Selective amygdala hypoactivity to fear in boys with persistent conduct problems after parent training.

Arjun Sethi, PhD, Suzanne O'Brien, MSc, James Blair, PhD, Essi Viding, PhD, Mitul Mehta, PhD, Christine Ecker, PhD, Nigel Blackwood, PhD, Moira Doolan, PhD, Marco Catani, PhD, Stephen Scott, PhD, Declan G.M. Murphy, PhD, Michael C. Craig, PhD

PII: S0006-3223(22)01658-4
DOI: https://doi.org/10.1016/j.biopsych.2022.09.031
Reference: BPS 15012

To appear in: Biological Psychiatry

Received Date: 7 April 2022
Revised Date: 23 August 2022
Accepted Date: 30 September 2022

Please cite this article as: Sethi A., Brien S.O', Blair J., Viding E., Mehta M., Ecker C., Blackwood N., Doolan M., Catani M., Scott S., Murphy D.G.M. & Craig M.C., Selective amygdala hypoactivity to fear in boys with persistent conduct problems after parent training., Biological Psychiatry (2022), doi: https://doi.org/10.1016/j.biopsych.2022.09.031.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc on behalf of Society of Biological Psychiatry.
Title: Selective amygdala hypoactivity to fear in boys with persistent conduct problems after parent training.


*Joint first author
**Joint last author

Arjun Sethi, PhD
Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
arjun.sethi@kcl.ac.uk

Suzanne O' Brien, MSc (Corresponding author)
Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
suzanne.o'_brien@kcl.ac.uk
0044 7479607245

James Blair, PhD
Child and Adolescent Mental Health Centre, Mental Health Services, Capital Region of Denmark, Copenhagen, Denmark
robert.james.blair@regionh.dk

Essi Viding, PhD
Division of Psychology and Language Sciences
University College London
e.viding@ucl.ac.uk

Mitul Mehta, PhD
Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
mitul.mehta@kcl.ac.uk

Christine Ecker, PhD
Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
christine.ecker@kcl.ac.uk

Nigel Blackwood, PhD
Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
nigel.blackwood@kcl.ac.uk

Moira Doolan, PhD
Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
moira.doolan@kcl.ac.uk

Marco Catani, PhD
Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
marco.1.catani@kcl.ac.uk

Stephen Scott**, PhD
Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
stephen.scott@kcl.ac.uk

Declan G.M. Murphy**, PhD
Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
declan.murphy@kcl.ac.uk

Michael C. Craig**, PhD
1 Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK
2 National Female Hormone Clinic Maudsley Hospital, London, UK
3 National Autism Unit, Bethlem Royal Hospital, London, UK
michael.c.craig@kcl.ac.uk

Short title
Amygdala hypoactivity predicts treatment response

Keywords
Antisocial behaviour (ASB); Conduct problems; Amygdala; Hypoactivity; Functional magnetic resonance imaging (fMRI); Parent training
STRUCTURED ABSTRACT

**Background:** Parenting interventions reduce antisocial behaviour (ASB) in some children with conduct problems (CP), but not others. Understanding the neural basis for this disparity is important because persistent ASB is associated with lifelong morbidity and places a huge burden on our health and criminal justice systems. One of the most highly replicated neural correlates of ASB is amygdala hypoactivity to another person’s fear. We aimed to assess whether amygdala hypoactivity to fear in CP children is remediated following reduction in ASB after successful treatment, and/or if it is a marker for persistent ASB.

**Methods:** We conducted a prospective, case-control, study of CP and typically developing (TD) boys. Both groups (aged 5-10 years) completed two MRI sessions (18±5.8 weeks apart) with ASB assessed at each visit. Participants included CP boys following referral to a parenting intervention group, and TD boys recruited from the same schools and geographical regions. Final functional MRI data was available for 36 TD and 57 CP boys. CP boys were divided into those whose ASB improved (n=27) or persisted (n=30) following the intervention. Functional MRI data assessing fear reactivity was then analysed using a longitudinal group (TD/improving CP/persistent CP) x timepoint (pre/post) design.

**Results:** Amygdala hypoactivity to fear was only observed in CP boys with persistent ASB and was absent in those whose ASB improved following intervention.

