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05. NOV 2007

Administration Board
Grupo BIAL
A Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

Re: Report on BIAL Fellowship Programme: Event-related potentials and temperament traits in ADHD and conduct disorder. (ref 119/04).

Dear Sir/Madame

We would like to thank BIAL very much for the support of this study which is now complete and here submit our final study report. The financial report was sent to BIAL foundation previously by us.

The aim of this study was to understand brain function involved in symptoms and temperament traits of ADHD and conduct disorder. The project includes 80 adolescent boys into the study (30 healthy individuals, 30 boys with ADHD, 20 boys with conduct disorder). We also made use of an international database of 245 children and adolescents to investigate maturational changes in brain function (see abstract 2 below).

A structured clinical interview was used to diagnose developmental problems including Attention Deficit and Hyperactivity Disorder (ADHD), oppositional defiant disorder (ODD) and Conduct Disorder (CD). A number of techniques were used to measure brain function including electroencephalography, event-related potentials and neuropsychology measures. Brain function assessment was performed using brain resource company techniques. We also used a number of self and parent report instruments to measure symptoms and temperament traits, in particular we were interested in callous/unemotional traits, emotional intelligence, affective problems,

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pragmatic language impairment, hyperactivity, impulsivity, and aggression.

Instruments used to measure these clinical variables included.

- 1) The antisocial process screening device (self and parent report)
- 2) An emotional intelligence questionnaire (self report)
- 3) The depression, anxiety and stress scale (DASS) (Self report)
- 4) The Children's Communication Checklist (CCC-2) (parent report)
- 5) The Conners-Wells Adolescent Self-Report Scale (CASS:L) (self report)
- 6) The Conners' Parent Rating Scale (CPRS-R:L) (parent report)
- 7) Buss and Perry Aggression Scale (self report)

Data from this project formed the basis of five Masters thesis and is currently being written up for publication. Abstracts from each thesis are presented below. Data have also been presented in poster form. If required we will be happy to forward BIAL full copies of the thesis and posters.

Please find attached two manuscripts which are currently in preparation. Full versions of these will be forwarded to BIAL as soon as they are in press. The first describes gender differences in the development of brain function as measured using event-related potential techniques. This study suggests that both linear and nonlinear maturational components exist that differ in topography and between boys and girls. The second study investigates these maturational processes in conduct disorder and suggests abnormal development of N200 over the right temporal regions. Right temporal N200 was significantly associated with callous unemotional traits a measure of empathy which is thought to index a particularly persistent subtype of conduct disorder. In comparison, left frontal function was associated with depression and narcissism in opposing ways. That is, depression and narcissism may reflect opposite ends of a spectrum extremes of which predispose to conduct problems. This work was also orally presented at the International Applied Neuroscience conference at the beginning of 2007. Please find attached a copy of the presentation. We are yet to write up our comparison between CD and ADHD patients, and as with the other manuscripts will forward this to BIAL as soon as it is published. Please let me know if further information is required. We trust that BIAL will be pleased with the outcome of project so far and look forward to further correspondence. Thank you.

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Sincerely,

Katya Rubia

Alex Sumich

Abstract 1

A PILOT STUDY EXPLORING THE RELATIONSHIP BETWEEN ASPECTS OF PERSONALITY, COMMUNICATION SKILLS AND PARENTING ENVIRONMENT IN A MALE ADOLESCENT SAMPLE WITH EXTERNALISING DISORDERS.

Background: High rates of comorbidity with other disorders is found in children with externalising psychopathology. Previous studies suggest temperamental traits, pragmatic language impairment and family environment may exacerbate behavioural problems.

Aims: To examine homogeneous and heterogeneous comorbidity in children with behavioural disorders and to study the impact of personality traits, communication skills and parenting style to the occurrence and maintenance of conduct problems.

Sample: Five boys (mean age: 13) with conduct problems and six controls (mean age: 15.16) participated in the study.

