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RUNNING HEAD: NEURAL RESPONSES TO CONFLICT/COOPERATION

Neural Responses to Feedback Regarding Betrayal and Cooperation in Adolescents with Anxiety and Mood Disorders

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Abstract

This study examined patterns of neural response to feedback regarding betrayal and cooperation in adolescents with anxiety/mood disorders and healthy peers. We compared performance on and neural activation patterns during the Prisoner's Dilemma (PD) game, an economic exchange task involving betrayal and cooperation, between age- and IQ-matched groups of adolescents with anxiety/depressive disorders (A/D) (*N*=13) and healthy controls (n=17). Participants were deceived to believe that their co-player (a pre-programmed computer algorithm) was another study participant. Although participants responded similarly following feedback that the co-player had cooperated with them on preceding trials, A/D adolescents were more likely than controls to cooperate following trials when the other player betrayed them. Further, A/D participants differed significantly from controls in patterns of neural activation in response to feedback that they had been betrayed. In particular, A/D participants showed more activation relative to baseline in the precuneus, cerebellum, and supramarginal gyrus than did controls. Groups did not, in contrast, differ significantly in patterns of activation in response to feedback that their co-player had cooperated with them. Our findings provide preliminary evidence that A/D adolescents may not only behave differently than do healthy peers when they encounter potential social obstacles, but that they may also engage a different set of neural resources. These findings offer a first step toward elucidating the mechanisms underlying social impairment in youth with internalizing disorders.

KEYWORDS: fMRI, anxiety, depression, cooperation, betrayal, interpersonal interaction, Prisoner's Dilemma

The literature in the past decade reflects a growing interest in neural mechanisms that support social cognition and behavior across development. A large number of studies in healthy adults and adolescents alike, for example, have found evidence that a core set of brain structures, including the amygdala, regions of the prefrontal cortex (PFC), and the anterior cingulate cortex (ACC) show activation during the processing of isolated social cues such as facial expressions of emotion (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Monk et al., 2003; Phillips, Drevets, Rauch, & Lane, 2003; Phillips et al., 2004; Whalen et al., 2001). Less is known about how the brain responds to more complex social experiences such as empathy, social rejection, cooperation, or acceptance but a growing literature suggests that that the neural regions engaged by such stimuli in healthy individuals overlap with those engaged by simpler stimuli such as emotionally expressive faces presented outside of a social context (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Eisenberger, Lieberman, & Williams, 2003; Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, in press; J. K. Rilling et al., 2008; Somerville, Heatherton, & Kelley, 2006).

Additional research suggests that atypical patterns of social cognition and behavior, such as those associated with different forms of internalizing psychopathology (e.g., bias to overperceive threat in individuals with social phobia or generalized anxiety disorder [GAD] (Mogg, Bradley, Millar, & White, 1995; Mogg, Philippot, & Bradley, 2004) or hypersensitivity to rejection in social anxiety disorder (Harb, Heimberg, Fresco, Schneier, & Liebowitz, 2002)), may reflect atypical functioning in underlying neural structures. Studies of individuals with anxiety disorders, for example, have yielded evidence of exaggerated amygdala and attenuated PFC responses to different emotional expressions (Killgore & Yurgelun-Todd, 2005; McClure, Monk et al., 2007; Monk et al., 2008; Shin et al., 2005; M. B. Stein, Goldin, Sareen, Zorrilla, &

Brown, 2002; Murray B. Stein, Simmons, Feinstein, & Paulus, 2007). Indeed, one recent study even suggests that specific disorders such as social phobia and GAD may be associated with specific and distinct patterns of neural response to such cues (Blair, Shaywitz et al., 2008). More elaborate social situations, such as those involving anticipated or experienced rejection or criticism also appear to elicit abnormal neural responses in adolescents and adults with anxiety disorders (ADs) (Blair, Geraci et al., 2008; Guyer et al., 2008). These studies provide primarily descriptive data; however, a better understanding of the neural correlates of atypical social cognition and behavior in individuals with ADs could ultimately contribute to the development of more precisely targeted diagnostic and treatment approaches.