**Conclusions:** Our findings suggest amygdala hypoactivity to fear is a marker for ASB that is resistant to change following a parenting intervention, and a putative target for future treatments.
INTRODUCTION:

Conduct problems (CP), characterised by a persistent pattern of antisocial behaviour (ASB), are the most common psychiatric disorder in children(1) and represent a significant individual, social and economic burden.(2–4) For example, the annual cost of youth crime in the UK has been estimated to be £8.5-11 billion.(2) However, the costs of severe CP extend beyond childhood, with a 5-10 fold increased risk of subsequent mental illness, substance abuse, criminality, unemployment and early death.(3–5) Youth with early onset CP (i.e. CP emerging between the ages of 5 and 10) are particularly likely to develop persistent ASB.(6,7) Therefore, understanding the mechanisms underpinning ‘early onset’ CP, and whether they are responsive to treatment, is of individual and social importance.

The current so-called ‘gold standard’ treatment for CP involves early intervention with manualised parent-training programmes.(8) These aim to reduce the severity of CP by improving parenting skills using, for example, praise and rewards, and more positive forms of punishment(9) to develop a positive parent-child relationship. Recent evidence, across multiple countries and settings,(10,11) suggest that these treatments can successfully mitigate ASB in children. Further, studies suggest that positive behavioural changes are typically long-lasting.(12) Although these findings are promising, other reports have suggested that up to 50% of children do not respond to current treatments.(13) As with many other psychiatric disorders, it is believed that heterogeneity in the brain mechanisms underpinning CP may partially explain the differential response profile.(14) Therefore, exploration of potential predictive markers of treatment response may increase our understanding of the brain mechanisms underpinning behavioural improvement or persistence.

One of the most widely reported neurocognitive associates of CP is reduced amygdala activity to affective stimuli; particularly others’ distress.(15,16) The clinical importance of this deficit has been supported by recent evidence suggesting a role of amygdala hypoactivity in: i) CP youths with co-occurring callous-unemotional traits(17–19) – a putative risk factor for
persistent ASB(7,20) and poor treatment response,(21) and ii) adult ASB(22) and psychopathy.(23) Consequently, it has been proposed that reduced amygdala activity is associated with lack of guilt, lack of empathy and increased instrumental aggression.(24,25) Amygdala hypoactivity is therefore a compelling candidate marker of treatment resistant ASB in children. However, to date there has been an absence of longitudinal treatment data assessing this.

Therefore, in the current study, we compared changes in brain and behaviour in a group of CP children, (pre and post the ‘gold-standard’ treatment for CP) in comparison to a typically developing (TD) control group (at two equivalent time points). Boys were assessed before and after the intervention, to characterise patterns of amygdala reactivity and persistence of ASB. CP boys were divided into those whose ASB persisted following the intervention, and those whose ASB improved (see methods for details). These groups were then compared in a longitudinal design (3 groups x 2 timepoints).

We tested two competing hypotheses:

(i) Amygdala hypoactivity to fear would be observed in CP boys, and ‘normalise’ (i.e. in the direction of TD controls) in CP children whose ASB improves, but not in those whose ASB persists (i.e. a group x time effect driven by the ‘improving group’).

(ii) Amygdala hypoactivity to fear would be selectively observed in CP children with persistent ASB (i.e. not in those whose ASB improves) and would not change during the course of the intervention (i.e. a group effect driven by the ‘persistent’ group).

Finally, as the presence of CU traits has been shown to be a reported risk factor for persistent ASB,(20,26) and poor treatment response,(21) we examined the influence of callous-unemotional traits on amygdala hypoactivity and treatment responsivity.
METHODS

Sample
The sample included 83 boys with CP, and 47 TD boys, aged 5-10 years old. CP boys were recruited from two parenting programmes (i.e. Incredible Years (IY) and Triple P). Each required parents to attend facilitated, weekly group sessions, over 10-12 weeks, and to complete 'homework' between meetings. CP was assessed at the beginning (i.e. <3 weeks after enrolment into the parenting programme), and after completion of the programme (18.5 ± 7.0 weeks from baseline assessment). Families were referred to parenting groups from Child and Adolescent Mental Health Services (CAMHS), Local Authorities, Charities, & Social Enterprises and attended weekly group training sessions. Boys were included if they met a pre-defined threshold of ≥ 3 on the CP scale of the Strengths and Difficulties Questionnaire (SDQ)(27). Typically developing (TD) boys were recruited from the same schools and geographical areas as CP boys and scanned at two equally spaced timepoints (17.6 ± 4.3 weeks). Inclusion criteria to the TD group required a score of <3 on the SDQ. TD boys and their families did not participate in the parenting programmes. For both groups boys with a clinical diagnosis of an autism spectrum disorder, neurological abnormality, or MRI contraindication were excluded from the study.

