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The Effects of Childhood Disruptive Disorder Comorbidity on P3 Event-related Brain Potentials in Preadolescents with ADHD

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Abstract

The present study examined the degree to which the P300 component of the visual brain event-related potential and associated task performance deficits often observed in children with attention-deficit hyperactivity disorder (ADHD) are attributable to comorbid childhood disruptive disorders using a community sample of 11-year olds from the Minnesota Twin Family Study. Subjects were divided into “ADHD-pure” (ADHD without oppositional defiant disorder, ODD, or conduct disorder, CD), “ADHD-comorbid” (ADHD with ODD or CD), and comparison (no childhood disruptive disorder) groups using DSM-III-R diagnoses. Results showed that ADHD-comorbid but not ADHD-pure subjects displayed significant P3 amplitude reduction and poorer task performance compared to controls. No group effects for P3 latency or reaction time were seen. Although ADHD-comorbid children had marginally more ADHD symptoms compared to ADHD-pure children, this did not account for their reduced P3, suggesting that the observed neurobehavioral deficits reflected the effects of co-occurring childhood disruptive disorders.

Keywords

ADHD; childhood disruptive disorders; comorbidity; P3; event-related potentials; disinhibition

1. Introduction

1.1. ADHD and disruptive disorder comorbidity

Attention-Deficit Hyperactivity Disorder (ADHD) is an impairing childhood psychiatric condition noted for its frequency in school-aged samples, treatment referrals (Offord et al., 1987), and adverse outcomes such as academic failure, negative peer relations, and incomplete independence as adults (Greene et al., 2002; Hinshaw, 2003; Offord et al., 1987). Currently, DSM-based diagnoses of ADHD are assigned using reportable features of inattention and/or disinhibition (American Psychiatric Association, 1994). Although diagnoses provide clinically useful information (Kendell & Jablensky, 2003), ADHD is likely a heterogeneous condition (Biederman et al., 1992) with multiple etiologic factors (Banaschewski et al., 2005). Uncovering these factors is complicated by its comorbidity with childhood disruptive conditions such as Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD). The frequent presence of these co-occurring disorders often leaves ambiguous the degree to which observed correlates are specific to ADHD or stem from the concomitant comorbidity. One way

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to address this issue is to examine how laboratory measures possibly linked to the pathophysiology of ADHD differentiate ADHD children with comorbid disruptive disorders from those without.

This study evaluates a set of brain measures from the P300 (P3) event-related potential (ERP) that putatively reflect disinhibitory dysfunctions associated with ADHD. The P3-ERP paradigm provides both psychophysiological (P3 amplitude, P3 latency) and behavioral performance measures (reaction time, total hits, false alarms) with potential utility for investigating these dysfunctions. Existing studies have repeatedly found P3 amplitude reductions (P3-AR) in ADHD subjects compared to non-ADHD controls. Findings associated with P3 latency and task performance have been less robust. However, many studies have not accounted for possible comorbidity with other disruptive disorders. In addition, possible effects of gender have received little attention. The current study systematically evaluates these P3 measures in a large epidemiological sample of preadolescent boys and girls divided into groups that allow for the assessment of disruptive comorbidity.

1.2. Findings from ERP studies of ADHD

Reflecting their perceived importance as possibly providing clues to ADHD's underlying pathophysiology, brain-related processes reflecting deficits in inhibitory control have received particular attention in ADHD research (Barkley, 1997; Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Hinshaw, 2003; Raine, 1997). P3 amplitude is thought to provide a psychophysiological signature of these deficits. Significant reductions in P3 amplitude elicited primarily from oddball tasks are noted predominantly in male ADHD versus non-ADHD subjects (see review by Barry, Johnstone, & Clarke, 2003), putatively reflecting behavioral disinhibition (Iacono, Carlson, Malone, & McGue, 2002), top-down failures of behavioral control (Nieuwenhuis, Aston-Jones, & Cohen, 2005), CNS hyperexcitability (Porjesz et al., 2005), or neuroinhibitory processes (Polich, 2007). This association is noted despite wide variation between studies in subject age (from age 6-17) or method used to obtain diagnoses (e.g., structured interviews, teacher ratings). Furthermore, P3-AR is reported for both auditory (Holcomb, Ackerman, & Dykman, 1986; Johnstone & Barry, 1996; Johnstone, Barry, & Anderson, 2001; Jonkman et al., 1997; Kemner et al., 1996; Kuperman, Johnson, Arndt, Lindgren, & Wolraich, 1996; Loiselle, Stamm, Maitinsky, & Whipple, 1980; Satterfield, Schell, & Nicholas, 1994; Satterfield, Schell, Nicholas, Satterfield, & Freese, 1990) and visual (DeFrance, Smith, Schweitzer, Ginsberg, & Sands, 1996; Holcomb, Ackerman, & Dykman, 1985; Jonkman et al., 1997; Kemner et al., 1996; Klorman, Salzman, Pass, Borgstedt, & Dainer, 1979; Lubar, Mann, Gross, & Shively, 1992; Michael, Klorman, Salzman, Borgstedt, & Dainer, 1981; Overtom et al., 1998; Robaey, Breton, Dugas, & Renault, 1992; Steger, Imhof, Steinhausen, & Brandeis, 2000; Strandburg et al., 1996; van der Stelt, van der Molen, Boudewijn Gunning, & Kok, 2001) P3 studies.

