the initial fixation cue forward-masking critical stimuli that subsequently appeared at fixation (e.g., Breitmeyer, 1984). Target displays consisted of a black cross target with horizontal and vertical axes of the same size as those used in Experiment 1. Target crosses appeared in either one of two peripheral locations (upper-left or lower-right visual field, counterbalanced across trials) with the centers of each cross-target lying on an imaginary diagonal line, 3.35° away from fixation. In critical trials, a black outline square (each side subtending 0.3° as in Experiment 1) appeared in addition to the cross-target in one of two peripheral locations, 3.35° above or below fixation and 3.35° from center of target cross (position counterbalanced between participants, see **Figure 3**). All possible stimuli (peripheral cross-targets and peripheral critical stimuli) lay equidistant from one another. Thus, when the cross appeared in the lower-right position, peripheral critical stimuli were presented only in the lower visual field and *vice versa* for upper visual field stimuli. The visual mask from Experiment 1 was used. A white background was maintained throughout (see **Figure 3**).

Target position was counterbalanced across participants with targets appearing in the upper visual field position on half the trials and in the lower position on the other half of trials. Target crosses were presented in the same position on the sixth and seventh (critical) trials for one group of participants (e.g., upper position followed by upper position) and in different positions to another group (e.g., upper position followed by lower position).

RESULTS

Participants who failed the visual control trial (7), the main target task (2); the critical trial target response (2); participants who gave uninterpretable responses (2); participants who were not naive to the experiment (3); and participants who could not understand instructions (2) were excluded from the analyses. Remaining participants were as follows: 7–8 years, low load (20) and intermediate load (20); 9–10 years, low load (24) and intermediate load (20); 11–12 years, low load (20) and intermediate load (20); 13–14 years, low load (16) and intermediate load (20); and adults, low load (16) and intermediate load (16).

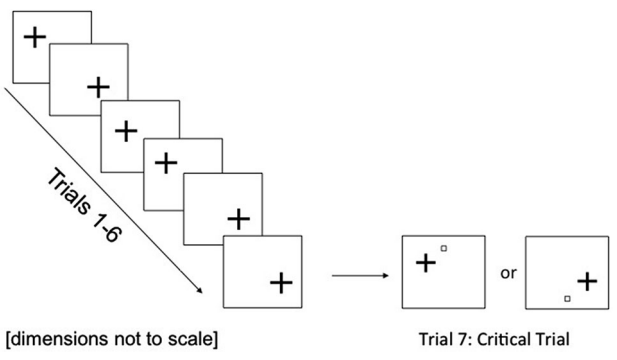

FIGURE 3 | Example of stimulus displays and trial sequence (intermediate load) used in Experiment 2. On the critical trial, the cross was equally likely to appear in the top left or bottom right of the screen and the critical stimulus was always presented in the same quadrant as the cross.

Overall awareness

Figure 4 presents the percentage of reported awareness for the critical stimulus as a function of age and perceptual load (low load vs. intermediate load). All of the participants who reported awareness of the critical stimulus (i.e., made a "Yes" response to the critical question) were able to describe correctly its location and at least two of its major features (shape, size or color).

χ^2 analyses revealed that rates of awareness reports significantly increased with age across participants aged 7–8 years to adults, (χ^2 (4, N = 192) = 52.13, $p < 0.0001$). The effect of age on awareness found in Experiment 1 is therefore replicated in the current experiment where both the attended cross-targets and the critical stimulus for which awareness was measured were presented in the periphery.

Post-hoc comparisons of awareness rates between different age groups (with Bonferroni-Holm corrected α-levels for multiple comparisons) revealed no difference in reported awareness between 7–8 year-olds (10/40) and 9–10 year-olds (13/44), (χ^2 (1, N = 84) = 0.22, p = 0.64). However, rates of awareness reports increased significantly from children aged 9–10 years to 11–12 years (25/40, χ^2 (1, N = 84) = 9.19, p = 0.002). Again, as in Experiment 1, there was no difference between the rates of awareness reports given by 11–12 year-olds and 13–14 year-olds (27/36, χ^2 (1, N = 76) = 1.37, p = 0.24), and in this experiment children aged 13–14 years did not report awareness significantly less often than adults (30/32, χ^2 (1, N = 68) = 4.39, p = 0.04). Therefore, in this experiment, rates of awareness rose with age between the age brackets of 7–10 years and 11–14 years (see **Figure 4**).

As in Experiment 1, significant developmental increases in awareness reports were evident under both low load (χ^2 (4, N = 96) = 24.60, $p < 0.001$) and intermediate load (χ^2 (4, N = 96) = 44.42, $p < 0.001$). Under low load, however, specific comparisons showed a significant increase only from 9–10 year-olds to 11–12 year-olds (13/24 reports vs. 18/20 reports, χ^2 (1, N = 44) = 6.73, p = 0.009) with no other significant differences between age groups ($p > 0.05$). Conversely, under intermediate load, a significant increase was seen between 9–10 to 11–12 year-olds (0/20 reports vs. 7/20 reports, χ^2 (1, N = 40) = 8.49, p = 0.003) and between 13–14 year-olds and adults (12/20 reports vs. 15/16 reports, χ^2 (1, N = 36) = 5.40, p = 0.002). Thus development of awareness outside the focus of attention is also evident in tasks that do not require disengagement from fixation.

Impact of perceptual load

The χ^2 analysis also revealed that significantly fewer awareness reports were given in the intermediate load group (36/96) than

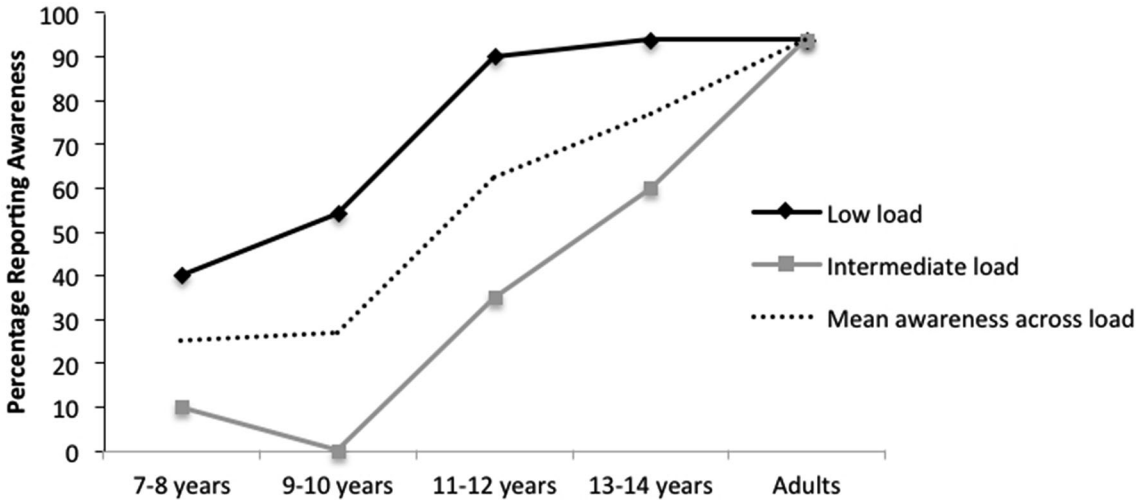

FIGURE 4 | Percentage of reported awareness of a peripheral critical stimulus (peripheral target) as a function of perceptual load (low vs. intermediate) and age, *N* = 192, in Experiment 2.

the low load group (69/96), χ^2 (1, N = 192) = 22.89, $p < 0.001$. These results replicate the previous findings regarding the effects of load on awareness in Experiment 1.

Separate χ^2 analyses showed that increasing perceptual load from low level to an intermediate level in the cross task caused a significant reduction in awareness for the critical stimulus at every age group of children. Awareness reports decreased from low load (8/20) to intermediate load (2/20) for 7–8 year-olds, (χ^2 (1, N = 40) = 4.8, p = 0.03); 9–10 year-olds, (13/24 vs. 0/20, χ^2 (1, N = 44) = 15.38, $p < 0.001$); 11–12 year-olds (18/20 vs. 7/20, χ^2 (1, N = 40) = 12.91, $p < 0.001$); and 13–14 year-olds (15/16 vs. 12/20, χ^2 (1, N = 36) = 5.4, p = 0.02). By contrast, there was no difference in the rates of awareness reported by adults under conditions of low load (15/16) vs. intermediate load (15/16) (see **Figure 4**). Thus children of ages up to 16 are more affected by an intermediate increase in the level of load, when compared to adults.

A 2 × 5 multi-way frequency analysis on the interaction of load (low, intermediate) by age (7–8, 9–10, 11–12, 13–14, adult) did not reach significance, χ^2 (4, N = 192) = 7.70, p = 0.10. However, a multi-way frequency analysis of load (low, intermediate) by age (9–10, 11–12, 13–14, adult) excluding the 7–8 year age group (which showed smaller effects of load on awareness, likely to be due to low baseline awareness levels) revealed a significant interaction, χ^2 (3, N = 152) = 8.25, p = 0.04. This interaction illustrated in **Figure 4** suggests that the effect of load on awareness became smaller as age increased.

The convergence of results across both tasks that involve and do not involve disengagement from fixation suggests an overall reduction in awareness outside the focus of attention that does not depend on the development of the ability to disengage from fixation. Overall, these findings support our hypothesis of smaller perceptual capacity in younger children compared to older children and in all children compared to adults.

EXPERIMENT 3

Experiments 1 and 2 demonstrate that for adults a moderate increase in the level of load did not affect the level of awareness for an unexpected critical stimulus. Based on previous research with similar tasks (Lavie and Cox, 1997; Cartwright-Finch and Lavie, 2007) we predicted that it would take a higher level of perceptual load to reduce awareness in a group of adult participants. To test this, and to confirm that for the tasks and experimental conditions (e.g., testing in the museum) used in Experiments 1 and 2 load does indeed modulate awareness in adulthood, we carried out a further task on an adult group with a higher level of perceptual load.

METHODS

Participants

Sixty-nine visitors to the Science Museum, London participated in the experiment. All reported normal or corrected-to-normal vision and were between 18–47 years old.

Apparatus and procedure

Apparatus and procedure were as in Experiment 1.

Stimuli

Stimuli were as in Experiment 2, but with low load (longer arm of cross subtended 3.9°; shorter arm subtended 0.7°) and high load (longer arm of cross subtended 3.9°; shorter arm subtended 3.31°) trials.

RESULTS

All participants performed the task adequately, with four or more correct line-length judgments entered. Excluded were participants who failed the final control trial (2), participants who provided unclear responses (2), and one participant who did not understand the awareness questioning. Remaining participants were divided equally between the two experimental groups: low load

(16) and high load (16). All of the participants who reported awareness of the critical stimulus (i.e., made a "Yes" response to the critical question) were able to describe correctly its location and at least two of its major features (shape, size or color). χ^2 analyses revealed that rates of awareness reports were significantly higher in the low load condition (15/16) than in the high load condition (2/16), (χ^2 (2, $N = 32$) = 21.20, $p < 0.01$).

Combining these data with those from the intermediate level of load in Experiment 2, one can see that rates of awareness under low (15/16) and intermediate (15/16) levels of load are equivalent and both are significantly greater than awareness in the high load condition (2/16) (see **Figure 5**). Experiment 3 confirms that increasing the level of load to a greater extent results in modulation of awareness for the critical stimuli in adult participants.

DISCUSSION

Our results reveal that awareness outside the focus of attention develops with age and that a small increase in the perceptual load of the attended task reduces awareness rates for children (aged 7–14 years) but not adults. The effects of age and load on awareness for a stimulus in the visual periphery converged across tasks that involved disengagement from fixation (Experiment 1) and tasks that did not involve this disengagement (Experiment 2). This demonstrates an overall increase in awareness outside the focus of attention with age. Note that this increase in awareness with age was found in tasks involving low and moderate levels of load. The fact that younger children were more prone to IB in such tasks provides support for our hypothesis that perceptual capacity is increased in older children compared to younger children with these levels of load disproportionately taxing the smaller capacity of the younger ages. This finding—combined with the fact that, across development, a small increase in the level of load that had no effect on awareness in adults significantly reduced the awareness for an unexpected critical stimulus—demonstrates a smaller perceptual capacity in younger children compared to older children and in all children compared to adults. In adults however, a higher level of perceptual load was required to modulate awareness (Experiment 3). This finding supports our proposal that development of attention involves maturation of awareness for information that is not part of the attended task. Consequently, the development of perceptual capacity plays an important part in the development of attention, in addition to the well-known development of cognitive control. An increase in capacity would lead to greater availability of resources, resulting in less of an impact (proportionately) of increases in the level of load.

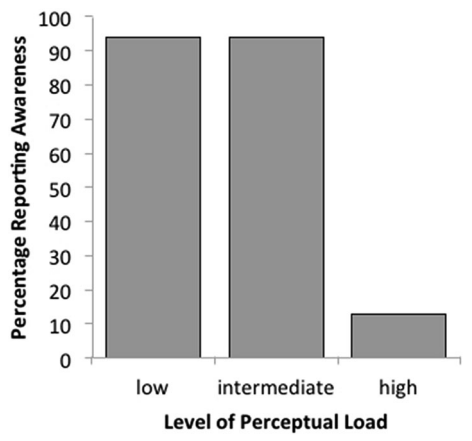

FIGURE 5 | Percentage of reported awareness of a peripheral critical stimulus (peripheral target) as a function of perceptual load (low vs. intermediate vs. high) in adults (Experiments 2 and 3).

It is perhaps important to note that alternative accounts for the present findings in terms of inability to follow verbal probing and instruction at younger ages are highly unlikely for the following reasons. All participating children were school age, which in the UK means they already have had 3–6 years of formal education (performance of 7–8 and 9–10 year-olds did not differ) and therefore much experience following verbal instructions. Moreover, due to exclusion criteria, all these children performed correctly on the control trial (and the cross task generally), indeed only 11 of 203 (Experiment 1) and 7 of 210 children (Experiment 2) were excluded for failing the control trial (failures that may have resulted from undiagnosed reduced visual acuity). Furthermore, the experimenter's notes indicated that the children of all ages generally expressed a high level of confidence in their awareness reports: typically either a clear "yes" and a point to the area in the screen where the critical stimulus appeared, or a flat "no". This suggests that they have clearly understood the question, and perhaps also that responses tended to be a direct reflection of their perceptual trace rather than the result of elaborate deliberation. This goes some way towards alleviating concerns regarding response criteria, although of course without formally measuring sensitivity verses criterion (e.g., using signal detection paradigms) alternative accounts for awareness in terms of effects on response criteria remain viable. An important extension of this work would be to examine the effects of load and age on awareness reports using a signal detection paradigm.

The development of global vs. local processing should also be considered here. Previous research has highlighted age-related changes in the bias for processing local over global scene features (and *vice versa*). Predominantly, a local processing bias is noted early in development with a global precedence effect emerging from age 5 (e.g., Poirel et al., 2008; Vinter et al., 2010), perhaps a consequence of immature hemispheric communication at younger ages (Moses et al., 2002; and see Smith and Chatterjee, 2008, for a review). Moreover, some suggest that this global precedence can in fact only be seen much later in development, with local precedence appearing to dominate perceptual organization until adolescence, followed by a gradual transition to more a global processing style (Dukette and Stiles, 1996; Mottron et al., 1999, 2003; Enns et al., 2000; Porporino et al., 2004; Kimchi et al., 2005; Scherf et al., 2009). However, evidence for the reverse pattern has also been found, with demonstrations that 6 and 10 year-olds showed strong global bias, stronger even than that of adults (Mondloch et al., 2003), and that infants show greater sensitivity to global than to local structure in visual stimuli

(Quinn and Eimas, 1986; Ghim and Eimas, 1988; Freeseman et al., 1993; Quinn et al., 1993; Frick et al., 2000). It has been argued that this contradiction may be due to differences in task parameters that differentially affect children's perceptual biases (Scherf et al., 2009).

Could these developmental changes in hierarchical processing account for the better ability to detect the critical stimulus in the periphery at older ages? For example, could the development of awareness of the critical stimulus in the periphery be attributed to the development of a more global processing strategy that encompasses both the task stimuli at fixation and the periphery? This is somewhat unlikely for the following reasons. The critical stimulus was in fact smaller in size than the lines used in the line-length discrimination task. It is therefore unclear whether development of global precedence with age would lead to increased awareness of this stimulus. In addition, the convergence of results across Experiment 2 (which, notwithstanding our first point, could be said to encourage a more global processing strategy because of the reduced spatial certainty and the presence of all stimuli in the periphery) and Experiment 1 (which could be said to encourage a more spatially-local processing strategy) suggest that this factor was unlikely to play a crucial role. Nevertheless, future research assessing awareness in tasks that involve both local and global elements of task displays under various levels of load (e.g., Navon Figures) could prove interesting in revealing any potential interactions between these factors.

INCREASED FOCUS IN YOUNGER CHILDREN

It is interesting to consider the flipside of the capacity development established in this study. The age-related increases in awareness outside the focus of attention demonstrate that there will be more cases where younger children are unaware of stimuli outside their more narrow focus of attention. In such situations younger children will appear to have a higher level of focus than older children, and under moderate increases in the task load children will be more focused than adults. This fits with anecdotal observations that children can appear more oblivious to their surroundings, and be harder to detract from their current object of focus.

Indeed, our conclusions are consistent with Memmert's (2006) findings (discussed earlier) that 8 year-old children exhibited lower awareness rates than 13 year-olds and adults on the IB task with the gorilla. However, the dynamic video clip paradigm that was used in this study allowed participants to freely move their eyes. Thus any reports of blindness to the "gorilla" while tracking the ball passes may be due to blurring on the retina caused by intersaccadic suppression during eye movement rather than inattention. In keeping with the well-established finding that orienting of gaze matures with age (Pearson and Lane, 1990), it is likely that children's reduced ability to reorient gaze from the ball to the "gorilla" has contributed to the observed differences in awareness between the age groups. In contrast, our task used short exposure durations, which preclude eye movement, and thus ensure that our findings reflect attentional effects rather than eye movements.

Our findings can therefore be more clearly attributed to a narrowing of attention which leads to the exclusion of irrelevant information under higher levels of perceptual load. Importantly this effect requires only small increases in perceptual load for children.

Note that although rates of IB were increased overall for the younger children (including in the low load condition) this does not suggest the low level of load was sufficient to exhaust their smaller capacity since a further reduction in awareness was found with the moderate increase in load for all ages, including the youngest. Indeed, an interesting prediction arises whereby finer grained increases in the levels of perceptual load would be sufficient to exhaust capacity for children of younger, but not older, ages. This would be an interesting direction for future research.

RECONCILING INCREASED FOCUS AND REDUCED COGNITIVE CONTROL

How do we reconcile the fact that children have, in some situations, higher levels of focus and yet reduced cognitive control? The key is firstly to consider the nature of the irrelevant distractor item. Cognitive control processes are only required to control against distractors that compete with the target stimulus for selection—for example, when the distractor is associated with a different target response or is a very salient stimulus such as a face. However, non-competing stimuli do not require cognitive control over selection. Therefore, when cognitive control processes are loaded (e.g., working memory) there is an increase in the level of processing of items that compete for the response, but not of non-competing irrelevant information (Carmel et al., 2012). This finding, together with our application of load theory to development suggests that smaller increases in cognitive control load will lead to increased distraction and greater processing of irrelevant competing distractors by younger children due to cognitive control immaturity.

In our study, however, the irrelevant distractor is non-competing as it is a small square presented while participants are performing a line discrimination task. The processing of non-competing distractors does not depend on cognitive control but depends instead on perceptual processes. With this in mind, a different developmental pattern of results is expected for the processing of these stimuli. Under low load (i.e., when perceptual capacity limits are not reached), we would not expect to see increased processing of irrelevant non-competing items with maturation. Indeed, we would expect this equivalent performance across age groups to remain even if cognitive control processes were loaded. Comparing our findings under low load with those of Huang-Pollock et al. (2002) demonstrates this dichotomy. In their study, the distractor competed for a response (letter distractor and letter search attended task) and, as predicted, under low load the children showed increased distractor processing. This interference was then eliminated by a smaller increase in perceptual load (than for adults). In our study, however, the irrelevant item was non-competing and we show the opposite pattern—distractor processing was lower in the children than the adults under both low and intermediate levels of perceptual load. While this was expected under intermediate levels of load (where the task loaded the children's smaller capacity, but not that of the adults) it was not predicted that age-related changes would be evident

under low load. As mentioned above, the lack of equivalent performance in this condition is likely due to age-related changes in the ability to disengage from the cross stimulus and shift the focus of attention. Future research involving the manipulation of cognitive control vs. perceptual load, and competing vs. non-competing distractors, would undoubtedly be fruitful.

IMPLICATIONS

The results we present here have implications for attentional performance in a number of situations. Given that a moderate rise in perceptual load leads to a greater increase in focused attention for younger children (compared to older children and adults), it is likely that performance on paradigms such as Garner and Stroop tasks could be improved in younger age groups by the addition of perceptual load—provided that these are performed with some separation between the relevant and irrelevant dimensions so that attention can be clearly engaged in the relevant task rather than the irrelevant processing with increased perceptual load. Aside from these experimental situations, our findings also have practical consequences whereby the modulation of perceptual load could be used to improve the focus of attention in young children, and hence the efficacy of learning tools.

The present findings that children have lower rates of awareness than adults and that a moderate increase in perceptual load that had no effect on awareness in adults, was sufficient to increase IB rates in children also have interesting neural implications. They imply that unattended stimuli in IB tasks should evoke less activity in children than adults due to their smaller perceptual capacity. Furthermore, these neural modulations would be found at lower levels of load in children, compared to the level needed to reduce neural response to unattended stimuli in adults.

Overall, our findings demonstrate that maturation involves the development of awareness outside the focus of attention and an increase in perceptual capacity. This leads to a greater likelihood of IB, namely enhanced focus and resistance to irrelevant intrusions into awareness in the younger children. This must be considered together with evidence of age-related changes in cognitive control processes to understand fully the development of selective attention. Looking at the development of the latter in isolation does not accurately reflect the full picture.

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Complexities in understanding attentional functioning among children with fetal alcohol spectrum disorder

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Parental reports of attention problems and clinical symptomatology of ADHD among children with fetal alcohol syndrome disorder (FASD) were assessed in relation to performance on standardized subtests of attentional control/shifting and selective attention from the Test of Everyday Attention for Children (TEA-Ch; Manly et al., 1998). The participants included 14 children with FASD with a mean chronological age (CA) of 11.7 years and a mean mental age (MA) of 9.7 years, and 14 typically developing (TD) children with no reported history of prenatal exposure to alcohol or attention problems with a mean CA of 8.4 years and a mean MA of 9.6 years. The children with FASD were rated by their caregivers as having clinically significant attention difficulties for their developmental age. The reported symptomatology for the majority of the children with FASD were consistent with a diagnosis of ADHD, combined type, and only one child had a score within the average range. These reports are consistent with the finding that the children with FASD demonstrated difficulties with attentional control/shifting, but inconsistent with the finding that they outperformed the TD children on a test assessing selective attention. These findings are considered within the context of the complexity in understanding attentional functioning among children with FASD and discrepancies across sources of information and components of attention.

Keywords: fetal alcohol spectrum disorder, attentional control, selective attention, attention deficit hyperactivity disorder, test of everyday attention for children, prenatal exposure to alcohol, attention deficit, attention switching

Common parental and anecdotal reports of general attentional problems among children with fetal alcohol spectrum disorder (FASD), a non-diagnostic umbrella term that refers to a spectrum of effects resulting from prenatal exposure to alcohol (PEA), seem consistent with high rates of clinical diagnoses of attention deficit hyperactivity disorder (ADHD) in this group. Yet, the complexity in evaluating general attentional processing from different perspectives and in relation to the many different components and theories of attention suggests a more nuanced reality. Accordingly, we examined the relationship among parental report of attentional problems and ADHD symptomatology in relation to performance on two standardized subtests of each of the essential attentional components of distractibility and cognitive control/switching among children with FASD as compared to typically developing (TD) children matched for mental age (MA).

The level of PEA is generally related to the extent of impairment associated with FASD, although the degree and type of impairment varies depending on a number of factors such as the timing of the PEA, maternal behaviors, and environmental conditions (Stratton et al., 1996; Chudley et al., 2005). Fetal alcohol syndrome (FAS), a specific pattern of birth defects associated with excessive maternal alcohol consumption during pregnancy, represents the most severe consequence of PEA. These birth defects, which historically included growth deficiency, a pattern of facial anomalies, and central nervous system dysfunction, were first described in the medical literature in the early 1970s (Jones and Smith, 1973; Jones et al., 1973). The criteria for FAS have remained largely the same during the past four decades, although they are now more clearly defined through the development of diagnostic procedures (e.g., Astley, 2004; Chudley et al., 2005; Hoyme et al., 2005).

According to the prevailing Canadian guidelines (Chudley et al., 2005), the term FASD includes the diagnoses of FAS, partial fetal alcohol syndrome (pFAS), and alcohol-related neurodevelopmental disorder (ARND). The diagnostic criteria for all three include PEA and significant brain dysfunction. A diagnosis of FAS also requires growth deficiency (i.e., weight and/or height $<$10th percentile) and certain characteristic facial features (i.e., short palpebral fissures, flat philtrum, and thin upper lip) along with PEA and significant brain dysfunction. Partial FAS is diagnosed when only two of the three characteristic facial features are present with or without growth deficiency. A diagnosis of ARND is provided when significant brain dysfunction has occurred as a result of PEA. Within this diagnostic framework, confirmed maternal alcohol use during pregnancy is necessary but not sufficient for an alcohol-related diagnosis, as brain dysfunction must also be evident. All individuals diagnosed with an alcohol-related disorder based on the Canadian guidelines are impacted by PEA and considered to have static encephalopathy (i.e., non-progressive brain damage) as a result.

Although all children with FASD present with broad deficits (i.e., significant impairment in three or more domains of brain

functioning), a specific profile of brain dysfunction unique to FASD has not been identified (Chudley et al., 2005). Rather, the literature seems to point to a "generalized deficit in processing complex information" (Kodituwakku, 2007, p. 199; for examples, see Aragón et al., 2008), as evidenced by findings of a wide range of reported cognitive deficits associated with PEA, including those of general cognition (Coles et al., 1991), learning and language (Mattson and Riley, 1998), executive function (Rasmussen, 2005), visual-spatial processing (Olsen et al., 1998), memory (Coles et al., 2010), and attention (Lee et al., 2004). Similarly, in a 25 year longitudinal study on the effects of PEA in a primarily middle-class population in Seattle, Streissguth (2007) identified problems throughout childhood in attention, visual-spatial memory, speed of information processing, IQ level, and arithmetic. In particular, attentional difficulties have been cited as sequelae of prenatal alcohol exposure that lead to many of the concomitant difficulties that are reported among individuals with PEA (Kopera-Frye et al., 1997).

THE ATTENTIONAL FUNCTIONING OF CHILDREN WITH PEA

The extent of the attention problems among children with FASD (e.g., Nanson and Hiscock, 1990; Oesterheld and Wilson, 1997; Malbin, 2002) led to a notion of attention problems as core deficits (Kopera-Frye et al., 1997). Disruption in attentional functioning as a consequence of PEA appears to be evident almost from birth (Streissguth, 2007); for example, PEA was significantly related to poor habituation to light in exposed human infants one or two days after birth (Streissguth et al., 1983). These problems appear to persist through infancy. In a study of the RTs (response times) of 6.5 month old infants drawn from a larger longitudinal study of the effects of PEA on infant cognition, Jacobson et al. (1994) found that prenatal alcohol exposure was associated with an increased latency to shift eye gaze to a visual stimuli after the stimulus was presented, which was thought to reflect slowed information processing. Similarly, in a study of attentional regulation among 6 month old infants with varying levels of PEA using cardiac-orienting responses in response to the presentation of auditory (tones) and visual (faces) stimuli, Kable and Coles (2004) found that infants whose mothers scored high on a substance abuse checklist took longer to reach the heart rate deceleration criteria following the onset of a new event as compared to infants whose mothers scored low on the checklist. This finding was thought to reflect difficulties in the initiation of attention, and suggested a decrease in the speed with which information is encoded.

Attention difficulties arising from PEA continue into childhood (e.g., Lee et al., 2004; Kooistra et al., 2010). For example, children with PEA often meet criteria for ADHD based on clinical interviews (Koren et al., 2003; Fryer et al., 2007; Kooistra et al., 2010), score higher than same-aged peers on behavioral questionnaires that assess attention problems (Nanson and Hiscock, 1990; Brown et al., 1991; Coles et al., 1997; Lee et al., 2004; Nash et al., 2006; Astley et al., 2009), and are rated as more inattentive at school than children of mothers who did not (Brown et al., 1991). Yet, even as children with PEA consistently present with behavioural symptoms of inattention (e.g., Fryer et al., 2007), they do not always demonstrate deficits on experimental or clinical measures of attentional functioning. One reason for this discrepancy might be that children with PEA who exhibit externalizing problems and hyperactivity are more difficult to manage and are, therefore, more likely to be referred to a clinic for diagnosis and treatment (Coles et al., 1997).

Attention control/shifting attention

Mirsky et al. (1991) defined the shift component of attention as the "ability to change attentive focus in a flexible and adaptive manner" (p. 112), and performance on the Wisconsin Card Sorting Task (WCST) was used to measure this aspect of attention in their model. Performance on the WCST appears to be related to rates of PEA with deficits commonly found among those with greater (Kodituwakku et al., 1995, 2001b; Coles et al., 1997; McGee et al., 2008; Vaurio et al., 2008), but not lower (Richardson et al., 2002; Burden et al., 2005), levels of PEA. For example, Astley et al. (2009) found that children with FASD who would be considered to have an alcohol-related disorder according to the Canadian diagnostic guidelines made significantly more errors on a computerized version of the WCST than both children without PEA and children with *mild ARND* (i.e., defined as PEA but significant impairment in less than three areas of brain function). Similarly, Connor et al. (2000) found that a clinical group of diagnosed adults with PEA consistently demonstrated extreme deficits on the WCST, whereas adults with lower levels of PEA did not.

The WCST may also not be a good measure of attention shifting for children with FASD, as it is a complex task that relies on broader abilities than attention, especially executive function which appears to be an area that is impaired among individuals with PEA (Connor et al., 2000; Kodituwakku et al., 2001a; Rasmussen, 2005). Accordingly, in an attempt to use an alternative paradigm of attention shifting, Mattson et al. (2006) administered a computerized experimental task that involved both the visual and auditory modalities to 9–14 years old children considered to have experienced heavy PEA. The children exposed to high levels of prenatal alcohol were slower than the TD children when required to switch back and forth between the auditory (high tone, low tone) and visual (red square, green square) stimuli that were each presented one at a time with varying interstimulus time intervals. As they were not less accurate than the TD children when full scale IQ was used as a covariate, Mattson et al. (2006) suggested that children with FASD were capable of switching between modalities, but that it required more cognitive effort for them.

Difficulties in shifting attention are supported by the performance of children with heavy PEA on other measures that involve an aspect of switching. For example, Vaurio et al. (2008) found that children with PEA who also met criteria for ADHD demonstrated significant difficulties in comparison to both TD children and children with ADHD on the Trail Making Test – Part B (e.g., Reitan and Wolfson, 1993) which requires switching between sequencing a set of numbers and letters. These findings are consistent with the performance of children diagnosed with an alcohol-related disorder. For example, Rasmussen and Bisanz (2009) and Astley et al. (2009) found that the children with FASD demonstrated significant difficulties switching between letters and

numbers on the Trail Making Test from the Delis-Kaplan Executive Function System (Delis et al., 2001).

Selective attention

Selective attention refers to the ability to direct attentional resources to a task and filter distracting stimuli (Mirsky et al., 1991). Children (Burden et al., 2005), adolescents (Streissguth et al., 1994), and adults (Connor et al., 1999) with PEA demonstrate difficulties on digit cancellation tasks used to assess selective attention. The attention shifting task administered by Mattson et al. (2006) also included visual and auditory focused attention conditions that required the participants to maintain focused attention to stimuli in one modality while ignoring visual and auditory distracters. Mattson et al. (2006) found that the children with PEA were less accurate in the focused attention conditions and consistently responded slower to visual stimuli than TD children, indicating a "consistent and significant deficit in visual focused attention" (p. 366).

THE PRESENT STUDY: ATTENTIONAL CONTROL AND SELECTIVE ATTENTION AMONG CHILDREN WITH FASD

The aim of the present study was to examine the attentional functioning of children with FASD in relation to MA matched TD children. We used a strict criterion for measuring PEA, by including only those children diagnosed with an alcohol-related disorder, rather than children exposed to prenatal alcohol. Children diagnosed with an alcohol-related disorder using the Canadian guidelines (Chudley et al., 2005) have been exposed to prenatal alcohol and are also *affected* by the exposure. This distinction is particularly important in the search for deficits exhibited by children with FASD, since not all children exposed to prenatal alcohol are later identified with FASD (Stratton et al., 1996). The dosage and timing of the prenatal alcohol experienced by children in this study, although not measured specifically, was sufficient to produce brain dysfunction.