Behavioural and clinical assessments
At each timepoint, the Parent Account of Childhood Symptoms (PACS) interview was used to assess CP symptoms as the primary outcome measure. This semi-structured clinical interview uses specific investigator-based criteria to assess both the frequency and severity of ASB (e.g. aggression, destruction of property, disobedience etc.) and is highly predictive of later psychosocial outcomes.(28) The PACS interview was administered by a member of the research team who was trained to use the instrument by a fully qualified clinician. To discern a clinically meaningful level of symptom improvement, a minimally important clinical difference (MICD) approach was employed.(29,30) Meta-analysis of parent training indicates a mean
change in symptoms of approximately 0.6 standard deviations (SD), associated with a high user reported satisfaction (~92%). Therefore, to ascertain an MICD, we used a cut-off of 2/3 of this (0.4 SD) to reflect successful treatment. In our study, SD was measured as a function of baseline CP PACS scores across the entire clinical cohort (i.e. CP children whose CP scores improved by 0.4 SD or higher following the intervention were classed as ‘improving’ and those whose CP scores did not improve by 0.4 SD were classed as ‘persistent’).

At both timepoints, clinical symptoms were additionally assessed using the parent forms of the SDQ,(27) Inventory of Callous-Unemotional Traits (ICU),(31) and the Conners 3 Short form ADHD assessment report.(32) Parents also completed the Alabama Parenting Questionnaire(33) at both timepoints. Boys completed the Wechsler Abbreviated Scale of Intelligence (WASI)(34) and parents completed sociodemographic measures at baseline only. Maternal education was used as a measure of Socioeconomic Status (SES). Children’s ethnicity was also reported by parents.

**MRI acquisition**

All participants underwent MRI scanning at each timepoint at the Centre for Neuroimaging Sciences, King’s College London, providing T1-weighted, T2-weighted, diffusion MRI, and functional MRI data with a total scan time of one hour. Prior to scanning, children were introduced to a mock scanning environment, where they were familiarized with the sounds of the MRI scanner, practiced entering the scanner and lying still, and were familiarized with the emotion processing task detailed below. Several studies have suggested the importance of these procedures for enhancing data quality in pediatric cohorts.(35,36)

Task based functional data was acquired using 218 volumes of T2* weight echo-planar imaging (EPI) data with 41 near-contiguous slices (3mm³ voxels, Matrix 64X64, slice gap =
3.3mm, FOV = 240mm), TE = 30ms, TR = 2000ms and Flip angle = 75°. In addition, T1-weighted MPRAGE structural imaging data acquired on a 3T GE Signa HDx with a 12-channel head coil located at the Centre for Neuroimaging Sciences at King’s College London, with a resolution of 1x1x1.2mm, matrix size of 256x256x196, flip angle of 11°, TE of 3016ms, TR of 7312ms, FOV of 270mm, and inversion time of 400ms.

**fMRI: Emotion processing task**

The fMRI paradigm employed was an implicit emotion processing task, which was modelled as an event-related design. The task consisted of 140 trials for a duration of 7 minutes and 36 seconds, where they were presented with a male or female face with either a fearful (60 trials), happy (60 trials) or neutral (20 trials) expression (37) for 1.5s in a randomised order. Faces expressing emotion were additionally morphed (50%, 100% or 150%) to display a range of intensities. During each trial, participants were asked to indicate whether the face belonged to a male or female individual by pressing a button with their index or middle finger when the image appeared on the screen. Each trial was followed by a variable intertrial interval of between 1 and 2s (mean 1.5s).

**MRI processing**

FMRI data were preprocessed using *fMRIPrep* 1.5.1rc1 (RRID:SCR_016216), which is based on *Nipype* 1.3.0-rc1 (RRID:SCR_002502). Details of the pre-processing pipeline can be found within eMethods 1 and eMethods 2 of the Supplementary Materials.