P3 latency is thought to reflect timing of stimulus categorization (Courchesne, Hillyard, & Courchesne, 1977; Kutas, McCarthy, & Donchin, 1977). Compared to P3 amplitude, latency is not consistently analyzed or reported in ADHD studies. Among those that do, results seem to suggest no latency differences between ADHD and control subjects (DeFrance et al., 1996; Holcomb et al., 1986; Johnstone & Barry, 1996; Johnstone et al., 2001; Klorman et al., 1979; Kuperman et al., 1996; Michael et al., 1981; Robaey et al., 1992; Satterfield et al., 1994; Satterfield, Schell, Nicholas, & Backs, 1988; Satterfield et al., 1990; Steger et al., 2000; van der Stelt et al., 2001), although some reports suggest significantly longer latencies (Holcomb et al., 1985; Strandburg et al., 1996) and even shorter latencies (Loiselle et al., 1980).

Although P3 task performance measures vary by study, most investigators include the measures (or related versions) assessed in the current report. We therefore limit our review to these

measures (reaction time, total hits, and false alarms). In general, behavioral performance results are inconsistent. For instance, among those studies examining response times, some find significantly longer reaction times in ADHD subjects compared to controls (Holcomb et al., 1985, 1986; Johnstone et al., 2001; Klorman et al., 1979; Loiselle et al., 1980; Overtom et al., 1998; Satterfield et al., 1994; Strandburg et al., 1996), but others do not (Johnstone & Barry, 1996; Jonkman et al., 1997; Jonkman et al., 2000; Satterfield et al., 1988; Satterfield et al., 1990; van der Stelt et al., 2001). More frequently reported are measures of accuracy (total hits or its variant “errors of omission”) and impulsive responding (i.e., response inhibition errors such as false alarms or “errors of commission”). However, like reaction time, these findings are inconsistent: some reports find that compared to controls, ADHD subjects commit more false alarms (Jonkman et al., 1997; Klorman et al., 1979; Loiselle et al., 1980; Lubar et al., 1992; Michael et al., 1981; Robaey et al., 1992; Satterfield et al., 1994; Satterfield et al., 1988; Satterfield et al., 1990; Strandburg et al., 1996; van der Stelt et al., 2001), and execute fewer target hits (Johnstone et al., 2001; Jonkman et al., 1997; Klorman et al., 1979; Loiselle et al., 1980; Michael et al., 1981; Overtom et al., 1998; Robaey et al., 1992; Strandburg et al., 1996; van der Stelt et al., 2001). However, others find no group differences for either false alarms (Holcomb et al., 1985, 1986; Johnstone & Barry, 1996; Winsberg, Javitt, Silipo, & Doneshka, 1993), or total hits (DeFrance et al., 1996; Holcomb et al., 1985, 1986; Johnstone & Barry, 1996; Johnstone et al., 2001; Kemner et al., 1996; Satterfield et al., 1988; Satterfield et al., 1990; Winsberg et al., 1993). In sum, results for P3 latency and task performance measures are variable, but P3-AR appears to be a fairly consistent accompaniment of ADHD.