The issue of developmental level was addressed by comparing the performance of children with FASD with the performance of TD children at the same developmental level, as indicated by MA as measured by the Leiter International Performance Scale – Revised (Leiter-R; Roid and Miller, 1997). Due to the typically lower MAs among children with FASD, comparing them with TD children of the same chronological age (CA) is potentially misleading, particularly on abilities such as those of visual attention in which developmental changes occur (e.g., Enns and Girgus, 1985; Pastò and Burack, 1997). Thus, comparisons with TD children of the same MA allow researchers to determine whether attentional performance is developmentally appropriate or problematic in relation to a priori differences in level of functioning that are not linked to FASD per se (for a discussion of relevant issues, please see Burack et al., 2004). In this study, the Leiter-R (Roid and Miller, 1997), an entirely non-verbal visual measure of cognitive ability, was used to estimate developmental level. Using this measure, children with FASD were matched to TD children on MA (mental age) so that group differences could then be attributed to characteristics unique to the children with FASD.

Attention is one of the brain domains recommended to be assessed during the neuropsychological assessment for FASD (Chudley et al., 2005); significant impairment in this domain could reflect a clinical diagnosis of ADHD and/or poor performance on clinical measures that require attention. In our study, the Conners' Rating Scale (Conners, 1997) was used to assess behavioral symptoms of ADHD, and subtests from the Test of Everyday Attention for Children (TEA-Ch; Manly et al., 1998) were used to assess visual attention, particularly selective attention, and attentional control/shifting. The TEA-Ch was considered an appropriate choice for children with FASD, as the test was designed to measure various components of attention without relying on other abilities, such as memory, verbal comprehension, or motor speed (Manly et al., 2001), any of which might be impaired in children with FASD (e.g., Stratton et al., 1996).

MATERIALS AND METHOD

PARTICIPANTS

The participants included 14 children (9 females) with FASD with a mean CA of 11.73 (SD = 1.36) years, a mean MA of 9.65 (1.47) years, and a mean brief non-verbal IQ (intelligence quotient) of 83 (10.59), and 14 TD children (9 females) with no reported history of PEA or attention problems with a mean CA of 8.42 (1.39) years, a mean MA of 9.59 (1.55) years, and a mean brief non-verbal IQ of 114.93 (9.92). The groups were matched on gender and within four months of MA based on the Leiter-R (Roid and Miller, 1997), a standardized measure of non-verbal intelligence. The children with FASD did not differ from the TD children on mean MA, $t(26) = 0.115$, $p = 0.909$, but were significantly older, $t(26) = 6.364$, $p = < 0.001$, and had significantly lower non-verbal IQs, $t(26) = -8.217$, $p = < 0.001$. Descriptive statistics for the two groups are presented in **Table 1**.

The children with FASD were recruited from the Asante Centre for Fetal Alcohol Syndrome, a FASD assessment and diagnostic centre located in the Fraser Region of British Columbia (BC) that provides assessment to individuals throughout BC. A staff member from the Asante Centre contacted legal guardians of children between 8 and 13 years of age who underwent a FASD assessment through the centre, and invited them to participate in the study. Twenty-two children were initially tested, but eight were eliminated from the study as the MAs of five children fell outside of the target developmental age range for this study (i.e., 7 to 12 years), two children did not have confirmed PEA, and a TD match was not found for one child. All of the children with FASD had been assessed in accordance with the Canadian diagnostic guidelines (Chudley et al., 2005) and received one of three alcohol-related diagnoses, FAS ($n = 1$), pFAS ($n = 3$), or ARND ($n = 10$). Eight of the participants with FASD were rated by the diagnostic team as having significant attention problems, four were rated as having mild to moderate attention problems, and only one was rated as having no attention problems (data for one participant was missing). Nine of the children with FASD had a confirmed diagnosis of ADHD. None of the children with FASD were living with their mothers and only two with their birth fathers; 6 with foster families; 4 with adoptive families; two with relatives. All of the children for whom the information was available ($n = 12$) experienced postnatal risk (e.g., multiple placements; abuse/neglect). Ten of the children for whom the information was known ($n = 11$)

Table 1 | Descriptive Statistics for the participants with FASD and TD participants.

Group	*N*	CA		MA		Brief non-verbal IQ		% Male	% Caucasian
		M	*SD*	*M*	*SD*	*M*	*SD*		
FASD	14	11.73	1.36	9.65	1.47	83.07	10.59	35.7	57.1
TD	14	8.42	1.39	9.59	1.55	114.93	9.92	35.7	92.9

CA, chronological age; MA, mental age; Brief IQ, brief non-verbal IQ score from the Leiter-R.

experienced other prenatal exposures in addition to alcohol (e.g., tobacco; marijuana). Five children regularly took medication to manage their attentional difficulties and the caregivers of these children were asked to not give the medication on the day of testing. Three of these children were tested off their medication. Two were on medication during the time of the assessment (one because the caregiver forgot and one because of the type of medication). The children who were tested off their medication had taken their last dose at least 24 hours before the testing session.

The TD children were recruited from communities in British Columbia through the use of community postings, school contacts, and the distribution of flyers to acquaintances and colleagues. Only a parent or caregiver knowledgeable about the child's prenatal history were included in the study.

MEASURES

The Leiter International Performance Scale – Revised (Leiter-R)

The Leiter-R (Roid and Miller, 1997) is a non-verbal measure of cognitive ability developed for use with individuals from 2 to 20 years of age. The Leiter-R is entirely non-verbal and performance is not timed. It is comprised of 20 subtests organized into the two major areas of Reasoning and Visualization (10 subtests), and Attention and Memory (10 subtests). Standard scores are generated for each of the composites under these major areas. The Brief IQ Composite (four subtests) was used to estimate the developmental level or the MA of the participants in this study.

The Conners' Rating Scale: Long Version – Parent Form (CPRS:L)

The CPRS:L (Conners, 1997) is a rating scale administered to caregivers of children and adolescents to aid in the assessment of ADHD and other comorbid issues. The CPRS:L includes scales that correspond to the DSM-IV diagnostic criteria for ADHD. The results of this rating scale were used as a measure of the degree to which each child displays clinically significant attention problems.

The Test of Everyday Attention for Children (TEA-Ch)

The TEA-Ch (Manly et al., 1998) was designed to assess various components of attention in children. The TEA-Ch is comprised of nine subtests that are used to measure focused (selective) attention, sustained attention, and attentional control/switching. The tasks are "game-like" and require little memory or verbal comprehension skills, which makes the TEA-Ch a potentially appropriate tool for use with children with disabilities such as FASD. The four subtests that involve visual attention were administered in this study. Two of the subtests involved selective attention (Sky Search and Map Mission), and the other two involved attentional control/switching (Creature Counting and Opposite Worlds). Norms from the TEA-Ch which were derived from 293 children and adolescents between the ages of 6 and 16 years.

1. On the *Sky Search* subtest, the children were required to quickly circle target pairs among distracters on paper. Sky Search includes a trial with no distracters in order to control for motor speed. Scores on the Sky Search task are based on the number of correctly identified targets, as well as the amount of time taken to identify each target.
2. On the *Map Mission* subtest, the children were required to locate as many target stimuli as possible on a city map within a time limit. Map Mission scores are based on the number of target shapes correctly identified on a display.
3. On the *Creature Counting* subtest, the children were required to switch between counting forward and backward in response to visual targets. Participant scores are based on accuracy in counting, and time taken to complete the task.
4. On the *Opposite Worlds* subtest, the children were first required to name aloud the numbers "1" and "2" that they saw displayed along a path on paper. In the "opposite world" they were required to say "1" when they saw a "2," and say "2" when they saw a "1." The scores on this subtest are based on the time taken to correctly complete the task.

PROCEDURE

Ethics approval was obtained from the Human Research Ethics Board at McGill University. The legal guardians and caregivers (when different) provided signed informed consent prior to testing. Verbal assent was also obtained from the participating child. In the case of the TD participants, the child's parent completed

Table 2 | Mean *T*-scores (standard deviations) based on MA for both groups on the Conners' subscales.

	FASD ($n = 13$)		TD ($n = 12$)	
Conners' subscale	***M***	***SD***	***M***	***SD***
Cognitive problems/inattention	79.08	8.78	45.75	2.22
DSM-IV index: inattentive	77.00	9.97	45.50	2.88
DSM-IV index: hyperactive-impulsive	72.92	13.20	50.92	4.34
DSM-IV index: total	76.77	10.66	47.75	3.31

a brief questionnaire to confirm that the child did not experience prenatal substance exposure, or have a history of learning, behavior, or attentional problems. The alcohol-related diagnosis, ratings for the attention-deficit hyperactivity brain domain and the postnatal risk, and other prenatal substance exposures for each of the children with FASD were obtained from the Asante Centre diagnostic assessment file.

All of the children were tested in a quiet room with limited distractions. The majority of the children with FASD were tested at the Asante Centre. One participant was tested in their home and another participant was tested at another community agency. The TD children were either tested at the Asante Centre, another community agency, or their school. All of the assessment measures were administered by an experienced clinician trained in test administration.

RESULTS

CAREGIVER RATINGS OF ATTENTION DIFFICULTIES

The mean ratings on the Conners' scale for each group are presented in **Table 2**. As expected, the participants with FASD were rated by their caregivers on the Conners' as having clinically significant attention difficulties for their developmental age. This was not the case for the MA-matched TD participants, who had significantly lower *T*-scores on all subscales. These conclusions were supported by the following evidence. The caregiver reported significant cognitive problems/inattention in relation to their MA ($M = 79.08$, $SD = 8.78$; range 67–90) for all of the children with FASD. None of the children with FASD scored within the average range on the diagnostic-oriented scale for ADHD, inattentive type, and only two scored within the average range on the diagnostically oriented scale for ADHD, hyperactive-impulsive type. The reported symptomatology for the majority ($n = 10$; 76.9%) of the children with FASD ($n = 13$) were consistent with a diagnosis of ADHD, combined type, as measured by the Conners' (i.e., *T*-score of 70 or above), and only one child had a score within the average range. None of the TD children displayed symptoms of ADHD.

GROUP COMPARISON ON THE TEA-Ch

The mean scores for each of the subtests from the TEA-Ch, which were administered to assess visual selective attention (the Sky Search and Map Mission subtests) and attention control/switching (the Opposite Worlds and Creature Counting subtests) are presented in **Table 3**. Differences between the groups as assessed by *t*-tests were found for only two comparisons. Inconsistent both with previous evidence from children with FASD and with their behavioral presentation, the children with FASD as a group scored within the average range for their developmental level on all but one of the standardized subtests (Creature Counting). The finding of average levels of focused attention on the TEA-Ch subtests in relation to developmental level is consistent with evidence from children with ADHD (Heaton et al., 2001).

Group comparisons on measures of attention control/shifting

The children with FASD and TD children did not differ in speed or accuracy on the Opposite Worlds task [Same World $t(25) = -0.251$, $p > 0.05$; Opposite World $t(25) = 0.469$, $p > 0.05$], however, the children with FASD demonstrated difficulties on Creature Counting as only three children with FASD performed within the average range for their MA on the accuracy component of this subtest. The children with FASD were less accurate in their counting than TD children matched on MA [$t(16.05) = -3.463$, $p = 0.003$], but did not differ from TD children on time taken to complete the task [$t(17) = 0.281$, $p > 0.05$]. However, timing was counted only for the seven children with FASD who accurately answered more than two of the seven trials.

Table 3 | Comparison of mean TEA-Ch subtest scores (calculated based on MA) between FASD and TD groups.

	FASD		TD			
Subtest	***n***	***M* (SD)**	***n***	***M* (SD)**	***t***	***p***
Selective attention subtests						
Sky search						
Correct	14	10.36 (2.21)	14	8.86 (2.35)	1.742	0.093
Timing per correct target	14	9.21 (2.94)	14	7.71 (2.34)	1.495	0.147
Map mission						
Targets found	14	11.79 (3.09)	14	8.86 (3.06)	2.519	0.018
Attention control/switching subtests						
Creature counting						
Correct	14	5.64 (1.65)	13	9.62 (3.82)	−3.463[a]	0.003
Timing	7	10.14 (3.08)	12	9.67 (3.80)	0.281	0.782
Opposite Worlds						
Same World	14	9.14 (2.57)	13	9.46 (3.93)	−0.251	0.804
Opposite World	14	8.79 (3.22)	13	8.31 (3.52)	0.369	0.715

[a] *df = 16.05 (unequal variances).*

Group comparisons on measures of selective attention

The children with FASD outperformed the TD children on the Map Mission task [$t(26) = 2.519$, $p = 0.018$], but did not differ from them on the time taken to find each target [$t(26) = 1.495$ $p > 0.05$] on the Sky Search task. The children with FASD also outperformed the TD children on the number of targets found on the Sky Search task, but this difference did not reach the conventional levels of statistical significance [$t(26) = 1.742$, $p = 0.09$].

DISCUSSION

The findings from this study provide insight into the complexity of the real-world perceptions and manifestations of attentional processing among children with FASD. This complexity is manifest as a gap between everyday observational and clinical methods of assessment. Consistent with previous evidence, the 14 children with FASD in this study, all of whom were impacted by PEA as assessed with the Canadian diagnostic guidelines (Chudley et al., 2005) and functioned at MAs between 7 and 12 years, received high ratings of attention problems by their caregivers that were commensurate with a high incidence of a clinical diagnosis of ADHD. Yet, their performance on clinical subtests of attention from the TEA-Ch (Manly et al., 1998) reflected a more nuanced pattern of attentional functioning.

These results also highlight the need to provide more fine-tuned accounts that include multiple sources of information about various components of attention. Consistent with previous evidence that individuals with FASD, especially those with high rates of PEA, appear to have difficulties with attentional shifting (e.g., Coles et al., 1997; Kerns et al., 1997; Kodituwakku et al., 2001a,b; Mattson et al., 2006), the children with FASD in this study performed below average for their MA, and significantly worse than the MA-matched TD children, on the Creature Counting subtest of the TEA-Ch, which is used to assess task switching, in this case, between counting forward and counting backward. However, this diminished performance might also be a function of the difficulties associated with arithmetic that have been reported among children with FASD (Streissguth et al., 1994; Goldschmidt et al., 1996; Howell et al., 2006; Jacobson et al., 2011).

In contrast, based on their performance on the Sky Search and Map Mission subtests of the TEA-Ch, the children with FASD demonstrated an ability to attend to relevant stimuli in the presence of distracters at a level that appeared to be consistent with their MA as based on non-verbal cognitive ability. Although discrepant with findings of impaired selective attention among children with FASD (Connor et al., 1999; Streissguth et al., 1999; Burden et al., 2005; Mattson et al., 2006), the findings of average or better levels of performance reported here are consistent with evidence that children with ADHD also perform within the average range on the visual selective attention subtests of the TEA-Ch (Heaton et al., 2001; Manly et al., 2001). As the behavior of both children with ADHD and those with FASD is characterized as distractible and inattentive (American Psychiatric Association, 1994; Hudziak et al., 2004), the commensurate findings from the two groups suggest that the subtests of the TEA-Ch may be measures of selective attention that are not confounded with other aspects of attention, such as vigilance or control, that have been cited as the source of the attentional problems at least among children with ADHD (Manly et al., 2001). Conversely, the TEA-Ch subtests may not be sufficiently sensitive to detect nuanced real-world attentional problems. Additionally, differences in methodologies, such as matching on CA rather than MA (Connor et al., 1999) and using RT, rather than accuracy, to assess selective attention performance (Mattson et al., 2006) could account for the discrepancies between this and other studies with regard to performance on the TEA-Ch by children with FASD.

The implications of this study must be considered within the constraints of research on persons with FASD. Due to the difficulties in recruiting participants who met the guidelines for FASD and were able to complete the task, the number of participants in this study precluded comparisons among subgroups with regard to variables such as the specific FASD diagnosis, gender, diagnosis of ADHD, medication history, developmental level, living situation, and other life circumstances. The findings may also have been affected by maternal smoking during pregnancy which was not considered in this study but has possible links with ADHD symptoms in children (Thapar et al., 2003; Langley et al., 2005), and, therefore, may account for some of the observed attentional difficulties among the children with FASD in this study. As is common, the group of children with FASD had a mean IQ score in the low average range, and therefore, was matched to the group of TD children on MA in order to ensure that any of the expected deficits in attention would be specific to the task rather than to a priori differences in developmental level. Although the inevitable outcome is that the children with FASD were chronologically older, this type of MA matching is advocated among developmental researchers in the study of attention and related areas of functioning among persons with lower IQ levels (for reviews, see Iarocci and Burack, 1998; Burack et al., 2001, 2004, 2013). The shortcoming of this matching strategy is that it eliminates the possibility of controlling for differences in verbal proficiency between participants, although the impact of verbal differences on our findings was likely minimal as the tasks were non-verbal and were successfully completed by the participants. In addition, despite being a common methodological practice, our a priori exclusion of TD children with documented attention problems may have exacerbated the finding of any group differences in attentional functioning between the groups.

In sum, these findings highlight three points essential to understanding the development of attention among children with FASD. One, the level of functioning exhibited by a child with FASD varies considerably, depending on which component of attention is assessed. Two, the clinical assessment of attentional problems as they are expressed in everyday life may be misleading when they are made in comparison to peers of the same CA, rather than the more appropriate comparison to peers of the same MA, which is a more accurate reflection of level of functioning for children with FASD whose general cognitive level is often lower than that of their peers. Thus, the CA comparisons would lead to both everyday impressions and clinical diagnoses of hyperactivity and ADHD, although the children might be behaving more appropriately in relation to MA. Three, parent, clinical, and experimental information are often quite discrepant, partly because they each tap into different aspects

of functioning, and partly because they entail different premises of inference.

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Differential diagnosis of sensory modulation disorder (SMD) and attention deficit hyperactivity disorder (ADHD): participation, sensation, and attention

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Differential diagnosis between sensory modulation disorder (SMD) and attention deficit hyperactivity disorder (ADHD) is often challenging, since these disorders occur at a high rate of co-morbidity and share several clinical characteristics. Preliminary studies providing evidence that these are distinct disorders have focused solely on body functions, using sophisticated laboratory measurements. Moreover, no studies have compared participation profiles of these populations. This study is the first to compare the profiles of these populations regarding both "body functions" (attention and sensation) and "participation," using measures applicable for clinical use. The study included 19 children with ADHD without SMD and 19 with SMD without ADHD (diagnosed by both pediatric neurologists and occupational therapists), aged 6–9, and matched by age and gender. All children underwent a broad battery of evaluations: the Evaluation of Sensory Processing, Fabric Prickliness Test (FPT) and Von Frey Test to evaluate sensory processing, and Test of Everyday Attention to evaluate attention components. The Participation in Childhood Occupations Questionnaire was used to evaluate participation. Results support significant group differences in all sensory components, including pain intensity to suprathreshold stimuli and pain "after sensation," as well as in tactile, vestibular, taste, and olfactory processing. No differences were found in attention components and participation. This study has both theoretical and clinical importance, inter alia, providing further evidence of two distinct disorders as well as indications of specific clinical instruments that might enable clinicians to implement differential diagnoses. In addition, results accord with other previous statements, which indicate that the clinical diagnosis of children with disabilities may not be a major factor in determining their participation profile.

Keywords: sensory modulation, attention deficit hyperactivity disorder, sensory processing, attention, participation, differential diagnosis

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent and intensively studied childhood developmental disorders (Barkley, 2003). It is characterized by a persistent pattern of inattention, and/or hyperactivity- impulsivity, to a degree that causes significant impairment of functional performance at home, school, and in social settings (American Psychological Association [APA], 2013). Estimated prevalence rates of ADHD vary greatly (Froehlich et al., 2007); however, the results of population surveys suggest that in most cultures ADHD occurs in about 5% of children (APA, 2013).

The literature indicates that ADHD is often accompanied by deficits other than those subsumed under the ADHD diagnosis. In fact, the subject of co-occurring deficits is one of the most frequently explored aspects of this disorder (Adesman, 2003; Gillberg et al., 2004). Findings of both clinical and community studies have revealed extremely elevated rates of co-occurrence between ADHD and other neuro-developmental disorders, predominantly related to motor (e.g., Pitcher et al., 2003), language (e.g., Cohen et al., 2000), cognitive (e.g., Frazier et al., 2004) and sensory functioning (e.g., Yochman et al., 2006). Pertaining to the sensory domain, children with ADHD frequently meet the criteria for sensory modulation disorder (SMD) as well (Miller et al., 2001).

SMD is characterized by difficulty in responding to sensory input in a graded and adaptive manner relative to the degree, nature, or intensity of the sensory input. Furthermore, individuals with SMD routinely respond to benign sensory input with exaggerated avoidant and defensive behaviors that are inappropriate to the environmental demands (Miller et al., 2007). These behaviors range from over to under- responsiveness to sensory stimuli and/or intensely seeking sensory stimuli, and may involve only one or multiple sensory systems (Dunn, 1997; Miller et al., 2007). Studies have shown that individuals with SMD present with behavioral and physiological features of sensory processing that are different from those of typically developing children (McIntosh et al., 1999a; Reynolds and Lane, 2008; Bar-Shalita et al., 2009a,b; Davies et al., 2010). For sensory processing

difficulties to be classified as a disorder, an individual's responses to sensory input must significantly impair his/her successful performance of daily activities and routines (Bar-Shalita et al., 2008). The prevalence of SMD is estimated to be 5–16% in the normal population (Ahn et al., 2004; Ben-Sasson et al., 2009; Gouze et al., 2009), similar to that of ADHD.

Differential diagnosis between SMD and ADHD is often challenging, since these disorders share several clinical characteristics. The behavioral responses of children with sensory over-responsivity in the face of adverse sensory stimulation may manifest as distractibility, impulsivity, hyperactivity, or some combination of these, which represent the core symptoms of ADHD (Miller et al., 2012). In addition to sharing behavioral characteristics, several studies have revealed a high prevalence of co morbidity—over half the children with ADHD may also exhibit SMD (Mangeot et al., 2001; Miller et al., 2001; Yochman et al., 2006)—increasing the difficulty of the differential diagnosis process. Researchers have employed both behavioral and physiological measures in an attempt to describe the unique sensory responsivity patterns of children with ADHD compared to those exhibited by typically developing children. Results of behavioral measures such as parent questionnaires, have indicated that children with ADHD are more sensitive to sensory stimuli, such as tactile, visual, auditory and oral, than typical children (Dunn and Bennet, 2002; Yochman et al., 2004). Studies that employed physiological measures, such as the central Somatosensory Evoked Potential (SEP) (Parush et al., 1997), and sympathetic markers of nervous system functioning using electro-dermal reactivity (EDR), (McIntosh et al., 1999a; Mangeot et al., 2001; Miller et al., 2001) have also indicated that the responses of a significant percentage of children with ADHD differ from those of typical children, suggesting stronger physiological reactivity.

Despite the similarity between children with SMD and those with ADHD with respect to these and other clinical characteristics, preliminary studies comparing the two populations have provided evidence that these disorders are indeed separate, each with its own unique profile. Thus, for example, results of a study that compared children with ADHD and tactile over-responsivity to children with ADHD without tactile over-responsivity, demonstrated significantly higher SEP amplitudes in the group with sensory modulation difficulties (Parush et al., 2007). In addition, the preliminary research of Lane et al. (2010) led them to suggest that patterns of salivary cortisol and electrodermal responsivity to sensation may distinguish between groups of children with ADHD with and without sensory over-responsivity. More recently, the study of Miller et al. (2012) revealed that children with SMD have larger EDR responses to sensory stimuli and exhibit more somatic complaints, anxiety and depression than children with ADHD.

The current study is comparative, examining differences between children with a sole diagnosis of ADHD to children with a sole diagnosis of SMD in an attempt to determine whether these disorders are distinct. While there are a very few studies that have compared such groups of children, their focus is mainly on body functions utilizing sophisticated equipment. In addition, to our knowledge, no other study has compared the participation profiles of these children across multiple areas of functioning. The World Health Organization (WHO) posits that participation is directly related to health and represents the highest level of functioning (WHO, 2001). Although only limited research has been performed with respect to the participation profiles among children with ADHD and/or children with SMD, the evidence to date suggests that the participation of these children is significantly impaired in various aspects of daily life compared to typically developing children (Cohn et al., 2000; Harpin, 2005; Dunn, 2007; Bar-Shalita et al., 2008; Engel-Yeger and Ziv-On, 2011). A comparison between these two diagnostic populations regarding the unique expression of their participation limitations may prove to be an additional important factor in their differential diagnosis.

The uniqueness of this study lies in it being the first to compare the profiles of ADHD and SMD regarding both "body functions" (sensation and attention) and "participation," through the use of clinically applicable measures. A better understanding of the specific features that distinguish between these two disorders can enable a more accurate differential diagnosis process, and may have a profound impact on intervention planning.

MATERIALS AND METHODS

PARTICIPANTS

Participants in the study were recruited from a major developmental center in Israel. Of the 63 children referred for the study, 15 were excluded due to their having a dual diagnosis of both ADHD and SMD. Ten other children could not be included because their parents chose to withhold their consent. Thus, the final sample was composed of 38 children; 19 children with ADHD without SMD (11 male, 8 female; mean age 6 years and 8 months [$SD = 7$ months]; age range 6–8.11 years) and 19 with SMD without ADHD (13 male, 6 female; mean age 6 years and 7 months [$SD = 8$ months]; age range 6–8.4 years). No group differences were found with respect to age [$t_{(36)} = 0.630$; $p = 0.533$] and gender [$\chi^2(1) = 452$; $p = 0.501$].

The ADHD group included children who scored as such on the CPRS-R:S (Connors, 1997) and as typically behaving on the Short Sensory Profile (McIntosh et al., 1999b). The opposite was true for the children included in the SMD group. Children in the SMD group scored as having definite deficits on the Short Sensory Profile and as typically behaving on the CPRS-R:S. To further verify the presence or absence of ADHD according to the DSM-IV criteria, as well as to exclude children with additional physical and/ or neurological deficits (e.g., cerebral palsy, ASD), all children underwent an additional evaluation by a developmental neurologist. Moreover, participants were evaluated by an occupational therapist to substantiate the presence or absence of SMD.

PROCEDURE

Following research approval and parental consent, children were recruited for the study according to the inclusion criteria. Prior to receiving therapeutic or medical intervention, each child was individually evaluated on a broad battery of evaluations by an established occupational therapist with 10 years of experience working with this population. In addition, mothers completed the relevant questionnaires. The examiner was blind as to group placement.

INSTRUMENTATION

Baseline measures

The short sensory profile (SSP; McIntosh et al., 1999b). A standardized parent-report questionnaire used to screen children between the ages of 3–10 for sensory modulation deficits as well as for research purposes. The questionnaire contains 38 items reflecting responsiveness to sensory input across sensory modalities, including tactile, auditory, visual, gustatory, olfactory stimuli, movement, and body position. Parents indicate their perception of the frequency with which their child exhibits atypical behavioral responses to sensory stimulation on a 5-point Likert scale ranging from 1 (always) to 5 (never). Higher scores represent more functional performance. A total score was calculated for each participant by summing the item scores. Construct validity of the SSP has been demonstrated using the "known-groups" procedure and factor analysis. Convergent validity was established through electrodermal response testing, which has shown that abnormal electrodermal responses are significantly associated with lower scores on the SSP. Cronbach's alpha coefficient values ranged from 0.70 to 0.90, demonstrating internal consistency reliability (McIntosh et al., 1999a). The Hebrew version of SSP was found to have good psychometric properties (Engel-Yeger, 2010).

Conners' Parent Rating Scale- Revised: Short Form (CRPS-R:S; Connors, 1997). The CRPS-R:S is a parent-report tool for 3–17 year old children to assess behaviors associated with ADHD according to the criteria referred to in the DSM-IV-TR (APA, 2000). Items also relate to various behaviors that may accompany attention disorders reflecting anxiety, conduct, and emotional problems. The CRPS-R: S includes 27 items grouped into four subscales: oppositional, Hyperactivity, Cognitive Problems/Inattention, and ADHD index. Each item is rated on a 4-point Likert scale ranging from 0 (not true at all/never) to 3 (very much true/very often) indicating the occurrence of the behavior over the previous month. Item scores are summed individually for each subscale and total subscale scores are compared to the standardized scores. The authors report medium—high internal consistency reliability (Cronbach's alpha 0.85 to 0.93) and test-retest reliability from 0.62–0.85, $p < 0.05$ for all the scales. The tool significantly discriminates between ADHD and non-ADHD populations ($p < 0.001$) and high criterion validity was reported (Kumar and Steer, 2003).

STUDY MEASURES

Sensory measures

Both the Fabric Prickliness Test (FPT) and the von Frey Monofilament Test used in this study (see below) are based on quantitative sensory testing (QST); a psychophysical approach used to characterize somatosensory hypersensitivity in a non-invasive but rigorous manner. Participants rate the subjectively perceived intensity of controlled graded levels of stimuli (Verdugo and Ochoa, 1992; Hansson et al., 2007; Arendt-Nielsen and Yarnitsky, 2009). Both tests have been shown to be valid methods of determining pain levels in children, as well as for measuring and comparing pain and pain "after sensation" between children with SMD and typically developing children (Bar-Shalita et al., 2009a,b).

The Fabric Prickliness Test. (FPT; Garnsworthy et al., 1988; Cervero et al., 1994). This test quantifies the level of pain evoked by the application of prickly fabrics to the skin. In the present study, 16 applications of three types of woolen fabrics with different levels of prickliness (least prickly, mildly prickly, and very prickly) were used for each child. The different fabrics were applied face down (to prevent visual identification) to the volar surface of the child's non-dominant forearm and presented sequentially in an identical pseudorandom order for each child. Using digits 2–4, the investigator rapidly tapped on each individual fabric, repeating this sequence until the child verbally indicated registering the sensation. At this point, the fabric was removed and the child was asked to rate the level of pain the fabric evoked using the Revised Faces Pain Scale (FPS-R; Hicks et al., 2001). This scale presents schematic drawings of six faces expressing increasing levels of distress typically experienced by individuals with pain. The faces correspond to a numerical rating scale ranging from 0 to 10 with increments of 2, with the higher score representing the highest level of pain. Pain "after-sensation" (the duration in which the sensation of pain continues to linger) was measured after the last fabric was scored by having the child indicate when he/she no longer feels the sensation. The first "after sensation" measurement was taken 15 s after the final FPT fabric was scored and measurements were then repeated at 1-min intervals thereafter. The time taken for the sensation to dissipate was recorded.

Pinprick pain (Smith and Nephew Rolyan; Menomonee Falls, WI). A series of Von-Frey filaments were used to test pinprick pain. Three stiff mono-filaments with variable bending forces were applied perpendicularly to the skin on the volar surface of the child's dominant forearm. Each filament was applied three times, for a total of 9 applications. The filaments elicit increasing levels of punctate pain by applying a bending force of 5.46, 5.88, and 6.10 on a log force scale (29 g, 75 g, and 127 g; 284.4 mN, 735.5 mN, 1245.4 mN, respectively). The filaments were applied in an identical pseudorandom order to each child. Children wore a blindfold during each application to prevent visual cues of the stimuli, which was then removed to rate pain intensity. Pain intensity was then rated using the FPS-R (Hicks et al., 2001) as detailed above.

The Evaluation of Sensory Processing Questionnaire. (ESP; Parham and Johnson-Ecker, 2002). The ESP is a standardized behavioral care-giver questionnaire designed to identify behaviors that are specifically indicative of sensory processing problems in 5–12 year old children. The ESP is the predecessor of the Sensory Processing Measure Home questionnaire (SPM) (Kuhaneck et al., 2007). The ESP provides scores of function in the visual, auditory, tactile, olfactory/gustatory, proprioceptive, and vestibular sensory systems. It is distinctive in that it contains only items that are specific to particular sensory systems (Parham and Johnson-Ecker, 2002). Each item is rated according to the frequency of the behavior using a 5-point Likert scale.

The standard score for each of the subscales enables the classification of children's functioning into one of three interpretive ranges: typical performance, probable dysfunction or definite dysfunction. Studies on the psychometric properties of the ESP revealed Cronbach's alphas of 0.83 or above on most scales (Johnson-Ecker and Parham, 2000) and inter-rater reliability; when examining mother- father agreement in their responses about their child, parent agreement was found across more than 75% of the items (Chang, 1999). LaCroix and Mailloux (1995) conducted a validity study in which parents were asked to rate their typically developing preschoolers according to the ESP items. On the majority of items, 75% or more of the parents responded that the items describe behaviors that are not typical of preschoolers. Criterion validity using contrasting groups showed that many of the items were rated significantly higher by children with autism (Vermass Lee, 1999) and children with sensory processing deficits (Johnson-Ecker and Parham, 2000) than by typically developing children.

