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BRIEF COMMUNICATION

Neuropsychological Functioning in Girls with Premature Adrenarche

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Abstract

Contemporary research indicates that brain development occurs during childhood and into early adulthood, particularly in certain regions. A critical question is whether premature or atypical hormone exposures impact brain development (e.g., structure) or function (e.g., neuropsychological functioning). The current study enrolled 40 girls (aged 6–8 years) diagnosed with premature adrenarche (PA) and a comparison group of 36 girls with on-time maturation. It was hypothesized that girls with PA would demonstrate lower IQ and performance on several neuropsychological tasks. The potential for a sexually dimorphic neuropsychological profile in PA was also explored. No significant univariate or multivariate group differences emerged for any neuropsychological instrument. However, effect size confidence intervals contained medium-sized group differences at the subscale level. On-time girls performed better on verbal, working memory, and visuospatial tasks. Girls with PA showed improved attention, but not a sexually dimorphic profile. These results, though preliminary, suggest that premature maturation may influence neuropsychological functioning. (*JINS*, 2012, *18*, 151–156)

Keywords: Puberty, Endocrine system diseases, Adrenal cortex hormones, Neuropsychological tests, Sexual development, Sex characteristics

INTRODUCTION

Gonadal hormones (e.g., testosterone, estradiol) rise in puberty and influence the development and functioning of the central nervous system (CNS) (Hines, 2004). Other hormones also act on the CNS. For instance, adrenal androgens such as androstenedione, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) also rise during the pubertal transition and influence brain function and development (i.e., "neuroactive" steroids; Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009). Certain brain regions are more susceptible to hormonal influences due to the developmental trajectories associated with each region (Huttenlocher, 1999). For example, neuroimaging research indicates that cerebral, white matter, and gray matter volumes increase in an age-dependent manner throughout childhood and adolescence (Giedd, 2008). These structural developmental trajectories are similar to trajectories of neural activity, particularly in the frontal and parietal regions (Whitford et al., 2007). Thus, regions of the brain associated with important higher-order skills such as flexible thinking, decision-making, maintaining information in mind and working with it (Huttenlocher, 1999), spatial processing, and attention (Schweinsburg, Nagel, & Tapert, 2005) undergo significant change during a developmental period characterized by rising hormones that influence the CNS.

The brain's exposure to hormones during periods of significant development can result in "organizational" effects

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(i.e., permanent changes in brain structure/behavior) or "activational" effects (i.e., temporary modification of target cells that facilitates specific behaviors; Hines, 2004). Sex differences on typically female- (e.g., motor dexterity, category fluency) or male-advantaged neuropsychological tasks (e.g., mental rotation, spatial perception; Hines, 2004) suggest that hormones activate prenatally organized, sexually dimorphic neural circuits or further organize the brain during puberty to manifest a female- or male-typed neuropsychological profile. Indeed, neuroimaging research supports sex differences in the development of most brain structures, such as an earlier peak in gray matter volume in females than males (Giedd, 2008). Further, regions of the brain that show sexual dimorphisms generally contain higher densities of sex hormone receptors, suggesting that hormones that change at puberty may directly impact brain development (Lenroot & Giedd, 2010). Yet, research findings with endocrine disordered populations are inconclusive, such that high concentrations of adrenal or gonadal androgens may or may not alter neuropsychological profiles (see reviews by Hines, 2004; Berenbaum & Beltz, 2011). Additionally, even though androgens may act to masculinize neural circuitry (Hines, 2004), research has not yet shown that premature androgen exposure in girls with PA yields a sexually dimorphic (i.e., male-typed) neuropsychological profile.

A critical question that remains is whether premature or atypical hormone concentrations impact brain development or functioning. Specifically, neuropsychological skills might be perturbed if the brain regions subserving those skills are exposed to atypically high concentrations of hormones, especially if exposure is premature or occurs during a period of significant brain development (e.g., Mueller et al., 2009). In contrast to brain regions demonstrating nearly complete development in early childhood (i.e., primary sensory regions), the prefrontal and parietal regions continue to develop long after the postnatal period and may be vulnerable to hormone-related disruptions in their developmental processes (e.g., synaptogenesis, pruning; Huttenlocher, 1999).