These P3 findings, however, should be evaluated in the context of two important features that most ADHD-ERP studies share: 1) the predominant use of clinic-referred subjects, and 2) the uncertainty regarding the contribution of comorbid disruptive disorders (ODD, CD). Most studies reviewed use clinic-referred samples. This is evident in both the visual and auditory studies. Clinic samples, although crucial, may draw on particularly severe ADHD that likely includes comorbid conditions (Waschbusch, 2002) that some have argued may constitute distinct clinical entities (Biederman, Newcorn, & Sprich, 1991). Thus, issues of effect specificity and result generality remain, especially if comorbidity is not accounted for. Although this is a general concern in ADHD research (see review by Tannock, 1998), this is an important issue for many ERP studies of ADHD which used clinic samples but did not account for disruptive comorbidity (DeFrance et al., 1996; Holcomb et al., 1985; Jonkman et al., 1997; Klorman et al., 1979; Loiselle et al., 1980; Satterfield et al., 1994; Satterfield et al., 1988; Satterfield et al., 1990; Steger et al., 2000; Strandburg et al., 1996), or did not make it clear whether these disorders were excluded in their ADHD subjects (Holcomb et al., 1986; Johnstone et al., 2001; Jonkman et al., 2000; Kemner et al., 1996; Michael et al., 1981; Winsberg et al., 1993). Such accounts are important because P3-AR is also associated with CD in older subjects (Bauer & Hesselbrock, 1999a, 1999b; Carlson, Katsanis, Iacono, & Mertz, 1999; Costa et al., 2000; Iacono et al., 2002; Kim, Kim, & Kwon, 2001) as well as in younger samples with either ODD or CD (Banaschewski et al., 2003, 2004; Baving, Rellum, Laucht, & Schmidt, 2006).

Only a few investigations have examined the effect of disruptive comorbidity on P3 measures in ADHD subjects. These studies employed multigroup designs that allowed for comparative assessments in ADHD groups with and without other disruptive disorders. Overall, these studies obtained discrepant results which are difficult to reconcile based on available information. Linden and colleagues (1996) showed that ADHD and ADHD+ODD groups both displayed auditory P3-AR, longer latencies, and reaction times compared to controls, with the two diagnostic groups not differing from each other. Wiersma and colleagues (2006) found that visual P3-AR and longer reaction times characterized both ADHD and ADHD+ODD/CD subjects from controls, while false alarms indexed only the former group. However, Banaschewski and colleagues (2003) found that ADHD subjects were most

psychophysiological (e.g., reductions in P3a amplitude) and behaviorally (e.g., longer reaction times) deviant compared to ODD/CD, ADHD+ODD/CD, and control subjects when assessed on a cue-condition of a visual task designed to elicit cognitive/motor preparation. On the other hand, when these same groups were compared on stimuli associated with motor response activation and inhibition, these investigators found that P3-AR indexed ADHD comorbidity severity, with the ADHD+ODD/CD subjects displaying the greatest P3-AR (Banaschewski et al., 2004). Iacono et al. (2002) provide conditional support to the former finding as they document pronounced P3-AR and fewer total hits in their subjects with “comorbid” ADHD (ADHD without controlling for disruptive comorbidity) but not “pure” ADHD subjects (ADHD excluding ODD and CD) compared to controls. This study of older adolescents is especially relevant to the current investigation because it is the only study to use the same visual task in a multigroup evaluation of ADHD subjects derived from a community sample.

1.3. Present Study

The current study evaluated the role of comorbidity on P3 outcomes using the largest epidemiological sample of preadolescent boys and girls in the current literature ($n = 1,136$). To separate the effect of disruptive comorbidity, ADHD subjects were divided into “ADHD-pure” (i.e., ADHD excluding ODD and CD) and “ADHD-comorbid” (ADHD including ODD or CD) groups. Furthermore, given that few ADHD studies have assessed the effects of gender and comorbidity on P3, these evaluations were made using a large sample of girls ($n = 572$). Based on the existing literature, we hypothesized that children with ADHD would show P3-AR and associated performance deficits. Because the one study that employed a community sample (Iacono et al., 2002) provided evidence that ADHD comorbidity might account for the P3-AR observed in ADHD children, we hypothesized that these deficits would be more apparent in ADHD children with comorbid childhood disruptive disorders than in those with “pure” ADHD. The current study thus represents an effort to extend the Iacono et al. (2002) findings, which were derived from 17-year old boys, to a large sample of 11-year olds that included girls. Because gender has not been systematically explored in ERP studies of ADHD, it is difficult to offer a gender-based hypothesis. However, since a growing number of magnetic resonance imaging (MRI) reports do show comparable anomalies in both female and male subjects (e.g., Castellanos et al., 2002) it may be inferred that similar ERP deficits will be observed in girls as well.