Method: A diagnosis of conduct disorder and/or oppositional defiant disorder was confirmed using the children's inventory for psychiatric syndromes (ChIPS). ChIPs was also used to screen for conduct problems in control participants. Self and parent assessments were also obtained using the strengths and difficulties questionnaire (SDQ), Antisocial Process Screening Device (APSD), Children's Communication Checklist-2 (CCC-2), and Alabama Parenting Questionnaire (APQ). Repeated measures multivariate analysis were used to test group and assessor differences in subscores from each assessment administered. In addition, linear regression was used to identify significant predictors from the APSD, CCC-2 and APQ subscores for each of the SDQ dimensions.

Results: Boys with conduct problems were found to have a more severe symptomatology and clinical diagnoses which included various other internalising and externalising disorders. The clinical group had significantly stronger antisocial personality traits and significantly lower general and pragmatic language scores. They also received more corporal punishment than the controls. The linear regression analysis showed that hyperactivity was predicted by poor pragmatic language skills and positive parenting. Conduct problems were predicted by callous-unemotional traits and peer problems and

low prosocial behaviour was predicted by impulsivity. Overall difficulty score was predicted by pragmatic communication deficits and positive parenting. Reword as above

Conclusions: Comorbidity, language communication deficits, temperament and family environment contribute to the maintenance and perseverance of conduct problems. Better understanding of the dynamics between these factors and their contribution to conduct problems has implications for effective treatment and intervention plans for boys with behavioural problems.

Abstract 2

SEX-DIFFERENCES IN MATURATION OF FRONTAL LOBE FUNCTION AS MEASURED BY EVENT-RELATED

Objective: Sex-differences exist in prevalence, symptom profile and brain function of conduct and attention deficit/hyperactivity disorders. Event-related potentials (ERP) have been used to study brain function in these disorders and in normal maturation. Maturation decreases in N200 amplitude -a measure of categorisation and executive function- are associated with improved reaction time and fewer commission errors. In contrast, P300, a measure of memory updating and response modulation, increases with age. Behavioural studies suggest girls have more effective frontal/executive function than boys at ages 12-13. Sex-differences in normal maturation of brain function have not been investigated using ERPs. An understanding of sex-differences in healthy maturation may offer insights into the aetiology of developmental disorders. **Method:** 245 healthy participants (n=110 girls and n=135 boys) aged 6-17 years completed an auditory oddball task at an international Brain Resource lab located in either UK, USA, Europe or Australia. A NeuroScan *Quik cap* (NuAmps amplifier; sampling rate=500Hz) was used to collect electroencephalographic data (reference=linked mastoids; ground=forehead; low pass filter =100Hz, 40dB; impedance< 5kOhms). Mean scores for N200 and P300 amplitude were calculated at left (F3 and F7) and right- (F4 and F8) frontal sites. Four groups were formed based on age (Group1: 6-8yrs n=40; Group2: 9-11yrs n=80; Group3: 12-14yrs n=69; Group4: 15-17yrs n=56). A repeated measures ANOVA was used to test for differences in N200 and P300 with *hemisphere* (left, right) as a within group factor and *age-group* (1, 2, 3, 4) and *gender* (boys, girls) as between groups factors.

Results: There were significant *group* and *group*sex* effects for N200 (group 1>2>3>4) and P300 (group 1<2<3<4). Girls had lower N200 than boys in group 4, but higher (trend level) N200 in groups 1 and 3. In boys, groups 1 and 2 had higher N200 than groups 3 and 4. For P300 in boys, group 3>2 =1, and group 4>1. In girls, group 1 had higher N200 than groups 3 and 4; and group 4 had lower N200 than all other groups; P300 was higher in group 4 than groups 1 and 2. A significant *hemisphere*group* effect in N200 was due to higher right than left N200 in groups 1 and 2. **Conclusion:** During oddball task performance, girls show a gradual increase in prepubescent brain function followed by more dramatic changes in late adolescence. Boys show greatest change at ages 12-14, but are then overtaken by girls.