PREMATURE MATURATION AND NEUROPSYCHOLOGICAL FUNCTIONING

Premature adrenarche (PA) is a specific form of clinically early maturation. PA is a biochemical phenomenon in which the normal developmental process of the adrenal gland occurs prematurely, resulting in increased concentrations of adrenal androgens (i.e., androstenedione, DHEA, DHEAS) and testosterone in girls and boys aged 8 or 9 years and younger, respectively (Ibanez, DiMartino-Nardi, Potau, & Saenger, 2000). In PA, atypically high concentrations of hormones occur during a period when the CNS is undergoing significant structural and functional change (e.g., synaptogenesis, pruning, integration; Giedd, 2008). As such, PA represents a natural experiment of the impact of prematurely high concentrations of hormones on brain development and functioning.

Few studies have considered the impact of atypical maturational timing on neuropsychological functioning. A seminal study with healthy adolescents found that spatial abilities of later maturing adolescents were superior to those of earlier maturers (Waber, 1976). However, maturational timing in this study was within the normal range. Rovet (1983) attempted to replicate these findings in a case-controlled study of children with precocious and clinically delayed puberty. Rovet found a spatial *strength* for early-maturing girls; verbal and spatial *weaknesses* were observed for early-maturing boys and a spatial *weakness* emerged for late-maturing girls. However, age ranges were wide (i.e., 4–16 years) with varying pubertal processes represented (and, therefore, varying hormonal exposures) across groups. Nass, Baker, Sadler, and Sidtis (1990) evaluated girls with PA and found that IQ and neuropsychological functioning were within the normal range. Nass's results were limited by a small sample ($N = 13$) and a wide age range (4–14 years) resulting in an inability to isolate the effect of the initial hormonal rise of PA on neuropsychological functioning. Nearly a decade later, Dorn, Hitt, and Rotenstein (1999) compared girls with PA (aged 6–8 years) to age-matched on-time peers. Results indicated lower IQ and neuropsychological functioning (e.g., verbal, working memory, visuospatial) for girls with PA. Although also limited by a small sample size, these results suggested that clinically early maturation and the associated rise in hormones may negatively influence neuropsychological functioning.

THE PRESENT STUDY

The existing literature concerning clinically off-time maturation and neuropsychological functioning is limited. The purpose of this study was to investigate the impact of clinically early maturation (i.e., PA) on neuropsychological functioning by comparing girls with PA to matched peers with on-time maturation. Based upon the potential for hormonal influences on prefrontal and parietal brain regions, this study compared girls on higher-order neuropsychological skills, spatial processing, attention, and other domains that may be sensitive to hormonal action (i.e., memory, attention, executive, psychomotor, visuospatial; Collaer, Geffner, Kaufman, Buckingham & Hines, 2002). Based upon findings of the most methodologically rigorous study of PA and neuropsychological functioning to date (Dorn et al., 1999), we hypothesized that girls with PA would demonstrate lower IQ and performance on several neuropsychological tasks (i.e., verbal, working memory, visuospatial) compared to on-time girls. Additionally, considering childhood as an important period for brain development, particularly in regions with high concentrations of sex hormone receptors, we explored whether premature and high concentrations of adrenal androgens in PA are associated with a sexually dimorphic (i.e., male-typed) neuropsychological profile.

METHOD

Participants

Forty girls with PA and 36 with on-time maturation were enrolled in this study. Inclusion criteria for the PA group

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included: aged 6 through 8 years, PA diagnosed by a pediatric endocrinologist, Tanner I breast (i.e., prepubertal; Marshall & Tanner, 1969), Tanner II or greater pubic hair, English speaking, estimated intellectual functioning ≥ 75, and no acute/chronic disorders or medications that could influence endocrine measures (e.g., congenital adrenal hyperplasia). Inclusion criteria for the on-time maturation group were the same as the PA group except that breast and pubic hair were Tanner stage I. Girls were matched on age (± 6 months), ethnicity, socioeconomic status (SES; ± 10 points), and body mass index (BMI; $\pm 20\%$) (see Table 1 for demographics).

Procedure

Girls were recruited through pediatric endocrine clinics, community clinicians, and advertisements and enrolled consecutively at two sites (Pittsburgh and Cincinnati). The study was approved by the Institutional Review Boards affiliated with each site and informed consent and assent were obtained. Approximately half of the girls were from each site (Pittsburgh: $n = 34$; 52.9% PA; Cincinnati: $n = 42$; 52.4% PA). Girls from Pittsburgh were younger than their Cincinnati counterparts ($t = -2.47$; $p < .05$), but this difference was within the matching criterion. No other significant site differences emerged.