2. Methods

2.1. Subjects

A community-based sample of 1,136 twins (564 boys and 572 girls in the Minnesota Twin Family Study) aged 11 years (range = 10-12) with event-related potential and diagnostic data served as participants. This sample comprised 11-year old twins selected to be broadly representative of twins born in the state of Minnesota (see Iacono et al., 1999, for details) supplemented with additional twin participants ($n=15$: 8 boys, 7 girls) who were recruited following identical procedures but who were found to have ADHD following a telephone screening interview with their mother that indicated such a diagnosis was likely (see Iacono, McGue, & Krueger, 2006, for details). All children gave written informed assent and a parent provided written informed consent for both the parent's and the child's participation.

These ADHD children were divided into two groups based on the presence of co-occurring disruptive disorders: 1) “ADHD-pure” group ($n = 39$: male = 22; female = 17) consisted of subjects who did not have diagnoses of ODD and CD; 2) “ADHD-comorbid” group ($n = 61$: male = 49; female = 12) included all ADHD subjects with a diagnosis of either CD or ODD. Controls ($n = 1,036$: male = 493; female = 543) did not have a diagnosis of ODD, CD, or

ADHD. Furthermore, 17 children with six ADHD symptoms were also removed from the control group. This was done to ensure that subthreshold ADHD cases that could potentially represent false negatives were excluded from analysis.

2.2. Interview and Assessment Procedure

Trained interviewers conducted in-person interviews with the child participants as well as their parents. Diagnostic information was obtained using modified versions of the Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Herjanic & Reich, 1982; Welner, Reich, Herjanic, Jung, & Amado, 1987). All DSM-III-R diagnoses were made at the probable (one symptom short of the eight needed for a definite diagnosis) or definite (all diagnostic criteria satisfied) levels of certainty using a best-estimate approach that combined mother and child reports and that has demonstrated construct validity in this sample (e.g., Burt, Krueger, McGue, & Iacono, 2001). Kappa reliabilities for diagnoses were as follows: ADHD (0.77), ODD (0.71), and CD (0.81).

2.3. P3 Event-related potential (ERP) procedure

P3 data were collected using the same visual rotated heads “oddball” paradigm and data processing procedures described in Iacono et al. (2002) who, as noted previously, examined P3-AR in 17-year old boys with ADHD. P3 amplitude obtained from this paradigm has been shown to provide a reliable and heritable (Katsanis et al., 1997; Yoon et al., 2006) marker of substance use disorders and other externalizing psychopathology that indexes both morbid (e.g., personal history; see review by Iacono et al., 2003) and premorbid (i.e., family history; see Begleiter, Porjesz, Bihari, & Kissin, 1984) concomitants over decades of research. During ERP recording, subjects were seated in a sound attenuated room, instructed to pay close attention to images appearing on a computer monitor, and asked to respond as quickly as possible by pressing either a left or right button when target stimuli appeared. Targets consisted of infrequently-occurring schematics of heads with a nose pointed vertically up or down on the screen and only one ear represented on either the left or right side. “Easy” targets ($n = 40$) consisted of heads with noses pointed towards the top of the screen with the left or right ear appearing directly on the side corresponding to the correct response button (e.g., nose pointed up with ear on left of head requires left button press). In contrast, “hard” targets ($n = 40$) consisted of heads facing towards the bottom of the screen with either left or right ear appearing on the head which corresponds to the *opposite* response button (e.g., nose pointed down with ear on left of head requires right button press). Consistent with past research using this rotated heads paradigm, easy and hard trials together composed “targets.” Subjects were also instructed to ignore frequently occurring, interspersed nontarget stimuli which consisted of ovals ($n = 160$).

All stimuli were displayed for 98 ms, with intertrial intervals randomly varying between 1-2 seconds. The ERP task took 15 minutes to complete. An electrode cap was used to record brainwave activity from three parietal sites: one over each hemisphere (P3 and P4) and one at midline (Pz). For this report, averaged data from all target stimuli at site Pz were examined, a practice consistent with the relevant extant P3 literature (e.g., Hill, Muka, Steinhauer, & Locke, 1995). Electrooculographic (EOG) data were recorded from a pair of electrodes at the supra-orbital ridge and the outer canthus of the eye. Impedances were kept below 5 k Ω for scalp electrodes and below 10 k Ω for EOG recordings. A ground electrode was placed on the right shin. All data were acquired using a Grass Model 12A Neurodata system and filtered with a passband of 0.01 to 30 Hz (half-amplitude). Data were digitized with 12 bits of resolution at a rate of 256 samples/second. Participants were not given any rewards for task performance, and were instructed to discontinue any psychotropic medications (including stimulants) 24-hours prior to assessment.