Attention measure

The test of everyday attention for children. (TEA-Ch; Manly et al., 1999). The TEA-Ch is a standardized measure designed to assess various components of attention in children aged 6–16. The test comprises nine "game-like" subtests that require visual, auditory, and motor skills to measure the child's ability to selectively attend, sustain attention, divide attention, switch attention and inhibit verbal and motor responses. The developers selected assessment tasks designed to minimize potential confounding factors such as motor speed, reading and writing and memory, so that the targeted attentional system be activated (Heaton et al., 2001). The current study employed the five subtests (Sky Search, Score, Creature Count, Sky Search Dual Task and Walk, Don't Walk) recommended by the developers to be used for screening purposes. The following is a description of the five subtests administered:

(1) Sky Search—Examines selective visual attention by measuring the speed and accuracy with which one scans a test sheet with numerous visual stimuli to select identical pairs of stimuli ("spaceships") from the unpaired distractor stimuli, while controlling for motor efficiency.
(2) Score—Assesses sustained auditory attention. The participant silently counts the number of target tones, which are presented at varying intervals.
(3) Creature counting —Examines attentional switching and control. The children are asked to repeatedly switch between forward and backward counting of visual stimuli aligned along a path in response to arrows pointing upward and downward. The target stimuli are located within an array of visual stimuli.
(4) Sky Search Dual Task—Assesses sustained and divided attention, indicating the ability to perform two tasks simultaneously. Respondents must identify identical pairs of visual stimuli from visual distractors (as in Sky Search), while simultaneously counting tones presented at fixed intervals.
(5) Walk, don't walk—Assesses sustained attention and response inhibition. Respondents progress along a paper path (marking steps with a pen) in response to a "go" sound, but are to refrain from doing so when hearing a "no-go" tone.

The TEA-Ch was standardized on 293 Australian children (Manly et al., 1999). Construct validity was established through factor analysis (Manly et al., 1999; Passantino, 2011). In addition, the criterion validity of various TEA-Ch subtests was examined by comparing them to other measures of attention. Passantino (2011) found statistically significant correlations between the Sky Search ($r = 0.40$, $p < 0.001$) and Map Mission ($r = 0.31$, $p < 0.01$) tasks and the Stroop measure; and between the Sky Search ($r = 0.69$, $p < 0.001$) and Map Mission ($r = 0.37$, $p < 0.001$) tasks and the Trails Test A. Studies have also found that children with ADHD performed significantly worse than typically developing children on the subtests assessing sustained attention and attentional control/switching, but not on the subtest of selective attention (Heaton et al., 2001; Manly et al., 2001). Test-retest reliability was assessed on a random subgroup of 55 children across age groups from the original sample and correlation coefficients ranging from 0.64 to 0.92 were obtained (Manly et al., 2001).

Participation measure

The participation in childhood occupations questionnaire (PICO-Q; Bar-Shalita et al., 2009a,b). This is a standardized reliable and valid caregiver questionnaire validated on an Israeli population of children. This questionnaire was designed to evaluate participation in four areas of functional activities: personal activities of daily living; academic activities; play and leisure, and habits and routines. Each item describes an activity that is scored according to three different scales: (1) level of activity performance, (2) level of enjoyment of the activity, and (3) frequency of performance of the activity. Each of these scales provides scores for each of the four individual performance areas. A total score is also calculated for each individual scale. In addition, this questionnaire provides descriptive data by having parents select one of nine characteristics or behavior patterns that they feel underlie their child's participation difficulties. Reliability has been established through internal consistency (Cronbach's $a = 0.86$–0.89) and test–retest ($r = 0.69$–0.86) measures. Content and construct validity have been demonstrated (Bar-Shalita et al., 2009a,b).

DATA ANALYSIS

Data were analyzed using both parametric and non-parametric statistics, depending on the variable's distribution. Multivariate analysis of variance (MANOVA) was used to analyze group differences in scores obtained on the ESP, the TEA-Ch and the PICO-Q. The von Frey and FPT did not meet criteria for normal distribution (Komogorov–Smirnov <0.05), therefore group comparisons were performed through the Mann–Whitney test.

In addition to the comparisons performed between the two diagnostic populations of this study, a comparison of the PICO-Q scores between children with ADHD and typically developing children, as well as between children with SMD and typically developing children was performed using one sample t-tests. This comparison was possible in view of the fact that data regarding the

functioning of typically developing Israeli children on the PICO was reported by Bar-Shalita et al. (2008).

RESULTS

DIFFERENCES BETWEEN GROUPS ON SENSORY MEASURES:

Results support significant group differences on all sensory measures, which indicate significantly greater sensory difficulties in the SMD group.

PINPRICK PAIN TEST

Significant differences were found between the groups on the overall Von-Frey filament test score ($Z = -2.24$; $p = 0.026$). The children with SMD reported higher scores as a response to punctate pain (median = 60) compared to children with ADHD (median = 30).

The fabric prickliness test

Significant differences were found between the groups in the level of pain elicited by the application of the fabrics ($Z = -2.367$; $p = 0.018$), such that children with SMD reported higher scores (median = 16) compared to children with ADHD (median = 4). In addition, significant group differences were found in the measures of pain "after-sensation" ($Z = -2.803$; $p = 0.005$). After the application of the last fabric of the FPT, the after pain sensation in children with SMD lingered longer (median = 2 min, 15 s) than the children with ADHD (median = 15 s).

The evaluation of sensory processing questionnaire (ESP)

The results of the MANOVA on the six subtest scores revealed a significant group effect [$F_{(1, 35)} = 5.950$; $p < 0.001$]. To examine the source of the effect, a univariate analysis of variance (ANOVA) was conducted for each of the individual subtests. The results indicate that the scores for the SMD group were significantly lower than the scores of the ADHD group in three of the six subtests (i.e., taste and smell, tactile and motion /vestibular) (**Table 1**).

Table 1 | Results of multivariate analyses of variance (MANOVA) comparing test scores on the ESP between children with ADHD and children with SMD.

Subsection	Children with ADHD ($n = 19$)		Children with SMD ($n = 19$)		*F*	*P*	Effect size (partial eta squared)
	M	*SD*	M	*SD*			
Hearing	41.42	6.736	38.53	6.834	1.73	0.197	0.046
Taste and smell	22.26	2.621	18.58	3.702	12.53	0.001	0.258
Body awareness	50.95	14.547	44.21	7.458	3.23	0.081	0.082
Touch	92.11	28.276	69.32	10.878	10.75	0.002	0.230
Motion (vestibular)	60.47	6.222	53.63	8.565	7.94	0.008	0.181
Vision	45.95	8.263	49.42	11.177	1.19	0.283	0.032

ESP, Evaluation of Sensory Processing; ADHD, attention deficit hyperactivity disorder; SMD, sensory modulation disorder.

DIFFERENCES BETWEEN GROUPS ON THE ATTENTION MEASURE

A comparison between groups using a MANOVA analysis revealed no significant group differences on any of the TEA-Ch subtests [$F_{(1, 27)} = 0.655$, $P = 0.686$], indicating that the children with ADHD did not perform worse than the children with SMD on the various attention sub-tests.

DIFFERENCES BETWEEN GROUPS IN THE PARTICIPATION MEASURE

Quantitative data

To determine group differences on the PICO- Q scores, a MANOVA was performed on the total scores of the three questionnaire scales (performance level, degree of enjoyment of activity and frequency of performance), as well as on the participation scores obtained in each performance area (daily care activities, academic activities, play and leisure and habits and routines). Only in the "degree of enjoyment" for "daily care activities" [$F_{(1, 36)} = 5.97$; $p = 0.020$] did the results reveal any significant difference between the groups, indicating that children with SMD enjoy these activities less ($M = 34.58$; $SD = 9.73$) than children with ADHD ($M = 41.05$; $SD = 6.21$).

Table 2 displays the results of a one sample *t*-test used to compare the participation of each of the experimental groups (ADHD, SMD) to typically developing children. Data regarding the typical sample was based on the information reported by Bar-Shalita et al. (2009a,b). Significant differences were found between children with SMD and typically developing children [$t_{(18)} = 6.011$, $p = 0.000$]; as well as between children with ADHD and typically developing children [$t_{(18)} = 3.72$, $p = 0.001$] on the total "level of performance" dimension of participation, indicating that both experimental groups obtained mean scores significantly below those reported for typically developing children. In contrast, no differences were found between the experimental groups compared to typically developing children on the dimensions of "enjoyment" and "frequency of performance."

Descriptive data

Different trends were found between the ADHD and SMD groups with respect to the responses of parents regarding their perception

Table 2 | Results of PICO-Q scores for the three dimensions of participation, according to study groups.

Dimension of participation	Children with ADHD $n = 19$		Children with SMD $n = 19$		Typical children $n = 34$	
	M	*SD*	M	*SD*	M	*SD*
Level of activity performance	127.95	22.92	121.79	17.88	148.53	10.04
Enjoyment of activity	127.58	19.65	118.11	21.19	127.18	12.11
Frequency of performance	75.63	17.28	70.42	4.55	67.60	12.05

PICO-Q, Participation in Childhood Occupations Questionnaire; ADHD, attention deficit hyperactivity disorder; SMD, sensory modulation disorder.

of the reasons underlying their children's participation difficulties. Thus, for example, a higher percentage of children with ADHD reportedly had difficulty due to poor quality of performance or the length of time they required to perform activities. In contrast, a higher percentage of parents reported that their children with SMD had difficulty due to inflexibility, fighting with their parents or refusing to participate (**Table 3**).

DISCUSSION

Children with ADHD demonstrate significant functional performance impairments at home, school, and in social settings (APA, 2013). In addition to the impairment caused by the core symptoms of ADHD, these children are at increased risk of associated deficits in various areas, including sensory processing (Mangeot et al., 2001; Miller et al., 2001). Thus, sensory processing ability is one of the many factors that need to be considered when assessing the reasons why a child with ADHD may be experiencing difficulties participating in daily activities. However, consideration of these issues in the evaluation and treatment of children with ADHD is often challenging due to the significant overlap of ADHD and SMD symptoms (Miller et al., 2001; Ahn et al., 2004; Gouze et al., 2009).

An important question raised in recent studies is whether ADHD and SMD are distinct disorders, the same disorder or comorbid disorders (Miller et al., 2012). To date, very few studies compared children who only meet the criteria for one or the other diagnosis—children with SMD without ADHD, and ADHD without SMD—so that the unique characteristics of each can be used to discriminate between the two conditions. Therefore, the purpose of this study was to compare children with a sole diagnosis of SMD and a sole diagnosis of ADHD on the central underlying symptoms of both disorders. Furthermore, due to the fact that participation is becoming increasingly important in the field of childhood disability, this study compared the participation profiles of children with SMD to those with ADHD in all areas of functioning.

Table 3 | PICO-Q: Comparison of behavior characteristics of children with ADHD and SMD underlying poor performance as reported by parents.

Behavior characteristics (as reported by parents)	Children with ADHD ($n = 19$)	Children with SMD ($n = 19$)
	% reported	%reported
Poor quality of performance	26.98	11.74
Performance time longer than expected	26.98	13.73
Completes task only with constant arguing /bribing/ lack of flexibility	17.10	35.79
Refuses to perform task	7.82	27.45
Does not follow appropriate rules of behavior	15.85	8.34
Performs the task too often	0.00	0.00
Does not perform task enough	5.27	2.95

PICO-Q, Participation in Childhood Occupations Questionnaire; ADHD, attention deficit hyperactivity disorder; SMD, sensory modulation disorder.

DIFFERENCES BETWEEN GROUPS ACCORDING TO SENSORY MEASURES

The results of this study demonstrated significant group differences on all sensory measures, indicating that the children in the SMD group had significantly greater sensory difficulties than those in the ADHD group.

Specifically, the parent-report measure (ESP) revealed significant group differences in several sensory systems (tactile, gustatory/olfactory and movement/vestibular). These findings are in line with the study performed by Miller et al. (2012), in which the SSP was used to compare four groups of children: children with SMD, with ADHD, with SMD + ADHD and typically developing children. Supporting the results of the current study, Miller et al. found that children with SMD obtained significantly poorer scores than children with ADHD in the areas relating to tactile, taste/smell, and movement sensitivity. However, they also found significant differences in visual-auditory sensitivity. It is important to note that Miller and colleagues found significant differences in these sensory domains between children with SMD and typically developing children, but not between children with ADHD and typically developing children. This supports the suggestion that the behavioral manifestations of these sensory systems may be more characteristic of children with SMD than children with ADHD and hence, may be useful in their differential diagnosis.

Although it is difficult to demonstrate the distinction between SMD and ADHD through behavioral analysis, data derived from parent report questionnaires are often an important component in the clinical diagnoses of both SMD and ADHD (Johnson-Ecker and Parham, 2000; Tripp et al., 2006; Reynolds and Lane, 2008). However, in addition to behaviors indicative of sensory processing *per se*, some sensory questionnaires also address clinically significant problem behaviors considered to be derivatives of sensory processing deficits—such as those related to attention and social-emotional functioning (Yochman et al., 2004), which can also be found among children with a broad range of disabilities including ADHD (Koziol and Budding, 2012). In contrast, the ESP was uniquely designed to identify behaviors that are indicative specifically of sensory processing problems in the various sensory systems (Johnson-Ecker and Parham, 2000). Given the clinical and theoretical importance of determining the characteristics that can distinguish between SMD and ADHD, researchers, and clinicians should consider using sensory processing evaluation tools with a higher level of specificity than those used to differentiate between SMD and typically developing children alone.

In addition to the ESP, psychophysical performance-based evaluations that are practical and appropriate for clinical use were employed. Previous research has shown that children diagnosed with SMD reported higher levels of pain than those reported by typically developing children in response to both pinprick (Von Frey monofilaments) and prickly fabrics, suggesting that children with SMD demonstrate a more vigilant nociceptive system. In

addition, pain "after-sensation" to prickly fabrics was found to linger for at least 5 min after the termination of the test among children with SMD (Bar-Shalita et al., 2009a,b).

The present study is the first to compare between children with SMD and ADHD using these psychophysical methods. Results of our study indicate that children with SMD reported significantly higher levels of pain than those reported by children with ADHD on both pinprick (von Frey monofilaments) and prickly fabrics. Moreover, the children with SMD reported feeling pain for a significantly longer time than the children with ADHD, indicating increased "after-sensation" to the stimuli. These results support the findings of Bar-Shalita et al. (2009a,b), suggesting that one of the definitive features of children with SMD is increased aversive responses to suprathreshold tactile stimuli—which reflects abnormal central processing of nociceptive input—as compared to typically developing children. The results of the present study add to the previous results by demonstrating that such responses are not typical of children with ADHD, suggesting that children with ADHD do not have abnormalities in processing suprathreshold noxious tactile sensations (Arendt-Nielsen and Yarnitsky, 2009).

Our finding that children with SMD experience significantly longer pain "after sensation" compared to children with ADHD is also noteworthy. Clinical parent reports regarding children with SMD often describe that their children feel aversive sensations long after the sensory stimuli has been terminated (i.e., feeling pain long after a child got hit, or continuing to display aversive smell responses from an object long after it has been removed). Our results regarding "after sensation" seem to be in accord with the limited research done on the habituation profiles of these populations. The few studies that assessed sympathetic "flight or fight" reactions of children with SMD in response to sensory stimuli as measured by electrodermal activity (EDA) found that these children exhibited exaggerated electrodermal responses to sensory stimulation, and habituate more slowly to repeated stimulation than do typically developing children (McIntosh et al., 1999a; Miller et al., 2001, 2012). However, the physiological reactivity profile of children with ADHD has been shown to be different from that of children with SMD. Variability exists with regard to the magnitude of their response to stimuli (Miller et al., 2012), being either smaller (Mangeot et al., 2001) or the same (Herpertz et al., 2001) as typically developing children, and a faster than normal habituation to repeated stimulation has been demonstrated (Mangeot et al., 2001; Miller et al., 2001). These results, together with the results of the present study, seem to suggest that there are differences between these populations regarding the ability of these children to habituate sensory stimuli.

In summary, the findings of group differences on these sensory measures provide additional supporting evidence that SMD is a separate clinical condition distinct from ADHD. With further research in larger samples, the clinical tests used in this study may prove to be useful for differential diagnosis.

DIFFERENCES BETWEEN GROUPS ON THE ATTENTION MEASURE

Although attention difficulties have been found to be characteristic of children with SMD (Dunn, 1997; Miller et al., 2012), as well as in children with ADHD, the assumption is that this difficulty is not a core symptom of the disorder as it is in ADHD, but rather a secondary behavioral manifestation of the sensory over-responsivity experienced by children with SMD to adverse sensory stimulation. Therefore, we hypothesized that children with SMD would perform better than children with ADHD on the measure of attention used. In contrast to our assumption, the MANOVA analysis revealed no significant group differences on any of the five TEA-Ch subtests administered (Sky Search, Score!, Creature Counting, Sky Search Dual Task, Walk Don't Walk).

Studies performed to attempt to discriminate between SMD and ADHD have mainly focused on areas related to the core symptoms of SMD. Only one other study, to our knowledge, compared these populations with regard to measures of attention. Unlike the findings of the present study, Miller et al. (2012) found that although both children with ADHD and children with SMD had significantly more attention problems compared to typically developing children, children with ADHD had significantly worse attention scores than children with SMD. These results were found on both the Parent Leiter international performance scale as well as on the and SNAP- IV parent rating scale for the assessment of ADHD. Nevertheless, no group differences were found on the Child Behavior Checklist (CBCL), a parent report scales which assesses a variety of behaviors, including attention problems. Miller et al. (2012) note that it is common to find differing results when measuring similar constructs with different tools.

Thus, a possible explanation for our results may be related to the instrument chosen for this study. The TEA-Ch was used to measure attention in this study because of its reported advantages. That is, it was found to be a reliable performance-based attention measure (as opposed to parent-report questionnaires) that relates to multiple components of attention, it is ecological valid, and is unique due to the game-like nature of the tasks. Nevertheless, according to the test developers the subtests of the TEA-Ch do not purport to measure attention directly. Rather, they measure differences in performance abilities believed to contribute significantly to inferred separable attention processes, including auditory and visual detection, counting ability, processing speed, and response speed among other factors (Manly et al., 1999). In addition, the studies utilizing the TEA-Ch with ADHD study samples are not always consistent with respect to their results regarding which attention components are impaired among children with ADHD compared to typically developing children (Manly et al., 1999, 2001; Heaton et al., 2001; Villella et al., 2001; Lajoie et al., 2005). This inconsistency has also been found in a number of other studies, using a variety of attentional measures (Wu et al., 2002; Berlin et al., 2003; Koschack et al., 2003).

The unsolved issue with regard to the classification and characterization of attentional components (Sergeant, 1996; Knudsen, 2007) as well as which attentional components are in fact impaired among children with ADHD (Wilding, 2005; Sutcliffe et al., 2006; Knudsen, 2007), causes further complications when trying to differentiate between developmental disabilities such as SMD and ADHD. There is also a question regarding the representativeness of our study sample. Specifically, the relative proportions of ADHD subgroups were not controlled for.

Future studies need to use more sensitive measures both in performance- based as well as behavioral inventories, which may shed light on the cognitive differences between SMD and ADHD.

Furthermore, it is important to relate to additional defining characteristics of ADHD, such as deficits in executive functions (Barkley, 2003; Wilding, 2005), which have not yet been sufficiently examined with respect to their presence or absence in SMD.

DIFFERENCES BETWEEN THE GROUPS ON THE PARTICIPATION MEASURE

In comparing the quantitative data obtained through the PICO-Q between children with SMD and ADHD, the only significant difference between the groups was that the children with SMD had a lesser "degree of enjoyment" for "daily care activities."

This is understandable, given that children with sensory over-responsivity experience these activities as unpleasant or threatening and not enjoyable. Children with over-responsivity are often characterized by behaviors such as limited preference for types of food, avoidance of various clothing materials, and/or dislike washing due to the feeling of running water or the smell of soap (Miller and Fuller, 2006; Reynolds and Lane, 2008).

Our findings indicate that, with the above exception, children with ADHD and children with SMD exhibit similar characteristics of participation in all three domains (level of activity performance, level of enjoyment and frequency of performance) and across multiple areas of function (activities of daily living, academic activities, play and leisure, habits, and routines).

A unique feature of this study is in comparing comprehensive participation profiles of children with ADHD and SMD across life situations. The majority of studies performed regarding the characteristics of participation among children with SMD and ADHD, have compared children with disabilities to typically developing children. On the whole, the results of these studies point to the fact that these children are at risk for limited participation in many aspects of daily life. This was also found to be the case in the present study, in which parents of both experimental groups rated the level of their child's participation abilities in activities throughout the day to be significantly poorer than those reported for typically developing children; a finding supporting those of previous studies both on SMD (Cohn et al., 2000; Dunn, 2001; Bundy et al., 2007; Bar-Shalita et al., 2008) as well as on ADHD (Cermak, 2005; Harpin, 2005).

By comparison, only a limited amount of studies have compared between different diagnostic populations in general, in order to identify the unique expression of participation limitations characteristic of different disability populations. Supporting the findings of the current study, these comparison studies seem to indicate a lack of significant group differences between clinical populations on participation measures. This is in accord with current perspectives on participation and health, indicating that the clinical diagnosis of children with disabilities is not a major factor in determining their participation profiles. Rather, meaningful participation in a given activity appears to depend on a variety of contextual and personal factors (King et al., 2003; Rosenberg et al., 2012).

Thus, for example, Law et al. (2004) examined the relationship between diagnosis, function, and participation among 427 children with physical disabilities. The sample was divided into one of two diagnostic categories—central nervous system-related disorders and musculoskeletal disorders. Using the Children's Assessment of Participation and Enjoyment (CAPE; King et al., 2004) the researchers revealed that when adjusted for age, gender and physical function, no significant differences were found in the participants' intensity, and diversity of participation over and above the level of function. Similar findings were also reported by Eriksson (2006) from a series of studies that included children with a variety of impairments (e.g., social skills, communication limitations, behavioral problems, low general health, visual impairments, physical impairments, and multiple impairments). She concluded that intensity and diversity of participation seems to be more related to personal and environmental factors than to disability type. Thus, further research should investigate the contribution of other confounding personal and environmental factors on the participation of children with disabilities in general, and when comparing between children with ADHD and SMD in particular.

It is interesting to note that the descriptive findings did find different trends between the groups with respect to parent's perceptions regarding the reasons underlying their children's participation difficulties. In fact, qualitative research on the unique expression of participation limitations of children with neurodevelopmental disorders is extremely limited. Due to the vast influence of participation on the development of competence, emotional well-being, and quality of life of a child (Law, 2002; Rosenberg et al., 2012), further studies should additionally explore the qualitative aspects of participation, which may provide a more in depth and informative approach to the study of the complex construct of participation.

CONCLUSIONS

The present study is, to our knowledge, the first to compare the profiles of ADHD and SMD regarding the core symptoms of each of these disorders as well as their participation profiles. In addition, the instrumentation selected was comprised solely of practical and clinically applicable measures. Certain limitations of the research need to be taken into account when relating to the findings. This study included a small convenience sample of children, inter alia due to the difficulty of identifying participants with only one of these diagnoses. In addition, controlling for subtypes of ADHD and SMD was not performed. Furthermore, although all children attended mainstream public schools, the cognitive abilities of these children were not directly evaluated and may have influenced their performance. A further possible limitation is that, although all the tools have adequate psychometric properties, some have not been specifically validated for the local population.

Taking these limitations into account, our findings provide a number of important contributions to the existing literature, with the aim of providing a more comprehensive and in-depth understanding of the relationship between these deficits. Given the high risk of comorbidity in children with ADHD, the American Academy of Pediatrics (APA, 2000) recommend that clinicians routinely and systematically screen for comorbidity over and above the behavioral symptoms of ADHD, which may have motivated the initial referral (Adesman, 2003). The clinical implications derived from the results of this study support the

practice of considering co-occurring sensory processing abilities among children with ADHD and may contribute to the process of differential diagnosis. Improved diagnostic accuracy is essential to providing a child with the most appropriate treatment.

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Using environmental distractors in the diagnosis of ADHD

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This study examined the effect of the incorporation of environmental distractors in computerized continuous performance test (CPT) on the ability of the test in distinguishing ADHD from non-ADHD children. It was hypothesized that children with ADHD would display more distractibility than controls while performing CPT as measured by omission errors in the presence of pure visual, pure auditory, and a combination of visual and auditory distracting stimuli. Participants were 663 children aged 7–12 years, of them 345 diagnosed with ADHD and 318 without ADHD. Results showed that ADHD children demonstrated more omission errors than their healthy peers in all CPT conditions (no distractors, pure visual or auditory distractors and combined distractors). However, ADHD and non-ADHD children differed in their reaction to distracting stimuli; while all types of distracting stimuli increased the rate of omission errors in ADHD children, only combined visual and auditory distractors increased it in non-ADHD children. Given the low ecological validity of many CPT, these findings suggest that incorporating distractors in CPT improves the ability to distinguish ADHD from non-ADHD children.

Keywords: ADHD, CPT, visual, auditory, distractibility, diagnosis, validity

INTRODUCTION

The diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) is predominantly based on behavioral symptoms. ADHD is characterized by persistent pattern of inattention and/or hyperactivity-impulsivity, which is maladaptive and inconsistent with a comparable level of developmental age [American Psychiatric Association (APA), 2013]. The DSM criteria classify the disorder into three general presentations– predominantly inattentive, predominantly hyperactive-impulsive, and combined presentation. Children who exhibit the behavioral symptoms of ADHD but demonstrate no functional impairment do not meet the diagnostic criteria (APA, 2013). One of the major difficulties in diagnosis ADHD is that decisions about the inappropriateness of behavior are based on subjective judgments of the observers. Despite efforts of standardization, there are no data to offer a precise estimate of when diagnostic behavior becomes inappropriate (Rader et al., 2009; Berger, 2011). Therefore, the behavioral characteristics remain subjective and maybe interpreted differently by different observers and in different cultures (American Academy of Pediatrics, 2000; Schonwald and Lechner, 2006). Significant variations in the prevalence rates around the world, based on variations in diagnostic methods, support the hypothesis of the role of diagnostic criteria bias (Rousseau et al., 2008).

Since ADHD diagnosis is a complex, multi-factorial task, it requires an integration of data. Typically, the data is assessed by clinical interview and observation, ratings of behavioral scales, and medical-neuro-developmental examination (Wolraich et al., 2011; APA, 2013). In schools and college settings the diagnosis of ADHD may provide additional secondary gains, such as specific academic advantages including additional time to complete assignments and tests, elimination of spelling penalties, advantageous seating in the classroom, testing environments that are free from distractions, etc. Given these benefits, there could be an impetus to feign or simulate the symptoms of ADHD (Sollman et al., 2010). With ADHD information readily accessible on the internet, today's students are likely to be symptom educated prior to evaluation, so ADHD can be readily feigned, particularly when symptoms assessment is based mainly on checklists (Sansone and Sansone, 2011).

Due to these diagnostic complexities and the subjective nature of the assessment instruments, efforts should be made so that the diagnosis of ADHD will be carefully undertaken through the integration of a number of sources of information and sophisticated testing. This attitude might explain the growing use of laboratory-based tools, such as the continuous performance tests (CPT), as complementary strategies in the assessment process.

The visual CPT, which was originally developed as a measure of vigilance and detection of deficits in sustained attention (Rosvold et al., 1956; Rutschmann et al., 1977; Cornblatt et al., 1988), has been widely used and is reported to be the most popular clinic-based measure of sustained attention and vigilance (Edwards et al., 2007). Despite the popularity of the CPT, many studies have questioned its reliability and validity for several reasons (McGee et al., 2000; Edwards et al., 2007; Skounti et al., 2007; Adams et al., 2009). Most CPT are based on a simple visual task that primarily measures the ability of subjects to focus attention and to remain vigilant over time (Shalev et al., 2011).

Typical visual CPT task requires the participant to sustain attention over a continuous stream of stimuli (single letters, shapes, or digits which are presented serially) and to respond to a pre-specified target (Kelip et al., 1997; Shalev et al., 2011). Traditionally, inattention is assessed in CPT by the number of omission errors, indicating the number of times the target was presented, but the participant did not respond, or by its

"inverse" measure calculating relative accuracy (the number of correct hits out of the total targets presented). Additional tested measure is the frequency of commission errors, indicating the number of times the participant responded to a non-target stimulus, which is an indicator of impulsivity. Most CPT paradigms assume that ADHD patients become more inattentive as the task progresses, therefore, increasing number of omission and commission errors over time indicate a difficulty to sustain attention over time, namely, to continue process the information effectively (Greenberg and Waldman, 1993). Contextual factors, such as distracting stimuli in the environment, can contribute to increased inattention (Adams et al., 2011). Therefore, sustained attention can be broadly characterized as the ability to concentrate on a specific stimulus over a period of time while excluding distracting stimuli (Shalev et al., 2011). When attending to a target stimulus in the environment, individuals must select the relevant information on which to focus (i.e., attend to the target) while simultaneously ignoring irrelevant information (Godijn and Theeuwes, 2003). Distracting stimuli might, therefore, have an effect on sustained attention by increasing the rate of omission errors in CPT. Therefore, we would expect an ADHD group of children to perform significantly different than non-ADHD peers in a CPT when measuring omission errors.

A major criticisms frequently voiced against the CPT refers to its low ecological validity, that is, the CPT ability to simulate the difficulties of ADHD patients in everyday life (Barkley, 1991; Rapport et al., 2000; Pelham et al., 2011). Being administrated in laboratory conditions (Gutiérrez-Maldonado et al., 2009), most CPT are usually free of distracting stimuli (apart from the non-target stimuli), which are thought to impair the cognitive performance of ADHD children (APA, 1994, 2000). This limitation may explain the loose association between CPT performance and behavioral measures of inattention and hyperactivity, such as those reported by parents and teachers in symptoms rating scales (DuPaul et al., 1992; McGee et al., 2000; Weis and Totten, 2004).

Some efforts have been made to assess distractibility in CPT. Presenting non-target stimuli is one option which is considered very subtle and based mainly on visual performance. In some cases, the CPT confidence index (reflecting the degree to which participants' responses match those of people diagnosed with ADHD) served as a measure of distractibility (Martin et al., 2009). Distractibility was based on the consistency of the response pattern and the degree to which this pattern was typical to ADHD population. However, this measure does not exclusively indicate distractibility but rather could characterize other attentional problems.

Several CPT include specific distractibility tasks. One of the widely used is the FDA approved Gordon Diagnostic System (Gordon and Mettelman, 1987). In the GDS CPT Vigilance task, a series of numbers are shown serially on a front display. The participant is asked to respond as quickly as possible when the number "1" is followed by the number "9." There are a total of 30 target sequences out of a total of 360 trials. Trials are divided into three blocks consisting of 120 stimuli and 10 target sequences each. The GDS CPT records the number of correct presses, omission and commission errors for both the total test as well as each of the three blocks of trials. In this task, distractors appear as numbers which are presented at a rate of one per second and are exposed for 200 ms each. The test takes approximately 6 min to complete (Kurtz et al., 2001). Although the GDS consistently discriminated ADHD children from control groups, there are mixed evidences regarding its ability to discriminate children with ADHD from various disordered controls and its associations with other measures of ADHD. The effect of distractors on its abilities is not clear (Christensen and Joschko, 2001).

Recently, Uno et al. (2006) developed a noise-generated CPT, which included neutral, geometric target/non-target stimuli and auditory/visual distractors (tone or irrelevant letter). This study found that while auditory noise strongly reduced impulsive and inattentive behaviors in ADHD relatively to non-ADHD children, visual distractors decreased the number of omission errors in ADHD children but increased it in non-ADHD children. However, the ecological validity of these trials is questionable due to the use of neutral stimuli. It has been suggested that ADHD children are more distracted when confronting with appealing, reinforcing or emotionally-loaded stimuli than with neutral ones (Blakeman, 2000; López-Martín et al., 2013).

Following the recommendation of Barkley (1991) and others (Rapport et al., 2000; Pelham et al., 2011) to improve the ecological validity of the CPT by evaluating the child's behaviors in more natural settings, virtual reality technologies incorporated typical stimuli of the learning environment (e.g., pencils dropping, chairs moving, airplane flying) into the CPT (Rizzo et al., 2006; Parsons et al., 2007; Adams et al., 2009). These methods consistently identified distractibility in ADHD children, probably due to better simulation of everyday life. However, these CPT tasks require sophisticated technologies that rarely exist in clinical and diagnostic settings.

