Parent-Adolescent Training on Neurofeedback and Synchrony

NCT03929263

Study Protocol and Statistical Analysis Plan

3/15/2019

SPECIFIC AIMS

Depression among adolescents has increased significantly over the past decade, and adolescent girls have a threefold incidence of depression as compared to their male peers.[1] Nearly 4 in 10 girls will experience a major depressive episode during adolescence.[1] Importantly, youth who experience difficulties with emotion regulation, which is the ability to manage emotions in order to engage in appropriate and goal-directed behaviors, are at greater risk for depression, and the parent-adolescent relationship strongly influences this risk.[2] The parent-adolescent relationship is thus a prime target for intervention and prevention efforts for adolescent depression. The overall impact of the proposed study will be the development of a protocol to promote parenting practices in support of adolescent emotion regulation that may ultimately be used as an intervention in adolescent depression. This study combines: (1) hyperscanning, an innovative approach using concurrent functional magnetic resonance imaging (fMRI) to simultaneously measure neural responses of two interacting individuals; and (2) real-time fMRI (rt-fMRI) neurofeedback, a method used for training participants to regulate activity in a specific brain region. Our preliminary studies suggest that neurofeedback is effective in reducing symptoms of depression, and that supportive parent-child relationships are associated with increased activation in brain regions important for emotion regulation during parent-child interactions and with fewer depressive symptoms in adolescents.

Our long-term research goal is to implement an effective parenting-based intervention for adolescent depression. Building on pilot data from past projects separately utilizing fMRI hyperscanning and neurofeedback, the objective of the current study is to develop a dyadic fMRI neurofeedback protocol using hyperscanning that will train mothers to regulate their daughters' activation in a brain region associated with emotion regulation (i.e., anterior insular cortex [aIC]), as well as to promote synchronous parent-child brain activity, which we and others have shown to be associated with positive emotional outcomes. The study will test this protocol for feasibility with ten mothers and their psychiatrically healthy adolescent daughters (ages 13-17), with the eventual goal to test this in a sample of depressed adolescents in a future study. Participants will complete a resting-state fMRI scan at the beginning and end of each hyperscanning session. Participants will also complete an ecologically valid emotion discussion task during hyperscanning, in which the daughter will describe a recent situation when she experienced strong negative emotions. The mother will then respond to the daughter while the mother is simultaneously receiving dyadic neurofeedback (dnf) of the daughter's aIC activation with the goal of decreasing it. Following the conversation, both participants will be asked to mentally reflect on the discussion while both receiving dnf representing the synchrony between the mother's and daughter's aIC activation. We have the following specific aims:

Aim 1. To develop and test the feasibility of a hyperscanning fMRI neurofeedback protocol in mothers and their adolescent daughters. Hypothesis 1A. Mothers will perceive that they are able to influence their daughters' aIC activation using the daughter's fMRI neurofeedback signal (e.g., dnf), based on rating scales presented at the end of each run (i.e., average rating of ability to move bar $\geq$ 5/10)**. Hypothesis 1B.** Mothers and daughters will be able to establish and maintain temporal synchronous aIC activation while reflecting on their interaction.

Aim 2. To determine preliminary effects of neurofeedback on neural activation and emotional experience during the dyadic social interaction. Hypothesis 2A. Mothers' own aIC activation while listening to their daughters will be positively correlated with that of their daughters' during the mothers' response. **Hypothesis 2B.** Stronger temporal synchrony and coupling between mothers' and daughters' aIC activation during the reflection condition will be associated with more validating statements made by the mother during the task and lower self-report ratings of negative emotions in both participants.

Aim 3. To identify short-term effects of neurofeedback training. Hypothesis 3A (Exploratory). Mothers' and daughters' neural activation of resting-state networks will be more temporally synchronous at the end of the hyperscanning session (following neurofeedback), as compared to their first resting-state fMRI scans in the hyperscanning session. **Hypothesis 3B.** Ratings of positive emotions will be higher and negative emotions will be lower following the hyperscanning session as compared to ratings taken before the scan.

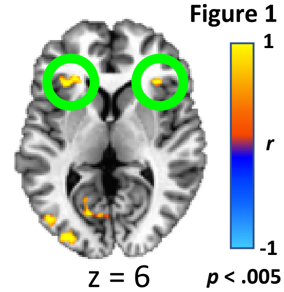
The expected outcome of the proposed study is a rt-fMRI neurofeedback-hyperscanning protocol that will be available for implementation in future studies with larger samples in order to study its effects on adolescent depression. The protocol and data from the first five dyads will be used for a K award submission in the fall of 2019. A manuscript will be prepared and submitted following the end of data collection in the summer of 2020. The protocol developed in this study will provide the foundation for future prevention and intervention efforts aimed at the effects of parenting on the development of emotion regulation skills and depressive symptoms.