**fMRI analysis**

Regressors for each condition of interest (Fear, Happy, Neutral) were entered into a single subject General Linear Model (GLM; SPM12). A parametric modulator encoding the intensity of the emotion was included in the conditions containing emotional valence (i.e. Fear and Happy). In addition, following Pruim et al. (41) mean signal for CSF and WM were included as
nuisance variables. Scans with framewise displacement (FD) exceeding 1mm were also deweighted in the model, (42) with the scans themselves interpolated from the surrounding volumes to mitigate the effects of residual motion artifacts on the data.

After this the regressors of interest for each analysis (parametric modulation of fear by intensity and parametric modulation of happy by intensity [hereafter, simply ‘Fear’ and ‘Happy’ respectively]) were entered into separate Linear Mixed Models (LMM) using 3dLME (AFNI) (43) using a 3 x 2 design modelling ‘group’ (improving, persistent, TD) and ‘time’ (pre-intervention, post-intervention) and a random subjects factor. Of particular interest, significant Time-by-Group effects were examined to assess for any changes in brain activity over time that differed according to clinical response profile i.e. improving, persistent, TD controls (Hypothesis 1). Secondly, significant group effects were examined to assess for any overall differences in amygdala activity between the groups (Hypothesis 2). Age, IQ, SES, child ethnicity, and ADHD symptoms were included as covariates.

In addition, to ensure that any remaining effects of motion did not influence the data, mean FD at each timepoint was included as a within-subjects covariate. (44) Following exclusions, no differences in the number of volumes censored or mean FD were observed between groups (Volumes: $F_{(2,77.5)}=1.1, \ p=0.338$; FD: $F_{(2,93.0)}=0.8, \ p=0.462$), timepoints (Volumes: $F_{(1,63.7)}=0.3; \ p=0.582$; FD: $F_{(1,65.6)}=1.8, \ p=0.189$), or their interaction (Volumes: $F_{(2,63.4)}=0.6, \ p=0.544$; FD: $F_{(2,65.4)}=0.4, \ p=0.651$). Resulting statistical maps were initially thresholded at an uncorrected threshold of $p_{unc} < 0.001$. Simulations using 3dClustSim (NN = 2, 2-sided clustering) assuming a mixed autocorrelation function (45) suggested a clustering threshold of 167 voxels for whole brain analysis. Due to the hypothesised importance of the amygdala, a small volume correction (SVC) approach was used here for our region of interest, with simulations recommending a cluster threshold of 2.1 voxels within this region. Finally, behavioural parameters of the task (% accuracy for gender discrimination and reaction time) were
analysed using identical LMMs to the fMRI data, excepting exclusions and covariates for motion.

**RESULTS**

Demographic and clinical data

Groups did not differ significantly in age, and time to follow-up (Table 1). Also, no significant between group differences were observed in ethnicity (Fisher’s Exact Test \( p=0.441 \)). Individuals whose ASB improved during the intervention (Improved ASB) and those whose ASB persisted (Persistent ASB) differed from controls on IQ and SES (Table 1); but there were no significant differences between ‘improvers’ and ‘persisters’.

The CP group overall showed a significant response to the intervention, showing reduced (Pre: 1.60±0.42, Post: 1.34±0.46; \( F_{(1,55.3)}=17.9, p<0.001 \)) ASB scores. A reduction in ADHD (Pre: 53.7±15.7, Post: 49.3±18.3; \( F_{(1,51.9)}=5.4, p=0.024 \)) and CU scores (Pre: 39.0±12.0, Post: 35.7±12.4; \( F_{(1,47.1)}=6.1, p=0.017 \)) was also observed, but no difference in internalising symptoms between the two timepoints was detected (Pre: 7.9±3.9, Post: 7.5±4.6; \( F_{(1,51.0)}=1.1, p=0.307 \)).