Up to date, distractibility symptoms are clinically and empirically assessed by a large variety of cognitive tasks, such as Digit Span Distractibility Test (Oltmanns and Neale, 1975), Flanker task (Botvinick et al., 1999), Filter Task (Ophir et al., 2009), or Delayed Oculomotor Response task (Adams et al., 2011). The majority of these tasks involve a competition of responses, so that the child has to inhibit his response to the irrelevant stimuli. These tasks were criticized for their low ecological validity (Blakeman, 2000; Van Mourik et al., 2007) because in everyday life, the child has to ignore a stimuli that is external to the task and not conflicting with task demands (e.g., a child is doing schoolwork while someone talks in the next room). Importantly, it is possible that when the distractors compete with the central task, reduced performance in ADHD could be a result of a greater difficulty in inhibiting conflicting stimuli that are incorporated in a task, rather than higher sensitivity to irrelevant stimuli. Separate reviews found that auditory-sustained attention on a CPT (Gentilini et al., 1989; Parasuraman et al., 1991) and verbal-sustained attention with the Paced Auditory Serial Attention Task (Gronwall, 1989) were impaired after mild traumatic brain injury (mTBI).

Taken together, the described findings may suggest that including meaningful and relevant distracting stimuli in CPT may improve its ecological validity.

The objective of this study was to examine the added value of incorporating everyday life visual and auditory distractors into a

visual CPT and the effect of the distractors on the ability of the CPT to discriminate ADHD from non-ADHD children. Using the rate of omission errors as an index of sustained attention, this study examined whether ADHD children are more distracted than non-ADHD children. We also examined if and which type of distractors improves the ability of the test to distinguish ADHD from non-ADHD children. In order to examine these questions, this study used a visual CPT which includes environmental distracting stimuli (MOXO-CPT; Berger and Goldzweig, 2010). We hypothesized that several factors may make the MOXO-CPT preferable in terms of ecological validity. First, it includes environmental auditory and visual stimuli that are typical of childrens' everyday life. In contrast to the majority of cognitive tasks, distracting stimuli in the MOXO-CPT are external to the task (i.e., not conflicting with task demands). This method allows measuring the sensitivity of ADHD children to irrelevant stimuli in the classroom (e.g., someone talking in the next room) rather than background stimuli (e.g., music) or distractors that are part of the cognitive task (Van Mourik et al., 2007). Finally, this CPT is a standard computerized task which is highly available in clinical practices.

METHODS

PARTICIPANTS

Participants were 663 children aged 7–12 years, 405 of which were boys and 258 were girls. The clinical group was composed of 345 children previously diagnosed with ADHD (Mean age, 9.39, $SD = 1.57$) and the control group was composed of 318 children without ADHD (Mean age = 9.48, $SD = 1.58$).

Participants in the ADHD group were recruited from children who were referred to out-patient pediatric clinics of a Neuro-Cognitive Center, based in a tertiary care university hospital. The referrals to the center were made by pediatricians, general practitioners, teachers, psychologists, or parents. The following were the inclusion criteria for participants in the ADHD group:

Each child met the criteria for ADHD according to DSM-IV-TR criteria (APA, 2000), as assessed by a certified pediatric neurologist. The diagnostic procedure included an interview with the child and parents, medical/neurological examination and filing of ADHD diagnostic questionnaires (DuPaul et al., 1998).

Participants in the control group were randomly recruited from regular primary school classes. The inclusion criteria for participants in the control group were: (1) score below the clinical cutoff point for ADHD symptoms on ADHD/DSM-IV Scales (DuPaul et al., 1998; APA, 2000) and (2) absence of academic or behavioral problems based on parents and teachers reports.

The exclusion criteria for all participants were: intellectual disability, other chronic condition, chronic use of medications, and primary psychiatric diagnosis (e.g., depression, anxiety, and psychosis). All participants (both groups) studied in regular classes in regular schools.

All participants agreed to participate in the study and their parents provided a written informed consent to the study, approved by the Helsinki committee (IRB) of Hadassah-Hebrew University Medical Center Jerusalem, Israel.

TOOLS

The MOXO continuos performance test

The current study employed the MOXO-CPT version (Berger and Goldzweig, 2010). The MOXO-CPT (Neuro Tech Solutions Ltd.) is a standardized computerized test designed to diagnose ADHD related symptoms. As in other CPT, the MOXO-CPT task requires a participant to sustain attention over a continuous stream of stimuli and to respond to a pre-specified target, but it also includes visual and auditory stimuli serving as measurable distractors. The test consists of eight stages (levels). Each level consists of 53 trials and lasts 114.15 s. The total duration of the test is 15.2 min. In each trial a stimulus (target or non-target) is presented in the middle of the computer screen for a duration of 0.5, 1, or 3 s and is followed by a "void" of the same duration (see **Figure 1**). Fifty-three stimuli are presented in each level, of which 33 are target

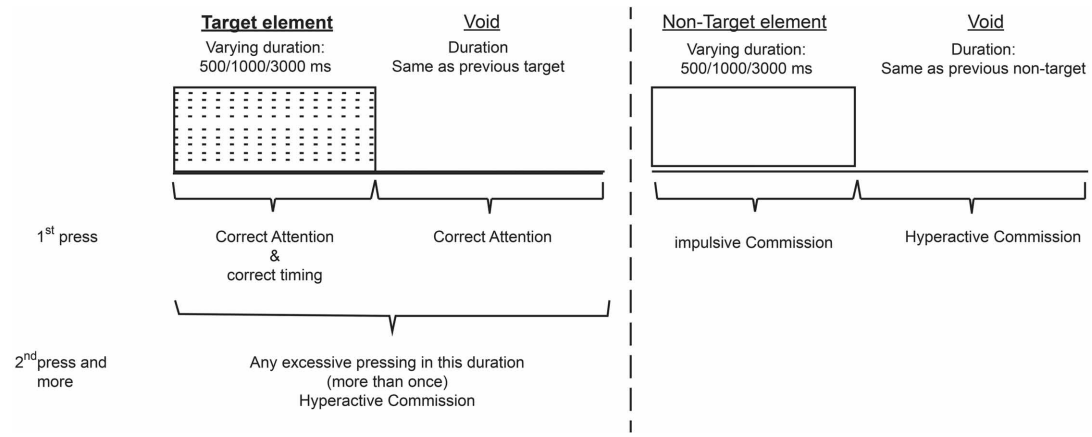

FIGURE 1 | Definition of the time line- Target and non-target stimuli were presented for 500, 1000, or 3000 ms. Each stimulus was followed by avoid period of the same duration. The stimulus remained on the screen for the full duration regardless the response. Distracting stimuli were not synchronized with target/non-targel's onset and could be generated during target/non-target stimulus or during the void period.

stimuli and 20 are non-target. Each stimulus remains on the screen for the full duration of the designated presentation time, regardless whether a response was given or not. This practice allows the measuring of the timing of the response as well as its accuracy.

The screen size is 125 high and 166 wide. The child is located 60 cm from the screen and is instructed to respond to target stimulus as quickly as possible by pressing the space bar once, and only once. The child is also instructed not to respond to any other stimuli but the target, and not to press any other key but the space bar.

Test Stimuli. Target and non-target stimuli—Both target and non-target stimuli are cartoon pictures free of letters or numbers (see **Figure 2**). The absence of letters and numbers in the stimuli is important given the fact that ADHD children tend to have learning difficulties (e.g., dyslexia, dyscalculia) that may be confound with CPT performance (Seidman et al., 2001). Target stimulus is always a cartoon image of a child's face. Non-target stimuli include five different images of animals (**Figure 1**). Both target and non-target stimuli are 41∗41 mm large and are always presented in the center of the screen.

Distracting stimuli—To simulate everyday environment, the MOXO-CPT included visual and auditory distracting stimuli which are not part of the non-target stimuli. The distracting stimuli are of various degrees of similarity to the target stimulus. Distractors were short animated video clips containing visual and auditory features which can appear separately or together. Overall, six different distractors were included, each of them could appear as pure visual (e.g., three birds moving their wings), pure auditory (e.g., birds singing), or as a combination of them (birds moving their wings and singing simultaneously). Each distractor was presented for a different duration ranging from 3.5 to 14.8 s, with a fixed interval of 0.5 s between two distractors. Visual distractors (**Figure 3**) included six different stimuli: a gong (presented for 6.8 s), a bowling ball (3.5 s), birds (9.25 s), warrior (Jedi) with a saber (14.8 s), a saber (6.8 s), and a flying airplane (8.6 s).

Visual distractors appeared at one of four spatial locations on the sides of the screen: down, up, left, or right. Visual distractors that appeared on the left/right axis were 200–400 pixels high and 100–200 wide. Visual distractors that appeared on the up/down axis were 100–200 pixels high and 100–600 wide. The distance between visual distractors and target/non-target stimuli is always 21 mm.

Auditory distractors included the six corresponding sounds of each visual distractor (e.g., a gong sound, sound of a bowling ball, birds singing etc.). The sound is delivered through loudspeakers located on both sides of the screen (about 60 cm distance from the child's ears). The sound intensity was about 70% of the maximal intensity of the loudspeakers. Distractors' onset was not synchronized with target/non-target's onset and could be generated during target/non-target stimulus or during the void period. All distracted were elements which characterize a typical child environment. This feature is unique to the MOXO-CPT in comparison to other CPT.

Test levels. The test comprised of eight levels, with 53 trials in each level. The stimuli and their presentation time are identical across all levels; however, the levels differ in the visual and auditory distractors present in the trials. Different levels of the MOXO-CPT were characterized by a different set of distractors: levels 1 and 8 did not include any distractors but only target and non-target stimuli, levels 2 and 3 contained pure visual stimuli, levels 4 and 5 contained pure auditory stimuli, and levels 6 and 7 contained a combination of visual and auditory stimuli. The sequence of distractors and their exact position on the display were constant for each level. The load of the distracting stimuli increased in the odd number levels: during the 2nd, 4th, and 6th levels only one distractor was presented at a time. During the 3rd, 5th, and 7th levels two distractors were presented simultaneously.

Performance indices. The MOXO-CPT includes four performance indices, the current study focuses on the rate of omission errors as an index of sustained attention:

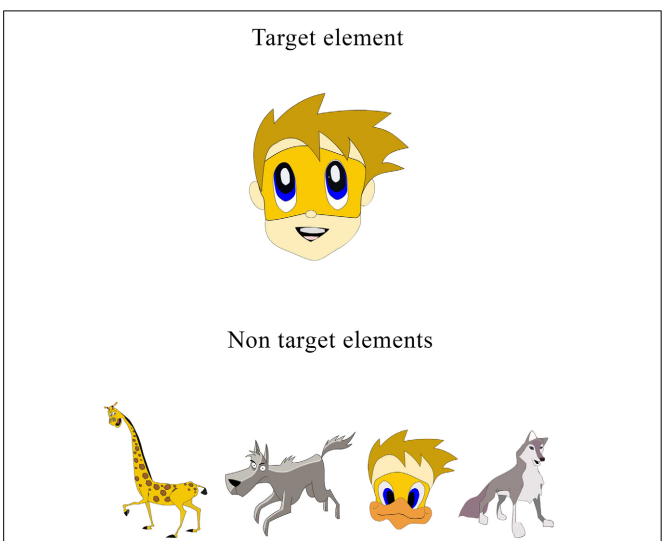

FIGURE 2 | MOXO-CPT target and non-target stimuli.

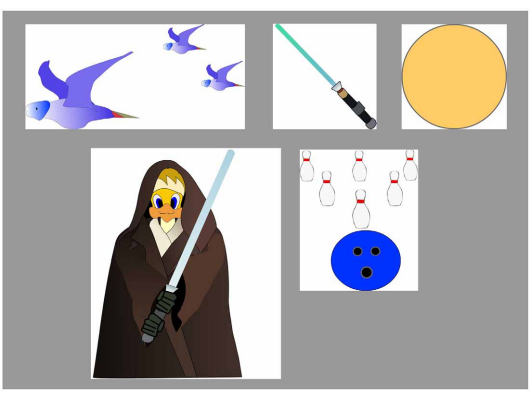

FIGURE 3 | MOXO-CPT visual distractors.

Attention: the number of correct responses (pressing the key in response to a target stimulus), given either during the stimulus presentation on the screen or during the following void period. The difference between the total number of the target stimuli and the number of correct responses produced the number of omission errors.
Timing: the number of correct given only while the target stimulus was still presented on the screen.
Impulsivity: the number of commission errors (responses to a non-target stimulus).
Hyperactivity: the number of all types of commission responses that are not coded as impulsive responses (e.g., multiple responses- pressing the keyboard's space bar more than once to target or non-target, random key pressing—pressing other keyboard button than the space bar). For more detailed description of performance indices see Appendix.

In this research we focused mainly on the index of omission errors. This index measures the number of times the child did not respond to target stimuli either during the stimulus presentation or during the void time. Hence, it can be regarded as a pure measure of difficulty in sustained attention which is not dependent on response speed.

PROCEDURE

The MOXO-CPT was administered by a technician who made sure that the child understood the instructions. The technician was present throughout the entire session. The examination room was clear of other distractors. All children (including the ADHD group) were drug naïve while performing the test.

DATA ANALYSES

All analyses were carried out using the SAS software for Windows version 9.2. First, Chi-square analysis and *t*-test for unpaired samples were used to examine group differences in background variables. Second, effects of background variables, ADHD, and test level on omission errors were examined through a Linear Repeated Measures model with Tukey's correction for multiple comparisons. Omission errors were the dependent variable, whereas age, gender, group, level were the independent variables.

*In addition, level * group interaction was calculated*

Between and within group effects were measured in every CPT condition (no distractors, visual distractors, auditory distractors, and a combination of visual and auditory distractors). For this purpose, every two identical levels were combined: levels 1 and 8 (no distractors), levels 2 and 3 (visual distractors) levels 4 and 5 (auditory distractors), and levels 6 and 7 (combination of visual and auditory distractors).

RESULTS

BACKGROUND VARIABLES

The two groups did not differ in age [$t_{(661)} = -0.81$, $p = 0.42$] but the percentage of boys in the ADHD group (68%, $N = 235$) was significantly higher than in the control group (54%, $N = 172$) [$\chi^2(1, N = 663) = 13.15$, $p < 0.001$]. However, when the effect of gender on omission errors was examined using a Linear Repeated Measures model, gender did not have a significant effect [$F_{(1, 659)} = 1.05$, $p = 0.31$].

EFFECTS OF DISTRACTORS ON OMISSION ERRORS IN ADHD AND NON-ADHD CHILDREN

In order to study the added value of the incorporation of distractors in the CPT for a better differentiation between AHDH and controls a linear repeated measures model with Tukey's correction for multiple comparisons was conducted.

This model included (a) between groups analysis of the differences in the rate of omission errors between ADHD and non-ADHD children, and (b) within-group analysis of the differences in omission errors between no distractors conditions and the three conditions which contained distractors (visual, auditory, and a combination of them).

First, analyses showed that while gender was not associated with CPT performance, age had a significant effect on it [$F_{(1, 659)} = 97.59$, $p < 0.001$].

When controlling for age and gender, group affiliation had a significant effect on the rate of omission errors [$F_{(1, 659)} = 92.59$, $p < 0.001$]. As can be seen in **Table 1**, ADHD children demonstrated higher rate of errors than non-ADHD children in all CPT conditions (no distractors, visual distractors, auditory distractors, and a combination of visual and auditory distractors). Most importantly, group * level interaction revealed that the differences between the two groups varied as a function of the task demands [$F_{(3, 659)} = 15.55$, $p < 0.001$]. Within-groups analysis indicated that for the ADHD group, omission errors were significantly higher in all distractors conditions compared to no-distractors. However, in the control group, only combined distractors resulted in an increase in omission errors (**Table 2**).

DISCUSSION

This study investigated the effects of environmental distractors on sustained attention of ADHD and non-ADHD children. Results showed that while ADHD children were negatively impacted by all types of distractors (visual, auditory, and a combination of them) non-ADHD children were affected only by the combination of visual and auditory stimuli. This finding confirms the sensitivity of ADHD children to environmental distracting stimuli and is consistent with other studies demonstrating higher distractibility of ADHD children in a variety of cognitive tasks (Adams et al., 2011; Pelham et al., 2011).

It is known that a variety of visual and auditory stimuli exists in the everyday environment of ADHD children and that problematic behavior first appear in the presence of such stimuli. Thus, our results support the idea that ADHD is indeed marked by high distractibility and that children with ADHD have difficulties to sustain attention in the presence of irrelevant environmental stimuli. These findings are in line with other studies that demonstrated higher distractibility of ADHD children during CPT and non-CPT tasks (Gumenyuk et al., 2005; Parsons et al., 2007; Adams et al., 2011; Pelham et al., 2011). Parsons et al. (2007), who used a virtual reality technology to simulate everyday distractibility in ADHD, have shown that during

Table 1 | Differences in Omission errors between ADHD and non-ADHD Children.

Level's number	Distractors type	ADHD ($N = 345$)		Control ($N = 318$)		Difference t (659)
		Omission errors		Omission errors		
		M	*SD*	*M*	*SD*	
1	Base line	1.80	2.57	0.80	1.30	6.18, $p < 0.001$
2	Visual[a]	3.21	3.38	1.19	1.32	10.53, $p < 0.001$
3	Visual[b]	2.73	3.09	1.18	1.42	8.46, $p < 0.001$
4	Auditory[a]	2.50	3.21	0.95	1.25	8.26, $p < 0.001$
5	Auditory[b]	2.74	3.86	0.97	1.39	7.84, $p < 0.001$
6	Combined[a]	3.52	3.90	1.58	1.64	8.50, $p < 0.001$
7	Combined[b]	3.45	4.17	1.75	2.17	6.57, $p < 0.001$
8	No distractors	2.26	3.19	1.21	1.95	5.01, $p < 0.001$

[a]*Low distractibility;* [b]*High distractibility; M, mean; SD, standard deviation.*

Table 2 | Level differences in Omission errors within each study group.

Level's number	Distractors type	ADHD ($N = 345$)			Control ($N = 318$)		
		Omission errors		Difference from baseline level $t_{(659)}$	Omission errors		Difference from baseline level $t_{(659)}$
		M	*SD*		*M*	*SD*	
1	Base line	1.80	2.57		0.80	1.30	
2	Visual[a]	3.21	3.38	−12.51, $p < 0.001$	1.19	1.32	−3.27, $p = 0.08$
3	Visual[b]	2.73	3.09	−8.46, $p < 0.001$	1.18	1.42	−3.31, $p = 0.07$
4	Auditory[a]	2.50	3.21	−6.04, $p < 0.001$	0.95	1.25	−1.23, $p = 0.99$
5	Auditory[b]	2.74	3.86	−6.63, $p < 0.001$	0.97	1.39	−1.11, $p = 0.99$
6	Combined[a]	3.52	3.90	−12.09, $p < 0.001$	1.58	1.64	−5.20, $p < 0.001$
7	Combined[b]	3.45	4.17	−10.06, $p < 0.001$	1.75	2.17	−5.53, $p < 0.001$
8	No distractors	2.26	3.19	−3.45, $p = 0.05$	1.21	1.95	−2.94, $p = 0.20$

[a]*Low distractibility;* [b]*High distractibility; M, mean; SD, standard deviation.*

distracting conditions, ADHD children were more hyperactive and produced more omission errors on the Conners' CPT-II as compared to non-ADHD children. Likewise, Gumenyuk et al. (2005) shown that when a novel sound appeared during a visual discrimination task, ADHD children showed higher rate of omission responses and different patterns of event-related potentials (ERP) (smaller amplitude over the fronto-central left-hemisphere during the early phase of P3a and a larger amplitude during its late phase compared to controls). These findings were attributed to the deficient control of involuntary attention in ADHD children that may underlie their abnormal distractibility.

On the other hand, our findings are inconsistent with other studies which indicated that auditory and visual distractors did not impair cognitive performance of ADHD children or even improved it (Abikoff et al., 1996; Uno et al., 2006; Söderlund et al., 2007; Van Mourik et al., 2007; Pelham et al., 2011). Uno et al. (2006) who specifically tested the effect of auditory noise on CPT performance, found that ADHD children produced fewer omission errors in the presence of auditory noise than in the no-noise condition. Similarly, Van Mourik et al. (2007) found that the occurrence of an irrelevant, novel sound prior to a visual stimulus decreased the rate of omission errors in ADHD children relatively to no-sound conditions. The positive effect of distracting auditory stimuli on the cognitive performance of ADHD patients is usually attributed to the increased arousal provoked by a novel signal (Uno et al., 2006; Van Mourik et al., 2007). It is possible that distractors in the MOXO-CPT failed to improve attention in ADHD children because of the little information they conveyed for the participant. It has been suggested (Parmentier et al., 2010) that the degree to which a novel, unexpected auditory sound may optimize performance depends on the amount of information it conveys. When a novel sound predicts another relevant stimulus, the system can take advantage of the auditory distractors to improve its functioning. In contrast to other CPT tasks (e.g., Uno et al., 2006; Van Mourik et al., 2007), distractors in the MOXO-CPT did not precede the target or were generated simultaneously with it, but rather were unsynchronized with it. This fact may lower the extent to which the sound included information necessary to optimize performance and may explain

why auditory distractors did not improve sustained attention in our study.

The diversity of our results from the studies mentioned above could also result from the type of distractors used. While some studies have used neutral stimuli (neutral tone/letter) as distractors (Gordon and Mettelman, 1987; Uno et al., 2006), the MOXO-CPT used more ecologically valid stimuli that are typically found in the child's environment. Since ADHD children have more difficulties in filtering meaningful distractors (Blakeman, 2000) they may fail to inhibit response to relevant or appealing stimuli. Another factor that may contribute to the high distractibility of ADHD children in this study is the method of distractors presentation. In several studies, auditory distractors served as a background noise while children performed another cognitive task (Abikoff et al., 1996; Pelham et al., 2011). In contrast, distractors in the MOXO-CPT vary in their type, in their length of presentation and in their location on the screen. This mode of presentation did not allow adjustment or de-sensitization to the distractors, therefore, kept them salient. Finally, methodological differences in distractors presentations may underlie the contrasting findings. While Gumenyuk et al. (2005) used headphones to present auditory distractors; Van Mourik et al. (2007) used a speaker. It is possible that auditory stimuli served as more potent distractors to ADHD children when presented by headphones than by a speaker because they drew the patient's attention spatially away from the visual targets. However, this argument is not enough to explain why auditory stimuli in the MOXO-CPT distracted ADHD children despite the use of a loudspeaker.

It can be argued that because levels in the MOXO-CPT are presented in a constant manner (namely level 1 to level 8), distractors' effect may be confounded with time effects. However, our findings suggest that it might not be the case. In the current study children in the control group did not perform more omission errors at the last level of the test (level 8) than at the first one (level 1). ADHD children performed marginally more omission errors in the last level (level 8), but it is a rather weak/marginal effect which does not seem a cause for concern. Moreover, in both groups, there was no linear increase in omission errors as the test progressed as we would expect if time was negatively associated with sustained attention.

The finding that both ADHD and control groups did not perform significantly more omission errors at the end of the test than at the beginning of it (i.e., both groups did not demonstrate clear fatigue effects) is in contrast to other studies indicating degraded performance in ADHD patients as the task progresses (McGee et al., 2004; Erdodi et al., 2010; Erdodi and Lajiness-O'Neill, 2013). According to Huang-Pollock et al. (2012), degraded performance over time in ADHD patients is more prominent in tasks that use sensory stimuli (i.e., discriminations of physical characteristics that differ in degree) than in tasks that use cognitive stimuli (i.e., stimuli that differ in kind, such as alphanumeric symbols) because of the lower level of effort in the latter type. *The fact that the MOXO-CPT, like most CPT tasks, relied on cognitive stimuli may explain why we failed to identify time effects on performance.* Nevertheless, time effect on CPT performance should be further addressed in future studies.

Several limitation of this study should be considered. First, participation in the study was based on a voluntary agreement of children and their parents. This self-selected sampling strategy tends to be biased toward favoring more cooperative and motivated individuals. Therefore, it is not possible to determine whether this sample also represents other children that were not recruited and whether cooperation is confounded with ADHD variables. This limitation is typical to most clinic-based ADHD studies around the world (Lee and Ousley, 2006; Gau et al., 2010). In addition, the clinics from which ADHD children were recruited were based in tertiary care hospital. Finally, the exclusion of ADHD children with severe comorbidities may limit the generalization of our results.

In light of the criticism voiced against the low ecological validity of many CPT (Rapport et al., 2000; Pelham et al., 2011), the current study provides evidence that adding environmental distractors to CPT impaired the ability of ADHD children to sustain attention and strongly increased their omission errors as compared to non–ADHD children. For non-ADHD children only a combination of visual and auditory stimuli created enough cognitive load to impair attention.

Future research should address the diagnostic utility of the test in larger spectrum of age, in samples with comorbid features, and in different sub-types of ADHD. In addition, future research should investigate the effects of medical treatment on the distractibility of ADHD children.

AUTHOR CONTRIBUTIONS

All authors contributed extensively to the work presented in this paper.

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APPENDIX

DESCRIPTION OF PERFORMANCE INDICES

Attention

This parameter included the number of correct responses (pressing the key in response to a target stimulus), which were performed either during the stimulus presentation on the screen or during the void period that followed. Thus, it was possible to evaluate whether the participant responded correctly to the target (was attentive to the target) independently of how fast he was. Knowing how many responses are expected, it was also possible to calculate the number of times the target was presented, but the patient did not respond to it (omission errors).

Timing

This parameter included the number of correct responses (pressing the key in response to a target stimulus) which were performed only while the target stimulus was still presented on the screen. This parameter did not include responses that were performed during the void period (after the stimulus has disappeared). According to the National institute of mental health (2012), inattention problems in ADHD may be expressed in "difficulties in processing information as quickly and accurately as others." Traditionally, difficulties in timing at a CPT are evaluated by mean response time for correct responses to the target (which is interpreted as a measure of information processing and motor response speed) and by the standard deviation of response time for correct responses to the target (which is interpreted as a measure of variability or consistency) (Greenberg and Waldman, 1993). In these paradigms the stimulus is presented for short and fixed periods of time and the response occurs after the stimulus has disappeared. Given the short, fixed presentation, accurate but slow participants may be mistakenly diagnosed as inattentive. While a group of patients would respond correctly if allowed more time, inattentive patients would not respond at all because they were not alert to the target. Therefore, the measurement of response time *per-se*, addresses only the ability to respond quickly, but not the ability to respond accurately. By implanting a void period after each stimulus and using variable presentation durations of the elements, the MOXO-CPT could distinguish accurate responses performed in "good timing" (quick and correct responses to the target performed during stimulus presentation) from accurate but slow responses (correct responses to the target performed after the stimulus presentation; during the void period). These two aspects of timing correspond to the two different problems of ADHD described by the National institute of mental health (2012); responding quickly and responding accurately.

Impulsivity

This parameter included the number of commission errors (responses to a non-target stimulus), performed as responses to the non-target stimuli. Usually, commission errors are coded in any case of inappropriate response to the target (e.g., pressing a random key) (Greenberg and Waldman, 1993). In contrast, the MOXO-CPT's impulsivity parameter considered as impulsive behavior only the pressings on the keyboard's space–bar in response to non-target stimulus. All other non-inhibited responses (e.g., pressing the keyboard more than once) were not coded as impulsive responses (as will describe in the next paragraph).

Hyperactivity

This parameter included all types of commission responses that are not coded as impulsive responses. Several examples are: (1) Multiple responses- pressing the keyboard's space bar more than once (in response to target/non-target), which is commonly interpreted as a measure of motor hyper-responsivity (Greenberg and Waldman, 1993). The MOXO-CPT considered as multiple responses only the second press and above (the first response would be considered as correct response with good timing, as correct response with poor timing, or as impulsive response, depends on the type of element appearing on the screen). (2) Random key pressing—pressing any keyboard button other than the space bar. By separating commission errors due to impulsive behavior from commission errors due to motor hyper-responsivity, it was possible to identify the multiple sources of response inhibition problems. Thus, the MOXO-CPT was able to differentiate impulsive responses from hyperactive responses.

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The effect of alpha-linolenic acid supplementation on ADHD symptoms in children: a randomized controlled double-blind study

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Background: Attention deficit-hyperactivity disorder (ADHD) is the most common neuro-developmental disorder in childhood. Its pharmacologic treatment mostly includes methylphenidate, yet many parents seek alternative, "natural," therapeutic options, commonly omega-3 fatty acids. Previous studies of supplementation with fish oil or long-chain omega-3 fatty acids to children with ADHD yielded mixed results. The use of alpha-linolenic acid (ALA), a medium-chained, plant-based omega-3 fatty acid (18:3 n-3), has not been sufficiently examined in this population.

Methods: Forty untreated children with ADHD, aged 6–16 years, were randomized to receive either 2 g/day of oil containing 1 g ALA or placebo, for 8 weeks. Before and after supplementation, the children underwent a physician assessment of ADHD symptoms and a computerized continuous performance functions test. The children's parents and teachers filled out Conners' and DSM questionnaires.

Results: Seventeen (42.5%) children completed the study, eight in the supplementation group, nine in the placebo group. Main drop-out reasons were capsule size, poor compliance, and a sense of lack of effect. No significant difference was found in any of the measured variables tested before and after supplementation, in both study groups. No between-group difference was found in the changes of the various measures of ADHD symptoms throughout the study period.

Conclusion: Supplementation of 2 g/day of oil containing 1 g ALA did not significantly reduce symptoms in children with ADHD. Future studies in this field should consider an alternative method to deliver the oil, a higher dose, and a larger sample size.

Keywords: fatty Acids, omega-3, attention, hyperactivity, ADHD, linolenic acids

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a childhood onset disorder with a relatively high global prevalence, ranging from 2.2–17.8% (Skounti et al., 2007). ADHD is considered the most common neuro-behavioral disorder of childhood, and one of the most prevalent chronic health conditions affecting school-aged children (Wolraich et al., 2011).

The pharmacologic treatment of ADHD mostly includes methylphenidate (Wolraich et al., 2011). Surprisingly, one study from Israel found that the prevalence of methylphenidate prescription use in the population was only 2.5% – a much smaller rate than the estimated prevalence of ADHD in Israel (Vinker et al., 2006). A possible explanation as to why a large proportion of children with ADHD are not adequately treated could be the stigmatization of methylphenidate. Indeed, many parents continuously seek alternative, "natural," therapeutic options other than methylphenidate (Berger et al., 2008). Omega-3 fatty acids are among the most common dietary supplements used in children with ADHD. The basis for this treatment stems from studies that identified low levels of omega-3 fatty acids in plasma phospholipids or red blood cell membranes of children with ADHD (Mitchell et al., 1987; Stevens et al., 1995; Antalis et al., 2006).

Several trials of supplementation with fish oil or long-chain omega-3 fatty acids [mostly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] to children with ADHD have been conducted, and yielded mixed results. Systematic reviews and meta-analyses on this topic summarized that there is currently no consensus that omega-3 fatty acids influence ADHD symptoms (Richardson, 2006; Chalon, 2009; Raz and Gabis, 2009; Bloch and Qawasmi, 2011; Gillies et al., 2012). One possible mechanism suggested for the common lack of effect is a relatively poor incorporation of these fatty acids into the brain. In a pioneering study, Vaisman et al. (2008) showed that consumption of EPA and DHA that were incorporated into phospholipids, resulted in higher

circulating levels and better executive functioning in children with ADHD, as compared with fish oil. The authors identified significant correlations between the chemical changes and the clinical effects. Another supplementation study with long chain omega-3 fatty acids conjugated to phosphatidylserine, in order to improve their absorption, also showed improved behavior of children with ADHD (Manor et al., 2012).

Fewer trials examined the effect of the plant-based alpha-linolenic acid (ALA), the parent medium-chain omega-3 fatty acid, on ADHD symptoms. In one published study, 200 mg ALA administered as flaxseed oil together with vitamin C were given to children with ADHD (Joshi et al., 2006). The authors noted increased levels of circulating EPA and DHA, with improvements in parent-rated ADHD symptoms of impulsivity, restlessness, inattention, and self-control. Yet the lack of control group in this study, the relying on parent report only, and the concomitant addition of vitamin C, prevent from drawing clear conclusions on the effect of ALA alone. In another study, children with ADHD received either a supplement containing 120 mg of ALA and 480 mg of linoleic acid and, or vitamin C as placebo, for 7 weeks (Raz et al., 2009). Treatment effects were measured using questionnaires and a computerized test of attention, and did not differ significantly between groups. Of note, these authors administered a relatively low dose of ALA, while also supplementing with a higher dose of the parent fatty acid of the omega-6 family which could inhibit conversion of ALA to the long chain omega-3 fatty acids through competition on the same enzymes. It still remains unknown whether supplementation of a higher dose of ALA could affect ADHD symptoms more than placebo.

The aim of the current study was to examine if supplementation with an ALA-rich sage oil can improve symptoms in children and adolescents diagnosed with ADHD.