From the grand average of the target trials, a computer algorithm identified P3 amplitude as the positive apex between 395-1000 milliseconds post-stimulus, while P3 latency was defined as the time interval between stimulus-onset to this apex in milliseconds. This algorithm was monitored by raters blind to diagnostic status who overrode it when, for example, two peaks of approximately equal amplitude occurred within 100 ms of each other. In these cases, the second peak was chosen (Squires, Squires, & Hillyard, 1975). Three P3 task performance measures were used: false alarms (i.e., number of nontarget stimuli (160 ovals) incorrectly identified as targets), reaction time (the average time it took for subjects to make a button press to identify target stimuli), and total hits (i.e., number of 80 targets correctly identified). False alarm and total hits data were skewed and respectively underwent log and arcsine transformations prior to analyses. A total of 22 subjects identified as outliers were dropped: 19 control subjects (13 males, 6 females) and 3 subjects from the ADHD-pure group (2 male, 1 female) due to having anomalous P3 (e.g., negative values with documented recording problems) and/or task performance data (e.g., no correctly identified hard targets). Thus, the final number of children within each group was: Controls ($n = 1,036$; male = 493; female = 543), ADHD-pure ($n = 39$; male = 22; female = 17), ADHD-comorbid ($n = 61$; male = 49; female = 12).

2.4. Statistical Analyses

The effect of the diagnostic grouping variable (Controls, ADHD-pure, ADHD-comorbid) on the P3 (amplitude, latency) and task performance (reaction time, false alarms, total target hits) outcome measures was assessed in separate two-way ANOVAs with group and gender as fixed effects. Participants were drawn from twin pairs which violate the assumption that all observations are independent and acts to artificially deflate variability. We therefore conducted all ANOVAs using PROC SURVEYREG in SAS (version 9.1), which calculates appropriate standard errors (Fuller, 1975) when data are clustered, as in this case. Standard deviations (SD) for all variables were then calculated by multiplying standard errors by the square root of the sample size (n). In this case n was defined as the number of unique twin pairs within each group: controls = 600, ADHD-pure = 37, ADHD-comorbid = 51. Means and standard errors were derived via PROC SURVEYMEANS.

Significant group main effects were followed by a pair of simple contrasts where the control group was compared with each diagnostic group separately (i.e., controls vs. ADHD-pure and controls vs. ADHD-comorbid). These contrasts were based on a priori hypotheses regarding P3 amplitude and performance variables, and a significance criterion of $\alpha < .05$ was used for all analyses with no further adjustments for multiple comparisons.

3. Results

Omnibus F-statistics are reported in text. Table 1 displays descriptive statistics (means, standard deviations) for P3 and task performance variables by group.

3.1. Gender Results

The main effect of gender was apparent for all P3 and task performance variables (all $F_s > 5.0$, all $p_s < .03$) except for P3 latency (Wald $F(1, 653) = 1.50$, $p = 0.22$). As the table shows, girls had larger P3 amplitudes than boys (2.59 μV difference). Behaviorally, boys were slower to react to targets but performed more accurately, identifying more target stimuli and committing fewer false alarms. Tests for group by sex interactions yielded non-significant results across all analyses (All $F_s < 1.56$, all $p_s > 0.22$). Thus, we restricted all analyses to examine the main effect of diagnostic group adjusting for sex.

3.2. P3 Task Performance

Although reaction time did not differentiate the groups (Wald $F(2, 653) = 1.69$, $p = 0.19$), significant group effects were detected for total hits and false alarms ($F_s > 4.0$, all $p_s < .01$). Two follow-up contrasts were then conducted to compare controls to each diagnostic group on total hits and false alarms. Results revealed that ADHD-pure subjects did not differ from controls on either performance measure. On the other hand, ADHD-comorbid children had fewer total hits (Wald $F(1, 653) = 9.05$, $p = 0.003$) and committed more false alarms (Wald $F(1, 653) = 8.32$, $p = 0.004$) compared to controls.