Abstract 3

NEUROBIOLOGICAL CORRELATES OF CALLOUS- UNEMOTIONAL TRAITS, NARCISSISM AND DEPRESSION IN ADOLESCENTS WITH CONDUCT PROBLEMS

Background:

Conduct Disorder (CD) is characterised by a persistent pattern of antisocial behaviour appearing during development. CD commonly occurs with comorbid depression and psychopathic temperament traits, and poorer outcomes are seen in individuals with these associated symptomologies. Neurophysiological correlates of these associated features of CD are currently unknown.

Objectives:

As the N200 event-related potential (ERP) deflection undergoes maturational change and is thought to index emotion, the current study sought to explore:

- (1) whether N200 alterations follow normal developmental patterns in CD;
- (2) whether N200 is associated with depression and/or anxiety in CD;
- (3) whether there are N200 ERP correlates of CU traits and narcissism in CD.

Methods:

20 adolescent males with CD and 31 healthy controls completed a visual continuous performance task (CPT-XX). Affective symptoms and psychopathic traits were assessed and N200 amplitudes were examined for effects of age and psychopathology.

Results:

N200 failed to show typical age related reductions as seen in healthy controls. N200 amplitude decreased as a function of depression at left frontal sites and was inversely correlated with narcissism in the same areas. Narcissism was a more significant predictor (31.8% at F7; 44.6% at FC3) than depression. CU traits strongly correlated with the right anterior temporal lobe, where depression made additive contribution.

Conclusion:

Normal development of N200 does not occur in adolescents with CD, and alterations to N200 seen during executive task-completion are linked to the frequently associated features of depression, CU traits and narcissism.

Significance:

Firstly, the current study provides evidence that deficits in CD may arise from abnormal developmental processes, and that neurophysiological links exist between this condition and its comorbid affective symptomologies. Furthermore, it lends support to the view that depression and narcissism lie on a continuum. In addition, these findings strongly indicate that CU temperament has a neurobiological basis, and lends support to the view that these traits signify a unique subtype of CD which shares many behavioural and neurological features seen in adult psychopathy.

Abstract 4

The Association between Event Related Potentials and the Conners-Wells' Adolescent Self Report Subscales in Conduct Disorder

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Objective: The neurobiology of clinical characteristics, including emotional problems, inattention and hyperactivity-impulsivity – in conduct disorder was studied using event-related potentials (ERPs).

Methods: 18 male participants (age 12-17 years) with conduct problems, of which 14 were right handed and 4 left handed, completed a Conners-Well's Self report and a visual continuous performance task. Electroencephalographic data was collected at multiple electrodes sites. N100, P200 and N200 event-related potentials were scored. The relationship was tested using correlation and linear regression techniques.

Results: A positive association was seen between the N100 amplitude at right anterior sites and emotional problems, whilst right posterior N200 amplitude showed a strong negative association with emotional problems. A further negative association was seen between the right centro-temporal N200 amplitude and emotional problems. The left central P200, right centro-temporal N200 and the right anterior N100 explained 72.4% of emotional problems. There was a negative correlation between the N100 amplitude at the right posterior sites as well a positive association with the N100 amplitude at the left posterior sites although this wasn't seen within the spearman's correlations. What's this all about?? The results also report an association between lower N200 amplitude at left anterior sites and hyperactivity. The posterior N100 and the left anterior N200 explained 60.9% of hyperactivity. Conduct problems and anger problems were both negatively associated with the right posterior N200 amplitude, while cognitive problems were linked to a raised left centro-temporal N100 and a lower N200 at left anterior sites. Right posterior N200 amplitude explained 45.1% of conduct problems, and explained 38.8% of anger problems. The left anterior N200 and the left central N100 accounted for 64.9% of the cognitive problems. The ADHD index was seen to have an association with raised left centro-temporal N100 amplitude and decreased N200 amplitude at the left anterior sites. The ADHD index also showed a strong association with lower N100 amplitude at the right posterior sites. The left central and right posterior N100 plus the left anterior N200 explained 90.9% of the ADHD index scores. The DSM-IV inattention results implied a negative correlation with the left anterior N200 amplitude, while the DSM-IV hyperactive-impulsive subscale was associated with lower N200 amplitude at the right posterior sites. The DSM-IV hyperactive-impulsive subscale was also seen to be