MATERIALS AND METHODS

PARTICIPANTS

The study population included 40 children and adolescents aged 6–16 years, recently diagnosed with ADHD, who were drug naïve and untreated, from two ambulatory ADHD specialty clinics in Israel. Exclusion criteria were refusal to undergo any or all of the testing procedures or to take the designated supplement; a history of chronic health conditions other than ADHD; or use of any chronic medications or dietary supplements, specifically methylphenidate or fatty acid/fish oil supplements. The study was approved by the Institutional Review Board of Hadassah Medical Center, Jerusalem, Israel, conducted according to the Declaration of Helsinki, and registered in a clinical trials registry before recruitment (#NCT00874536). At least one parent signed an informed consent form, and each participant verbally agreed to participate.

INTERVENTION

The study participants were randomized 1:1 to receive either 2 g/day of sage oil or an identical appearing lactose placebo in gel capsules. Participants were instructed to consume two gel capsules daily. The composition of sage oil varies slightly by crop year, and is 50–54% ALA, 20–23% oleic acid, 16–18% linoleic acid, 6–7% palmitic acid, and 2–3% stearic acid (Tulukcu et al., 2012). This corresponds to a supplementation of 1 g/day of ALA, a dose that had been shown previously in adults to elevate the concentrations of omega-3 fatty acids (Barceló-Coblijn et al., 2008). The supplementation period lasted 8 weeks.

RANDOMIZATION

Both types of capsules were supplied in identical amounts in solid plastic bottles. The bottles were numbered consecutively and coded by a person uninvolved in the study, and each participant received three bottles that contained all pills necessary for the study duration. Each ADHD clinic received half of the bottles, numbered consecutively. The children that agreed to participate in the study received their designated bottles in consecutive order. All study participants, parents, teachers, and study personnel were blinded to the allocation until completion of all data collection.

OUTCOMES AND DATA COLLECTION

The primary outcomes at study end were ADHD symptoms, as assessed by validated questionnaires and a computerized continuous performance test (CPT, see below). Each child met the criteria for ADHD according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR criteria (American Psychiatric Association, 2000), as assessed by a physician certified in ADHD diagnosis and treatment.

The diagnostic procedure included an interview with the child and parents, filing of DSM-based ADHD diagnostic questionnaires, and a medical and neurological examination. Parents and teachers filled the appropriate Conners' rating scales (Conners, 1997a,b).

We used the MOXO-CPT, which is a standardized computerized test designed to diagnose ADHD-related symptoms (Berger et al., 2009). The total duration of the test is 15 min, and it is composed of eight levels of 53 trials each. In each trial, a stimulus in the form of a cartoon picture (designated as "target" or "non-target") is presented for 500, 1000, or 3000 ms, followed by a "void" period of the same duration, during which the tested individual should respond by pressing the keyboard "space" bar as quickly as possible. In each level, 33 target and 20 non-target stimuli are presented. The tested participant is instructed not to respond to any other stimuli except the target, and not to press any other key but the space bar, and only once. The response timing and accuracy is measured after each stimulus. The test includes distracting stimuli that are presented to the tested participant. These distractors are short animated video clips, containing visual, and auditory features. Six different distractors are included, each of them could appear as only visual, only auditory, or as a combination of both. Each distractor is presented for a different duration ranging from 3.5–14.8 s, with a fixed interval of 0.5 s between two distractors. Distractor onset is not synchronized with target/non-target onset, and could therefore appear either during the stimulus events or during the void period. The burden of the distracting stimuli increases during the test.

The MOXO-CPT measures four performance indices: attention, timing, impulsivity, and hyperactivity. The attention index corresponds to the number of correct space bar keystrokes in response to a target stimulus. This index is considered a pure measure of sustained attention, because it measures correct responses

independently of the response time. The timing index is the number of correct responses given quickly, still within the period that the target stimulus is present on screen. The impulsivity index is the number of responses performed following a non-target stimulus. The hyperactivity index is the total number of commission responses that are not coded as impulsive responses (e.g., multiple keystrokes in response to a target stimulus, responses performed in the void period after a non-target stimulus, random key pressing). Other measures of the MOXO-CPT are described in detail elsewhere (Berger et al., 2013; Cassuto et al., 2013).

The same assessment tools were used after 8 weeks of supplementation in both groups. At this final assessment visit, missing pills in the bottles were counted, to assess adherence.

STATISTICAL ANALYSIS

The differences in questionnaire scores and CPT results between baseline to end-of-study values within each group were compared by the Wilcoxon signed-ranks test. The differences in clinical data, questionnaire scores, and CPT results between study groups at baseline and at trial end were compared by the Mann–Whitney *U* Test. The between-group differences in the changes of questionnaire scores and CPT results were also compared by the Mann–Whitney *U* Test. Proportions were compared using Fisher's exact test. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

Twenty children were included in each group, and received their designated supplement. After 8 weeks, only 17 participants remained in the study, and underwent the post-supplementation assessment: nine in placebo group (six males, three females, mean age 10.9 $\pm$ 2.3 years) and eight in the oil group (four males, four females, mean age 11.1 $\pm$ 3.0 years). Reasons for dropout were difficulty to take the capsules due to size or taste (n=7), a subjective sense of lack of effect ($n = 4$), loss of contact ($n = 5$), or lack of interest to perform the second assessment ($n = 7$). None of the participants complained about the most common intolerance to fish oils, namely a "fishy" smell and aftertaste.

PARENT QUESTIONNAIRES

Table 1 presents data from parent questionnaires, regarding their perception of their children's behavior, before and after the supplementation period. There were significant differences between study groups at baseline in two of the three scales, indicating worse ADHD behavior in the omega-3 group. There were also significant differences between groups at trial end in all scales, again in the direction of worse behavior. However, there were no significant between-group differences in the changes from pre- to post-supplementation values in any of the measured parameters.

TEACHER QUESTIONNAIRES

Table 2 presents data from teacher questionnaires, regarding their perception of the children's classroom behavior, before and after the supplementation period. There were no significant differences between study groups at baseline or at trial end in any of the tested parameters. Additionally, there were no significant between-group differences in the changes from pre- to post- supplementation values in any of the measures.

DSM criteria

Scores of DSM-criteria questionnaires also did not differ between placebo and omega-3 groups. Respective scores at baseline were 11 (range 6–17) and 13 (range 6–17), $p = 0.29$, with no measurable change in any of the values at trial end [11 (range 6–17) and 13 (range 6–17), $p = 0.47$].

COMPUTERIZED CONTINUOUS PERFORMANCE TEST

Table 3 presents data from the MOXO-CPT that the children undertook before and after the supplementation period. There were no significant differences between study groups at baseline or at trial end in any of the tested parameters. Additionally, there were no significant between-group differences in the changes from pre- to post- supplementation values in any of the measures.

DISCUSSION

The aim of this study was to examine if supplementation with an oil rich in ALA can improve behavior and function in children and adolescents with ADHD. Using several validated questionnaires and a CPT, we found no evidence for a significant effect in any direction. Although we did identify significantly higher post-supplementation scores in the parent Conners' questionnaires in the omega group, these were attributed to baseline differences; there were no significant differences between the changes in these questionnaire scores between groups. A decrease in the parent Conners' DSM-IV questionnaire score was seen in the placebo group only, with no other index of improvement in any other measure in this group. We believe that this does not truly reflect clinical improvement, and is probably a random finding resulting from multiple comparisons.

Several previous studies of fish oil/long chain omega-3 supplementation to children with ADHD have been performed, with recent meta-analyses showing no significant clinical effect (Bloch and Qawasmi, 2011; Gillies et al., 2012). It should be noted that one meta-analysis on this topic did identify a small, statistically significant effect – but which is clinically much lesser than that obtained by methylphenidate and other medications (Bloch and Qawasmi, 2011). Therefore, from a clinical point of view, there is currently no evidence to support choosing omega-3 fatty acids over methylphenidate for ADHD treatment. The authors explained the discrepancy between their own findings and the null effect seen in most individual trials, by the small sample sizes used in the single studies. They calculated that in order to obtain sufficient statistical power to identify the small effect of omega-3 in ADHD compared to placebo, clinical trials would require a sample of approximately 330 children. The authors stated that the omega-3 fatty acid supplementation trials examining childhood ADHD used 26–117 participants only. Conversely, the Cochrane meta-analyses (Gillies et al., 2012), which included 13 trials with 1011 participants overall, concluded that there is little evidence that omega-3 fatty acid supplementation provides any benefit for the symptoms of ADHD in children and adolescents.

Table 1 | Data from parent Conners' questionnaires at baseline and study end in both groups.

	Placebo ($n = 9$)			Omega-3 ($n = 8$)			*p*-value between changes***
	Pre	**Post**	***p*-value**	**Pre**	**Post**	***p*-value**	
Parent Conners' ADHD Index	62 [47–70]	62 [46–64]	0.19	76* [71–90]	79** [54–89]	0.68	0.79
Parent Conners' Global Index	68 [49–80]	71 [42–76]	0.50	85* [78–90]	77** [72–90]	0.46	0.42
Parent Conners' DSM-IV: total	65 [50–79]	62 [45–69]	0.04	78 [63–89]	87** [64–90]	0.89	0.22

Data is presented as median and [range].
**Significantly different ($p < 0.05$) from the corresponding baseline value of the placebo group.*
***Significantly different ($p < 0.05$) from the corresponding post-supplementation value of the placebo group.*
****p-value of the comparison between the pre-post changes in each group.*

Table 2 | Data from teacher Conners' questionnaires at baseline and study end in both groups.

	Placebo ($n = 9$)			Omega-3 ($n = 8$)			*p*-value between changes*
	Pre	**Post**	***p*-value**	**Pre**	**Post**	***p*-value**	
Teacher Conners' ADHD index	59 [59–75]	61 [59–69]	0.27	69 [53–89]	69 [58–87]	0.67	0.26
Teacher Conners' Global Index	63 [60–64]	64 [60–85]	0.65	65 [58–68]	72 [56–90]	0.25	0.76
Teacher Conners' DSM-IV: total	62 [57–75]	61 [57–67]	0.18	63 [46-90]	66 [56–90]	0.28	0.17

Data is presented as median and [range].
**p-value of the comparison between the pre-post changes in each group.*

Table 3 | Data from the MOXO performance test at baseline and study end in both groups.

	Placebo ($n = 9$)			Omega-3 ($n = 8$)			*p*-value between changes*
Measure	**Pre**	**Post**	***p*-value**	**Pre**	**Post**	***p*-value**	
Timing	167 [114–253]	158 [54–208]	0.87	125 [23–194]	178 [130–214]	0.14	0.20
Reaction time	0.47 [0.39–0.60]	0.54 [0.10–0.65]	0.50	0.54 [0.05–0.67]	0.52 [0.42–0.66]	0.89	0.88
Impulsivity	14 [2–130]	7 [1–96]	0.73	7 [0–23]	21 [5–157]	0.14	0.20
Attention	230 [166–264]	244 [58–263]	1.00	178 [24–258]	242 [196–256]	0.22	0.53
Hyperactivity	48 [7–293]	29 [0–435]	0.50	20 [4–151]	61 [10–569]	0.35	0.27

Data is presented as median and [range].
**p-value of the comparison between the pre-post changes in each group.*

To our knowledge, only two studies that utilized plant-based omega-3 fatty acids in ADHD were published to-date (Joshi et al., 2006; Raz et al., 2009). Both used relatively small amounts of ALA (200 and 120 mg, respectively). In the study by Joshi et al. (2006), increased levels of circulating EPA and DHA were found, demonstrating that even a much lower dose than that used in our study (yet when combined with vitamin C), is sufficient to increase concentrations of omega-3 fatty acids in the body. The improvement seen in most measures in that study, such as total hyperactivity score, restlessness, impulsiveness, and inattentiveness, was very large, around 1 SD. Nevertheless, the lack of placebo-control group and the addition of vitamin C, prevent from isolating the individual effect of ALA *per se*. Collectively, there is still a wide gap in our knowledge regarding the effects of omega-3 fatty acids in ADHD, which is even greater in the field of plant-based ALA. The main reasons are the large variations in the types of fatty acids used (omega-3 with or without omega-6, fish- or plant-based oils, etc.), in their dosages, in the proportions between EPA and DHA, and in the different characteristics and numbers of participants in each study.

We recognize that our trial has several limitations. Firstly, we had a relatively small sample size with a high dropout rate, attributed both to the reported inconvenience of consuming 2 g of oil per day, and to the subjective feeling of a lack of effect by the participants or their parents. Recruiting a larger sample size of newly diagnosed, non-medicated children for such a trial may be a challenge, as many parents do request an immediate and efficient treatment once their child is initially diagnosed with ADHD. Secondly, we chose a wide age range of 6.5–16 years, which might have caused a wide variation in test results, especially in the computerized test. Baseline data of the DSM questionnaire also showed a wide range of disturbance, as reflected by the range of DSM scores seen. We *a priori* chose a wide age range and included participants from both sexes in order to increase generalizability, yet eventually this might have been a drawback. Lastly, the dose used might have still been too low to increase the amount of brain EPA and DHA. While this dose has been shown to elevate omega-3 fatty acids concentrations in red blood cells in adults (Barceló-Coblijn et al., 2008), we would expect at least the same effect in children and adolescents; however, examining the brain content of these fatty acids in children following supplementation is currently not possible.

The strengths of the study were its randomized, placebo-controlled design; the choice of non-medicated, otherwise healthy children; and the concomitant use of several validated tools that directly assessed the child, as well as parent and teacher perceptions of his behavior.

In summary, in this study, supplementation of 1 g/day of ALA using an ALA-rich oil to children and adolescents with ADHD did not improve any behavioral measure, as tested by several validated questionnaires and a computerized CPT. We do acknowledge that a major limitation to the trial was the relatively small sample size, attributed to a relatively high dropout rate. Nevertheless, our findings are in concert with many other studies which used both ALA and long-chain omega-3 fatty acids. Given the high dropout rate, and in light of previous research and anticipated effect size, we recommend recruiting much larger numbers of participants, and possibly using a higher ALA dose in future similar studies.

AUTHOR CONTRIBUTIONS

Gal Dubnov-Raz contributed to study design, conductance, data analysis, and drafted the first manuscript. Zaher Khoury contributed to study conductance and data analysis. Ilana Wright and Itai Berger contributed to study design, conductance, and data analysis. Raanan Raz contributed to study design and data analysis. All authors contributed significantly to the manuscript text, and approved its final version.

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A meta-analysis of visual orienting in autism

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Background: Visual orienting is inconsistently reported to be impaired in autism.

Methods: We conducted a meta-analysis on visual orienting in autism. We focused on studies that used a Posner-type task. A total of 18 research papers published between 1993 and 2011 were included in our meta-analysis. We examined the effects of differences in experimental design as well as differences in participant samples. We examined both orienting reaction times of participants with autism, and the effect size relative to comparison group in each experiment.

Results: We found that participants with autism oriented across conditions (mean orienting effect = 40.73 ms), which was of an overall smaller magnitude than that of comparison groups (Cohen's $d = 0.44$). Participants with autism were most impaired on arrow cue tasks, and least impaired on eye-gaze cue tasks, more impaired with rapid trials, and the impairment increased with age.

Conclusions: Variations in experimental design and participant age group contribute to whether participants with autism appear impaired at visual orienting. Critical gaps exist in the literature; developmental studies are needed across and comparing broader age ranges, and more attention should be focused on basic endogenous orienting processes.

Keywords: visual orienting, Posner task, autism, meta-analysis, attention

INTRODUCTION

In the classroom, as in the world, children can only learn about that which they attend. Selecting where to attend in the world is termed orienting. While the skill of visual orienting in autism has been of interest to researchers for the past 20 years there is no consensus in the literature as to how, if at all, visual orienting differs in autism. Clarifying the research on visual orienting will improve our understanding of the neurodevelopmental trajectory of autism. The single most widely used task for measuring visual orienting is the Posner task (Posner, 1980). Different variants of this task have been used by investigators to study visual orienting in autism, arriving at often contradictory results. Our goal was to analyze the published corpus of papers that have used a variant of the Posner task in persons with autism in an attempt to clarify the murky question about the nature of visual orienting in autism.

In a typical Posner task, participants are instructed to detect, localize, or identify a target when the target appears. Targets are preceded by cues that validly, invalidly, or neutrally prime a target's location. Participants are faster to respond to a target in a validly cued location than an invalidly cued location because attentional resources are directed to the cued location in advance of the target appearance. The reaction time advantage of valid over invalid is referred to as the *orienting effect*. In studies employing a neutral condition, the advantage of a valid over a neutral cue is referred to as the *benefit* of the valid cue and the disadvantage of an invalid relative to a neutral cue is referred to as the *cost* of the invalid cue.

Visual orienting is often classified in two ways: exogenous and endogenous, although there has been considerable debate recently about this distinction with respect to the formerly synonymous distinction of automatic and voluntary orienting (e.g., Enns and Trick, 2006; Ristic and Kingstone, 2012). We will operationally define exogenous and endogenous in the following manner: exogenous orienting occurs in response to an external stimulus, which causes an individual's attention to be drawn toward the location of that stimulus—the cue and cued locations are the same. An oft-cited example is directing attention toward a flash of lightening. Endogenous orienting, on the other hand, occurs in response to some kind of symbolic cue (or indicator) directing attention to a specific location but away from the cue—the cue and cued locations are not the same. Arrows, pointing gestures, and directional eye-gaze are examples of endogenous cues. Attention is directed away from these cues toward the direction that they specify. Endogenous orienting is often considered as being more 'goal-driven' than exogenous orienting. Namely, an individual's goals and motivations will have a greater impact in the way they redirect attention during endogenous relative to exogenous orienting tasks. Both types of orienting have been studied with individuals with autism.

Early studies reported deficits in exogenous orienting in autism (Casey et al., 1993; Harris et al., 1999) leading to conclusions that orienting as a whole is impaired in autism. These conclusions were challenged on the basis that these earlier studies had poorly matched comparison groups. A later study reported that exogenous orienting was intact when the developmental level of participants was taken into account (Iarocci and Burack, 2004). Pruett et al. (2011) reported likewise that children with autism showed remarkably similar patterns to typically developing children on exogenous and endogenous orienting, including to peripheral, arrow, and eye-gaze cues conditions, and with high

proportions of valid trials, rendering the cue predictive of target locations, or equal proportions of valid and invalid trials, rendering the cue non-predictive. The only condition on which children with autism differed was predictive peripheral cues. In short, more recent studies of exogenous visual orienting in autism, using more appropriate comparison groups, have concluded that exogenous orienting is not as impaired as previously thought.

Likewise, early research on endogenous orienting in autism was mixed. On the one hand, Wainwright-Sharp and Bryson (1993) reported that adults with autism did not orient in response to rapidly presented central arrow cues, although they did orient for longer cues. In contrast, several other studies reported orienting patterns in autism that were either similar to comparison participants (Kuhn et al., 2010; Greene et al., 2011) or were unusual in terms of laterality (Vlamings et al., 2005) as well as in time-course and magnitude (Senju et al., 2004; Landry et al., 2009). Various attempts have been made to explain the underlying mechanisms. Burack et al. (1997) suggested that interpreting the symbolism of the cue, not orienting *per se*, is the challenging aspect of the task for individuals with autism. Landry et al. (2009) postulated a temporal explanation specific to acting upon symbolic information independent of reflexive responses to exogenous cues. Explaining mechanisms, however, requires a more complete understanding of the behavioral deficits. Critically, a complete understanding of endogenous orienting to non-social cues is needed to understand endogenous orienting to social cues, just as a complete understanding of exogenous orienting provides context for understanding endogenous orienting.

These inconsistencies are compounded by the heterogeneity of both research designs and participant characteristics employed in the research. These issues need to be resolved in order to contextualize orienting in the neurodevelopmental course of autism. Thus, to better characterize the nature of the deficits in visual orienting in autism, we carried out an exploratory meta-analysis to examine the effects that a number of variables might have on visual orienting performance in individuals with autism; these variables include cue type (e.g., gaze, arrow, or peripheral cue), contingency (predictive vs. non-predictive designs), aspects of task timing, complexity of response demands, and demographic variables such as age and IQ. Specifically, our goal was to examine the effects of these variables on both measured orienting within the autism samples, as well as the degree to which autism samples differed from comparison groups. We restricted our search to Posner type tasks as these are the most frequently employed tasks used to measure visual orienting in populations with autism. While theoretically informative, related tasks such as the Gap-Overlap (e.g., Landry and Bryson, 2004; Elsabbagh et al., 2009), a non-cued task measuring the temporal properties of disengagement in orienting, and the Attention Network Test (e.g., Keehn et al., 2010), a more complex task that combines orienting with other aspects of attention, have been used in a very limited number of studies with participants with autism and thus direct comparison would not be appropriate.

METHOD

SAMPLE OF STUDIES

A literature search was conducted using Pubmed and search terms "visual orienting" OR "exogenous orienting" OR "attention cuing" OR "attention cueing" OR "Posner task" AND autism" for articles published prior to March 2011, resulting in 125 articles. Of these, 90 were excluded as they were not experiments containing a Posner type task, and 14 were excluded as they did not include at least one participant group diagnosed with autism or autism spectrum disorders. Two studies were excluded as no reaction times were reported (Rinehart et al., 2002; Renner et al., 2006). One additional study was excluded as the experimental task examined orienting in several modalities simultaneously (Courchesne et al., 1994). Eighteen research papers met criteria, reporting a total of 21 experiments. Three experiments included saccades as the only dependent measure of reaction time; these were not included in the overall analyses, but are described for comparison.

MODERATOR VARIABLES

We recorded demographic and experimental design data from each of the studies to serve as potential moderator variables. These variables are summarized in **Table 1**.

DEPENDENT MEASURES

We recorded mean reaction times and standard deviations for each condition [valid, invalid, neutral, by Stimulus Onset

Table 1 | Demographic and experimental design data collected from target studies.

DEMOGRAPHIC DATA	
Participant ages	Mean and standard deviation of the autism sample
Number of participants	Number of participants with autism and number of comparison participants
Sex	Number of males and females included
Mental age and IQ	Mean, standard deviation, and range, of all IQ measures and/or mental age equivalents reported in the study, as well as IQ test name
Information on comparison group	Age, IQ, mental age, and sex of comparison participants (mean, standard deviation, and/or range)
DESIGN ASPECTS	
Alerting tone	Yes or no
Cue	Described
Stimulus onset asynchrony (SOA)	All SOAs (ms) included in the study; SOA is the elapsed time from cue onset to target onset
Fixation point	Yes or no
Pre-cue stimulus	Yes or no. If yes, described
Neutral condition	Yes or no
Target stimulus	Described
Inter trial interval (ITI)	ITI in ms, and whether feedback was given during this ITI
Overlap	Was there temporal overlap between the cue offset and target onset, yes or no
Type of response	Detection, localization, or identification

Asynchrony (SOA) and task]. Where raw reaction times and standard deviations /error were not reported in the manuscript, study authors were contacted if the study was recent; otherwise data was estimated from graphs (2 studies). One study was dropped (Ristic et al., 2005) because estimates could not be made from the graphs. Two dependent measures were extracted from the data to be analyzed:

(a) Reaction time measure of the magnitude of the orienting effect (invalid RT- valid RT) for participants with autism. The magnitude of the orienting effect provides us with a descriptive measure of orienting performance in autism independent of comparison groups. This allows us to examine which variables influence orienting within autism, without judgments relative to a comparison group. This measure addresses the question *do individuals with autism orient?*
(b) Cohen's *d* effect sizes, a standardized measure of the difference between group means. Cohen's *d* effect sizes (autism vs. comparison group) were calculated separately for invalid and valid RTs. Cohen's *d* effect sizes provide us with an examination of whether orienting is *intact* or *impaired* relative to comparison groups across different types of task, SOA, and age of participants, or whether there are baseline reaction time differences between groups. This measure addresses the question *are individuals with autism impaired at orienting?*

All data were analyzed using R (R Development Core Team, 2012) and the R packages *lme4* (Bates et al., 2012) and *languageR* (Baayen, 2007). Each dependent measure was analyzed using linear mixed effects models (LME), an extension of linear regression that allows the specification of nested random effects. This method was chosen to control for the effect of "Study". Analyses were weighted by the sample size of each study. Normality and homogeneity were checked by visual inspection of plots of residuals against fitted values. Models were compared using likelihood ratio tests, and MCMC-estimated *p*-values are presented throughout.

RESULTS

Demographic data was sufficient to include mean age as a variable, although the range included in some studies was so large that this should be interpreted cautiously. Ten included children 7–12 years old, four included adolescents and four included adults. Reported measures of IQ were so diverse that they could not be meaningfully included in the analysis. We classified whether the comparison group was well-matched for developmental level with the autism group, whether by reported mental age or by combined age and IQ. We use the inclusive term of comparison group, however, in no study was the comparison group explicitly identified as anything other than typically developing. Nine experiments were judged as having reasonably well matched comparison groups (50%), six were judged as unknown because information was missing or the range of IQs/mental ages in the autism group extended substantially lower than the comparison group, and three were judged as poorly matched in that the IQs/mental ages of the groups differed substantially (although one of these used IQ as a covariate in analyses; we used the covariate estimated means in our analyses). This data is presented in **Table 2**.

The variety of designs employed are shown in **Table 3**. Two experiments used alerting tones, 15 included fixation points, and five included a pre-cue stimulus. Four experiments included exogenous cues, seven included arrow cues, and eight included eye-gaze cues. Four experiments included predictive cues (ranging from 67–80% valid cues), 13 included non-predictive cues, and one included counter-predictive cues. Six studies included neutral conditions. The SOAs ranged from 100–1100 ms, and in nine experiments the cue and target overlapped temporally. In only one experiment did participants have to identify the target and filter competing distracter symbols, rather than simply localize or detect. Five studies did not report inter-trial interval lengths.

MAGNITUDE OF THE ORIENTING EFFECT IN AUTISM ACROSS STUDIES

Overall, the mean RT orienting effect for participants with ASD was 40.73 ms (95% C.I 33.82–47.64); as this is significantly greater than 0 ($t_{(125)} = 11.67$, $p < 0.001$), the general finding across studies is that participants with ASD orient. The next question was which factors influence orienting performance. Fixed effects (predictors) included in the model were *Task* type (exogenous, arrow, or eye-gaze cue), *SOA*, *Contingency*, whether the cue and target temporally *Overlap,* and mean *Age* of participant sample. The random effect included in the model was *Study*. The analysis was weighted by the sample size of each study. The best fitting model included Task, SOA, and Contingency (log likelihood ratio = −768.93). Orienting RT differed as a function of Task; orienting RT magnitude was weaker in Eye Gaze than Arrow cuing ($\beta = -18.47$, $p = 0.001$), but there was no significant difference between Exogenous and Arrow cuing ($\beta = -1.34$, $p = 0.58$, *ns*). SOA was negatively associated with orienting RT ($\beta = -0.03, p = 0.001$). Contingency contributed significantly to the model but the positive association with orienting RT was only a trend ($\beta = 0.67, p = 0.08$). Age was not associated with orienting RT, nor was the categorical distinction of whether the cue and target overlapped temporally during the task; models including these predictors did not significantly improve model fit. These associations are depicted in **Figure 1**.

EFFECT SIZES RELATIVE TO COMPARISON GROUPS

Cohen's *d* is a standardized measure of the difference between participants with autism and their comparison groups. As such, larger values are indicative of larger autism impairments. For the purposes of interpretation, Cohen's $d > 0.8$ is considered to be a large effect, >0.5 is a medium effect, and >0.2 is a small effect. Overall a mean Cohen's *d*-value of 0.44 (95% C.I. 0.37–0.50) was found, indicating that overall a small autism impairment was observed as the effect size was significantly greater than 0, $t_{(105)} = 12.90$, $p < 0.001$. The next question was what factors influence impairment. Fixed effects (predictors) included in the models were *Cue* (valid or invalid), *Task* type (exogenous, arrow, or eye-gaze cue), *SOA*, *Contingency*, mean *Age* of participant sample, whether there was cue-target *Overlap* (Y/N), and whether groups were well *Matched* (Y/N/Unknown). The random effect included in the model was *Study*. The analysis was weighted by

Table 2 | Age and IQ details of participants with autism and comparison groups.

Study	*n*	# Male participants	Age mean (*SD*) or ± *SE* as reported	Age range	IQ and/or mental age	Are groups well matched?
			AUTISM GROUP			
Casey et al., 1993	10	all	29.2 (8.6)	19–41	WAIS full scale IQ 82(13), 65–107	No—Substantial IQ difference (Adults, Age matched only)
deJong et al., 2008	30	24	10.7 ± 1.8		Dutch version of WISC full 108.4 ± 2.6; verbal 113.3 ± 2.7; perf 101.4 ± 3.1	Yes—Age and IQ (HFA)
Goldberg et al., 2008	22	16	10.47 (1.77)	8–13	WISC full 100.6 (15.54)	No—IQ difference, but used as covariate
Greene et al., 2011	22	20	12.95 (2.46)	9–17	WASI or WISC full 103.25 (13.93)	Yes—Age and IQ (HFA)
Harris et al., 1999 Autism group*	7	all	7.82 (1.7)		PPVT 46.6 (11.1) IQ 87.7 (12.3)	No—Substantial IQ difference (Children, Age matched only)
Harris et al., 1999 PDDNOS group*	5	4	4.21 (0.8)		PPVT 72.0 (18.9) IQ 105.4 (13.7)	Unknown—small but FSIQ isn't as badly matched
Iarocci and Burack, 2004	14	11	11.6 (4.9)		K-BIT mental age 7.2 (0.99)	Yes—Mental age matched
Kylliainen and Hietanen, 2004	12	11	9;11 (1;10)	7;4–14;1	WISC-R FS 91(17), perf 95(16), verbal 90(19); MA 9;3 (2;11), 6;8–16;0	Yes—Mental age matched
Landry et al., 2009	18	na	11.52(3.07)		perf.(WASI)—99.50(15.53) WASI blocks—29.39(20.70) WASI matricies—21.22(7.11); PMA—11.51(3.74)	Yes—Mental age matched
Pruett et al., 2011	27	22	11.1 (1.2)	9–12	WISC scaled blocks 12.3 (2.8) scaled vocab 10.3 (2.6)	Yes—Age and IQ (HFA)
Rutherford and Krysko, 2008	23	22	25.9 (9.6)	18–52	WAIS full 100.1 (15.0) 76–145; verbal 102.6 (14.8) 77–144; perf 96.9 (16.0) 74–136	Yes—Age and IQ (HFA)
Senju et al., 2004—Experiment 1	11	8	10.11	9.7–12.6		Unknown—CA matched and no IQs; presumed to be normal range based on educational placement
Senju et al., 2004—Experiment 2	26	23	9.6	7.6–12.3		Unknown—CA matched and no IQs; presumed to be normal range based on educational placement
Swettenham et al., 2003—Experiment 1	15	na	10;2 (0;9)	8;8–11;2	Raven's progressive matrices raw 37.6 (10.3)	Yes—Age and IQ (HFA)
Swettenham et al., 2003—Experiment 2	15	na	10;2 (0;9)	8;8–11;2	Raven's progressive matrices raw 37.6 (10.3)	Yes—Age and IQ (HFA)

(Continued)

Table 2 | Continued

Study	*n*	# Male participants	Age mean (*SD*) or ± *SE* as reported	Age range	IQ and/or mental age	Are groups well matched?
Uono et al., 2009	11	8	17.5 ± 6.5	9–30	Japanese versions of WAIS or WISC full = 107.73 (9.05); viq 107.55 (13.06); piq 104.55 (10.43)	Unknown—Comparison group contains more restricted age range, no children, and no IQ measures (although normal range is assumed, not indicated if they are undergraduates or community sample)
Vlamings et al., 2005	19	16	22.53 (4.96)			Unknown—CA matched and IQs not reported (only reported to be "in normal range" as per selection criteria)
Wainwright-Sharp and Bryson, 1993*	11	all	20.4	13–27	Raven's progressive matrices standard score 5–95; PPVT Standard Score 89, 64-122	Unknown—range of scores on standardized tests extends much lower in ASD group
			TYPICALLY DEVELOPING COMPARISON GROUP			
Casey et al., 1993	10	all	29.6 (5.2)	22–35	124 (16), 97–148 WAIS-R subtests	
deJong et al., 2008	30	24	10.6 ± 1.6		WISC full 111.5 ± 2.2; verbal 116.3 ± 2.5; perf 100.6 ± 2.5	
Goldberg et al., 2008	49	24	10.41 (1.42)	8–13	113.53 (14.59)* sig diff!!	
Greene et al., 2011	21	19	13.19 (2.44)	10–17	full 110.48 (14.10)	
Harris et al., 1999 Autism group*	15	14	7.44 (0.9)		IQ 115 (8.3)	
Harris et al., 1999 PDDNOS group*	15	14	7.44 (0.9)		IQ 115 (8.3)	
Iarocci and Burack, 2004	14	9	5.7 (0.64)		K-Bit mental age 6.4 (0.29)	
Kylliainen and Hietanen, 2004	12	11	8;11 (2;10)	6;1–16;0	WISC-R FS 106 (7), perf 102 (7), verbal 109 (8); mental age 9;5 (2;10), 6;6–16;0	
Landry et al., 2009	16	na	11.00 (2.66)		WASI—114.44 (13.69) WASI blocks—38.87 (17.85) WASI matricies—24.07 (4.92); PMA—12.49 (3.74)	
Pruett et al., 2011	25	20	11 (1.2)	9–12	WISC scaled block 11.8 (2.5) scaled vocab 11.2 (2.1)	
Rutherford and Krysko, 2008	23	22	26.5 (9.5)	18–53	WAIS full 104.4 (13.4) 77–135; verbal 104.4 (11.4) 79–125; perf 103.7 (16.0) 75–138	
Senju et al., 2004—Experiment 1	14	6	11.1	10.0–12.2		
Senju et al., 2004—Experiment 2	38	25		7.7–12.5		

(Continued)

Table 2 | Continued

Study	*n*	# Male participants	Age mean (*SD*) or ± *SE* as reported	Age range	IQ and/or mental age	Are groups well matched?
Swettenham et al., 2003—Experiment 1	15	na	10;2 (0;9)	8;8–11;2	Raven's progressive matrices 37.7 (10.4)	
Swettenham et al., 2003—Experiment 2	15	na	10;2 (0;9)	8;8–11;2	Raven's progressive matrices 37.7 (10.4)	
Uono et al., 2009	11	8	19.5 ± 2.2	18–26		
Vlamings et al., 2005	19	all	23.05 (3.70)			
Wainwright-Sharp and Bryson, 1993*	11	all	20.6	14–27	Raven's progressive matrices standard score 90–99; PPVT 117, 97–133 (std)	

**not included in effect size analysis (missing data).*

the sample size of each study. The best fitting model included *Task, SOA,* and *Age*, log likelihood ratio = −176.3. Participants with autism were more impaired on Arrow than Eye Gaze ($\beta = -0.22, p < 0.001$) conditions, with no significant difference between Arrow and Exogenous conditions ($p = 0.22$), impairment increased with age ($\beta = 0.03$, $p = 0.016$), and decreased as SOA increased ($\beta = -0.0002$, $p = 0.015$). These associations are shown in **Figure 2**. Models including *cue*, *contingency*, *overlap*, and *matched* did not improve model fit.

