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Selective Amygdala Hypoactivity to Fear in Boys With Persistent Conduct Problems After Parent Training

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ABSTRACT

BACKGROUND: Parenting interventions reduce antisocial behavior (ASB) in some children with conduct problems (CPs), 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 children with CPs 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 boys with CPs and typically developing (TD) boys. Both groups (ages 5–10 years) completed 2 magnetic resonance imaging sessions (18 $\pm$ 5.8 weeks apart) with ASB assessed at each visit. Participants included boys with CPs following referral to a parenting intervention group and TD boys recruited from the same schools and geographical regions. Final functional magnetic resonance imaging data were available for 36 TD boys and 57 boys with CPs. Boys with CPs were divided into those whose ASB improved (n = 27) or persisted (n = 30) following the intervention. Functional magnetic resonance imaging data assessing fear reactivity were then analyzed using a longitudinal group (TD/improving CPs/persistent CPs) $\times$ time point (pre/post) design.

RESULTS: Amygdala hypoactivity to fear was observed only in boys with CPs who had persistent ASB and was absent in those whose ASB improved following intervention.

CONCLUSIONS: Our findings suggest that 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.

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Conduct problems (CPs), characterized by a persistent pattern of antisocial behavior (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 United Kingdom has been estimated to be £8.5 to £11 billion (2). However, the costs of severe CPs extend beyond childhood, with a 5- to 10-fold increased risk of subsequent mental illness, substance abuse, criminality, unemployment, and early death (3–5). Youths with early-onset CPs (i.e., CPs emerging between 5 and 10 years of age) are particularly likely to develop persistent ASB (6,7). Therefore, understanding the mechanisms underpinning early-onset CPs, and whether they are responsive to treatment, is of individual and social importance.

The current so-called gold standard treatment for CPs involves early intervention with manualized parent training programs (8). These aim to reduce the severity of CPs 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), suggests that these treatments can successfully mitigate ASB in children. Furthermore, studies suggest that positive behavioral 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 CPs 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 behavioral improvement or persistence.

One of the most widely reported neurocognitive associates of CPs 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 1) youths with CPs who have co-occurring callous-unemotional (CU) traits (17–19)—a

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putative risk factor for persistent ASB (7,20) and poor treatment response (21) and 2) 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 this study, we compared changes in brain and behavior in a group of children with CPs (before and after the gold standard treatment for CPs) in comparison with a typically developing (TD) control group (at 2 equivalent time points). Boys were assessed before and after the intervention to characterize patterns of amygdala reactivity and persistence of ASB. Boys with CPs were divided into those whose ASB persisted following the intervention and those whose ASB improved (see Methods and Materials for details). These groups were then compared in a longitudinal design (3 groups $\times$ 2 time points).

We tested 2 competing hypotheses: 1) Amygdala hypoactivity to fear would be observed in boys with CPs and would normalize (i.e., in the direction of TD control group) in children with CPs whose ASB improves, but not in those whose ASB persists (i.e., a group $\times$ time effect driven by the improving group); and 2) Amygdala hypoactivity to fear would be selectively observed in children with CPs who exhibit 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 CU traits on amygdala hypoactivity and treatment responsivity.

METHODS AND MATERIALS

Sample

The sample included 83 boys with CPs and 47 TD boys between 5 and 10 years of age. Boys with CPs were recruited from 2 parenting programs (i.e., Incredible Years and Triple P). Each required parents to attend facilitated, weekly group sessions, over 10 to 12 weeks, and to complete homework between meetings. CPs were assessed at the beginning (i.e., $<$3 weeks after enrollment into the parenting program) and after completion of the program (18.5 $\pm$ 7.0 weeks from baseline assessment). Families were referred to parenting groups from Child and Adolescent Mental Health Services, local authorities, charities, and social enterprises and attended weekly group training sessions. Boys were included if they met a predefined threshold of $\geq$3 on the CP scale of the Strengths and Difficulties Questionnaire (27). TD boys were recruited from the same schools and geographical areas as boys with CPs and scanned at 2 equally spaced time points (17.6 $\pm$ 4.3 weeks). Inclusion criteria to the TD group required a score of $<$3 on the Strengths and Difficulties Questionnaire. TD boys and their families did not participate in the parenting programs. For both groups, boys with a clinical diagnosis of an autism spectrum disorder, neurological abnormality, or magnetic resonance imaging (MRI) contraindication were excluded from the study.