One approach to probing neural responses to complex social stimuli uses classic economic exchange tasks, such as the Prisoner's Dilemma Game (J. Rilling et al., 2002; J. K. Rilling et al., 2008) and the Ultimatum Game (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003), that simulate potentially rewarding or punitive interpersonal interactions for use in conjunction with physiological techniques such as fMRI. These tasks have the advantage of enabling researchers to manipulate participants' experiences of emotionally charged social interactions in tightly controlled ways that vary on a trial by trial basis; the Prisoner's Dilemma (PD) game, for example, permits turn-by-turn evaluation of interactions that involve cooperation or betrayal. Prior research using the PD game has shown that during mutually cooperative trials, healthy adult women show a activation in brain regions associated with reward processing (e.g., ventromedial and orbital PFC, nucleus accumbens, caudate nucleus, rostral ACC) (J. Rilling et al., 2002). In a subsequent study, Rilling and colleagues (2008) found that healthy adults showed different patterns of activation during trials involving unreciprocated cooperation, or betrayal by the co-player, than during mutually cooperative trials. Specifically, whole brain analyses

indicated greater activation during unreciprocated cooperation in bilateral insula, left lingual gyrus, bilateral thalamus, and middle frontal gyrus. Anatomical region of interest (ROI) analyses also indicated significantly greater activation in the left hippocampus and less activation in the bilateral ventral striatum. This experimental paradigm thus provides a potential basis for comparing neural patterns of activation associated with mutually cooperative interactions and betrayal between individuals with anxiety disorders (AD) and healthy peers.

In previous behavioral research (McClure et al., 2007), we found significant differences between adolescents with and without anxiety and/or depressive disorders in patterns of response during the Prisoner's Dilemma (PD) game. Of particular interest were findings that adolescents in the Anxious/Depressed group were significantly more likely than controls to cooperate following co-player cooperation, even though they had the potential to win more money during the interaction if they betrayed the other player. Additionally, in self-report ratings made at the end of the game, Anxious/Depressed participants, particularly girls, reported more anger toward their co-players than did controls. We interpreted these behavioral and emotional differences as suggestive that Anxious/Depressed youths place a particularly high value on positive interpersonal exchanges, even when they must sacrifice short-term financial rewards to sustain them. Further, we suggested that Anxious/Depressed youths may find it more distressing than healthy peers when others do not work with them to avoid negative interactions.

The present study was designed to extend and elaborate on our prior research by comparing patterns of neural response during the PD game between adolescents with and without ADs. In light of evidence that anxious adolescents respond distinctively to unwelcome feedback at both emotional and neural levels (Guyer et al., 2008), we focused explicitly on neural activation during feedback regarding either co-player cooperation or co-player betrayal.

We hypothesized that AD participants would show a different pattern of activation than healthy peers during feedback regarding betrayal. Although we examined activation within the whole brain, we focused in particular on structures such as the amygdala and regions of the PFC, which have been associated with processing of emotional and social cues.

Method

Participants

A total of 24 A/D adolescents and 43 psychiatrically healthy youth were recruited from the community via advertisement and referral by physicians and other health care practitioners. Only those participants for whom a) post-task debriefing confirmed that they had believed they were playing a real co-player, and b) usable fMRI data were generated, were included in the final sample. An additional 6 controls were excluded to ensure that groups were matched on age. Thus, data were analyzed from 13 A/D adolescents and 17 controls. All participants were enrolled in a larger ongoing treatment study of A/D youth that was approved by the National Institute of Mental Health Institutional Review Board. Prior to participation, parents provided written informed consent and youth granted written assent. Participants and their parents were informed at consent that they would receive misinformation at some point during the study; debriefing after the study concluded indicated that there were no adverse reactions as a consequence of deception or any other aspect of the study.

Each participant and a parent was administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL) (Kaufman et al., 1997) to determine psychiatric diagnoses. All K-SADS-PL interviews were conducted by clinicians who demonstrated excellent inter-rater reliability (all kappa values > .90). To be included in the AD group, participants had to meet DSM-IV criteria for an anxiety disorder; exhibit a high level of

symptoms, as indicated by a score > nine on the Pediatric Anxiety Rating Scale (PARS) (RUPP, 2001) that persisted during a three week trial of supportive therapy; and show impairment in global function as indicated by a score < 60 on the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). Exclusion criteria for both AD and comparison groups consisted of: use of any psychotropic medication; DSM-IV psychiatric diagnoses other than anxiety disorders, major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD) or oppositional defiant disorder; medical illness; pregnancy; substance abuse; history of head injury involving loss of consciousness, or IQ of less than 70.