Next, we examined any differences in symptoms across timepoints (i.e. ASB, CU traits, ADHD and internalising symptoms) or symptom change between the improved and persistent CP groups. Apart from the differences in ASB observed following treatment (GroupxTime: \( F_{(1,47.7)}=63.1, p<0.001 \)), symptom levels (i.e. no Group effect. ASB: \( F_{(1,64.7)}=0.2, p=0.656 \), ADHD: \( F_{(1,66.3)}<0.1, p=0.994 \), ICU: \( F_{(1,62.9)}=0.3, p=0.596 \), Internalising: \( F_{(1,65.1)}<0.1, p=0.924 \)) and changes in symptoms (i.e. no GroupxTime interaction. ADHD: \( F_{(1,51.3)}=0.1, p=0.779 \), ICU: \( F_{(1,49.1)}=1.0, p=0.319 \), Internalising: \( F_{(1,50.2)}<0.1, p=0.945 \)) did not differ according to CP clinical
response group. Means and standard deviations for all symptoms pre and post treatment are shown in Table 2.

fMRI

Our first prediction, that improvement in ASB would be related to amygdala activity, was not supported and the group by time interaction was absent.

However, our second prediction, that amygdala hypo-activity to fear would be associated with persistence of ASB following treatment was supported. We found a significant overall group effect across timepoints (cluster size\(k\) = 36, MNI coordinates = -32, 2, -22; \(F=11.06\); Figure 1). Post hoc tests revealed that this was driven by reduced right amygdala responsivity to fear in the persistent ASB group when compared to the control group (cluster size\(k\) = 48, MNI coordinates = -32, 2, -22; \(Z=4.37\); Figure 1).

When we additionally examined the effects of CU traits within the model, we found no main effect of CU or interaction with group, time, or group*time for either condition. Further, no significant effects were observed in the happy condition.

For completeness, we also performed whole brain analyses for the above contrasts. Here, we observed a significant group by time interaction to fear in medial sensory motor regions (\(k = 214, MNI = 6, 18, 60; F=13.39\); Supplementary eFigure 1). This was driven by a reduction over time in the improving ASB group compared to the others. Supplementary results can be found in eResults 1 and 2, and eFigure 2 in the Supplement.

DISCUSSION

In this study we compared changes in brain and behaviour in CP boys, pre and post parenting intervention, and compared these to TD boys assessed over equivalent timepoints. Consistent
with prior studies in CP children; i) parenting intervention successfully reduced ASB, CU traits and ADHD symptoms,(12,46) and ii) a subgroup of CP boys did not improve following the intervention.(13)

In addition, we found amygdala hypoactivity to fear in CP boys with ASB that persisted following treatment, but not in CP boys whose ASB improved. This finding provides the first direct evidence for a widely held view(17,18,47) that amygdala hypoactivity to fear underpins particularly stable forms of ASB, and suggests that more malleable forms of childhood ASB are underpinned by distinct neural mechanisms. We believe that these findings are important to our understanding of the neural correlates underlying treatment response in CP, but they also raise several significant questions that need to be addressed by future studies.

Firstly, contrary to one of our a priori hypotheses, we found no evidence of reduced amygdala hypoactivity to fear in CP boys whose ASB improved following intervention. Although we observed an association between improvement in ASB and sensorimotor activity, it would be highly tenuous to offer any interpretation of a relationship based on a task designed to probe affective processing. It may be that improvement in ASB is underpinned by different mechanisms not probed by the current task. Specifically, previous work has highlighted the importance of reinforcement learning in CP,(25,48,49) and early interventions for CP implicitly target the restructuring of reward and punishment schedules.(50) We anticipate that emerging techniques employing machine learning(51) will be better able to fractionate out these different neural subtypes and determine their value in predicting treatment response.

Secondly, unlike some previous studies, we did not find an association between severity of CU traits with either treatment response,(7,8,12) or amygdala reactivity to fear.(17–19,21) This may have been due to several factors, including the younger age range of our cohort compared to most prior neuroimaging studies(17–19) (although similar deficits have been observed in behavioural studies of younger age groups(52)). Another, more likely, possibility is that CU traits can arise from more than one neurocognitive profile - consistent with recent
observations in different ‘subtypes’ of psychopathy.(53) Finally, it is possible that the phenotype of CU traits indexed by the ICU differs somewhat to that indexed by other assessment tools used to measure CU traits. For instance, previous research has used a range of assessments to classify participants into those with high versus low CU traits (i.e. Youth Psychopathic Traits Inventory (YPI)(54,55) Antisocial Process Screening Device (APSD),(56,57) Psychopathy Checklist: Youth Version (PCL:YV)(48,58) in addition to the ICU).(17)

This, in combination with our finding of neurocognitive dissociation between persistent and improving ASB, supports growing evidence that there is substantial neurocognitive heterogeneity within this group that requires further investigation. These findings may also have significant utility for future research into novel treatments. For instance, amygdala hypoactivity to fear could be used as a biomarker to fractionate out a CP subgroup that are targeted with a treatment that upregulates amygdala activity to fear.