Study visits were conducted in a General Clinical Research Center. Demographic and anthropometric data were collected. Girls completed a neuropsychological battery, while caregivers completed demographic information and a diagnostic interview about their children in a separate room.

Measures

Participant age and family were assessed by parent report. Height and weight were objectively measured and used to calculate BMI (kg/m^2). Pubertal stage in both groups was assessed by physical examination by a trained clinician using Tanner stages for breast and pubic hair development (by palpation and visualization; Marshall & Tanner, 1969). Next, a fixed neuropsychological battery was administered to all participants. The most valid and reliable instruments of domains sensitive to hormonal action (per work in the area of sex differences in other endocrine disordered populations; Collaer et al., 2002) were selected. The following instruments were individually administered in one session and scored by a trained research assistant under a neuropsychologist's supervision.

California Verbal Learning Test-Child Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994): a brief assessment for children as young as 5 years old to evaluate strategies used to learn and remember rote verbal information.

Digit Vigilance Test (DVT; Lewis, 1995): a measure of sustained attention during rapid visual tracking and accurate selection of target stimuli that has demonstrated good validity and reliability in children.

Wechsler Intelligence Scales for Children-Third Edition (WISC-III; Wechsler, 1991): an assessment of general intellectual ability for children 6 years or older and the most updated version during data collection. IQ was calculated using the most reliable two-subtest short-form combination (Sattler & Saklofske, 2001).

Wisconsin Card Sort Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993): measures executive skills for children as young as 6 years-old.

Rey-Osterrieth Complex Figure Test (ROCFT; Osterrieth, 1993): a widely used measure of sensory-motor, perceptual, planning, and organizational abilities normed for children 6 years or older. The immediate copy and 30-minute delay tasks were administered.

Grooved Pegboard (Trites, 1977): assesses manipulative dexterity and psychomotor speed in children as young as 5 years-old.

Category Fluency Test (Butters, Granholm, Salmon, Grant, & Wolfe, 1987): category fluency tests are widely used, sensitive assessments of verbal fluency in children as young as 5 years-old (e.g., Korkman, Kirk, & Kemp, 2007).

Statistical Analyses

Normality of variables for the full sample was demonstrated. Results of the full sample were replicated in a right-handed subsample ($n = 69$). Therefore, analyses for the full sample are reported. Group differences in matching and inclusion variables were explored using t tests and a χ^2 test. Group differences on neuropsychological instruments were examined using multivariate analysis of variance (MANOVA) to limit inflation of Type 1 error. The alpha for the MANOVA series was adjusted to .01 to control for family-wise error. To balance the potentially inflated Type 2 error associated with the large number of comparisons with a small sample size, effect size confidence intervals were calculated and only medium to large-sized effects (partial $\eta^2 \geq .10$; Cohen, 1988) were interpreted.

Table 1. Sample demographics by group

	On-Time ($n = 36$)	PA ($n = 40$)	
	M (SD)	*M (SD)*	*t*
Age (years)	7.53 (.77)	7.65 (.90)	−1.53
SES	47.06 (11.07)	43.73 (13.10)	1.19
Height (cm)	123.72 (7.03)	128.53 (6.77)	−3.03**
Weight (kg)	26.48 (6.01)	31.58 (8.99)	−2.94**
BMI	17.14 (2.68)	18.86 (4.08)	−2.19*
	n (%)	*n* (%)	χ^2 (*df*)
Ethnicity			1.79 (2)
Caucasian	26 (72)	23 (58)	
African American	7 (20)	12 (30)	
Other	3 (8)	5 (12)	

Note. On-Time = on-time maturation; PA = premature adrenarche; SES calculated using Hollingshead scale (1975); BMI = body mass index; significant differences determined by independent samples *t*-tests and chi-square test; *$p < .05$; **$p < .01$.

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Table 2. Group differences for neuropsychological instruments