All 13 AD participants met DSM-IV criteria for at least one anxiety disorder: generalized anxiety disorder (GAD; n=7), separation anxiety disorder (SAD; n=6), social phobia (n=3), specific phobia (n=4). Of these participants, 8 were diagnosed with two or more anxiety disorders, three had comorbid MDD, and three had comorbid ADHD. All members of the control group were free of current or past psychiatric disorders.

As detailed in an earlier publication (McClure, Parrish et al., 2007) and consistent with prior research (Birmaher et al., 2003; Kendall et al., 1997; RUPP, 2001), we treated four disorders: major depression, generalized anxiety disorder (GAD), social phobia, and separation anxiety disorder, as a loosely unified group of internalizing conditions. We elected to do so because of the high rates of comorbidity among participants in the AD group, the limited number of participants meeting criteria for only one disorder (n=2) and small numbers of participants within each specific diagnostic category.

AD and comparison groups did not differ according to age, $t(28)=1.28$, $p> .05$, sex, $\chi^2(1)=.14$, $p> .05$, or IQ, $t(27)= .87$, $p> .05$ (See Table 1 for all demographic information).

Procedures

While undergoing an MRI scan, participants played a version of the Prisoner's Dilemma game (J. Rilling et al., 2002). Each player completed four games with a computerized confederate, whom they had been deceived to believe was a human co-player at a remote location. An examiner told each participant at the beginning of the session that during the fMRI scan, he or she would play a game with a study participant at another research site via a wireless computer network. Participants received no further information about the co-player until the end of the task. The examiner then trained participants to play the game, explaining that they must decide, during each of 20 trials, whether or not to cooperate with the other player. Depending on the conjunction of the two players' choices regarding cooperation on each trial, each would receive a specified amount of money: mutual cooperation yield monetary gains of two dollars for both players, mutual non-cooperation (defection) yielded one dollar for both players, and trials in which one player cooperated and the other defected would yield one dollar for the cooperator and three dollars for the defector. During training each participant completed 10 practice trials. Participants were informed during training that after completing the scan they would be paid the amount that they earned during one of the four games (selected randomly at the end of the task).

We have described the PD game version in detail in a prior publication (McClure, Parrish et al., 2007); briefly, however, each game consists of 20 trials (see Figure 1), during which two players (the participant and a computerized co-player) independently and simultaneously cooperate with or "defect from" (not cooperate with) each other with the goal of winning money. The participant indicates his or her choice via key press (1="cooperate", 2="not cooperate"). During most trials, the computerized co-player uses an algorithm based on human patterns of play (J. Rilling et al., 2002), to generate its "choice." This "choice" varies according to the

human participant's choices in the preceding two trials; to ensure that each participant experiences periodic defection by the co-player there is also a 50% likelihood that the computer will defect after four consecutive rounds of mutual cooperation. To provide some consistency among players in the experience of the game, the computer always cooperates during the first trial and defects during the final two trials. After both players submit their choices, the computer screen displays the outcome of the trial and running totals of both players' cumulative earnings.

After every five trials, participants reported their current emotional responses to the other player. Specifically, all participants rated (on a 100-point scale represented on the screen by a sliding bar; ratings could range from 1 = most negative to 100 = most positive) how they felt toward the other player. Additionally, after completing the last game, each participant completed an X-item questionnaire about their experiences during the entire session. Subsequently, an examiner debriefed participants about the deception involved in the task and the motivation for its use, following guidelines for ethically appropriate authorized deception (Wendler & Miller, 2004).

Measures

The PD task was presented in four XX-minute runs. Each run consisted of 20 game trials and 4 fixation trials. The game trials (see Figure 1) varied in duration from 11.5 to 16.1 seconds and each consisted of three components: a) a selection component that lasted 4600 ms, b) an interval that varied from 2300 to 9600 ms, and c) a feedback component that lasted 4600 ms. Four fixation trials varying in duration from 11.5 to 16.1 seconds appeared randomly during each game to provide a baseline. The intertrial interval was 1 second.

fMRI Data Acquisition and Preprocessing

A General Electric (Waukesha, WI) Signa 3 Tesla magnet was used for all scans. Participants viewed task stimuli via a head coil-mounted mirror; stimuli were projected onto a screen at the foot of the scanner bed. During scanning, foam padding was used to limit head movement. Participants rated task stimuli using a hand-held, two-button response box (Research Services Branch, NIMH, Bethesda, MD).