Although the current study has several strengths, such as being the first longitudinal study to examine the effect of brain and behavioural change in CP, several limitations should be addressed.

Firstly, the sample in this study consisted of male participants only. In recent years several studies have identified differences in brain structure and function between male and female youth with CP,(59–61) therefore future longitudinal studies including both genders are warranted, to investigate if female children with treatment-resistant CP present a similar neurobiological profile to their male counterparts.

Secondly, it should be acknowledged that although task-based fMRI studies are a major focus for biomarker development, recent reviews have highlighted the limited individual test-retest reliability observed in task-fMRI.(62,63) However, even though the ability to make individual-level predictions based on fMRI data is limited, there is still evidence to suggest that task-
based fMRI is a well-validated tool for making group-level inferences (64) (e.g. with regards to phenotypes associated with clinical response (improving, persistent)). Future work attempting to predict treatment response on the individual level could use alternative modalities that are reportedly more reliable predictors of disease biomarkers, such as multi-modal MRI (65).

In conclusion, we have found an association between amygdala hypoactivity to fear in CP boys with more persistent ASB following parenting intervention. Further studies, using a wider range of imaging modalities (67,68) are now needed to explore other neural correlates that predict behavioural improvement or persistence. It is hoped that this will enable us to better understand the CP phenotype and, ultimately, to develop and target more effective treatments.
Acknowledgment

We would like to thank the Medical Research Council (MRC) (MR/M013588) for funding the study. We would also like to acknowledge and thank Ms Raj Seraya Bhatoa, Ms Iruni Wanigasekara and Ms Laura Lennuyeux-Comnene for their assistance with the study.

Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.
REFERENCES:

2. The youth justice system in England and Wales: Reducing offending by young people (2010):


Table 1. Key Demographic Data
Table 2. Key behavioural data at baseline and follow-up.
FIGURES

**Figure1.** Figure on the left represents a significant group effect (across the 3 groups) on fear processing in the right amygdala. The figure on the right represents *post hoc* tests between the Controls vs. Improving, Controls vs. Persistent and Improving vs. Persistent. Our findings show that children with persistent ASB have significantly reduced amygdala activity in response to modulated fear processing (across both timepoints), in comparison to the typically developing control group. There was no evidence of amygdala hypoactivity to fear in children whose ASB improved over time. *Significant at p=0.001. Figures reflects the raw means and standard deviations.*
<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Improved</th>
<th>Persistent</th>
<th>Omnibus Test</th>
<th>Ctrl Vs Imp p</th>
<th>Ctrl Vs Pers p</th>
<th>Imp Vs Pers p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>27</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>8.5 (1.5)</td>
<td>8.7 (1.4)</td>
<td>9.1 (1.2)</td>
<td>F(2,90)=1.2, p=0.313</td>
<td>0.129</td>
<td>0.509</td>
<td>0.395</td>
</tr>
<tr>
<td>Followup time (Weeks)</td>
<td>17.3 (4.4)</td>
<td>19.8 (7.3)</td>
<td>17.5 (5.2)</td>
<td>F(2,86)=1.7, p=0.180</td>
<td>0.940</td>
<td>0.091</td>
<td>0.141</td>
</tr>
<tr>
<td>ADHD (Conners)</td>
<td>17.0 (10.7)</td>
<td>53.7 (12.6)</td>
<td>53.7 (18.8)</td>
<td>F(2,90)=75.2, p=0.001*</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.997</td>
</tr>
<tr>
<td>IQ</td>
<td>109.2 (15.1)</td>
<td>101.6 (13.8)</td>
<td>99.6 (12.1)</td>
<td>F(2,90)=4.3, p=0.016*</td>
<td>0.008</td>
<td>0.030</td>
<td>0.586</td>
</tr>
<tr>
<td>SES</td>
<td>5.7 (2.2)</td>
<td>3.8 (2.5)</td>
<td>3.6 (2.3)</td>
<td>F(2,90)=8.0, p=0.001*</td>
<td>0.001</td>
<td>0.001</td>
<td>0.778</td>
</tr>
</tbody>
</table>