DISCUSSION

We conducted a meta-analysis of the research examining visual orienting in autism. We focused exclusively on Posner-type visual orienting experiments as these are the most frequently used tasks permitting direct comparison across studies. We examined two dependent measures. The first dependent measure was orienting reaction times, to assess whether individuals with autism orient and what conditions influence the magnitude of orienting. The second dependent measure was Cohen's *d* effect sizes, a standardized measure of the differences between groups, thus providing a metric of impairment. We concluded that overall, participants with autism orient, and this orienting is impaired relative to comparison participants. The average Cohen's *d* effect size across studies was 0.44, a small effect.

In considering the question of whether orienting is impaired in autism, we also have to consider the multitude of factors that may influence orienting, both in terms of differences in experimental design as well as differences in participant samples. We found that individuals with autism were most impaired on arrow cuing tasks and least impaired on eye-gaze cuing tasks, were more impaired at shorter SOAs, and that relative impairment increased with age. Nevertheless, even under the most favorable conditions, participants with autism were impaired, and the effect size was small. There is not enough data to examine which combinations of favorable conditions might eliminate the autism disadvantage, although one could speculate based on the experiments in which effect sizes are less than $d = 0.2$, summarized in **Table 4**; little to no autism impairment was found in studies that all included younger participants, in non-predictive exogenous or eye-gaze conditions.

Critically, participants with autism were not differentially influenced on invalid vs. valid trials (invalid mean $d = 0.45$, valid mean $d = 0.41$, $p = 0.64$), thus the impairment may simply reflect a general task impairment reflecting slower reaction times; there also was no evidence for *cue* interacting with other variables. The manner with which the data is presented in the literature does not permit calculating an effect size for the invalid–valid orienting effect itself, only for calculating effect sizes separately fo valid and invalid RTs. The vast majority of papers report valid and invalid RTs, along with standard deviations for valid and invalid RTs. From this data we were able to calculate the orienting effect (invalid - valid) but we are unable to derive a standard deviations in order to calculate the effect size for each study. For descriptive purposes we can plot the difference in orienting effects for autism and comparison samples. **Figure 3** presents the differences in orienting RT (invalid - valid RT) between autism and comparison samples. Most values are negative, reflecting larger orienting RTs among participants with autism (autism mean = 40 ms; comparison mean = 20 ms). Presented as a function of task, the box-plot shows the median orienting RT difference between samples is lowest in eye-gaze tasks, with autism samples producing an orienting effect that is on average differing by less than 10 ms from that of comparison groups. In arrow tasks, autism samples differ by an average of 20 ms, and in exogenous tasks by an average of 30 ms.

Eye gaze cuing was the most frequently used in the literature, accounting for slightly more than half of the included studies, but the effect size for arrow cues was 0.2 *d* higher than for eye gaze, suggesting further research is needed on non-social endogenous cues. Impairment was also noted for exogenous cuing, however, high variability and two poorly matched experiments using this design also suggest further research is needed on this task. Only one study examined all three tasks in both predictive and non-predictive conditions, in a well-matched sample of children (mean age 11), finding group differences only on predictive exogenous cues at the shorter SOA (Pruett et al., 2011).

Table 3 | Designs employed in orienting tasks.

Study	Alerting tone	Fixation point	Pre-cue stimulus	Cue	Predictive?	Neutral condition	SOA	Target stimulus	Non-target stimulus	Overlap (cue and target at same time)
Casey et al., 1993	No	Yes, central plus sign, with 2 boxes on either side (5 s)	No	exogenous	Yes, valid 80%	Yes, either both got inner boxes or neither	100 ms, 800 ms	* in center of box L or R	No	Yes
deJong et al., 2008	No	Yes, fixation dot (1100–1700 ms)	Yes	Gaze cue	No, valid 50%	No	813 ms	black dot to L or R	No	Yes
Goldberg et al., 2008	No	Yes, fixation cross (750 ms)	No	Gaze cue	No, valid 50%	No	200 ms, 700 ms	* to L or R	No	No
Greene et al., 2011	No	Yes, central cross (700 ms)	No	Arrow and gaze cues	No, valid 50%	Yes, doubly inverted arrow or look straight	300 ms	X' to L or R	No	Yes
Harris et al., 1999	No	Yes, central white cross. With green boxes on L and R	No	Exogenous	Yes, valid 67%	Yes, both boxes brighten (1/6)	200 ms, 1000 ms	* to L or R	No	Yes
Iarocci and Burack, 2004	Yes	No	No	Exogenous	No, valid 50%	Yes (center)	150 ms	O/+ to R, L, or midpoint	Yes, 4 distractor symbols (50%)	No
Kylliainen and Hietanen, 2004	No	Yes, central cross (1000 ms)	No	Gaze cue	No, valid 50%	Yes, look striaght	200 ms, 800 ms	* to L or R	No	No
Landry et al., 2009	No	No	No	Arrow cue	No, valid 50%	No	200 ms, 400 ms, 700 ms, or 1100 ms	X' to L or R	No	No
Pruett et al., 2011	No	Yes, fixation cross, neutral arrow or face (1, 1.5, or 2s)	No	Exogenous, arrow, and gaze cues	50% and 80% valid	No	150 ms, 800 ms	* to L or R	No	Yes

(Continued)

Table 3 | Continued

Study	Alerting tone	Fixation point	Pre-cue stimulus	Cue	Predictive?	Neutral condition	SOA	Target stimulus	Non-target stimulus	Overlap (cue and target at same time)
Rutherford and Krysko, 2008	No	Yes, fixation point (1s or 2s)	No	Gaze cue	No, valid 50%	No	100 ms, 800 ms	white astrix on photo to R or L	No	Yes
Senju et al., 2004—Experiment 1	No	Yes, central cross (675 ms)	Yes, eyes-closed face or square—900 ms	Arrow and gaze cues	No, valid 50%	No	100 ms, 300 ms, 700 ms, or 1,000 ms	* to L or R	No	No
Senju et al., 2004—Experiment 2	No	Yes, central cross (675 ms)	Yes, eyes-closed face or square—900 ms	Arrow and gaze cues	Counter (valid 20%)	No	100 ms, 300 ms, 700 ms	* to L or R	No	No
Swettenham et al., 2003—Experiment 1	No	Yes, central cross 1 or 2s	Yes, eyes forward 500 ms	Gaze cue	No, valid 50%	No	100 ms, 800 ms	* to L or R	No	Yes
Swettenham et al., 2003—Experiment 2	No	Yes, central cross 1 or 2 s	Yes, eyes forward 500 ms (inverted)	Gaze cue	No, valid 50%	No	100 ms, 800 ms	* to L or R	No	Yes
Uono et al., 2009	No	Yes, fixation cross (600 ms)	No	Gaze cue	No, valid 50%	No	460 ms	T' to L or R	No	Yes
Vlamings et al., 2005	No	Yes, neutral arrow or gaze (500 ms)	No	Arrow and gaze cues	No, valid 50%	No	1500 ms	A' to L or R	No	No
Wainwright-Sharp and Bryson, 1993	Yes	Yes, central, asteirx 1–2 s	No	Arrow cue	Yes, valid 80%	Yes, line	100 ms, 800 ms	Cross to L or R	No	No

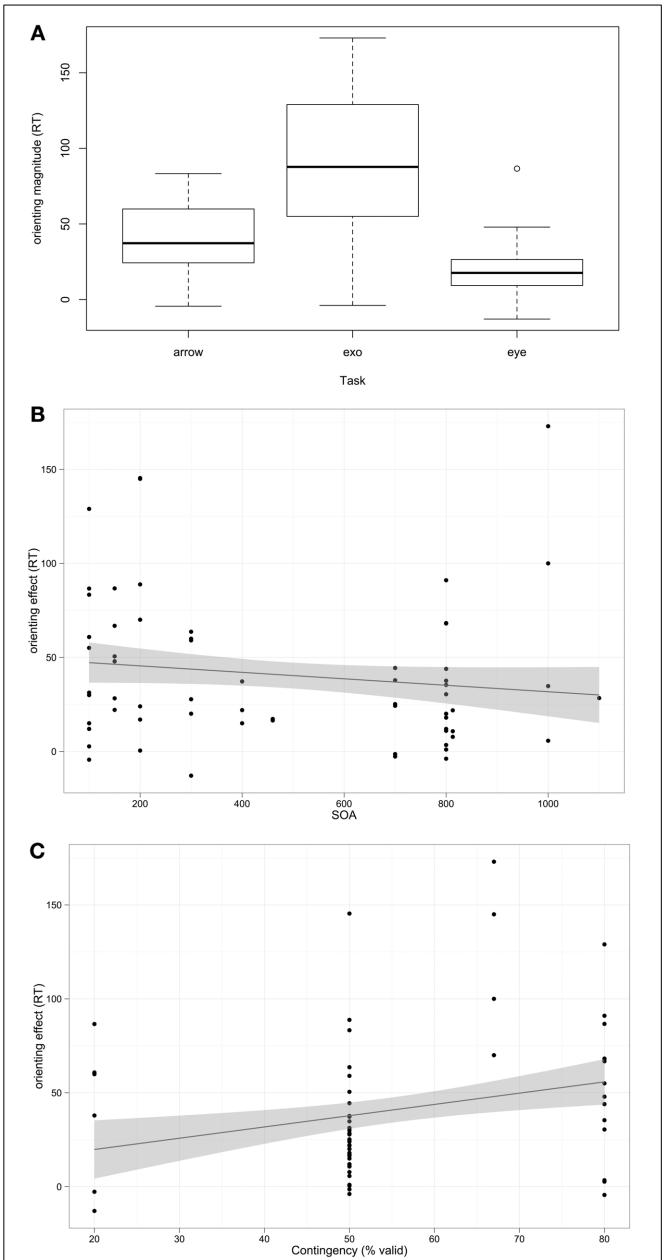

FIGURE 1 | Associations between predictors and orienting magnitude RT among participants with autism. (A) Box-plot of orienting effect across task types. **(B,C)** Scatterplots with linear regression line of best fit.

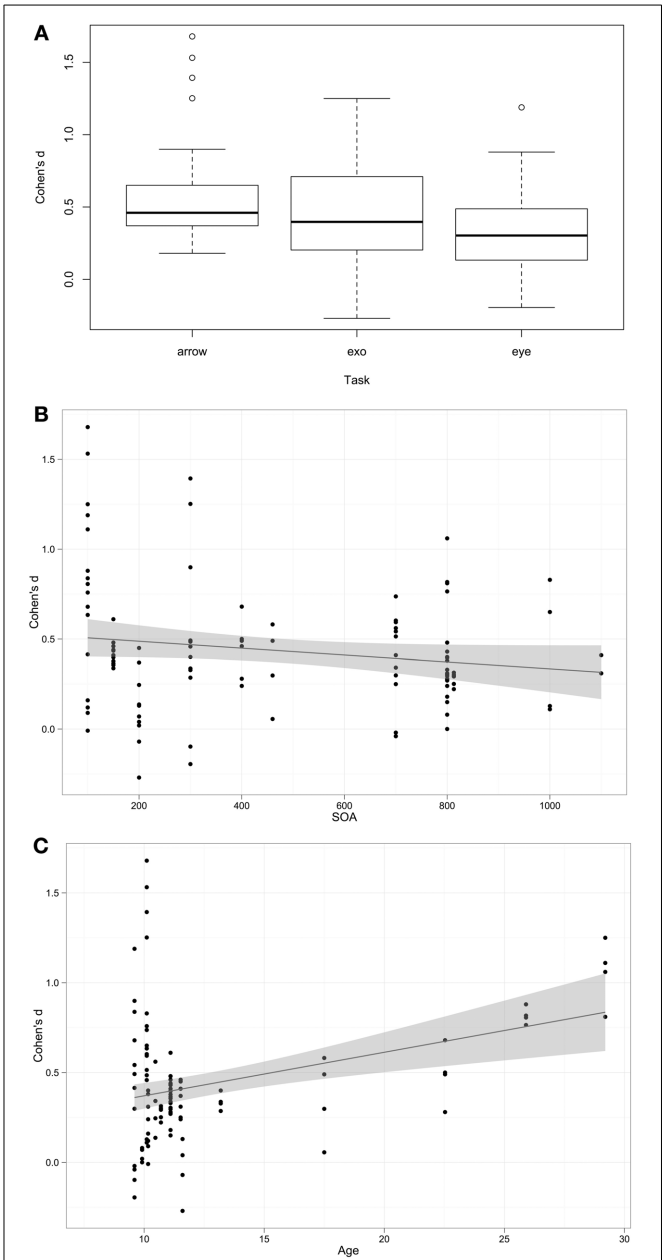

FIGURE 2 | Association between predictors and Cohen's d effect size. (A) Box-plot of Cohen's *d*-values across task types. **(B,C)** Scatterplots with linear regression line of best fit.

We hypothesize that the same experiment, carried out with adolescents and adults, would show increasing group differences with age.

Contingency, while influencing orienting reaction times, did not contribute to impairment; participants with and without autism were equally influenced by the contingency of a task. The diversity in contingencies represented in the literature is less than optimal. Nearly ¾ of studies used a non-predictive contingency, and only one study used a counter-predictive contingency. The lack of evidence for an influence of contingency on impairment may reflect this imbalance. Future research should incorporate a wider range of contingencies, and examine contingency as a factor in performance. Of particular concern is the limited number of predictive endogenous cuing experiments completed by participants with autism.

There was an interesting temporal element to the autism orienting impairment; SOA was negatively associated with orienting RT, and was also negatively associated with Cohen's *d* effect sizes. In other words, individuals with autism were most impaired in the context of rapid trials. This conclusion was previously drawn

Table 4 | Magnitude of the orienting effects (invalid—valid RT) and overall Cohen's d effect sizes for each experiment, presented in descending order from largest autism impairment to largest autism advantage.

Study	Cue	Autism orienting effect (RT)	Comparison orienting effect (RT)	Cohen's d
Casey et al., 1993	Invalid	85.75	26.50	1.16
Casey et al., 1993	Valid	85.75	26.50	0.96
Senju et al., 2004—Experiment 1	Valid	35.46	6.65	0.82
Rutherford and Krysko, 2008[a]	Valid	13.50	5.00	0.82
Rutherford and Krysko, 2008[a]	Invalid	13.50	5.00	0.81
Senju et al., 2004—Experiment 1	Invalid	35.46	6.65	0.72
Senju et al., 2004—Experiment 2	Invalid	38.27	−8.90	0.54
Kuhn et al., 2010[b]	Valid	18.18	19.57	0.54
Kuhn et al., 2010[b]	Invalid	18.18	19.57	0.51
Vlamings et al., 2005	Invalid	18.50	18.50	0.50
Vlamings et al., 2005	Valid	18.50	18.50	0.48
Landry et al., 2009	Invalid	31.78	18.85	0.41
Pruett et al., 2011	Invalid	36.16	18.82	0.40
Goldberg et al., 2008	Valid	−0.47	14.25	0.40
Uono et al., 2009	Valid	16.90	17.80	0.39
Greene et al., 2011	Invalid	45.70	40.15	0.36
Pruett et al., 2011	Valid	36.16	18.82	0.34
Uono et al., 2009	Invalid	16.90	17.80	0.32
Landry et al., 2009	Valid	31.78	18.85	0.31
Greene et al., 2011	Valid	45.70	40.15	0.31
Senju et al., 2004—Experiment 2	Valid	38.27	−8.90	0.29
deJong et al., 2008	Invalid	13.48	11.00	0.29
deJong et al., 2008	Valid	13.48	11.00	0.27
Swettenham et al., 2003—Experiment 1	Valid	24.00	30.00	0.26
Swettenham et al., 2003—Experiment 1	Invalid	24.00	30.00	0.24
Swettenham et al., 2003—Experiment 2	Valid	11.50	26.50	0.24
Goldberg et al., 2008	Invalid	−0.47	14.25	0.24
Swettenham et al., 2003—Experiment 2	Invalid	11.50	26.50	0.12
Chawarska et al., 2003—Experiment 2[b]	Valid	−6.00	−1.00	0.07
Kylliainen and Hietanen, 2004—orienting	Invalid	12.50	22.50	0.05
Kylliainen and Hietanen, 2004—orienting	Valid	12.50	22.50	0.04
Iarocci and Burack, 2004	Invalid	117.10	79.15	−0.02
Iarocci and Burack, 2004	Valid	117.10	79.15	−0.07
Chawarska et al., 2003—Experiment 2[b]	Invalid	−6.00	−1.00	−0.10
Chawarska et al., 2003—Experiment 1[b]	Valid	9.00	12.00	−0.76
Chawarska et al., 2003—Experiment 1[b]	Invalid	9.00	12.00	−1.18
Wainwright-Sharp and Bryson, 1993[c]	–	25.48	29.00	NA
Harris et al., 1999[c]	–	122.00	80.00	NA

Positive values > d = 0.2 indicate autism impairment. Negative values < d = −0.2 indicate autism advantage. Orienting effects are the RT difference between invalid and validly cued conditions. Cohen's d-values were calculated separately for invalid and validly cued conditions within each experiment.

[a] eye gaze condition only.

[b] saccadic RT (not included in analyses).

[c] insufficient data to calculate effect size.

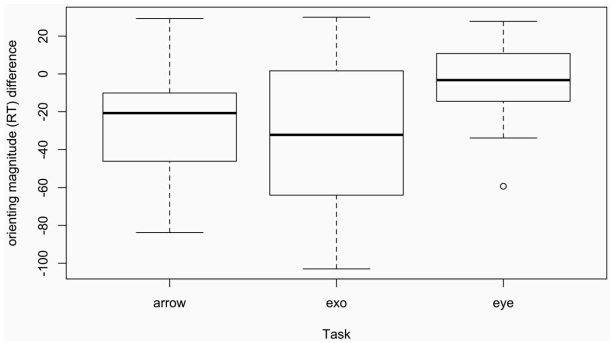

FIGURE 3 | Differences between autism and comparison participants in magnitude orienting RT. Negative values denote larger orienting effects in autism.

and competing theories have been put forth to explain the underlying mechanisms (Burack et al., 1997; Landry and Burack, 2009; Landry et al., 2009), but further research will be needed to tease this pattern apart. This temporal impairment may have very important implications for early development and education, as slowing down the pace of a social interaction may allow the younger child with autism a greater opportunity to orient to various cues, and *keep-up* with the interaction. Thus, we might expect parents or interventionists who are better able to synchronize to the child will achieve better results. For example, Baker et al. (2010) reported that while there were no differences in maternal sensitivity between a group with emergent ASD and a group without ASD, among the ASD mother-child dyads, sensitivity was associated with greater language gains from 18–36 months. Sensitivity to pacing of interactions may be an underlying factor in this association and should be the focus of future investigation.

Interestingly, while there were no effects of age upon orienting RT, there was a significant association between age and Cohen's *d* effect size. The implications are two-fold. First, if the effect size gets larger as the participant sample gets older, the likelihood that a given study will conclude orienting is impaired in autism depends in large part on the age at which participants are tested. For example, Iarocci and Burack (2004) argued that their more appropriate matching procedures eliminated the exogenous orienting impairment reported by previous studies, however, it could also be due to their younger participant sample. Half of all studies included children in the 7–12 year old range, and these were more likely to conclude that there was no autism impairment. Why this is such a popular age group is unclear. Studies of even younger children, while not included in the analyses as they only recorded saccadic RT, are consistent with this age effect in that toddlers showed Cohen's *d* effect sizes ranging from 0.38 to −1.18, with most closer to 0 (Chawarska et al., 2003), an effect that is arguably driven by age more than the simple change from manual response to saccadic RT; Kuhn et al. (2010) measured saccadic orienting responses in adults with ASD and found a moderate effect of $d > 0.50$.

While this may appear inconsistent with the evidence from Gap-Overlap experiments that find orienting differences in infancy predict later autism diagnosis (Zwaigenbaum et al., 2005; Elsabbagh et al., 2013), these are qualitatively different tasks. The Gap-Overlap is a non-cued orienting task and the autism impairment reported is one of disengagement; infants with autism exhibit more "sticky attention" to the central stimulus when it remains onscreen overlapping with the peripheral target stimulus. Similar results are also reported for toddlers with autism (Landry and Bryson, 2004). The Posner task on the other hand is a *cued* orienting task. We found that nearly half of the experiments included in this analysis contained temporally overlapping cues and targets, and thus we might have expected that participants with autism would be more impaired when the task contained overlapping cues and targets. We did not find this to be the case, overlapping tasks elicited a mean $d = 0.45$ while non-overlapping tasks elicited a mean $d = 0.42$. Furthermore, Chawarska et al. (2010) did not find stickier attention in toddlers with autism, in fact the toddlers with autism were less sticky when the stimuli were faces and groups didn't differ when the central stimulus was a non-social non-cue. Future studies will need to explore the potential ways in which early "sticky attention" could compromise children's acquisition of cued orienting. For example, an early overgeneralized sticky attention could signal that the child with autism is not differentiating relevant and meaningful environmental cues, while the typically developing infant is separating the signal from the noise and is both attracted to and has more difficulty disengaging from important signals.

Second, it no longer seems appropriate to ask whether orienting is impaired or not in autism, if the impairment is one that builds with age. The potential impact of slowed orienting in childhood, adolescence, or adulthood needs to be further examined. This age-related change also needs to be explored in greater depth. It does not appear to be the case that orienting effect RTs necessarily change with age, but it may be that typically developing adolescents and adults evidence greater overall speed increases with age than do individuals with autism. Given the limited number of studies and variability of designs, we were unable to explore interactions among factors, however, it is imperative that future studies approach the question developmentally, testing children as young as possible on identical tasks, and including a wider age range on the saccadic-based tasks that are appropriate for the youngest children.

The results of our meta-analysis clearly show the following three general conclusions:

First, individuals with autism orient in response to the three most frequently used cues. Second, individuals with autism evidence a temporally based impairment in visual orienting that increases with age. Third, gaps in the research exist in that the vast majority of research has been conducted with participants in late childhood using non-predictive cues, especially eye-gaze cues. Orienting effects, the magnitude of reaction time advantage of valid vs. invalid cues, were small across all studies employing this method, and Cohen's *d* effect sizes were variable, ranging from no autism impairment to substantially large autism impairments measured. The disproportionate number of studies using this methodology is not surprising given the characterization of autism as a disorder of *social* communication and behavior, with gaze aversion being a stereotypic diagnostic symptom; researchers therefore hypothesize that social orienting of attention could be a pivotal skill or core deficit and research resources are disproportionately directed toward that goal. We conclude that more research needs to be conducted on participants at different ages, ideally longitudinal, and using more consistent methods to measure orienting. What was most surprising was the paucity of research using non-predictive exogenous cues and predictive arrow cues, given these are the staples of adult cognitive research on the topic of orienting.

It is clear that visual orienting is an important area of research in autism, with group differences reported even for infants at high-risk of developing autism and predicting those that receive a later diagnosis (Zwaigenbaum et al., 2005; Elsabbagh et al., 2009, 2013). Future studies examining orienting in younger children and more comprehensively across the lifespan are needed to better understand the course of endogenous orienting to both social and non-social cues and how subtle atypicalities in endogenous orienting might influence other emerging skills.

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Cognitive functions of regularly cycling women may differ throughout the month, depending on sex hormone status; a possible explanation to conflicting results of studies of ADHD in females

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Attention Deficit/Hyperactivity Disorder (ADHD) is considered as a model of neuro-developmental cognitive function. ADHD research previously studied mainly males. A major biological distinction between the genders is the presence of a menstrual cycle, which is associated with variations in sex steroid hormone levels. There is a growing body of literature showing that sex hormones have the ability to regulate intracellular signaling systems that are thought to be abnormal in ADHD. Thus, it is conceivable to believe that this functional interaction between sex hormones and molecules involved with synaptic plasticity and neurotransmitter systems may be associated with some of the clinical characteristics of women with ADHD. In spite of the impact of sex hormones on major neurotransmitter systems of the brain in a variety of clinical settings, the menstrual cycle is usually entered to statistical analyses as a nuisance or controlled for by only testing male samples. Evaluation of brain structure, function and chemistry over the course of the menstrual cycle as well as across the lifespan of women (premenarche, puberty, cycling period, premenopause, postmenopause) is critical to understanding sex differences in both normal and aberrant mental function and behavior. The studies of ADHD in females suggest confusing and non-consistent conclusions. None of these studies examined the possible relationship between phase of the menstrual cycle, sex hormones levels and ADHD symptoms. The menstrual cycle should therefore be taken into consideration in future studies in the neurocognitive field since it offers a unique opportunity to understand whether and how subtle fluctuations of sex hormones and specific combinations of sex hormones influence neuronal circuits implicated in the cognitive regulation of emotional processing. The investigation of biological models involving the role of estrogen, progesterone, and other sex steroids has the potential to generate new and improved diagnostic and treatment strategies that could change the course of cognitive-behavioral disorders such as ADHD.

Keywords: menstrual cycle, sex hormones, cognitive functions, attention deficit/hyperactivity disorder, gender

INTRODUCTION

Behavioral, biochemical, and physiological data in animals demonstrate that gonadal steroid hormones estrogen, progesterone and testosterone have an effect on behavior and modulate neuronal activity (McEwen and Alves, 1999; Pfaff et al., 2000; McEwen, 2002; Pfaff, 2005). These hormones not only influence ovulation and reproductive behavior but may also have an effect on cognitive functions, affective state, vulnerability to drugs of abuse, and pain sensitivity (Bromberger and Kravitz, 2011; McEwen et al., 2012). While the influence of sex hormones on emotional states is supported by a wide body of animal data and reflected in diverging prevalence rates for men and women for psychiatric diseases, much too little is known about the impact of estrogen progesterone and testosterone on cognitive functions in women (Schmidt et al., 1998; Bloch et al., 2000). Common psychiatric disorders in women, such as depression and anxiety (Soares and Zitek, 2008) are associated with cognitive biases to emotional information. Furthermore, hormonal transitions across women's lifespan, such as the premenstrual period (Rapkin and Akopians, 2012), postpartum (O'Hara, 2009) and menopause (Freeman, 2010) have been shown to be highly vulnerable to mood disorders, whereas alterations in the cognitive function during these periods were little investigated. The menstrual cycle offers a unique opportunity to study whether and how subtle fluctuations of sex hormones can influence cognitive functions.

THE MENSTRUAL CYCLE AND HORMONAL PROFILES DURING WOMEN'S LIFE SPAN

Most women (80%) experience regular menstrual cycle from menarche to menopause, whereas the rest have irregular cycles (Münster et al., 1992). Overall, approximately 15% of reproductive age cycles are 28 days in length (Vollman, 1997) divided into follicular and luteal phases. Significant changes in hormonal levels occur during the menstrual cycle. At the early follicular phase levels of estrogen, progesterone and testosterone are very low, while toward the mid-follicular days blood levels of estrogen and testosterone begin to rise, reaching maximal levels a little before ovulation (Griffin and Ojeda, 2004; Terner and De Wit, 2006). The rise in estrogen level is accompanied by a drop in follicle stimulating hormone (FSH) level. Ovulation occurs 40–44 h after a luteinizing hormone surge and a milder FSH surge. The luteal phase is characterized by moderate estrogen and increasing progesterone production by the corpus luteum. Estrogen decreases from moderate level at the midluteal phase to its lowest level just before the onset of menstruation. Progesterone levels rise after ovulation, peak approximately 7 days post ovulation on and fall rapidly just before menstruation to undetected levels (Griffin and Ojeda, 2004; Terner and De Wit, 2006). Details are presented in **Figure 1**.

Before menarche and after menopause estrogen and progesterone levels are usually un-measurable. In premenopausal years, and depletion of the follicular reserve of the ovary, the cycle length tends to shorten, and anovulatory cycles are more frequent, until its cessation during menopause.

IMPACT OF SEX HORMONES ON BRAIN STRUCTURE AND FUNCTION

It has been established that sex hormones act on the central nervous system and influence the organization of neural circuits during the prenatal period (Collaer and Hines, 1995; McEwen, 2001). While men have greater overall brain volume than women, relative to total volume, sex-specific regional differences exist. Men have larger amygdala and hypothalamus, while women have larger caudate and hippocampus. These regional differences may be related to the distribution of estrogen (hippocampus) and androgen (amygdala) receptors. Sex hormones are known to directly influence the hypothalamus and the hippocampus: areas that are implicated in emotional processing, perception and memory, as well as in the interpretation of sensory information (Fanselow and Dong, 2010; Hines, 2010).

As it becomes clearer that hormonal transition periods across the life span of women also affect brain organization, some newly neuroimaging studies have started addressing the relevance of subtle hormonal fluctuations across the menstrual cycle on brain architecture, connectivity, metabolism and blood flow. For example, there is some evidence that estrogen in postmenopausal women increases regional cerebral blood flow (Resnick et al., 1998; Maki and Resnick, 2000; Kaya et al., 2008), thus estrogen may account for some of the variability in blood flow and metabolism in women's brain. Regional cerebral metabolic rate of glucose (CMRglu) varies significantly with menstrual cycle phase suggesting that there are acute hormonal effects on brain glucose metabolism (Reiman et al., 1996).

Genetic and hormonal differences are the two most obvious possible causes for gender differences in neuro-cognitive-behavioral aspects (Mahone, 2010). Sex steroids are major modulators of mammalian brain function, regulating neurotransmitters and influencing neuronal differentiation, growth, and synapse formation (Miodovnik et al., 2012). Exposure to varying levels of sex steroids early in development can lead to permanent changes in behavior (Morris et al., 2004). Sex hormones were found in a variety of clinical settings to impact major neurotransmitter systems of the brain. Women tend to have more active serotonin (5-HT transporter, 5-HT1A and 5-HT2A receptors) (Fink et al., 1998), dopamine (DA transporter) and GABA (neurotransmitter levels) systems. Estrogen and progesterone are involved in several aspects of brain function, such as brain development, synaptic plasticity, and modulation of neurotransmitter systems [e.g., serotonin, norepinephrine, γ-aminobutyric acid (GABA), glutamate] (Rubinow and Schmidt, 2006). Estrogen and progesterone receptors are found in brain areas involved with the stress response and mood regulation including the hypothalamus, hippocampus, amygdala, and prefrontal cortex (Lokuge et al., 2010; Bromberger and Kravitz, 2011).