A localizer and a manual shim procedure preceded each functional scan. For functional image acquisition, each brain volume contained XX contiguous XX mm axial slices acquired parallel to the AC/PC line using a single shot gradient echo with T2* weighting with a repetition time (TR) of 2300 ms and echo time (TE) of 23 ms. Voxel dimension was 3.3 x 3.75 x 3.75 mm. Matrix size was 64 mm x 64 mm and field of view (FOV) was 24 cm. A high resolution anatomical image was also acquired using a T1-weighted standardized magnetization prepared spoiled gradient recalled echo sequence to aid with spatial normalization using the following parameters: 124 1 mm axial slices, TR of 8100 ms, TE of 32 ms, flip angle of 15°, NEX = 1, matrix size of 256 x 256 mm, bandwidth = 31.2 KHz, and FOV of 24 cm.

Data Analysis

Behavioral rating data collected during the scan, as well as responses on the post-task questionnaire, were analyzed using SPSS 14.0 (Chicago, IL). FMRI data were preprocessed and analyzed using SPM2(?). Standard preprocessing of echo-planar imaging (EPI) data included slice time correction, re-slicing to 1mm isotropic voxels, motion correction, spatial smoothing with a 6 mm full-width half-maximum Gaussian smoothing kernel, a bandpass filtering algorithm, and normalization of blood oxygen level-dependent (BOLD) signal intensity to percentage signal change using each subject's voxel-wise time series mean as a baseline. Movement artifact was mitigated by using motion correction parameters in the statistical model

as nuisance covariates along with a covariate for mean intensity and linear drift. In addition, any participant who moved more than 3 mm in any plane was excluded.

The statistical model was XX. The basis function was set to the onset of each event type. Event types consisted of two self-appraisal conditions. Self-appraisal events occurred when participants evaluated how peers would perceive them (Figure 1B), and were binned according to (1) *Peers of High Interest* and (Pauls, Alsobrook, Goodman, Rasmussen, & Leckman) *Peers of Low Interest* to the participant for a chat session. A general linear model was then used to determine the beta value and *t*-statistic for each event type at each voxel (Neter, Kutner, Machtsheim, & Wasserman, 1996). Contrasts of whole-brain BOLD activation were created for each individual for each event type. This was followed by a second group-level, random-effects analysis of individual contrast values. A regression analysis was included in the group-level analysis to assess the main effects of the contrasted event ().

After initial analysis, values for specific functionally-defined ROIs identified in the group analysis were generated. These functional ROIs, based on clusters that survived both statistical thresholds, were used to generate average contrast values for each participant. Mean activation values within each functional ROI cluster were then extracted for graphical presentation and further analysis with SPSS. Additionally, to explore age-and-sex-related variation in behavioral responses, an age-group variable was created, thus facilitating analyses of between-group differences.

Results

Behavioral Findings

All means for all dependent variables are presented in Table 2.

Results of Students t-tests indicated that groups did not differ significantly in the number of games won, $t(28) = 0.77$, $p = .45$, or the average amount of money earned, $t(28) = 0.54$, $p = .59$. Greenhouse-Geisser corrected results of a repeated-measures ANOVA examining group differences in patterns of play during the game indicated a significant main effect, $F(1, 28) = 5.66$, $p < .05$, with AD participants less likely than controls to defect following co-player cooperation, but not following co-player defection. AD participants' feelings toward their co-players became more negative during the course of each game than did controls; results of paired samples t-tests comparing differences between initial and final ratings averaged across all four games were marginally significant for AD participants, $t(12) = 2.16$, $p = .05$, but not controls, $t(16) = .08$, $p > .05$ (see Figure 2). For AD participants, average ratings were consistently lower at the end of games than at the beginning.

Comparisons of patients' and controls' post-task interview responses revealed a significant main effect of XX, F(X) = XX, p < .X.

References

Birmaher, B., Axelson, D. A., Monk, K., Kalas, C., Clark, D. B., Ehmann, M., et al. (2003). Fluoxetine for the treatment of childhood anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(4), 415-423.

Blair, K., Geraci, M., Devido, J., McCaffrey, D., Chen, G., Vythilingam, M., et al. (2008). Neural Response to Self- and Other Referential Praise and Criticism in Generalized Social Phobia. *Arch Gen Psychiatry, 65*(10), 1176-1184.