3.3. P3 Amplitude and Latency

Figure 1 displays the grand mean P3 amplitudes by group collapsed across sex, and indicates how similar P3 morphology was for the ADHD-pure and control subjects as well as how different both groups were compared to the ADHD-comorbid children. This observation is further highlighted by the overall statistical results (Wald $F(2, 653) = 4.32$, $p = 0.01$) and follow-up comparisons which revealed that the ADHD-comorbid subjects displayed significantly attenuated amplitudes compared to controls (5.08 μV difference, $p = 0.003$), whereas ADHD-pure children did not (0.81 μV difference, $p = 0.66$). Latency did not differentiate the groups (Wald $F(2, 653) = 0.14$, $p = 0.87$).

3.4. Summary

In sum, our findings indicate that the association between P3-AR and task performance variables with ADHD is conditioned on the co-occurrence of disruptive comorbidity. Thus, P3-AR and poor task performance (fewer total hits and more false alarms) characterized ADHD cases with disruptive disorder comorbidity, but not subjects with ADHD alone.

3.5. Follow-up Analyses

3.5.1. Comparing diagnostic group ADHD symptom counts—Although ADHD-comorbid subjects alone displayed P3-AR, this group could have a more severe version of ADHD characterized by a greater number of ADHD symptoms. Were this the case, group differences could be attributed to differences in the expression of ADHD rather than to the comorbidity per se. To evaluate this possibility, comparisons were made between diagnostic groups (ADHD-comorbid vs. ADHD-pure) on the total number of ADHD symptoms derived from the combined mother and child reports. Results fell just short of significance (Wald $F(1, 80) = 4.12$, $p = 0.05$). Nevertheless, to further evaluate the possibility that the number of ADHD symptoms was driving the P3 effect, both ADHD-pure and ADHD-comorbid subjects were first combined and then split into two groups reflecting the top ($n=15$; every subject had ≥ 11 symptoms) and bottom ($n=25$; every subject had seven ADHD symptoms, the minimum necessary for a diagnosis at the “probable” level) of the ADHD symptom distribution. These groups were then compared on P3 amplitude. Results were non-significant: Wald $F(1, 80) = 0.96$, $p = 0.33$.

3.5.2. Stimulant Medication Use in Diagnostic Groups—For this study, participants who were prescribed stimulant drugs did not take them on the day of testing. To evaluate the possibility that the pure and comorbid groups differed in their likelihood of ever having been prescribed stimulants, the proportions of ever-medicated children in the two groups were compared. Medication data for seven diagnostic subjects were unavailable (i.e., 3 and 4 subjects were missing medication data from the ADHD-pure and comorbid groups, respectively). The percentages of remaining diagnostic children medicated in the pure and comorbid groups were 25.0% and 33.3%, respectively, a non-significant difference, $\chi^2(1, N = 93) = 0.7$, $p = 0.39$, thus rendering unlikely the possibility that differences in past medication status could account for ADHD group differences.

3.5.3. Accounting for group differences in total misses and its impact on P3 amplitude

Finally, in most ADHD-ERP studies to date, the potential impact of significant target detection differences on P3 amplitude was not systematically addressed. Many studies, including the current study, include missed trials in the P3 averaging process which may be associated with smaller P3. Therefore, diagnostic subjects (e.g., ADHD-comorbid) with more target misses may display P3-AR because they are not paying attention to some of the target trials rather than because they are processing these trials differently. A key example is provided by Jonkman et al. (1997) who documented both P3-AR and fewer target hits in ADHD subjects compared to non-ADHD controls. However, they found that P3 amplitudes to hit trials only did *not* significantly differ between groups when miss trials were excluded. In order to address this important issue, we re-analyzed P3 amplitude using total misses as a continuous covariate. The main group results in fact became slightly enhanced (Wald $F(2, 653) = 4.67, p = 0.01$), with contrast results remaining the same (5.08 μV difference between the ADHD-comorbid vs. Control groups).

4. Discussion

4.1. P3-ERP results

The current study highlights the considerable importance of accounting for disruptive disorder comorbidity when determining P3 associations in ADHD. This study demonstrated that significant psychophysiological (P3-AR) and behavioral (fewer target detections, greater false alarms) correlates of disinhibitory psychopathology are more accurately attributed to children with both ADHD and comorbid disruptive disorders than those children presenting ADHD alone.