Behavioral and Clinical Assessments

At each time point, the Parental Account of Childhood Symptoms interview was used to assess CP symptoms as the primary outcome measure. This semistructured clinical interview uses specific investigator-based criteria to assess both the frequency and severity of ASB (e.g., aggression, destruction of property, disobedience) and is highly predictive of later psychosocial outcomes (28). The Parental Account of Childhood Symptoms 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 approach was used (29,30). Meta-analysis of parent training indicates a mean change in symptoms of approximately 0.6 standard deviations (SDs), associated with a high user-reported satisfaction ($\sim$92%) (8). Therefore, to ascertain a minimally important clinical difference, we used a cutoff of two-thirds of this (0.4 SD) to reflect successful treatment. In our study, SD was measured as a function of baseline CP Parental Account of Childhood Symptoms scores across the entire clinical cohort (i.e., children with CPs 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 time points, clinical symptoms were additionally assessed using the parent forms of the Strengths and Difficulties Questionnaire (27), Inventory of Callous-Unemotional Traits (ICU) (31), and the Conners 3 Short Form attention-deficit/hyperactivity disorder (ADHD) assessment report (32). Parents also completed the Alabama Parenting Questionnaire (33) at both time points. Boys completed the Wechsler Abbreviated Scale of Intelligence (34), and parents completed sociodemographic measures at baseline only. Maternal education was used as a measure of socioeconomic status. Children's ethnicity was also reported by parents.

MRI Acquisition

All participants underwent MRI scanning at each time point at the Centre for Neuroimaging Sciences, King's College London, providing T1-weighted, T2-weighted, diffusion MRI, and functional MRI (fMRI) data with a total scan time of 1 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 were acquired using 218 volumes of T2*-weighted echo-planar imaging data with 41 near-contiguous slices (3 mm^3 voxels, matrix 64 $\times$ 64, slice gap = 3.3 mm, field of view = 240 mm), echo time = 30 ms, repetition time = 2000 ms, and flip angle = 75°. In addition, T1-weighted magnetization-prepared rapid acquisition gradient-echo structural imaging data were acquired on a 3T GE Signa HDx (GE Healthcare) with a 12-channel head coil located at the

Centre for Neuroimaging Sciences at King's College London, with a resolution of 1 × 1 × 1.2 mm, matrix size of 256 × 256 × 196, flip angle of 11°, echo time of 3016 ms, repetition time of 7312 ms, field of view of 270 mm, and inversion time of 400 ms.

fMRI: Emotion-Processing Task

The fMRI paradigm used was an implicit emotion-processing task, which was modeled 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 1.5 seconds in a randomized 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 varying between 1 and 2 seconds (mean 1.5 seconds).

MRI Processing

fMRI data were preprocessed using fMRIPrep 1.5.1rc1 (38,39) (RRID:SCR_016216), which is based on Nipype 1.3.0-rc1 (39,40) (RRID:SCR_002502). Details of the preprocessing pipeline can be found in the Supplemental Methods.