Blair, K., Shaywitz, J., Smith, B. W., Rhodes, R., Geraci, M., Jones, M., et al. (2008). Response to Emotional Expressions in Generalized Social Phobia and Generalized Anxiety Disorder: Evidence for Separate Disorders. *Am J Psychiatry, 165*(9), 1193-1202.

Brotman, M. A., Schmajuk, M., Rich, B. A., Dickstein, D. P., Guyer, A. E., Costello, E. J., et al. (2006). Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry, 60*(9), 991-997.

Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *PNAS, 100*(9), 5497-5502.

Eisenberger, N. I., Lieberman, M. D., & Williams, K. D. (2003). Does Rejection Hurt? An fMRI Study of Social Exclusion. *Science, 302*(5643), 290-292.

Guyer, A. E., Lau, J. Y. F., McClure-Tone, E. B., Parrish, J., Shiffrin, N. D., Reynolds, R. C., et al. (2008). Amygdala and Ventrolateral Prefrontal Cortex Function During Anticipated Peer Evaluation in Pediatric Social Anxiety. *Arch Gen Psychiatry, 65*(11), 1303-1312.

Guyer, A. E., McClure-Tone, E. B., Shiffrin, N. D., Pine, D. S., & Nelson, E. E. (in press). Probing the neural correlates of anticipated peer evaluation in adolescence. *Child Development*.

Harb, G. C., Heimberg, R. G., Fresco, D. M., Schneier, F. R., & Liebowitz, M. R. (2002). The psychometric properties of the Interpersonal Sensitivity Measure in social anxiety disorder. *Behaviour Research and Therapy, 40*, 961-979.

Hariri, A. R., Mattay, V. S., Tessitore, A., Fera, F., & Weinberger, D. R. (2003). Neocortical modulation of the amygdala response to fearful stimuli. *Biological Psychiatry, 53*(6), 494-501.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., et al. (1997). Schedule for affective disorders and schizophrenia for school-age children-present lifetime version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(7), 980-988.

Kendall, P. C., Flannery-Schroeder, E., Panichelli-Mindel, S. M., Southam-Gerow, M., Henin, A., & Warman, M. (1997). Therapy for youths with anxiety disorders: a second randomized clinical trial. *Journal of Consulting & Clinical Psychology, 65*(3), 366-380.

Killgore, W. D. S., & Yurgelun-Todd, D. A. (2005). Social anxiety predicts amygdala activation in adolescents viewing fearful faces. *Neuroreport, 16*(15), 1671-1675.

McClure, E. B., Monk, C. S., Nelson, E. E., Parrish, J. M., Adler, A., Blair, R. J. R., et al. (2007). Abnormal attention modulation of fear circuit activation in pediatric Generalized Anxiety Disorder. *Archives of General Psychiatry, 64*(1), 97-106.

McClure, E. B., Parrish, J. M., Nelson, E. E., Easter, J., Thorne, J. F., Rilling, J. K., et al. (2007). Responses to Conflict and Cooperation in Adolescents with Anxiety and Mood Disorders. *Journal of Abnormal Child Psychology, 35*(4), 567-577.

Mogg, K., Bradley, B. P., Millar, N., & White, J. (1995). A follow-up study of cognitive bias in generalized anxiety disorder. *Behav Res Ther, 33*(8), 927-935.

Mogg, K., Philippot, P., & Bradley, B. P. (2004). Selective attention to angry faces in clinical social phobia. *J Abnorm Psychol, 113*(1), 160-165.

Monk, C. S., Klein, R. G., Telzer, E. H., Schroth, E. A., Mannuzza, S., Moulton, J. L. I., et al. (in press). Amygdala and nucleus accumbens activation to emotional facial expressions in adolescents at risk for major depression. *Am J Psychiatry*.

Monk, C. S., McClure, E. B., Nelson, E. E., Zarahn, E., Bilder, R. M., Leibenluft, E., et al. (2003). Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage, 20*(1), 420-428.

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., et al. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *The American Journal of Psychiatry, 163*(6), 1091-1097.

Monk, C. S., Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Louro, H. M. C., et al. (2008). Amygdala and Ventrolateral Prefrontal Cortex Activation to Masked Angry Faces in Children and Adolescents with Generalized Anxiety Disorder. *Arch Gen Psychiatry, 65*(5), 568-576.

Neter, J., Kutner, M. H., Machtsheim, C. J., & Wasserman, W. (1996). *Applied linear statistical models* (4 ed.). Chicago: Irwin.