These findings at age 11 replicate and extend the study by Iacono et al. (2002) who found that ADHD-comorbid (but not ADHD-pure) 17 year-old boys displayed P3 abnormalities (P3-AR, less total hit detection) compared to controls. However, our findings are somewhat discrepant from the few existing multigroup studies reviewed previously. These studies suggested that P3-AR operates as a general index for ADHD, with or without comorbid disruptive disorders (Linden, 1996; Wiersma, 2006), or as a quantitative marker related to disruptive disorder comorbidity with the greatest deficits seen in children with ADHD+ODD/CD (Banaschewski et al., 2004). These differences may relate to recruitment source as these studies employed clinic-referred samples who may present more severe forms of these disorders. Indeed, the finding that P3-AR generally indexes disorders in both single and comorbid forms parallels findings in older subjects presenting differentiated externalizing psychopathology. For example, P3-AR indexes antisocial personalities (Bauer, O'Connor, & Hesselbrock, 1994; Costa et al., 2000), substance use disorders (Iacono et al., 2002; Malone, Iacono, & McGue, 2001), and comorbidity amongst these disorders in adolescent and adult samples. On the other hand, early forms of these disorders may be relatively undifferentiated (Lilienfeld, 1994), especially in younger epidemiological samples. Thus, in these samples, it may be the case that a particularly severe combination of disinhibitory features with relatively early expression elicits P3-AR, which this study identifies as ADHD disruptive disorder comorbidity.

The notion that such children are at increased risk for disinhibitory dysfunction is further supported by their apparent failure to inhibit responses to non-target stimuli during the ERP oddball task. Such task performance deficits putatively reflect executive-level inhibitory dysfunctions that may be primary to disorders like ADHD (Barkley, 1997; Nigg, 2000; Tannock, 1998) and may be more apparent in ADHD children with comorbid disruptive disorders (e.g., see meta-analysis by Waschbusch, 2002). The latter point is underscored by a recent study which found that a polymorphism in the gene for the COMT enzyme putatively linked to executive functioning distinctively indexed a subtype of ADHD children manifesting antisocial behavior (Caspi et al., 2008). Moreover, this association held in both clinic and

epidemiological samples. Thus, with the early presence of brain anomalies and associated neurocognitive deficits that may reflect a distinct genetic vulnerability, these children may be at risk for developing severe antisociality (Moffitt, 1993), or becoming ‘fledgling psychopaths’ (Lynam, 1998) warranting early intervention and longitudinal follow-up investigations.

4.2. Gender and ADHD-P3

The inclusion of gender analyses in relation to ADHD-P3 outcomes sets needed groundwork in this literature. Although the smaller number of diagnosed females preclude more definitive statements of gender effects on these measures, our findings offer the prospect that P3 indices may be helpful in identifying young female cases at heightened risk for disinhibitory psychopathology. Future studies using larger female samples are needed given the growing number of studies documenting significant risk for disruptive comorbidity in girls with ADHD (Biederman et al., 1999; Biederman et al., 2006; Hinshaw, 2002; Mikami & Hinshaw, 2003), as well as the potential dysfunctions associated with such comorbidity (see meta analysis by Gaub & Carlson, 1997).

4.3. ADHD and the externalizing factor

Overall, the finding that ADHD disruptive disorder comorbidity, but not ADHD alone, is associated with P3-AR adds to our understanding of recently proposed hierarchical models of disinhibitory psychopathology in adolescents that view individual disorders as facets of a highly heritable latent externalizing factor that accounts for the comorbidity among the various externalizing disorders (Krueger et al., 2002; Young, Stallings, Corley, Krauter, & Hewitt, 2000). An important question is which disorders should be included as part of this externalizing spectrum. P3 amplitude is a heritable index (van Beijsterveldt & van Baal, 2002; Yoon, Iacono, Malone, & McGue, 2006) that is itself a facet of the externalizing factor (Patrick et al., 2006). Moreover, the P300-externalizing association can be attributed entirely to mutual genetic effects (Hicks et al., 2007); a finding that adds to other evidence that P3-AR is an endophenotype reflecting the underlying genetic risk for externalizing (Frederick & Iacono, 2006; Iacono, Malone, & McGue, 2003). As we have illustrated elsewhere (Yoon et al., 2006), an endophenotype can be used to refine our understanding of clinical phenotypes in that whether the endophenotype is associated with a clinical disorder informs us about the nature of that disorder. In this case, the P3 findings suggest that ADHD per se does not share genetic liability with the externalizing latent trait.