5-HT functions to coordinate complex sensory and motor patterns during a variety of behavioral states and is implicated in the pathology of mood disorders, sleep and eating disorders, and schizophrenia. There is an association between estrogen and schizophrenia. A deficiency in estrogen exposure may impact gray matter cortical thickness, which may be reversed by higher levels of estrogen that may induce or activate neuroprotective mechanisms (van der Leeuw et al., 2013). The results of this and other studies fit both the estrogen deficiency and protection hypothesis (Begemann et al., 2012; McEwen et al., 2012).

Interestingly, studies on the effects of exogenous sex steroids in postmenopausal women have demonstrated higher 5HT2A binding throughout the cerebral cortex in women treated with estradiol plus progesterone replacement (Moses et al., 2000). Dopaminergic function is also enhanced in women. DA is important for reward processes including the reinforcing effects of most drugs of abuse, and has been implicated in a variety of neuropsychiatric disorders including Parkinson's disease. The DA transporter, which functions to regulate synaptic DA availability, is higher in women compared to men (Lavalaye et al., 2000; Mozley et al., 2001; Staley et al., 2001). Healthy women may have higher presynaptic dopaminergic tone in striatum and higher extrastriatal DA receptor density and availability compared to men (Kaasinen et al., 2001; Laakso et al., 2002). The availability of D2 receptor may vary with fluctuations in sex steroid hormones across the menstrual cycle (Wong et al., 1988).

Although not as well studied, differences between men and women have been reported for other receptor systems. These include the cholinergic system, which is involved in memory and cognition; the GABAergic system, the major inhibitory neurotransmitter system involved in mood and memory; and the opioid system, which is involved in pain and reward processes. Women express higher numbers of cortical muscarinic acetylcholine receptors (Yoshida et al., 2000). Women have also higher cortical GABA levels than men as measured with magnetic resonance spectroscopy (MRS; Sanacora et al., 1999). GABA levels

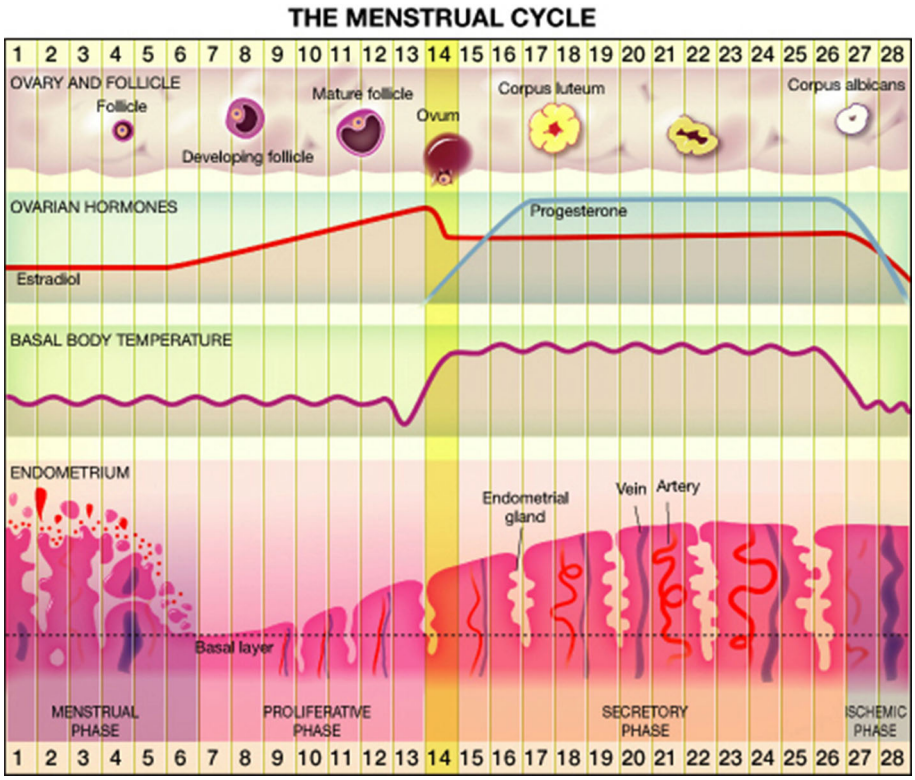

FIGURE 1 | The menstrual cycle.

vary across the menstrual cycle (Epperson et al., 2002) such that cortical GABA levels declines between the follicular and luteal phase in healthy women, and increases in women with premenopausal dysphoric syndrome. This indicates that GABA neurotransmission in tightly regulated by the menstrual cycle.

SEX DIFFERENCES ON BRAIN COGNITIVE PERFORMANCE

Women are believed to have better verbal skills and inferior spatial abilities than men. In women, IQ correlates with gray matter volume of the frontal lobe and Broca's area, which is involved in language (Haier et al., 2005), whereas in men it correlates with the volume of the frontal and parietal lobes; suggesting that men and women use different brain areas to achieve a similar IQ. Scarce literature has analyzed cognitive performance in women in respect to their menstrual cycle phase or hormonal status. In the few instances that the menstrual cycle phase was the primary research aim, typically the research focused on cognitive domains, using mental rotation or language tasks (Masters and Sanders, 1993; Fernández et al., 2003; Bell et al., 2006; Frings et al., 2006; Schoning et al., 2007; Pletzer et al., 2011). Women in the early follicular phase were inferior to men at a task requiring response inhibition to obvious versus less obvious stimuli; however, no sex differences in neural activation were associated with different performance levels (Halari and Kumari, 2005). A similar study determined that sex differences in performance on verbal and spatial cognitive tasks were not significantly related to endogenous hormone levels in men and women during the early follicular phase of the menstrual cycle (Halari et al., 2005).

HORMONAL IMPACT ON BRAIN COGNITIVE PERFORMANCE

Both androgens and estrogens have been shown to influence the organization of neural structure and function (Miodovnik et al., 2012). The prenatal hormonal levels influences the development of brain structures involved not only in sexual behaviors but also in cognition, memory, aggression and mood, resulting in a multitude of phenotypes that vary both within and between the sexes (McCarthy et al., 2009). The mechanisms underlying the sexual differentiation of the brain, however, are complex and incompletely understood. Sex steroids may act directly on sexually dimorphic regions of the brain; they may affect the spatial patterning of sex steroid receptors across brain regions; or they may impact the pituitary-gonadal axis, i.e., negative feedback from excess estradiol would result in decreased gonadotropin release and, subsequently, diminished testosterone serum levels (Rubinow and Schmidt, 1996; Miodovnik et al., 2012).

Previous studies have explored the link between sex hormones and other female-related mood disorders such as premenstrual dysphoric disorder (PMDD), (unipolar) postpartum depression, perimenopausal depression, and bipolar disorder (Schmidt et al., 1998; Bloch et al., 2000; Frey and Dias, 2014).

Several (not many) studies have investigated the impact of fluctuating sex hormone levels during the menstrual cycle on the interplay between emotion and cognition in healthy regularly cycling women. This lack of knowledge is remarkable, considering the evidence for major emotional disorders occurring specifically during normal hormonal swings in the lifespan of women. A recent review of the literature by Sacher et al.

(2013) summarized neuroimaging studies that showed that menstrual cycle phase affected the reaction to emotional stimuli and reward, as evidenced by behavioral biases in reaction time and neural activation. In line with this evidence, the menstrual cycle also appeared to impact a neural network implicated in cognitive control of emotion. It was suggested by these authors that the menstrual cycle be considered as a modulating factor when examining the behavioral and neural response to emotional stimuli.

SEX DIFFERENCES IN ADHD AS A MODEL FOR COGNITIVE FUNCTION

As with many neurodevelopmental disorders, the prevalence of attention deficit/hyperactivity disorder (ADHD) differs in males and females (American Psychiatric Association, 2013). ADHD is considered as a model of neuro-developmental cognitive functions and disorders (Pennington, 2006). Yet, relatively very little is known about the role of sex hormones in the pathophysiology of ADHD, and only recently has ADHD in females become the focus of clinical studies, while most previous research included mainly males (Gross-Tsur et al., 2006; Skogli et al., 2013). Males are at least twice more likely to be identified with ADHD than females (American Psychiatric Association, 2013). Research on gender differences suggests that girls may be consistently under identified and under diagnosed because of differences in the expression of the disorder among boys and girls (Skogli et al., 2013). The precise mechanisms underlying this sex difference are poorly understood and scarcely studied. Genetic and hormonal factors cited as potential causes of the male preponderance in ADHD but other factors, however, may contribute to this disparity (Mahone, 2010). Limitations inherent in the DSM nomenclature may contribute to the under-diagnosis of ADHD in females, rating scales may not adequately capture symptom severity among females, teachers are more likely to refer males than females for treatment for ADHD (Sciutto et al., 2004; Waschbusch and King, 2006). Thus, functional difficulties among females with ADHD may go unrecognized and untreated, and it remains unclear to what extent biological factors (genes, hormones) drive the preponderance of males diagnosed with ADHD (Lemiere et al., 2010; Mahone, 2010). Recent electroencephalogram (EEG) study has demonstrated that girls' EEG activity failed to replicate differences found previously in mixed-sex groups (Dupuy et al., 2013). The authors concluded that this reinforces the notion that it is no longer appropriate to apply the male-based literature to all ADHD groups, rather, the use of single-sex subject groups is necessary in EEG research of ADHD (Dupuy et al., 2013). Most studies regarding ADHD in females suggest confusing and non-consistent conclusions. Some suggest that ADHD school-age girls have far more impairment than their healthy female peers, with significant deficits in internalizing and externalizing disorders, and greater impairment in academic, social, and family domains (Biederman et al., 1999; Gershon, 2002; Zalecki and Hinshaw, 2004). Others suggest that ADHD in school-age boys and girls is more similar than different (Arcia and Conners, 1998; Castellanos et al., 2002; Yang et al., 2004). None of these studies examined the possible relationship between sex hormones and ADHD symptoms. As reviewed above, there is a growing body of literature showing that sex hormones have the ability to regulate intracellular signaling systems that are thought to be abnormal also in ADHD. Thus, it is conceivable to believe that this functional interaction between sex hormones and molecules involved with synaptic plasticity and neurotransmitter systems may be associated with some of the clinical characteristics of women with ADHD (Frey and Dias, 2014).

The investigation of biological models involving the role of estrogen, progesterone, and other sex steroids has also the potential to generate new and improved diagnostic and treatment strategies that could change the course of cognitive-behavioral disorders such as ADHD in women.

SUMMARY

Sex differences in brain morphology, function and neurochemistry are likely to impact normal and abnormal behavior and function. Until the role of sex hormones in the female human brain is understood, it is important to take into account critical variables, such as menstrual cycle phase, hormonal status (e.g., post partum, perimenopause, menopause), and external hormonal use (e.g., combined oral contraception, hormonal replacement therapy at menopause). In spite of the impact of sex hormones on major neurotransmitter systems of the brain in a variety of clinical settings, the menstrual cycle is usually entered to statistical analyses as a nuisance regressor (Lonsdorf et al., 2011), or controlled for by only testing male samples (Karama et al., 2011). The menstrual cycle offers a unique opportunity to study whether and how subtle fluctuations of sex hormones and specific combinations of sex hormones influence neuronal circuits implicated in the cognitive regulation of emotional processing.

We suggest that the menstrual cycle should be considered as a modulating factor when examining cognitive response to emotional information in women. Furthermore, with the introduction of sensitive tests to measure cognitive performance and imaging techniques to visualize brain morphology and study its neurochemistry, it is now becoming possible to carefully analyze cognitive performance in women by their menstrual cycle phase, or current hormonal status. This may lead to better understanding of the sex hormone impact on women's brain in health as well as in ADHD and may resolve the inconsistency of the findings in women with ADHD.

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The co-occurrence of autism and attention deficit hyperactivity disorder in children – what do we know?

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Symptoms of attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) often co-occur. The DSM-IV had specified that an ASD diagnosis is an exclusion criterion for ADHD, thereby limiting research of this common clinical co-occurrence. As neurodevelopmental disorders, both ASD and ADHD share some phenotypic similarities, but are characterized by distinct diagnostic criteria. The present review will examine the frequency and implications of this clinical co-occurrence in children, with an emphasis on the available data regarding pre-school age. The review will highlight possible etiologies explaining it, and suggest future research directions necessary to enhance our understanding of both etiology and therapeutic interventions, in light of the new DSM-V criteria, allowing for a dual diagnosis.

Keywords: autistic spectrum disorders, attention deficit hyperactivity disorder, diagnostic and statistical manual, co-morbidity, co-occurrence

INTRODUCTION

In the last decade, studies have reported increased prevalence of both attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorders (ASD). While ADHD is defined by impaired functioning in the areas of attention, hyperactivity, and impulsivity, whereas ASD is characterized by core social dysfunction and restrictive-repetitive behaviors, studies show that between 30 and 50% of individuals with ASD manifest ADHD symptoms (particularly at pre-school age), and similarly, estimates suggest two-thirds of individuals with ADHD show features of ASD (Davis and Kollins, 2012). Recent findings from the Autism Treatment Network (ATN) database suggest that co-occurrence of ADHD and ASD is associated with a lower quality of life and poorer adaptive functioning than in any one of these conditions (Vora and Sikora, 2011). Both disorders often include difficulties in attention, communication with peers, impulsivity, and various degrees of restlessness or hyperactivity. Both are more common in boys than in girls, and present, at least partially, at pre-school age. Both disorders have a known genetic pre-disposition, with comorbidity within the same individual and across family members, and both syndromes cause significant behavioral, academic, emotional, and adaptive problems in school, at home, and elsewhere. (Rao and Landa, 2013).

Evidence for common neurobiological substrates has been found through similarities in neuropsychological profiles in individuals with both disorders (Gargaro et al., 2011; Rommelse et al., 2011). It has been shown that children with ADHD have pragmatic language difficulties similar to children in the ASD spectrum (Bishop and Baird, 2001). Further neuropsychological similarities are suggested by a study of emotional recognition and theory of mind, which showed that children with ADHD could not be distinguished from those with ASD (Buitelaar et al., 1999). A study on social perspective taking showed children with ADHD used lower levels of social perspective taking coordination in their definition of problems, identification of feelings, and evaluation of outcomes than children without ADHD, and these differences persisted after the role of language abilities, intelligence, and oppositional and conduct problems were taken into account (Marton et al., 2009).

Despite the growing body of research pointing at the frequent co-occurrence of these two disorders, the previous DSM-IV-TR has not allowed a dual diagnosis. The DSM-V, in its revised ADHD diagnostic criteria, recognizes the frequency of this co-occurrence and allows, for the first time, a co-morbid diagnosis of ADHD with autism spectrum disorder. This new attitude will not only allow for more efficient clinical management of these children, but will also clear the way for a more precise scientific understanding of the overlap of these two disorders. While most research to date has documented developmental trajectories for ADHD and ASD separately, little is known regarding their co-occurrence, particularly at young pre-school age. PUBMED was searched using the definition "co-occurrence of ASD and ADHD in pre-school children." This led to only 35 studies, and therefore search was broadened to include the more general definition of the "co-occurrence of ASD (or social-communication difficulties) and ADHD in children." More than 150 articles were eventually reviewed.

ADHD (SYMPTOMS) IN CHILDREN WITH ASD

A significant percentage of children with ASD seeking services at clinical centers present with comorbid symptoms of ADHD, with rates ranging between 37% (Gadow et al., 2006) and 85% (Lee and Ousley, 2006) across studies conducted in the United States

and Europe (Rao and Landa, 2013). ADHD was the third most common disorder identified in a community sample of 5–17 years old children (Leyfer et al., 2006), with 31% of the sample meeting full ADHD criteria and another 24% with subsyndromal ADHD symptoms. This is lower than reported rates of ASD and ADHD in clinic samples (Rao and Landa, 2013). Very few studies have looked at the epidemiology of co-existing disorders in pre-school age children diagnosed with ASD. Two year-old twins ($n = 312$) from the Boston University Twin project were studied by Ronald et al. (2010) for autistic-like traits and ADHD behaviors using Child Behavior Checklist (CBCL) answered by their parents. Controlling for cognitive abilities and socioeconomic status, autistic like traits correlated positively with ADHD behaviors ($r = 0.23$–0.26), a lower correlation than described for older children. In a recent survey by Carlsson et al. (2013), 198 pre-school Swedish children (age 4.5–6.5 years) with ASD who treated in a habilitation center, were assessed for such disorders. They found language problems in 78%, intellectual disability in 49%, below average motor function in 37%, and severe hyperactivity in 33%.

Lecavalier et al. (2009) has lately shown the validity of DSM-IV syndromes in a group of 229 pre-schoolers with ASD, using confirmatory factor analysis (CFA). Despite very high factor loading with the general ADHD combined factor, several items had non-significant loadings with the specific ADHD hyperactive–impulsive factor. In other words, the verbal items from the hyperactive–impulsive sub scale were negatively correlated with the other motor items suggesting hyperactivity–impulsivity has two components: physical and verbal. The authors comment that this is a good example of how the clinical features of ASD might alter the clinical presentation of a co-occurring DSM-IV defined (pre-school) ADHD. In a study by Sikora (Sikora et al., 2012), as part of the Autism Speaks ATN, data was collected from 14 sites in the US and Canada. Participants between the age of 2 and 17.9 years were included if they met DSM-IV and/or Autism Diagnostic Intervention Schedule (ADOS) diagnostic criteria for ASD, if they were cared for at an established ATN site, if parents was fluent in English, and it was the language spoken with the child at least 75% of the time. Parents were asked to complete the CBCL and the pediatric quality of life inventory (PedsQL) and were also interviewed to complete the Vineland Adaptive Behavior Scales (VABS-II). Cognitive scores were used as covariates. Of the whole study group, 1737 participants were 2–5 years old. Of these, 40% had elevated T score in 1 of the 2 ADHD-related scales, and 18.8% had both ADHD-related scales T scores (>70) elevated. The ASD + ADHD group had lower scores on both the VABS-II and the PedsQL. The authors conclude that over one third of children with ASD have some comorbid ADHD symptoms, and their presence is related to greater problems in adaptive skills and poorer overall quality of life, and suggest primary care providers should screen for symptoms of ADHD in their patients with ASD, and consider these symptoms when developing a care plan.

ASD SYMPTOMS (SOCIAL-COMMUNICATION DIFFICULTIES) IN CHILDREN WITH ADHD

Social problems are not part of the core diagnostic criteria for ADHD, but children with ADHD experience significant social difficulties (Cantwell, 1996; Friedman et al., 2003). ADHD children are more often rejected by their peers, and have fewer friends (Hoza et al., 2005; Mikami, 2010). In many cases, these difficulties are viewed as a direct result of the ADHD core symptoms. Inattentive behaviors may lead a child to miss social cues, impulsiveness may result in upsetting peers, and hyperactivity hinders participation in organized activities and leads to avoidance of peers. It is estimated that approximately 50–60% of ADHD children experience rejection by their peers (Barkley et al., 1990). In fact, many ADHD children are disliked within minutes of the initial social interaction (Pelham et al., 1985) and then denied further opportunities to practice social skills, which lead to further rejection (Milich et al., 1982). Specific play behaviors have been linked with rejection of ADHD children and include being bossy, intrusive, inflexible, controlling, annoying, explosive, argumentative, easily frustrated, inattentive during organized sports/games, and violating the rules of the game (Pelham et al., 1985; Whalen et al., 1985; Klassen et al., 2004; Young et al., 2005). Social functioning by ADHD subtype varies somewhat according to rater (e.g., teachers, parents, and peers); however, the general consensus is that all ADHD subtypes are at risk for peer rejection (Carlson and Mann, 2000; Hodgens et al., 2000). The presence of co-morbid psychiatric disorders tends to exacerbate social impairments in children with ADHD (Greene et al., 1996; Antshel and Remer, 2003). This is significant when considering that over 2/3 of individuals with ADHD have a co-morbid psychiatric disorder (Cantwell, 1996) with rates reported to be 15–75% with mood disorder, 25% with anxiety, and 30–50% with conduct disorder (CD). Others (Biederman et al., 1991; Eiraldi et al., 2000) have found that anxiety and depression together accounted for 30% of the variance in social impairment in ADHD. Children with both ADHD and a learning disability have also been found to have greater peer relations difficulties than children with only a learning disability (Flicek, 1992).

This profile of social difficulties differs, however, from that observed in ASD, in which impairment in the basic understanding of social realm is central, such as a lack of emotional reciprocity and engagement with others, and the low interest or enjoyment in social interaction. Cantwell (1996) described a type of social difficulty in ADHD by a "lack of savoir faire," and estimated that this social naivety may affect some 20% of ADHD children and adolescents. Recent research suggests that many individuals with ADHD may experience social impairments that are more consistent with those observed in ASD. In children with a primary diagnosis of ADHD, the level of autistic symptomatology corresponded to the severity of ADHD subtype; children with the combined type of ADHD-demonstrated the most autistic symptoms (Reiersen et al., 2007). In a study recently published by Kotte et al. (2013), a positive autistic traits (AT) profile operationalized from the CBCL, was significantly overrepresented among ADHD children vs. controls (18 vs. 0.87%; $P < 0.001$).

Recent research suggests many individuals with ADHD may experience social impairments consistent with those observed in ASD. Santosh and Mijovic (2004) characterized the social impairments in children with ADHD as associated with either relationship difficulty (conduct and affective problems), or with social-communication difficulty. Children with the latter were

more likely to exhibit repetitive behaviors, speech and language impairment, and developmental problems similar to ASD. Other investigators have described deficient empathy and facial affect recognition in children with ADHD (Sinzig et al., 2008; Uekermann et al., 2010). Other studies have also pointed at the increased rate of autistic symptoms in samples of children with ADHD. Grzadzinski et al. (2011) confirmed the presence of a sub group of children with ADHD and elevated ratings of core ASD traits not accounted for by ADHD or behavioral symptoms. The ADHD group with AT revealed greater ODD behaviors than those with ADHD-only. Most of the studies conducted in middle or late childhood have shown that a substantial proportion of children with ADHD show significant autistic symptoms (Santosh and Mijovic, 2004; Holtmann et al., 2007; Nijmeijer et al., 2008). Very few studies have looked at pre-school children with ADHD, in an effort to identify early "comorbid" ASD symptoms, perhaps because an ASD diagnosis is usually made at pre-school age, while a primary ADHD diagnosis is often delayed to late pre-school or early school age.

IMPACT OF COMORBID ADHD AND ASD

Diagnostic constraints have limited research on co-occurring ADHD and ASD, because many studies, in accordance with the DSM-IV, have excluded individuals with other psychiatric or developmental difficulties (Davis and Kollins, 2012). There is preliminary evidence that when ADHD is comorbid with ASD, the risk for increased severity of psychosocial problems increases (Gadow et al., 2004; Yerys et al., 2009). Research comparing individuals with both diagnoses to individuals with a single diagnosis suggest that co-occurring symptoms are associated with greater impairment than a single diagnosis. By both parent and teacher reports children with ADHD and ASD (Rao and Landa, 2013) experience more difficulty in daily life. Furthermore, these co-occurring conditions may be less responsive to standard treatments for either disorder. Children 4–8 years old with ASD, whose parents report significant symptoms of ADHD, show lower cognitive functioning, more severe social impairment, and greater delays in adaptive functioning than children with ASD-only.

Sikora et al. as part of the activities of the ATN (Sikora et al., 2012) collected data on children with ASD across 14 sites in the US and Canada. Children were between ages 2 and 17.9 years. They were divided into groups based on whether their parents rated them as having clinically significant scores on ADHD problems subscales from the CBCL. 56.6% of the sample was young children between 2 and 5 years. Analysis revealed that those with ASD+ADHD symptoms had lower scores in all the areas measured. Psychosocial health summary, school functioning, physical functioning, emotional, and social functioning scores were all lower than those of the children with ASD alone ($P < 0.0001$). In another study by Gadow et al. (2004), PDD and non-PDD clinic groups showed equally severe ADHD and oppositional defiant disorder symptoms. As measured by parent and teacher referenced rating scale (ECI-4), Mulligan et al. (2009) compared autism symptoms in 821 ADHD probands, 1050 siblings, and 149 controls by using the Social-Communication Questionnaire (SCQ). Latent class analysis yielded five classes; class 1 (31%) had very few autism symptoms and low comorbidity; classes 2–4 were intermediate; class 5 (7%) had high autism symptoms and comorbidity. The cluster with the highest mean SCQ score (class 5) had the highest prevalence of co-morbid oppositional defiant disorder, CD, language disorder, and motor disorder. Other evidence supports more ODD symptoms in children with both disorders when using teacher rating rather than parent ratings (Guttmann-Steinmetz et al., 2009). These findings, however, describe mostly school age children, while there is a lack of psychiatric comorbidity studies in younger children with both conditions.

Several investigators have found (Sinzig et al., 2008; Rao and Landa, 2013) a higher percentage of children with both ASD+ADHD were classified as having significant cognitive delays than children with ASD-only (61 vs. 25%). Kotte et al. (2013) had reported ADHD children with high score on the AT profile of the CBCL, were significantly more impaired than control subjects in psychopathology, interpersonal, school, family, and cognitive domains. Yerys et al. (2009) reported on elevated rates of externalizing problem behaviors as well as greater impairment in executive functioning in children with comorbid ASD and ADHD, compared with children with ASD-only. Children with high functioning autism (HFA) and attention problems scored significantly below the children with HFA only, on the verbal memory and delayed recall measures, supporting the proposition that children with both disorders differ not only on a clinical level but also on a neurocognitive level (Andersen et al., 2013).

Only one study has looked at the relationship between the two disorders as they develop over time. St Pourcain et al. (2011) have followed 5,383 singletons (the Avon Longitudinal Study of Parents and Children-ALSPAC) ages 4–17 years and assessed multiple measures of hyperactive–inattentive traits and autistic social-communication impairment at multiple time points. Autistic symptoms were more stable than those of ADHD behaviors, which showed greater variability. Trajectories for both traits were strongly, but not reciprocally interlinked, such that the majority of children with a persistent hyperactive–inattentive symptomatology also showed persistent social-communication deficits, but not vice versa. Shared predictors, especially for trajectories of persistent impairment were maternal smoking during the first trimester, which included familial effects and a teenage pregnancy. The authors conclude that patterns of association between ASD and ADHD symptoms change over time, and propose to remove exclusivity criteria for these diagnoses in the DSM-V, as has already been done.

POSSIBLE ETIOLOGIES FOR THE CO-OCCURRENCE OF ASD AND ADHD

Due to the previous DSM-IV diagnostic constraints, research concerning the possible etiologies of the co-occurrence of ADHD and ASD is scarce. The central focus of available research is in the fields of neuropsychology, genetics, and neuroimaging.

Although there are some important differences between the two disorders, as mentioned in the introduction, ASD and ADHD share many similar impairments in developmental and cognitive domains. Both are more common in males, have a strong comorbidity with intellectual disability, and are also associated with other specific learning and developmental difficulties, notably language, reading, and motor problems. Executive functions (EF) deficits

are common in both disorders, together with response inhibition deficit. EF measures hardly discriminated between ADHD and HFA, but compared to children with ADHD, the HFA group showed more difficulty with cognitive flexibility and planning (Cooper et al., 2014). Children with ADHD have pragmatic language difficulties similar to children in the ASD spectrum (Bishop and Baird, 2001). Further neuropsychological similarities are suggested by a study of emotional recognition and theory of mind which showed that children with ADHD could not be distinguished from those with ASD (Buitelaar et al., 1999).

Rommelse et al. (2010) suggest a variety of hypotheses to explain co-occurrence, but the two most likely explanations may be that the two are independent disorders occurring together by association with a third independent factor, or alternatively they share a common underlying etiology. The authors believe the latter is the most likely model and that both disorders share a common genetic basis. Their view is supported by several family, twin, and molecular genetic studies. Both family (Holtmann et al., 2007; Guttmann-Steinmetz et al., 2009) and twin studies (Reiersen et al., 2007; Ronald et al., 2010) provide support for the hypothesis that ADHD and ASD originate from partly similar familial/genetic factors. About 50–72% of the contributing genetic factors in both disorders show overlap. These shared genetic and neurobiological underpinnings form an explanation why both disorders occur so frequently within the same patient and family.

Two related family studies originating from the IMAGE (Holtmann et al., 2007; Guttmann-Steinmetz et al., 2009) cohort have examined the rates and severity of ASD in probands with ADHD and their siblings. Mulligan et al. (2009) measured autism symptoms using the SCQ and compared 821 ADHD probands, 1050 siblings, and 149 controls. Affected and unaffected male (but not female) siblings had higher ASQ scores than controls. The phenotypic correlation between ASD and ADHD was slightly higher for males (0.63) than for females (0.49). Using a modified method of the deFries–Fulker analysis, the authors conclude that 56% of the cross-correlation (=0.18), could be explained by shared genetic influences on ADHD and ASD. In another study by Nijmeijer et al. (2008), using the same cohort, 256 sibling pairs and 147 controls were studied, using the Children Social Behavior Questionnaire (CSBQ). This instrument measures less severe variants of ASD. Similar to Mulligan's study, sibling correlations for ASD were significant, but contrary to the earlier study, correlations were higher in female probands (0.44), than male probands (0.23). Also, siblings correlations for ASD were higher in older than younger children, indicating an increased genetic influence on ASD within ADHD families over time. In this study, cross correlations were not significant, suggesting independent familial factors give rise to ADHD and ASD.

In a twin study, mentioned earlier (Reiersen et al., 2007), AT were examined in 8 years old ADHD twins ($N = 6771$), using parent and teacher questionnaires. Phenotypic correlations were 0.54 for parent and 0.51 for teacher data. The authors concluded that genetic correlations between ASD and ADHD symptoms were all >0.50. Similar results were reported in a study of young adult twins ($N = 674$), using a self reported measures of ADHD and ASD. A bivariate model indicated that the genetic correlation between ADHD and ASD was 0.72. Models with additive genetic effects and unique environmental effects fitted the data best, with no evidence for sex differences. While the limitation of most of these studies is the use of rating scales rather than direct clinical measures to evaluate either ADHD or ASD, together they do point at a genetic correlation between the two diagnoses.

Linkage studies and Genome Wide Association Studies (GWAS) have specifically addressed this co-occurrence, pinpointing to some promising pleiotropic genes, loci, and single nucleotide polymorphisms (SNPs). Their authors comment that there is an urgent need for better designed and powered studies to tackle this complex issue. A recent study (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) using GWAS data from the Psychiatric Genomic Consortium (PGC), for cases and controls in five psychiatric disorders including ADHD and ASD, did not find any significant genetic correlation between ASD and ADHD, using common SNP's. Analyses revealed that there were modest shared genetic influences between ADHD and AT as well as some common environmental influences explaining their co-variability. The contribution of assortative mating and parent-of-origin effects to the co-occurrence of ASD and ADHD has been investigated by van Steijn et al. (2012) in 121 families with at least one child diagnosed with ASD, and one or more biological sibling. All children and parents were carefully screened for the presence of ASD and ADHD. The authors concluded that cross-assortative mating for ASD or ADHD does not explain the frequent co-occurrence of these disorders within families. They did show, however, that parental ADHD is predictive of offspring' ASD but not vice versa, hinting that risk factors underlying ASD may overlap to a larger degree with risk factors underlying ADHD than vice versa.

In autism, as opposed to ADHD, anatomical studies found larger total brain and white matter volumes in most cortical brain regions and in the cerebellum, caudate, and globus pallidum (Piven et al., 1996). A shared anatomical dysmorphology between the two disorders appears to be a smaller corpus callosum. In functional neuroimaging, the most consistent findings has been that of reduced frontal and parietal activation across a wide range of tasks in ASD (Baron-Cohen et al., 1999), which may not be different for ADHD. Geurts et al. (2013) tested whether there is a relationship between gray matter (GM) volume and autism and ADHD symptom severity by using structural MRI. They found that self-reports on symptom severity of both disorders correlated with GM volume in the left inferior frontal gyrus, but each disorder symptom severity was correlated separately with different cortical areas. They conclude it seems to be an oversimplification to typify psychiatric disorders solely as extremes of brain structure abnormalities. Di Martino et al. (2013) used voxel wise network centrality, functional connectivity metrics indexing local [degree centrality (DC)] and global (eigenvector centrality) functional relationships across the entire brain connectome, in resting state functional magnetic resonance imaging data from 56 children with ASD, 45 children with ADHD, and 50 typically developing children. In both clinical groups, cortical and sub cortical areas exhibited centrality abnormalities, some common to both disorders (in the precuneus), but others were disorder-specific. Secondary analyses differentiating children with ASD into those with or without ADHD-like comorbidity [ASD(+) and ASD(−), respectively] revealed that the ASD(+) group shared ADHD-specific abnormalities in basal

ganglia. By contrast, centrality increases in temporolimbic areas characterized children with ASD regardless of ADHD-like comorbidity. The authors conclude that their work provides evidence for both shared and distinct underlying mechanisms at the large-scale network level. These and other neuroimaging studies in the future might lead to better understanding of the neuro-circuitry involved in the co-occurrence of ASD and ADHD.