Ctrl=controls; Imp=Improved; Pers=Persisters; ADHD (Conners)= attention deficit hyperactivity disorder (Conners' ADHD Rating Scales); IQ=intelligent quotient; CU=callous-unemotional; PACS=parental accounts of children's symptoms; SDQ=Strength and difficulties questionnaire;
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Improved</th>
<th>Persistent</th>
<th>Omnibus Test: Group</th>
<th>Omnibus Test: Time</th>
<th>Omnibus Test: Group*Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP symptoms T1</td>
<td>0.63 (0.34)</td>
<td>1.74 (0.37)</td>
<td>1.44 (0.42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PACS)</td>
<td></td>
<td></td>
<td></td>
<td>F(1,169)=253.71, p&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP symptoms T2</td>
<td>0.56 (0.36)</td>
<td>1.20 (0.45)</td>
<td>1.59 (0.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PACS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP symptoms T1</td>
<td>1.00 (1.28)</td>
<td>5.50 (1.95)</td>
<td>6.07 (2.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SDQ)</td>
<td></td>
<td></td>
<td></td>
<td>F(1,159.72)=1.41, p&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP symptoms T2</td>
<td>0.86 (0.86)</td>
<td>3.93 (2.50)</td>
<td>5.48 (2.58)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SDQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CU traits T1</td>
<td>14.94 (6.82)</td>
<td>34.82 (9.24)</td>
<td>35.28 (14.19)</td>
<td>F(1,54.08)=0.08, p=0.775</td>
<td>16.56, p&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1,159.15)=2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CU traits T2</td>
<td>16.13 (7.85)</td>
<td>31.69 (12.45)</td>
<td>33.09 (10.30)</td>
<td>F(1,159.15)=0.66, p=0.105</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Pos P) T1</td>
<td>13.55 (1.90)</td>
<td>13.02 (2.25)</td>
<td>13.04 (2.09)</td>
<td>F(1,53.38)=0.40, p=0.530</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1,159.45)=16.39, p&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Pos P) T2</td>
<td>13.77 (1.77)</td>
<td>13.93 (1.53)</td>
<td>13.68 (1.79)</td>
<td>F(1,159.45)=0.937, p=0.334</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Incon Dis) T1</td>
<td>7.38 (2.29)</td>
<td>8.68 (2.49)</td>
<td>8.56 (1.85)</td>
<td>F(1,52.70)=0.40, p=0.863</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1,161.25)=0.94, p&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Incon Dis) T2</td>
<td>7.61 (2.62)</td>
<td>7.34 (2.25)</td>
<td>7.40 (1.73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Poor Sup) T1</td>
<td>3.41 (0.88)</td>
<td>4.18 (1.81)</td>
<td>4.27 (1.99)</td>
<td>F(1,52.15)=1.79, p=0.186</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1,144.39)=2.75, p=0.099</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Poor Sup) T2</td>
<td>3.37 (1.03)</td>
<td>3.80 (1.38)</td>
<td>4.43 (2.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Involv) T1</td>
<td>12.64 (1.63)</td>
<td>12.51 (1.63)</td>
<td>12.40 (1.63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Involv) T2</td>
<td>12.64 (1.63)</td>
<td>12.44 (1.74)</td>
<td>12.30 (1.73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Corp Pun) T1</td>
<td>3.97 (1.26)</td>
<td>4.17 (1.51)</td>
<td>4.42 (1.15)</td>
<td>F(1,52.31)=1.28, p=0.262</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1,157.89)=0.97, p&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APQ (Corp Pun) T2</td>
<td>3.88 (1.32)</td>
<td>3.41 (0.94)</td>
<td>4.00 (1.61)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CP* = conduct problems; *PACS* = parental accounts of children’s symptoms; *SDQ* = Strength and difficulties questionnaire; *CU* = callous-unemotional; *APQ* = Alabama Parenting Questionnaire; *Pos P* = Positive Parenting; *Incon Dis* = Inconsistent Discipline; *Poor Sup* = Poor supervision; *Involv* = Involvement; *Corp Pun* = Corporal Punishment.

1 The omnibus tests were run on the improving versus persisting groups only.