4.4. Limitations

Although we found that children with ADHD alone did not display P3 abnormalities, these children may nevertheless suffer other inhibitory dysfunctions not tapped by our P3 task. For example, a growing body of work suggests that weak frontal activation during response inhibition tasks may serve as ‘cognitive endophenotypes’ for ADHD (see review by Aron & Poldrack, 2005). In addition, different studies use somewhat different procedures to elicit P3, including tasks that use auditory stimuli that may be more easily detected than the moderately difficult visual stimuli used in this study. Therefore, although the visual rotated heads task we used has been used in dozens of studies over the last 25 years, we cannot be certain to what degree our results depend on this particular task or how comparable our findings are to studies presenting stimuli that differ on various parameters (e.g., modality, difficulty level). Furthermore, evidence indicates that the P3 response itself is not a unitary phenomenon but may encompass important time-frequency or oscillatory components associated with critical cognitive functions (e.g., Karakas, Erzen, & Basar, 2000a; Karakas, Erzen, & Basar, 2000b). Thus, it may be the case that these measures may reveal fundamental dysfunctions not captured fully by P3 amplitude at a single scalp site. Such questions can be addressed using

denser electrode montages in conjunction with time-frequency decomposition (Bernat, Malone, Williams, Patrick, & Iacono, 2007) and evolving neuroanatomical source localization techniques (see review by Michel et al., 2004). Such methods are currently being pursued in our lab. Furthermore, even though this community-based sample offers unique research opportunities, it is nevertheless comprised of predominantly Caucasian twin participants from Minnesota, potentially limiting generalizability to samples similarly composed.

4.5 Conclusion

Despite these limitations, the findings of this study mirror closely those of Iacono et al. (2002) who, using a different sample but the same procedure, also found that comorbid ADHD, but not pure ADHD, was associated with P3-AR. Taken together, these two community-based studies suggest that to the extent that P3-AR is associated with ADHD, this association arises due to the presence of comorbid childhood disruptive disorders.

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Figure 1.

Grand average waveforms as a function of diagnostic status. Waveforms were generated using a low-pass filter at 10-Hz for presentation purposes only. “Controls” refer to subjects with no diagnosis of any childhood disruptive disorder. “ADHD-pure” refers to ADHD without oppositional defiant disorder (ODD) or conduct disorder (CD). “ADHD-comorbid” refers to ADHD with either ODD or CD.

Table 1

P3 and task performance descriptives by gender and comparison groups

Measure	Groups ¹			
	Gender Means ²		Controls (n = 1,036)	ADHD-comorbid (n = 61)
	Boys (n = 564)	Girls (n = 572)		
P3 amplitude (µV)	35.71 (8.89) ^b	38.30 (9.02) ^b	37.31 (9.06) ^a	32.23 (10.21) ^a
P3 latency (ms)	581.17 (74.92)	574.03 (73.92)	577.39 (73.71)	576.39 (91.75)
Reaction time (ms)	1247.48 (191.01) ^b	1151.13 (184.63) ^b	1194.48 (193.47)	1255.39 (273.89)
Total Hits	76.65 (4.54) ^b	74.96 (5.59) ^b	75.94 (4.90) ^a	73.19 (8.28) ^a
No. of false alarms	0.54 (1.81) ^c	0.68 (2.16) ^c	0.48 (1.47) ^a	2.20 (6.35) ^a

¹“Controls” refer to subjects with no diagnosis of any childhood disruptive disorder. “ADHD-pure” refers to ADHD without oppositional defiant disorder (ODD) or conduct disorder (CD). “ADHD-comorbid” refers to ADHD with either ODD or CD.

²Gender means are presented for all participants without regard to group membership.

^aGroup means differ significantly at $p < .01$ after adjusting for sex

^bGender means differ significantly at $p < .001$

^cGender means differ significantly at $p < .05$

Note: Descriptive statistics for behavioral performance variables (total hits, false alarms, reaction time) are given in their original metric for interpretability. Reaction time refers to the averaged response time to target stimuli in milliseconds; total hits refer to the number of correctly identified target stimuli of the 80 presented; false alarms refer to the number of *non*-target stimuli (160 presented) incorrectly identified as targets.