fMRI Analysis

Regressors for each condition of interest (fear, happy, neutral) were entered into a single-subject general linear model (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 cerebrospinal fluid and white matter were included as nuisance variables. Scans with framewise displacement (FD) exceeding 1 mm 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 using 3dLME (AFNI) (43) using a 3 × 2 design modeling group (improving, persistent, TD) and time (preintervention, postintervention) and a random subjects factor. Of particular interest, significant time × 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, and TD control groups (hypothesis 1). Next, significant group effects were examined to assess for any overall differences in amygdala activity between the groups (hypothesis 2). Age, IQ, socioeconomic status, 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 time point 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: $F_{2,77.5} = 1.1$, $p = .338$; FD: $F_{2,93.0} = 0.8$, $p = .462$), time points (volumes: $F_{1,63.7} = 0.3$; $p = .582$, FD: $F_{1,65.6} = 1.8$, $p = .189$), or their interaction (volumes: $F_{2,63.4} = 0.6$, $p = .544$; FD: $F_{2,65.4} = 0.4$, $p = .651$). Resulting statistical maps were initially thresholded at an uncorrected threshold of $p_{unc} < .001$. 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 hypothesized importance of the amygdala, a small-volume correction approach was used here for our region of interest, with simulations recommending a cluster threshold of 2.1 voxels within this region. Finally, behavioral parameters of the task (% accuracy for gender discrimination and reaction time) were analyzed using identical linear mixed models to the fMRI data, excepting exclusions and covariates for motion.

RESULTS

Demographic and Clinical Data

Groups did not differ significantly in age or time to follow-up (Table 1). In addition, no significant between-group differences were observed in ethnicity (Fisher's exact test $p = .441$). Individuals whose ASB improved during the intervention (improved ASB) and those whose ASB persisted (persistent ASB) differed from control subjects in IQ and socioeconomic status (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; $F_{1,55.3} = 17.9$, $p < .001$) ASB scores. A reduction in ADHD (pre: 53.7 ± 15.7, post: 49.3 ± 18.3; $F_{1,51.9} = 5.4$, $p = .024$) and CU (pre: 39.0 ± 12.0, post: 35.7 ± 12.4; $F_{1,47.1} = 6.1$, $p = .017$) scores was also observed, but no difference in internalizing symptoms between the 2 time points was detected (pre: 7.9 ± 3.9, post: 7.5 ± 4.6; $F_{1,51.0} = 1.1$, $p = .307$).

Next, we examined any differences in symptoms across time points (i.e., ASB, CU traits, ADHD, and internalizing symptoms) or symptom changes between the improved and persistent CP groups. Apart from the differences in ASB observed following treatment (group × time: $F_{1,47.7} = 63.1$, $p < .001$), symptom levels (i.e., no group effect; ASB: $F_{1,64.7} = 0.2$, $p = .656$, ADHD: $F_{1,66.3} < 0.1$, $p = .994$, ICU: $F_{1,62.9} = 0.3$, $p = .596$, internalizing: $F_{1,65.1} < 0.1$, $p = .924$) and changes in symptoms (i.e., no group × time interaction; ADHD: $F_{1,51.3} = 0.1$, $p = .779$, ICU: $F_{1,49.1} = 1.0$, $p = .319$, internalizing: $F_{1,50.2} < 0.1$, $p = .945$) did not differ according to the CP clinical response group. Means and SDs for all symptoms before and after treatment are shown in Table 2.

Functional MRI

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

However, our second prediction that amygdala hypoactivity to fear would be associated with persistence of ASB following treatment was supported. We found a significant overall group effect across time points (cluster size [*k*] = 36, Montreal Neurologic Institute (MNI) coordinates = −32, 2, −22; $F = 11.06$) (Figure 1). Post hoc tests revealed that this was driven

Table 1. Key Demographic Data

Measure	Control, n = 36, Mean (SD)	Improved, n = 27, Mean (SD)	Persistent, n = 30, Mean (SD)	Omnibus Test	Control vs. Improved, p	Control vs. Persistent, p	Improved vs. Persistent, p
Age, Years	8.5 (1.5)	8.7 (1.4)	9.1 (1.2)	$F_{2,90}$ = 1.2, p = .313	.129	.509	.395
Follow-up Time, Weeks	17.3 (4.4)	19.8 (7.3)	17.5 (5.2)	$F_{2,86}$ = 1.7, p = .180	.940	.091	.141
ADHD[a]	17.0 (10.7)	53.7 (12.6)	53.7 (18.8)	$F_{2,90}$ = 75.2, p = .001[b]	<.001	<.001	.997
IQ	109.2 (15.1)	101.6 (13.8)	99.6 (12.1)	$F_{2,90}$ = 4.3, p = .016[b]	.008	.030	.586
SES	5.7 (2.2)	3.8 (2.5)	3.6 (2.3)	$F_{2,90}$ = 8.0, p = .001[b]	.001	.001	.778