	On-time maturation			Premature adrenarche					
	n	Mean	*SD*	*n*	Mean	*SD*	*F*	partial η^2	95% CI
California Verbal Learning Test-Child Version							1.03	.11	
List A Total Trials 1–5	36	42.03	10.78	39	42.13	9.72	.00	.00	.00–.00
List A Trial 1 Free Recall	36	5.92	1.98	39	5.79	1.89	.07	.00	.00–.04
List A Trial 5 Free Recall	36	9.86	2.64	39	10.13	2.38	.21	.00	.00–.07
List A Short Free Recall	36	8.19	2.98	39	8.26	3.06	.01	.00	.00–.00
List A Short Cued Recall	36	9.50	2.6	39	9.41	2.16	.03	.00	.00–.01
List A Long Free Recall	36	9.75	2.27	39	8.97	2.39	2.07	.03	.00–.13
List A Long Cued Recall	36	10.11	2.51	39	9.79	2.65	.28	.00	.00–.07
List B Free Recall	36	4.69	1.28	39	5.41	2.09	3.14	.04	.00–.16
Digit Vigilance Test							1.08	.03	
Commission Errors[a]	36	.14	.49	39	.21	.47	.36	.01	.00–.08
Omission Errors[a]	36	38.42	19.50	39	32.59	19.47	1.67	.02	.00–.12
WISC-III							.70	.06	
IQ[†]	34	108.44	18.22	39	106.05	16.50	.44	.01	.00–.08
Block Design	36	20.58	12.11	40	19.93	11.23	.08	.00	.00–.04
Coding	33	43.45	10.63	40	41.95	12.62	.47	.01	.00–.09
Digit Span Backward	36	4.36	1.91	40	3.80	1.40	2.04	.03	.00–.13
Digit Span Forward	36	7.97	1.84	40	7.68	1.53	.60	.01	.00–.09
Vocabulary	33	20.00	7.30	40	20.45	6.08	.21	.00	.00–.07
Wisconsin Card Sort Test							.55	.06	
Perseverative Errors[a]	34	27.94	20.48	39	29.85	25.83	.12	.00	.00–.06
Perseverative Responses[a]	34	32.79	26.94	39	36.21	35.12	.21	.00	.00–.07
Categories Completed	34	3.85	2.03	39	4.03	2.17	.01	.00	.00–.01
Total Correct	34	64.97	15.34	39	66.05	16.02	.09	.00	.00–.05
Errors[a]	34	47.53	26.45	39	47.69	27.92	.00	.00	.00–.00
Trials To First Category[a]	34	24.85	28.90	39	24.08	32.16	.12	.00	.00–.06
Failure To Maintain Set[a]	34	.88	.91	39	1.03	1.14	.35	.01	.00–.08
Nonperseverative Errors[a]	34	19.59	13.26	39	17.82	14.30	.30	.00	.00–.08
Rey-Osterrieth Complex Figure Copy							.71	.02	
Copy	31	18.53	9.64	39	15.88	8.79	1.44	.02	.00–.12
Delay	31	7.89	5.87	39	6.81	5.28	.66	.01	.00–.10
Grooved Pegboard (seconds)							.31	.01	
Dominant[a]	33	43.85	12.16	40	48.58	14.41	.04	.00	.00–.02
Non-Dominant[a]	33	47.03	14.10	40	43.25	12.37	.21	.00	.00–.07
Category Fluency Test									
Total Words	33	14.61	4.29	40	14.15	4.28	.21	.00	.00–.07

Note. Neuropsychological tests were administered in the order of presentation; a small and approximately equal number of participants across groups did not complete all measures due to time and/or difficulty following test instructions; shaded rows represent omnibus *F* for MANOVAs by instrument; instruments consisting of only one subscale are represented by a single *F*; [a]higher score = poorer performance; [†]IQ = standard score for the Wechsler Intelligence Scale for Children Third Edition as estimated by the Vocabulary and Block Design short-form; $*p < .05$.

RESULTS

Sample characteristics have been described earlier (Dorn et al., 2008). In brief, results indicated that girls with PA were significantly taller, heavier, and had higher BMIs than on-time girls (Table 1). Consistent with the sampling strategy, all girls were Tanner stage I breast, but on-time girls were Tanner stage I pubic hair and PA girls were Tanner stages II (58%) and III (43%) pubic hair. Approximately half of the girls in the PA group (52.5%) evidenced axillary hair.

Addressing the primary aim, a series of MANOVAs identified no significant univariate effects or multivariate main effects of group for any single neuropsychological instrument (omnibus *F*'s = .21–1.08; $p > .05$) (see Table 2). However, effect size confidence intervals for several subscales contained medium-sized group differences favoring on-time girls [i.e., CVLT List A Long Free Recall, WISC-III Digit Span Backward, ROCFT (Copy and Delay)]. In addition, confidence intervals contained two medium-sized group differences that favored girls with PA (i.e., CVLT List B Free Recall; DVT Omission Errors). With regard to the secondary aim of exploring the presence of a sexual dimorphism among girls with PA, our results did not show group differences favoring PA girls in typically male-advantaged tasks (tasks involving spatial skills; e.g., WISC-III Block Design and ROCFT Copy).