TREATMENT OF CO-OCCURRING ADHD AND ASD

Much evidence supports the use of medications to treat symptoms of ADHD in typically developing school age children (Subcommittee on Attention Deficit/Hyperactivity Disorder et al., 2011). ADHD medications have shown their efficacy in pre-school children (PATS study), but with less efficacy and more side effects than in school age children (Riddle et al., 2013). For ASD, medications target comorbid behavioral symptoms like irritability, hyperactivity, and aggression, rather than the core social and communication deficits. Several medications have demonstrated the potential to treat repetitive/stereotyped behaviors, but efficacy data has not been strong. Only two medications, to date, have been formally approved for use in ASD, and they both target irritability; Risperidone and Aripiprazole (Abilify) (Owen et al., 2009; Canitano and Scandurra, 2011; Williams et al., 2013). Despite limited research on the pharmacological treatment in ASD, there is a significant increase in the use of psychoactive medications in this group in recent years, in part due to an increase in the use in ADHD medications in ASD children with ADHD symptoms. Frazier et al. (2011) have recently used data on psychotropic medication from the first wave of the National Longitudinal Transition Study 2, a nationally representative study of adolescents ages 13–17 in special education, and have shown that youths with ASD+ADHD had the highest rates of use (58.2%), followed by youths with ADHD-only (49.0%) and youths with ASD-only (34.3%). Youths with ASD, both ASD-only and ASD+ADHD, used medications across a variety of medication classes, whereas stimulants were dominant among youths with ADHD-only.

STIMULANT MEDICATIONS

Methylphenidate and atomoxetine (Frazier et al., 2011) are both typically used to treat ADHD and are also effective in ASD. Santosh et al. (2006) conducted a retrospective and an open-label prospective trial to compare response to stimulants (methylphenidate or dextroamphetamine) between children with ASD and ADHD and children with ADHD alone, and found no significant differences in treatment response or side-effect profiles between groups. However, other studies suggest that response rates of methylphenidate may differ in ASD as compared to what is reported in typically developing children with ADHD alone. The National Institute of Mental Health Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) (MTA Cooperative Group, 2004) reported response rates of 70–80% as compared to the 49% reported in the Research Units of Pediatric Psychopharmacology (RUPP) Autism Network trial of methylphenidate (Arnold et al., 2012). In terms of tolerability, 18% of subjects in the RUPP trial withdrew, yet discontinuation rates were quite low in the MTA study (1.4%). While methylphenidate may improve irritability in ADHD without ASD, it appears to worsen irritability in some patients with ASD.

Reduction in ADHD symptoms has been the primary outcome measure of most studies of co-occurring ADHD and ASD. A secondary analysis of the RUPP evaluated the effects of methylphenidate on social-communication skills and self-regulation in 33 children with ASD. Weekly dedicated observations over a 4-week period, indicated that methylphenidate use was associated with several positive social outcomes; including improved initiation of joint attention, improved response to bids for joint attention, and better affective and self-regulation.

NON-STIMULANT MEDICATIONS

In the only controlled study of atomoxetine (Jahromi et al., 2009), results were significantly better than placebo, but the sample size was small and only 7 of 16 children (43%) were considered responders. Overall, both methylphenidate and atomoxetine appear to effectively treat ADHD-related symptoms in ASD (MTA Cooperative Group, 2004; Arnold et al., 2006, 2012; Posey et al., 2006; Santosh et al., 2006; Jahromi et al., 2009; Murray, 2010), but atomoxetine demonstrated better tolerability than stimulants in individuals with co-occurring ADHD and ASD. Response rates may, however, be lower in ASD plus ADHD, than in ADHD alone, and symptoms of inattention may be less likely to respond than symptoms of hyperactivity and impulsivity. Atomoxetine effectiveness may vary as a function of level of impairment, measured by cognitive ability or by ASD symptom severity (Arnold et al., 2006; Posey et al., 2006). Finally, treatment success may be limited by tolerability. Many studies have demonstrated efficacy for antipsychotics, and since the RUPP trial with risperidone this medication in particular has consistently shown benefit for hyperactivity in ASD (Murray, 2010; Matson et al., 2011; Sharma and Shaw, 2012). In 2006, The United States Food and Drug Administration approved risperidone for the treatment of irritability in ASD in children and adolescents 5–16 years of age. However, significant concerns about tolerability remain and suggest that benefits of this medication must be carefully weighed against the risks. Evidence from controlled studies of alpha-2 agonists for ADHD-related symptoms in ASD is inconsistent and response rates are relatively low. Open-label studies of guanfacine (Intuniv) appear promising but additional controlled studies are needed. A retrospective analysis (Posey et al., 2004) of 80 patients indicated reduction in hyperactivity and inattention among children with ASD and higher cognitive functioning. Alpha-2 agonists may be a reasonable alternative or augmentation strategy and have the advantage of being relatively benign. Amantadine may be considered in the treatment of ASD but its use for ADHD-related symptoms is not yet supported by research (Hosenbocus and Chahal, 2013). Other medications like melatonin, antioxidants, acetylcholinesterase inhibitors, and naltrexone, are currently considered off-label for ASD, but further randomized controlled trials are necessary (Rossignol, 2009).

For all medication categories except MPH, no studies are available on pre-school children.

PSYCHOSOCIAL INTERVENTIONS

An up to date literature survey on psychosocial interventions in children with both ADHD and ASD has not revealed any results. In a comprehensive review on the treatment of these co-occurring conditions Davis and Kollins (2012) mention that there are similarities across approaches to treat both disorders. In both, treatment uses conditioning procedures, which have evolved in time to draw on a social learning theory (Brookman-Frazee et al., 2006). Whereas both ADHD and ASD include behaviorally oriented parental intervention, the role of the family is conceptualized in a different way; for ADHD "parent training" involves teaching parents to manage the behaviors of their children, in ASD "parent education" places more emphasis on individualized treatments that provide parents with tools to promote their child's (social) skill development. Davis and Kollins suggest that bridging between these two strategies might benefit those with comorbid disorders.

While many studies have shown the importance of combining medication and psychosocial interventions (mostly parental education) for children with ADHD, there are only a few studies on the combined medication and behavioral approach in ASD children. Aman et al. (2009) primarily targeted frequent tantrums, self-injury, and aggression in a trial of risperidone treatment and parent training, but the combined effects on hyperactivity were also examined. Results indicated that children who received the combined treatments had lower rates of aggression and greater reduction in hyperactivity (requiring lower risperidone dose), as compared with children who received medication only.

Studies on psychosocial interventions in pre-school children with co-occurring ASD and ADHD are lacking.

SUMMARY AND FUTURE DIRECTIONS

Research specifically focusing on co-occurring ADHD and ASD has only recently evolved, being previously limited by the DSM-IV exclusion criteria. What we have so far learned is that both disorders frequently co-occur, and when they do, they cause greater morbidity, and create a more complicated clinical challenge. The new DSM-V, allowing for a dual diagnosis, will hopefully facilitate research, by eliminating the exclusion of many patients and allowing the study of broader phenotypes. Most recent research focuses on etiology and clinical presentations, with less direct work on treatment and early intervention protocols. Very few studies have looked at pre-school children presenting with both conditions, on the impact of early intervention in this age group and its effect on developmental trajectory. Furthermore, many of the above quoted studies have used parent and/or teacher rating scales to assess clinical profiles, rather than direct clinical diagnoses of the two co-existing disorders. In the future, as a dual diagnosis is "officially" possible, studies using direct clinical assessment of both comorbid diagnoses are essential.

Future research should tackle two major hypotheses regarding the frequent co-occurrence of ASD and ADHD. The first is that ADHD and Autism are distinct, yet overlapping disorders which may share some common etiology, probably genetic. The second hypothesis is that the co-occurrence of autistic symptoms and ADHD "stands alone" as a distinct clinical disorder, with a distinct etiology, and a different developmental trajectory. These two hypotheses should be examined by studying the developmental trajectories in co-occurring ASD and ADHD, by defining common co-morbidity profiles in both, and by understanding differences and similarities in social perception, motor functions and language, cognition, and EF in each disorder and in the co-occurring "phenotype." Defining early "endophenotypes" as suggested by Rommelse et al. (e.g., heritable vulnerability traits that form a link between genes and observable symptoms, e.g., neuroimaging, neuropsychological functions) of both disorders, should serve to increase the chance of identifying genetic markers for each one and for both together (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

In 2010, Gillberg et al. have coined the ESSENCE concept (Gillberg, 2010) an acronym for early symptomatic syndromes eliciting neurodevelopmental clinical examinations, pointing to the fact that major problems in at least one developmental domain before age 5 years often signals major problems in the same or overlapping domains years later. They suggest "There is no time to wait," implicating intervention should be the main goal, and not necessarily the categorical diagnosis. They go on to suggest intervention should be broad, addressing the multiple aspects of developmental disorders at this young age. Future studies should focus on early identification and intervention strategies in this specific "co-morbid" group, with an emphasis on pre-school children, using prospective design, even before pathophysiology is fully understood.

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Extreme prematurity and attention deficit: epidemiology and prevention

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EXTREME PREMATURITY AND ATTENTION IMPAIRMENT

Preterm infants are at increased risk for a wide range of developmental disorders, including sensory, motor, cognitive, and other brain disorders (Lorenz et al., 1998; Bhutta et al., 2002; Aarnoudse-Moens et al., 2009), and the risk is highest for those infants born before 28 weeks gestation, i.e., extremely preterm or extremely low gestational age infants (Wood et al., 2005; Serenius et al., 2013). As large cohorts of extremely preterm infants have reached school age, the prevalence of brain dysfunctions that affect academic success has been quantified, and antecedents and correlates of these problems have been better characterized. The most prevalent of these is attention deficit/hyperactivity disorder (ADHD) (Hack et al., 2009; Johnson et al., 2010).

Based on screening questionnaires, such as the Child Behavioral Checklist (Hille et al., 2001) and the Strengths and Difficulties Questionnaire (Elgen et al., 2002; Samara et al., 2008; Delobel-Ayoub et al., 2009), children born extremely preterm perform worse than full term children on attention scales. Using Diagnostic and Statistical Manual-based criteria, extremely preterm children have a risk of ADHD that is four times that of full term controls (Johnson et al., 2010; Scott et al., 2012).

Some studies report an association of extreme prematurity with the inattention type of ADHD but not the hyperactivity/impulsivity type (Hack et al., 2009; Johnson et al., 2010; Johnson and Marlow, 2011), while others report associations with both types of ADHD (Anderson et al., 2011; Scott et al., 2012). In one sample, inattentive behaviors were explained by sequential memory problems, while hyperactive behaviors were explained by global intellectual impairment (Nadeau et al., 2001). The attention impairment among preterm infants affects a range of domains of attention including selective attention, sustained attention, attention encoding, shifting attention, and divided attention (Mulder et al., 2009; Anderson et al., 2011).

In the general population ADHD is associated with conduct disorder (Nock et al., 2006), but this does not appear to be the case among preterm infants (Elgen et al., 2002; Hack et al., 2009; Johnson et al., 2010; Scott et al., 2012). Extremely preterm infants with ADHD are more likely to have cognitive impairment than those without ADHD, and in one study there was no association between extreme prematurity and ADHD among infants without cognitive impairment (Johnson et al., 2010). Impaired attention is a likely contributor to extremely preterm children's increased risk of cognitive impairment and behavioral problems (Weijer-Bergsma et al., 2008). Moderately preterm children exhibit some developmental catch up in selective attention so that the difference between these children and term children narrows with increasing age (Mulder et al., 2009).

RISK FACTORS FOR ATTENTION IMPAIRMENT AMONG EXTREMELY PRETERM INFANTS

Social disadvantage is more prevalent among mothers delivering prematurely (Paneth, 1995), and is a risk factor for attention problems during childhood among preterm infants (Hack et al., 2009; Lindstrom et al., 2011; Scott et al., 2012). This variable conveys information about a variety of factors including race, maternal psychosocial stress, and mother's education (Adler et al., 2012). In unselected samples, maternal smoking, which is associated with preterm delivery, has been associated with attention impairment (Nomura et al., 2010).

The strong inherited contribution to ADHD (Thapar et al., 2012) appears to be less important among preterm infants (Johnson and Marlow, 2011). Male sex, which is predictive of more severe neonatal illness after preterm birth, is associated with the hyperactive type of ADHD among extremely low birth weight children (Hack et al., 2009). Neonatal illnesses which occur frequently after extremely preterm birth, such as necrotizing enterocolitis and chronic lung disease, could explain the smaller contribution of genetics in this group. In one extremely preterm cohort, necrotizing enterocolitis was predictive of impaired selective attention but not other attention domains (Anderson et al., 2011). At school age, children who had recovered from neonatal chronic lung disease, as compared to preterm children without chronic lung disease, had more attention problems, based on teacher's report (Gray et al., 2008). However, in two other cohorts no neonatal factors were predictive of an attention problem (Hack et al., 2009; Johnson et al., 2010). In another cohort of extremely preterm children, an Apgar score less than 8 at 5 min was associated with a higher risk of using medication for ADHD (Lindstrom et al., 2011).

Among very low birth weight infants, intraventricular hemorrhage (and presumably the accompanying brain damage) (Indredavik et al., 2010) and subnormal head growth (Peterson et al., 2006) are associated with attention problems. In

a large prospective study, white matter injury was associated with a 2.7-fold increase in the risk of ADHD at 6 years of age (Whitaker et al., 1997). Ultrasound is only modestly sensitive for detection of white matter abnormalities (Maalouf et al., 2001; Inder et al., 2003; Miller et al., 2003). More sensitive imaging techniques, using magnetic resonance imaging (MRI) also have identified structural correlates of attention impairment. Among adolescents who had very low birth weight, thinning of the corpus callosum and reduced white matter volume were associated with attention deficit but were not associated with hyperactivity (Indredavik et al., 2005). Diffuse tensor imaging, which identifies disruption or disorganization of white matter tracts, indicates that reduced fractional anisotropy of the external capsule and middle and superior fascicles is associated with higher inattention scores on the ADHD Rating Scale IV (Skranes et al., 2007).

INFLAMMATION AND CEREBRAL WHITE MATTER DAMAGE IN EXTREMELY PRETERM INFANT

Even when an infection is distant from the brain, maternal and neonatal infections are associated with perinatal brain damage (Dammann and O'Shea, 2008). Administration of endotoxin to a variety of immature experimental animals results in cerebral damage, and the damage is mediated by inflammation-related molecules including cytokines, chemokines, adhesion molecules, and matrix metalloproteinases (Wang et al., 2006). A range of clinical disorders in humans has been associated with perinatal infection and inflammation, including ultrasound-defined white matter injury, microcephaly, cerebral palsy, cognitive impairment, behavioral dysfunctions, and psychiatric illness (Hagberg et al., 2012).

Biomarkers of perinatal infection and inflammation include neutrophil infiltration of the placenta (Holzman et al., 2007) and inflammation-related proteins in the amniotic fluid and neonatal blood. Clinical initiators of inflammation include maternal infections (McElrath et al., 2011), lung injury induced by mechanical ventilation (Bose et al., 2013), necrotizing enterocolitis (Martin et al., 2013), and neonatal sepsis (Leviton et al., 2012).

In a large cohort of extremely preterm infants, the ELGAN cohort, both clinical indicators (McElrath et al., 2009; Martin et al., 2010) and biomarkers of inflammation (Leviton et al., 2010) have been associated with perinatal brain damage and subsequent developmental impairment at 2 years of age. In this cohort, persistent/recurrent elevations of seven inflammation-related proteins, defined as an elevation on at least 2 days a week or more apart in the first 2 weeks of life, are associated with a 2- to 3.9-fold increase in the risk of an attention impairment identified at 2 years of age using the Child Behavioral Checklist [manuscript under review].

Maternal or neonatal infections occur in a majority of pregnancies that result in an extremely preterm birth, yet the prevalence of ADHD among the offspring is typically less than 20%, suggesting that inflammation requires other factors, which could include genetic susceptibility, to contribute to the occurrence of ADHD. In a genetically isolated community with a high prevalence of ADHD, severe maternal respiratory infection was associated with a 3.3-fold increase in risk, suggesting that genetic factors could modify associations between inflammation and ADHD in humans (Pineda et al., 2007). In a preclinical model, inflammation-induced attentional impairments and abnormalities in dopamine neurons were more severe in mice genetically deficient in Nurr1, which plays important roles in differentiation, migration, and survival of dopaminergic neurons (Vuillermot et al., 2012).

MIGHT INTERVENTIONS TO REDUCE PERINATAL INFLAMMATION DECREASE THE RISK OF ATTENTION IMPAIRMENTS AMONG EXTREMELY PRETERM CHILDREN?

ANTENATAL INTERVENTIONS

The consistent association of perinatal inflammation and brain disorders, including attention impairment, suggests that immuno-modulatory interventions might decrease the risk of attention problems in extremely preterm infants.

Antenatal treatment of the mother with glucocorticoids might modulate inflammation's effects on the brain. For example, antenatal glucocorticoids decrease the risk of cerebral palsy (Roberts and Dalziel, 2006). However, in two randomized clinical trials of antenatal steroids, attention abilities were not improved, nor was the risk of ADHD reduced, by this intervention (Dalziel et al., 2005; Crowther et al., 2007).

Maternal infection is a frequent initiator of preterm labor (Romero et al., 2007), and often is accompanied by a fetal systemic inflammatory response (Gotsch et al., 2007). However, antenatal antibiotic treatment of mothers with preterm labor, but without overt infection, does not decrease the risk of attention problems in the offspring (Kenyon et al., 2008a,b).

Antenatal treatment with magnesium sulfate reduces the risk of cerebral palsy in offspring of mothers who develop preterm labor prior to 30 weeks gestation (Rouse, 2007). However, the effect of this intervention on attention problems has not been reported (Doyle et al., 2009).

Children of obese mothers are more likely than children of women with a pre-pregnancy weight in the normal range to have a low Bayley Scales Mental Development Index at age 2 years (Hinkle et al., 2012) and a lower reading score at kindergarten age (Hinkle et al., 2013). Since maternal pre-pregnancy obesity is associated with later inflammation in the offspring (Leibowitz et al., 2012), interventions that reduce maternal obesity could reduce the risk of attention problems in the offspring.

POSTNATAL INTERVENTIONS

Postnatal strategies to decrease inflammation-related perinatal brain injury include interventions to prevent initiators of inflammation and broader strategies to modulate inflammation.

The three most obvious initiators of systemic inflammation are bacteremia (Leviton et al., 2012), mechanical ventilation (Bose et al., 2013), and necrotizing enterocolitis (Martin et al., 2013). Our hope is that whatever reduces the occurrence of these three major complications in the NICU will reduce the later occurrence of attention problems.

Broader strategies to modulate inflammation include those that shorten or minimize the intensity of inflammation once initiated. For example, caffeine reduces the risk of chronic lung disease, an inflammatory pulmonary condition,

and decreases the risk of neurodevelopmental impairment. Unfortunately, the effects of perinatal caffeine on attention problems have not been reported (Schmidt et al., 2007).

Although postnatal steroids decrease lung inflammation (Halliday et al., 2009, 2010), no evidence has been offered to date that attention abilities are improved by postnatal steroids (Yeh et al., 2004). Similarly, human milk is associated with a reduced risk of necrotizing enterocolitis (Sisk et al., 2007), but other than a small pilot randomized trial of sphingomyelin-fortified human milk (Tanaka et al., 2013), evidence is lacking of an effect of human milk on attention in extremely preterm infants.

Other potential approaches to broadly reduce systemic inflammation have been suggested by preclinical studies. In animal models of perinatal brain injury which either directly or indirectly involve inflammation, (Hagberg et al., 2002; Wang et al., 2006, 2009; Thornton et al., 2012) injury can be attenuated by hypothermia (Fukuda et al., 2001; Tomimatsu et al., 2001, 2003), melatonin (Robertson et al., 2013), pentoxifylline (a methyl xanthine) (Dilek et al., 2013), and erythropoietin (Kumral et al., 2007). Hypothermia is an effective neuroprotective agent in humans born near term (Jacobs et al., 2013), and will be studied in preterm infants [ClinicalTrials.gov identifier: NCT01793129]. Melatonin and erythropoietin also are being studied as neuroprotective strategies for preterm infants [ClinicalTrials.gov identifier: NCT00649961 (melatonin) and NCT01378273 (erythropoietin)]. As mentioned above, caffeine, a methyl xanthine, appears to be neuroprotective in preterm infants although data about it effect on attention is lacking.

In addition to acute interventions, strategies might be found for attenuating the sustained disruption to brain development that persists months and perhaps years after an initial insult to the immature brain. The mechanisms underlying sustained disruption appear to include sustained inflammation as well as epigenetic changes, in which case an extended window of opportunity for intervention might exist (Fleiss and Gressens, 2012).

SUMMARY

Extremely preterm infants have an increased risk of attention problems and a better understanding of the antecedents of these problems can lead to prevention strategies. Perinatal systemic inflammation, an antecedent of structural and functional brain disorders in extremely preterm infants, appears to be an antecedent of attention problems. Interventions to prevent initiators of inflammation or modulate systemic inflammation might decrease the risk of attention problems among children born extremely preterm.

AUTHOR CONTRIBUTION

T. Michael O'Shea wrote the initial draft of the paper. L. Corbin Downey and Karl K. C. Kuban revised the paper. All authors approved the final version.

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Elevating hope among children with Attention deficit and hyperactivity disorder through virtual reality

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INTRODUCTION

Children with attention deficit and hyperactivity disorder (ADHD) suffer from a variety of emotional and social difficulties including high levels of depression, anxiety, poor regulation, other executive malfunctions, and lack of satisfying social experiences (Bird et al., 1993; Greene et al., 2001; Gillberg et al., 2004; Barkley, 2006; Klimkeit et al., 2006; Daviss, 2008; Elia et al., 2008; McQuade and Hoza, 2008; Anastopoulos et al., 2011; Larson et al., 2011). Pharmaceutical treatment of ADHD may be effective for ameliorating the manifestations of ADHD but there may also be a need for supplementary psychotherapeutic interventions (Chronis et al., 2006).

Engendering hope is an ancillary supportive therapy that can provide individuals with ADHD the positive coping skills and appropriate psychic framework for handling the challenges that they confront. Hope, in this context, is a psychological construct that relates to the ability of individuals to set themselves meaningful goals, to find channels to reach these goals, and to consistently work toward achieving these goals (Snyder et al., 1991).

A potential tool for instilling hope in patients with ADHD is virtual reality (VR) (Riva, 2005). VR is an advanced form of human-computer interface that allows the user to *interact* with, and feel *present* within a computer generated environment. Similar to Descartes' deceiving god but with nobler intentions, researchers are utilizing models of immersive virtual therapy that enable individuals with physical/mental challenges such as chronic pain to set meaningful goals and visualize alternative realities where their pain or disability is minimized (Magora et al., 2006). For example, Hoffman et al. (2011) have presented VR systems that facilitate distraction thereby reducing perceived pain in individuals undergoing painful medical procedures such as non-pharmacologic analgesic for acute burn pain (Hoffman et al., 2011). In addition, we have recently introduced a combined VR-biofeedback system that allows individuals with chronic headache to learn to reduce their physiological arousal, following which, they can their view virtual image as headache free (Shiri et al., 2012a). Utilizing VR for generating hope in ADHD children whom have significant difficulties in creating and holding images is especially challenging as it based on forming a durable interface with computer-based VR programs.

Recently, we have utilized a self-face recognition paradigm to enhance the verisimilitude of a VR-generated substituted reality (Shiri et al., 2012a, 2013). Self-face recognition programs have been successfully utilized for post-stroke disability and pain reduction. Self-face recognition creates a unique cerebral activity pattern which does not occur even when significant others, such as family members are recognized. Viewing a smile has the potential of activating brain structures that are related to reward and positive emotions. Positive emotions may enhance creative thinking and improve cognitive processes, necessary for effective coping with various challenges (Muehlberger et al., 2011). Although specific relationships between activation of reward structures and positive emotions need to be examined utilizing brain imaging techniques, a recent study suggested that static pictures of emotional facial expressions activate brain structures that are involved in the processing of emotional stimuli (Johnson et al., 2010). Similarly, a sequence of emotional facial expressions changes occur, different brain networks are involved. For example, it was found that the onset of happy and the offset of angry expressions induced significant activation in the left dorsal striatum (Johnson et al., 2010). These findings would suggest that the VR paradigm may be useful for children with ADHD as the interaction of salient brain activity created by self-face recognition together with the activation of reward brain centers produce a platform that is both cerebrally robust and emotionally positive for self-confidence and growth.

THEORETICAL BACKGROUND

While the neurocognitive aspects of ADHD have been studied intensely, the secondary emotional, behavioral, and social co-morbid aspects of ADHD are less-well understood. These difficulties include of depression, anxiety, and social adaptation difficulties (Bird et al., 1993; Greene et al., 2001; Gillberg et al., 2004; Barkley, 2006; Klimkeit et al., 2006; Elia et al., 2008; McQuade and Hoza, 2008; Anastopoulos et al., 2011) which can have both short and long-term ramifications. Current interventions for emotional and behavioral symptoms associated with ADHD include pharmacotherapy and

psychotherapy. Psychodynamic (Gilmore, 2000, 2002; Conway, 2012) and cognitive behavioral therapy (Safren et al., 2010; Antshel et al., 2011, 2012) are two types of psychotherapeutic approaches that have been utilized for ADHD and shown to be beneficial. The drawback of psychotherapy is that it is expensive, not always available, and may be challenging in the setting of ADHD in which children have difficulty in focusing. There is a need for novel approaches toward treating the secondary, but often devastating manifestations of ADHD. Here we suggest a cost-effective and immediately accessible therapeutic paradigm that utilizes VR to create hope in the form of vivid therapeutic and optimistic self images.

Hope is defined in terms of agency and pathways (Snyder et al., 1991). Agency relates to the motivational components necessary for consistent and sustained efforts that are requisite for achieving goals. Pathways refer to the perceived methods for achieving established goals. Hope has been shown to be a significant factor in coping with various difficult or challenging situations. For example, high levels of hope predict better academic performance (Rand, 2009) and self-efficacy (Davidson et al., 2012). In a recent work (Shiri et al., 2012b), we have found that hope is associated with improved mental and physical health parameters among individuals with post-polio syndrome who are generally in poor physical and mental health due to the residual effects of polio. While little can be done to change the physical limitations associated with the post-polio syndrome, those with higher levels of hope perceived themselves to be healthier and have a greater quality of life.

In light of these findings, we plan to examine the effect of elevating levels of hope among children with ADHD as a method for improving their coping skills as assessed in specific emotional, behavioral, and social domains. Setting meaningful goals, finding ways to reach these goals and achieving the necessary motivation are processes that by themselves are rewarding and increase the chance of attaining set upon goals.

Instilling hope has been traditionally achieved through psychotherapy and specific goal setting as part of cognitive behavioral therapy. A main element of this therapeutic approach is to provide accessible pathways for achieving the goals and providing the appropriate motivation that encourages patients to strive toward accomplishing set upon goals. Similarly, VR is a technique which allows users to visualize goals in a vivid and sharp manner. The verisimilitude inherent in VR allows for viewing specific goals as though they were real. This is particularly important for children with ADHD, given the difficulties these children often experience in imaging, which is a necessary prerequisite for increasing hope (Abraham et al., 2006).

Regarding the ability to visualize goals, VR can compensate for the limited ability of humans to imagine and keep desired images actively. A continuous re-activation of the visual representations is required to keep the image within visual memory (Kosslyn et al., 2006). Visualizing goals is particularly difficult and often impossible for individuals with a wide range of chronic limitations including ADHD (Abraham et al., 2006). VR can compensate for these limitations by providing the desired scenes through the use of specially constructed software programs. The sense of presence (the sense of "being there") is efficiently achieved by VR, and thereby serves as a potent replacement to guided imagery by providing expressive optimistic images even to individuals with difficulty to follow imagery suggestions (Riva, 2003).

ADHD is diagnosed mainly at a young age, and most of the patients are children and adolescents. Such computerized technologies are particularly appealing to this age group which in turn increases their enthusiasm and adherence to treatment.

PRELIMINARY STUDIES

In previous work related to stroke rehabilitation (Hoffman et al., 2011) and coping with chronic headache in children (Shiri et al., 2012a), we adopted a self-face recognition VR paradigm. The perspective embodied in this paradigm is different from other VR systems which provide a first person (egocentric) perspective. This paradigm was implemented in light of recent neuropsychological findings suggesting that self-face recognition is faster and more accurate than recognition of strange faces or even highly familiar faces and is characterized by unique bilateral activity (Keyes and Brady, 2010). It has been suggested that self-face recognition creates a unique activation of limbic structures in the right hemisphere in conjunction with left-sided associative and executive regions and that that produces a significant experience of self-awareness (Kircher et al., 2001).

In a pilot study of post-stroke patients, we tested the feasibility and efficacy of a novel motion capture VR system that allows for integrated self-face viewing and mirror visual feedback. This potential rehabilitation tool was tested on 6 post-stroke patients with paretic upper limbs. The system via the novel interface between the patient and the VR system allowed for the replacement of the impaired arm by a virtual arm. Upon making small movements of the paretic arm, patients viewed themselves virtually performing healthy full-range movements. Each patient received 10 sessions of treatment. During the duration of the therapeutic intervention, all participants succeeded in learning how to operate the system. Subject performance within the virtual environment and a set of clinical-functional measures recorded before the VR treatment, at 1 week and after 3 months indicated neurological status and general functioning improvement as shown by a variety of parameters (Hoffman et al., 2011). For example, patients were assessed as to their ability to pick up a fruit, and all 6 improved. Objective measurements of function also showed before and after intervention (Table 1). Although there was no control group and the numbers were small, the findings were sufficiently encouraging for our group to proceed with a second study.

In the subsequent study of pediatric headache (migraine and tension), ten children participated in a single arm prospective study to determine the efficacy of a combined intervention consisting of biofeedback based techniques of relaxation coupled to a VR system. The VR algorithm was designed so patients were led by their virtual self from a painful state to a relaxed pain free state. Biofeedback was based on a reduction of galvanic skin response which is a measure of relaxation. The subjects underwent 10 sessions, and at

the end, several outcomes were measured including measurements of pain, quality of life, and a survey related to the efficacy of the intervention (Shiri et al., 2012a). Selected parameters are shown in Table 2. Subjects felt that the intervention was helpful and most would recommend the treatment to others. Quality of life and perceived severity of headache measured before and after the intervention were significantly improved, and perceived limitations on activity related to headache pain was also mitigated (close to statistical significance).

CONCLUSION

Based on the preliminary results from these pilot studies, we suggest that implementing a self-face viewing paradigm may be particularly effective in drawing patients' attention and in generating sound neural processing of the virtual scenery, especially neural networks within the mirror neuron system (Uddin et al., 2005). Both the subjective improvement in hand function among stroke patients and the reduction of pain in chronic headache suggest that VR could have a role in instilling hope in individuals with ADHD and facilitate behavioral changes.

The virtual classroom used for evaluation and treatment of ADHD is a familiar and well studied model used to examine various neuropsychological abilities in an environment that simulates a real classroom (Rizzo et al., 2006). In the paradigm that is being developed, we propose that children with ADHD view themselves as achievers of significant, yet realistic goals. Measureable outcomes of this paradigm will be increasing levels of motivation and self-efficacy as assessed in various learning, behavioral, and social settings. Examples of third person VR that can be employed include programs for children who are easily distracted in the classroom setting. These children can view themselves sitting and focusing on specific tasks assigned by the teacher. Children who are disruptive and have explosive behavior at home can view themselves as sitting and doing homework in an orderly and structured manner. The challenge in developing specific VR programs is to identify behaviors that are amenable to modification and are within the capabilities of the children with ADHD.

In future studies we would like to examine the utility of a VR-based intervention to enhance the self-image of children and adolescents with ADHD. Picturing oneself performing a desired behavior from a third-person perspective has the potential of causing individuals to adopt attitudes that are concordant and harmonious with the content drawn in the pictures (Libby et al., 2007). This in turn provides the subjects with hope that they can achieve specific goals and this enhances self-confidence and motivation. Positive emotions produced by viewing a human smile induce a reduction in physiological and psychological stress as shown by Kraft et al. (Kraft and Pressman, 2012), who showed that smiling participants had lower heart rates during stress recovery as compared to controls. Higher levels of positive emotions are associated with greater engagement with the coping process, and individuals are more likely to think through their behavioral options before acting (Tugade et al., 2004).

In conclusion, elevating hope among children with ADHD utilizing a self- face recognition paradigm specifically designed for the needs of children with ADHD has the potential for providing an emotionally positive experience that is therapeutically beneficial in treating the cognitive impairments.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnhum.2014.00198/abstract

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