Pauls, D. L., Alsobrook, J. P., 2nd, Goodman, W., Rasmussen, S., & Leckman, J. F. (1995). A family study of obsessive-compulsive disorder. *Am J Psychiatry, 152*(1), 76-84.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry, 54*(5), 504-514.

Phillips, M. L., Williams, L. M., Heining, M., Herba, C. M., Russell, T., Andrew, C., et al. (2004). Differential neural responses to overt and covert presentations of facial expressions of fear and disgust. *Neuroimage, 21*(4), 1484-1496.

Rilling, J., Gutman, D., Zeh, T., Pagnoni, G., Berns, G., & Kilts, C. (2002). A neural basis for social cooperation. *Neuron, 35*(2), 395-405.

Rilling, J. K., Goldsmith, D. R., Glenn, A. L., Jairam, M. R., Elfenbein, H. A., Dagenais, J. E., et al. (2008). The neural correlates of the affective response to unreciprocated cooperation. *Neuropsychologia, 46*(5), 1256-1266.

Rissman, J., Eliassen, J. C., & Blumstein, S. E. (2003). An event-related FMRI investigation of implicit semantic priming. *J Cogn Neurosci, 15*(8), 1160-1175.

RUPP. (2001). Fluvoxamine for the treatment of anxiety disorders in children and adolescents. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. *New England Journal of Medicine, 344*(17), 1279-1285.

Sanfey, A. G., Rilling, J. K., Aronson, J. A., Nystrom, L. E., & Cohen, J. D. (2003). The neural basis of economic decision-making in the Ultimatum Game. *Science, 300*(5626), 1755-1758.

Shaffer, D., Gould, M., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., et al. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry, 40*, 1228-1231.

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., McMullin, K., Martis, B., et al. (2005). A Functional Magnetic Resonance Imaging Study of Amygdala and Medial

Prefrontal Cortex Responses to Overtly Presented Fearful Faces in Posttraumatic Stress Disorder. *Arch Gen Psychiatry, 62*(3), 273-281.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for Pain Involves the Affective but not Sensory Components of Pain. *Science, 303*(5661), 1157-1162.

Somerville, L. H., Heatherton, T. F., & Kelley, W. M. (2006). Anterior cingulate cortex responds differentially to expectancy violation and social rejection. *Nature Neuroscience, 9*(8), 1007-1008.

Stein, M. B., Goldin, P. R., Sareen, J., Zorrilla, L. T. E., & Brown, G. G. (2002). Increased Amygdala Activation to Angry and Contemptuous Faces in Generalized Social Phobia. *Arch Gen Psychiatry, 59*(11), 1027-1034.

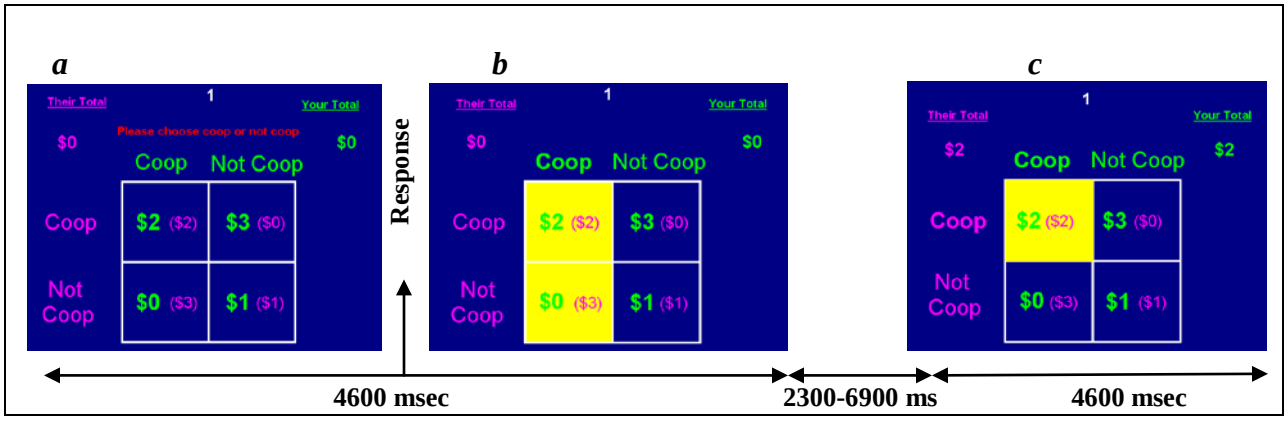
Stein, M. B., Simmons, A. N., Feinstein, J. S., & Paulus, M. P. (2007). Increased Amygdala and Insula Activation During Emotion Processing in Anxiety-Prone Subjects. *Am J Psychiatry, 164*(2), 318-327.