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DISCUSSION

The current research examined neuropsychological functioning among young girls with clinically off-time maturation and their typically maturing peers. Study hypotheses were generated based on a small number of prior studies evaluating neuropsychological functioning in samples with atypical maturational timing and contemporary research concerning the susceptibility of the developing brain to hormones that change during puberty.

Though results of a preliminary study suggested that IQ significantly differed between girls with PA and on-time maturation (Dorn et al., 1999), results of this research did not support significant group differences in IQ. Moreover, results indicated that the neuropsychological functioning of the two groups was largely comparable. Although underpowered for detecting significance at the subscale level, effect sizes provided important information about possible nuances of neuropsychological functioning in these two groups. In particular, several potentially medium-sized effects were observed that favored on-time girls. Largely consistent with a prior investigation of girls with PA (Dorn et al., 1999), the medium-sized effect sizes favoring girls with on-time maturation generally included tasks involving verbal and working memory (CVLT List A Long Free Recall; WISC Digit Span Backward) and visuospatial (ROCFT) skills.

Two medium-sized effects favoring girls with PA were also identified. These findings are complex and deserve discussion. The potentially stronger performance of the PA group on the measure of proactive interference (i.e., CVLT List B) must be interpreted within the context of the aforementioned weaker memory performance relative to on-time girls. Specifically, individuals with deficits in memory processes (e.g., consolidation) show *less decrement* in proactive inhibition because the influence of the "old" learned information is absent or diminished (Vanderploeg, Crowell, & Curtiss, 2001). This likely explains that girls with PA did *not* out-perform on-time girls. The finding of fewer omission errors on the measure of sustained attention is less straightforward. One potential explanation relates to research showing that hormones may support sustained attention to some degree (e.g., Ritsner, Gibel, Ratner, Tsinovoy, & Strous, 2006). Ultimately, neuropsychological findings were not consistent with a sexually dimorphic neuropsychological profile for girls with PA. Specifically, girls with PA did not demonstrate a markedly male-advantaged neuropsychological profile (i.e., better performance on spatial tasks) in comparison to their on-time counterparts.

LIMITATIONS

Certainly, some neuropsychological tests may have demonstrated floor effects, our small sample size was underpowered for purposes of identifying statistically significant differences at the subscale level, and effect size confidence intervals were wide. Despite these limitations, which are common to this type of research (Berenbaum & Beltz, 2011), this study represents the largest, most comprehensive prospective evaluation of neuropsychological functioning in girls during the initial hormonal rise of PA. To our knowledge, the largest study of young children with PA includes 73 participants and collected only biological data (i.e., Laakso, Utriainen, Laakso, Voutilainen, & Jääskeläinen, 2010). For purposes of replicating our effects, 73 participants would not achieve adequate power to achieve statistical significance (more than 250 girls with PA would be required to show significance at the subscale level; Cohen, 1988). Based upon the lack of studies comprehensively evaluating neuropsychological functioning within large samples of youth during the active hormonal rise of PA, we argue that our results *should* be interpreted, but with caution. Additionally, observed group differences were only modestly sized (i.e., medium effects, small score differences) and this research did not directly evaluate whether differences were associated with impairment. Thus, results should not be considered for guiding clinical practice and replication and extension of these findings is an essential future direction for research.

CONCLUSIONS

Atypical hormonal histories during early maturation (like those of PA) are rare, but the information gained from these children may provide insight into hormonal influences on neuropsychological functioning in important ways (Hines, 2004). Currently, most available evidence regarding hormonal effects on neuropsychological functioning is based upon animal and adult human studies. Moreover, experimental manipulations of hormone concentrations during child and adolescent development represent ethical and methodological challenges. Therefore, natural models of hormonal alteration during periods of significant brain development are essential for expanding our understanding of the influence of hormones on human brain development and functioning. Larger samples and longitudinal studies of children with PA are necessary for determining whether neuropsychological functioning is impacted by premature exposures to pubertal hormones (i.e., activational influences) and, if so, whether these effects are permanent alterations in functioning that persist after hormone concentrations have normalized (i.e., organizational influences; Berenbaum & Beltz, 2011). To complement studies such as ours, neuroimaging studies investigating puberty-related changes in brain structure and function are needed, as most studies outline brain development in terms of age and do not directly evaluate puberty-specific changes (Giedd, 2008).

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