ADHD, attention-deficit/hyperactivity disorder; SES, socioeconomic status.
[a]Conners ADHD Rating Scales (32).
[b]Significant at $p < .005$.

by reduced right amygdala responsivity to fear in the persistent ASB group when compared with 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. Furthermore, 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 × time interaction to fear in medial sensory motor regions (k = 214, MNI coordinates = 6, 18, 60; F = 13.39) (Figure S1). This was driven by a reduction over time in the improving ASB group compared with the others. Supplemental results can be found in the Supplement and Figure S2.

DISCUSSION

In this study, we compared changes in brain and behavior in boys with CPs, before and after parenting intervention, and compared these with TD boys assessed over equivalent time points. Consistent with previous studies in children with CPs, parenting intervention successfully reduced ASB, CU traits, and ADHD symptoms (12,46), and a subgroup of boys with CPs did not improve following the intervention (13).

In addition, we found amygdala hypoactivity to fear in boys with CPs who exhibited ASB that persisted following treatment, but not in boys with CPs 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 CPs, but they also raise several significant questions that need to be addressed by future studies.

First, contrary to one of our a priori hypotheses, we found no evidence of reduced amygdala hypoactivity to fear in boys with CPs whose ASB improved following intervention. Although

Table 2. Key Behavioral Data at Baseline (T1) and Follow-up (T2)

Outcome Measure	Control, Mean (SD)	Improved, Mean (SD)	Persistent, Mean (SD)	Omnibus Test[a]: Group	Omnibus Test[a]: Time	Omnibus Test[a]: Group × Time
CP Symptoms T1 (PACS)	0.63 (0.34)	1.74 (0.37)	1.44 (0.42)	–	–	$F_{1,169}$ = 253.71, p < .001[b]
CP Symptoms T2 (PACS)	0.56 (0.36)	1.20 (0.45)	1.59 (0.44)			
CP Symptoms T1 (SDQ)	1.00 (1.28)	5.50 (1.95)	6.07 (2.33)	–	–	$F_{1,159.72}$ = 14.11, p < .001[b]
CP Symptoms T2 (SDQ)	0.86 (0.86)	3.93 (2.50)	5.48 (2.58)			
CU Traits T1	14.94 (6.82)	34.82 (9.24)	35.28 (14.19)	$F_{1,54.08}$ = 0.08, p = .775	$F_{1,159.15}$ = 16.56, p < .001[b]	$F_{1,159.15}$ = 2.66, p = .105
CU Traits T2	16.13 (7.85)	31.69 (12.45)	33.09 (10.30)			
APQ (Pos P) T1	13.55 (1.90)	13.02 (2.25)	13.04 (2.09)	$F_{1,53.38}$ = 0.40, p = .530	$F_{1,159.45}$ = 16.39, p < .001[b]	$F_{1,159.45}$ = 0.937, p = .334
APQ (Pos P) T2	13.77 (1.77)	13.93 (1.53)	13.68 (1.79)			
APQ (Incon Dis) T1	7.38 (2.29)	8.68 (2.49)	8.56 (1.85)	$F_{1,52.70}$ = 0.40, p = .863	$F_{1,161.25}$ = 29.94, p < .001[b]	$F_{1,161.25}$ = 0.018, p = .894
APQ (Incon Dis) T2	7.61 (2.62)	7.34 (2.25)	7.40 (1.73)			
APQ (Poor Sup) T1	3.41 (0.88)	4.18 (1.81)	4.27 (1.99)	$F_{1,52.15}$ = 1.79, p = .186	$F_{1,144.39}$ = 2.75, p = .099	$F_{1,144.39}$ = 1.09, p = .297
APQ (Poor Sup) T2	3.37 (1.03)	3.80 (1.38)	4.43 (2.03)			
APQ (Involv) T1	12.64 (1.63)	12.51 (1.63)	12.40 (1.63)	$F_{1,54.14}$ = 0.086, p = .771	$F_{1,158.86}$ = 0.489, p = .486	$F_{1,158.86}$ = 0.416, p = .520
APQ (Involv) T2	12.64 (1.63)	12.44 (1.74)	12.30 (1.73)			
APQ (Corp Pun) T1	3.97 (1.26)	4.17 (1.51)	4.42 (1.15)	$F_{1,52.31}$ = 1.28, p = .262	$F_{1,157.89}$ = 22.97, p < .001[b]	$F_{1,157.89}$ = 0.494, p = .483
APQ (Corp Pun) T2	3.88 (1.32)	3.41 (0.94)	4.00 (1.61)			