Wendler, D., & Miller, F. G. (2004). Deception in the pursuit of science. *Archives of Internal Medicine, 164*(6), 597-600.

Whalen, P. J., Shin, L. M., McInerney, S. C., Fischer, H., Wright, C. I., & Rauch, S. L. (2001). A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion, 1*(1), 70-83.

Figure 1. Trial structure. During the first part of the selection phase of the trial (Figure 1a), the participant indicates a decision to cooperate or not cooperate with a co-player by pressing a computer key (1 for “cooperate”, 2 for “not cooperate”). A matrix shows the player’s options (columns), as well as the co-player’s options (rows) and the payoffs (player payoff in green print, co-player payoff in pink) for each conjunction of choices. Winnings accumulate continuously across all 20 trials. If both players cooperate across all trials, the long-term payoff is highest; however, the short-term (single trial) payoff for an individual player is highest if he/she defects and the co-player cooperates. During the second part of the selection phase, the option that the player has selected is highlighted in yellow (In Figure 1b, the player cooperated).Each player is blind to the other player’s selection until the feedback phase of the trial (Figure 1c), when the conjunction of both players’ choices is displayed, along with a running total of each player’s winnings (Figure 1c).

Figure 1


a
b
c
Their Total
Your Total
1
Please choose coop or not coop
$0
$0
Coop
Not Coop
Coop
Not Coop
$2 ($2)
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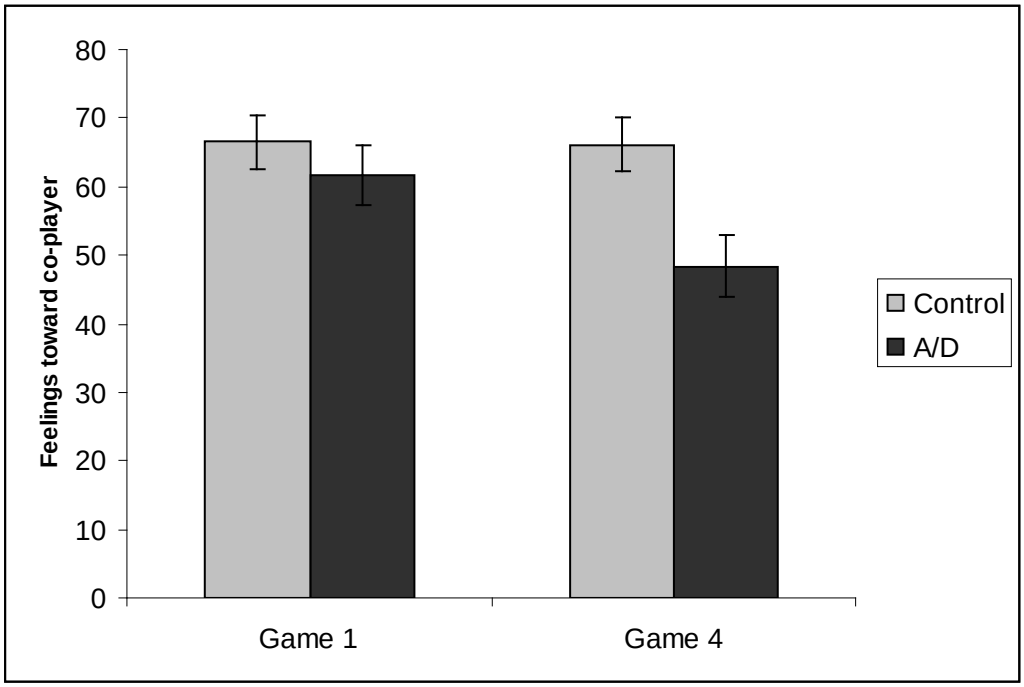
$0 ($3)
$1 ($1)
Response
$2
$2
4600 msec
2300-6900 ms
4600 msec

Figure 2


80
70
60
50
40
30
20
10
0
Feelings toward co-player
Game 1
Game 4
Control
A/D