positively associated with right anterior and right posterior P200 amplitudes. The left anterior N200 explained 64.2% of the DSM-IV inattention scores while the right posterior N200 and P200 plus the right anterior P200 explained 72.8% of the DSM-IV IV hyperactive-impulsive scores.

Conclusions: Reduced right centro-temporal N200 amplitude is associated with emotional problems. This association is not dissimilar to the association between reduced N200 and depression. Areas of the brain including the dorsolateral prefrontal cortex and superior temporal gyrus regions, the anterior cingulate and hippocampus are thought to be responsible for this reduced N200. Our results also support previous studies that suggest that the P200 is positively correlated with emotional problems. The results also suggest that reduced N200 in the left anterior sites is associated with disruption to the Frontal Inhibitory System and that Inhibition is an essential psychological function, and refers to the ability to withhold a planned response, to interrupt a response that has been started and to protect an ongoing task from interference and to delay a response and that inattention may reflect an inability to inhibit attention to irrelevant information, with impulsivity being a manifestation of general cognitive disinhibition. Reduced N100 is also associated with hyperactivity and is an age specific effect processing problem.

ABSTRACT 5

NEUROBIOLOGY OF EVENT-RELATED POTENTIALS AND PRAGMATIC/SOCIAL COMMUNICATION DEFICITS IN CONDUCT DISORDER

Background:

Children with conduct disorder display numerous cognitive deficits, and are also at increased of development a number of psychiatric disorders as adults. Higher incidence of pragmatic language impairments have previously been reported. The process in pragmatic language in communication can be viewed as consisting of complex interactions between linguistic, cognitive and sensorimotor processes, which take places both within and between individuals. During social interactions, the right ventromedial prefrontal cortex is thought to integrate the literal meaning of the words

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being said with social and emotional knowledge of the situation through experience (or episodic memory retrieval of verbal and non-verbal information and the social and emotions associated with it).

Method:

Event related potential (ERPs) measures will be used to investigate the neurobiology of conduct disorder and the communication deficits associated.

ERPs were recorded during a visual-continuous performance task (Visual-CPT) in 18 males aged 12 to 18 years with conduct disorder.

Child communication checklist 2nd edition (CCC-2) assessment will be used to measure communication competence to identify pragmatic language impairment (PLI) and specific language impairment (SLI).

Results:

Firstly, a large percentage of children with conduct disorder (CD) were found to have severe impairment in their pragmatic language and autistic-like behaviours as those with autistic spectrum disorders (ASD), scoring comparable GCC and SIDC scores on the CCC-2 assessment.

Secondly, children with CD and pragmatic deficits had reduced P300 peak amplitudes specifically over the right prefrontal cortex. GCC scores were negatively correlated with P300 amplitudes at both Fp1 ($p = 0.001$, $r = -0.79$) and Fp2 ($p = 0.01$, $r = -0.57$) areas. SIDC scores showed a positive trend with P300 amplitudes at Fp2 ($p = 0.02$, $r = 0.53$).

Thirdly, the mean reaction time to non-targets in the visual-CPT were negatively correlated with P300 amplitudes at F7 (inferior left frontal lobe), and the mean false positive response measure showed a positive trend to both the F3 and F4 area.

Conclusion:

The findings suggest that in a large number of children with CD, their conduct problems rather than their language had been the major concern all these years, which could have addressed rather than excluding them in managing their antisocial outcomes. The antisocial behaviour in CD may be an externalization of their frustration in their language and pragmatic difficulties in communication. It also

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suggest that CD and ASDs may exist on a continuum in terms of their symptomatology or may coexist, which have not been considered before.