APQ, Alabama Parenting Questionnaire; Corp Pun, Corporal Punishment subscale; CP, conduct problem; CU, callous-unemotional; Incon Dis, Inconsistent Discipline subscale; Involv, Involvement subscale; PACS, Parental Accounts of Children's Symptoms; Poor Sup, Poor Supervision subscale; Pos P, Positive Parenting subscale; SDQ, Strength and Difficulties Questionnaire.
[a]The omnibus tests were run on the improving vs. persisting groups only.
[b]Significant at $p < .001$.

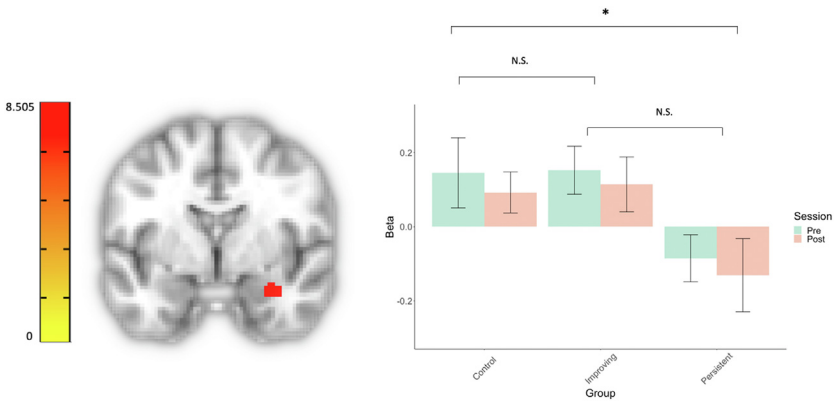

Figure 1. The figure on the left represents a significant group effect (across the 3 groups) on fear processing in the right amygdala. The figure on the right represents post hoc tests between the control vs. improving, control vs. persistent, and improving vs. persistent groups. Our findings show that children with persistent antisocial behavior have significantly reduced amygdala activity in response to modulated fear processing (across both time points) in comparison with the typically developing control group. There was no evidence of amygdala hypoactivity to fear in children whose antisocial behavior improved over time. *Significant at p = .001. Figures reflect the raw means and standard deviations. N.S., not significant.

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 CPs (25,48,49), and early interventions for CPs implicitly target the restructuring of reward and punishment schedules (50). We anticipate that emerging techniques using machine learning (51) will be better able to fractionate out these different neural subtypes and determine their value in predicting treatment response.

Second, 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 with that in most previous neuroimaging studies (17–19) [although similar deficits have been observed in behavioral 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 from 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 (54,55), Antisocial Process Screening Device (56,57), Psychopathy Checklist: youth version (48,58), and 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 is targeted with a treatment that upregulates amygdala activity to fear.

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

First, 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 youths with CPs (59–61), and therefore, future longitudinal studies including both genders are warranted to investigate if female children with treatment-resistant CPs present a similar neurobiological profile to their male counterparts.

Second, 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-based 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 regard 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 multimodal MRI (65).

In conclusion, we have found an association between amygdala hypoactivity to fear in boys with CPs who exhibit more persistent ASB following parenting intervention. Further studies, using a wider range of imaging modalities (66,67), are now needed to explore other neural correlates that predict behavioral 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.

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