SIGNIFICANCE: Depression is a debilitating illness that often begins during adolescence. In 2015, an estimated 3 million adolescents aged 12 to 17 in the U.S. had at least one major depressive episode in the past year – an increase of 44% over the past ten years.[3] The peak onset of depression is around age 15.[4] For adolescent females, rates of depression are three times that of adolescent males, with some studies indicating that 50% of females will have an episode of depression during adolescence.[5] Furthermore, higher rates of depression in females persist into adulthood, with serious consequences for social and emotional health and well-being.[6] Therefore, it is critical to research and understand the precursors to the onset of adolescent depression and identify intervention targets that forestall depressive episodes and the resulting health effects. **Parenting and emotion regulation** are two key factors that affect risk for depression, with a significant impact on the development of mental health during childhood and adolescence.[7,8] Emotion regulation difficulties are a core vulnerability that underlie adjustment problems that emerge during adolescence, including depression.[9,10] How parents react to and socialize their children's emotion regulation is critical to youth's mental health.[11,12] Numerous studies show better emotion regulation among children of emotionally supportive parents compared to emotionally unsupportive parents who ignore and sometimes denigrate their children's emotions.[13] Children who have warm, open, and supportive relationships with their parents have more positive emotional and mental health outcomes.[13] Fostering such relationships may therefore aid in the prevention of and intervention for adolescent depression. Parenting influences emotion processing and emotion regulation neurocircuitry, as well as the development of psychopathology.[14] Supportive parenting is associated with adaptive structural changes in limbic-striatal brain regions over time[15] and adaptive functional responses to emotional stimuli.[16,17] Parents and adolescents with more synchronous resting-state networks have similar daily emotional synchrony, and adolescents who have greater synchrony with their parents also show higher levels of emotional competence.[18] When listening to critical comments made by their mothers, adolescents exhibit increased brain activity (relative to neutral comments) in subcortical-limbic regions but decreased activity in regions subserving cognitive control of emotion, such as the dorsolateral prefrontal cortex (dlPFC) and caudal anterior cingulate cortex.[19] These findings suggest that typically developing adolescents fail to recruit cognitive control networks to help them regulate emotion when listening to critical comments from their mothers. Using a similar task in a study conducted with adolescent girls, Dr. Amanda Morris (a mentor on the current proposal) and colleagues demonstrated that symptoms of anxiety and depression are associated with a blunted left amygdala response to maternal criticism and praise paired with increased right amygdala response to criticism.[20] Taken together, these regions (dlPFC, anterior cingulate, amygdala) constitute an emotion regulation network in which the aIC plays a key role. Adolescents' regulation of the aIC through neurofeedback influences information flow between the amygdala and higher cortical structures such as the dlPFC.[21] Additionally, across numerous studies depressed adolescents show hyperactivation of the right aIC.[22] Parenting effects on aIC activation can be seen in child maltreatment, which is also associated with increased aIC activation.[23] **Collectively, these findings support the scientific premise that parenting influences adolescents' emotion regulation-related neurocircuitry, and parenting alters functioning in brain regions that support emotional reactivity and regulation in response to feedback from parents.**

INNOVATION: This study will integrate two cutting-edge, state-of-the art neuroimaging methods: hyperscanning and neurofeedback. This is the first study to our knowledge to simultaneously scan two individuals while they are interacting and being provided with real-time dnf. Using these techniques, mothers will be able to see in real-time how what they say to their daughter affects her brain function, and they will be able to use this feedback to respond more effectively and supportively to her. This will also be the first study to our knowledge to utilize a neurofeedback signal indicative of inter-brain synchrony. Parent-child neural synchrony has been shown to be associated with emotional health,[18] and this study provides the opportunity for mothers and daughters to receive neurofeedback on inter-brain synchrony in order to enhance it. Due to the high ecological validity of this paradigm, we expect effects to generalize to future real-world interactions between the participants after study completion.

PRELIMINARY DATA: The proposed emotion discussion task has been used in previous studies with parents and adolescents.[24,25] Our lab has experience with both hyperscanning and neurofeedback with parent-adolescent dyads. In the past 18 months, 40 parent-adolescent dyads completed a free-speech conflict discussion task while undergoing hyperscanning. The currently proposed project builds on acquired experience and acquired data and analyses. Preliminary analyses provide support for targeting the aIC as a key region for emotion regulation within the context of the parent-adolescent relationship. Our recent project included a task wherein each participant was led to believe the other had made a costly error during a cooperative game. A whole-brain analysis using the AFNI program 3dTcorrelate was conducted to identify brain regions where parent and adolescent activity was correlated during the ‘costly error’ condition, and evidence for co-activation was found in bilateral aIC (Figure 1). aIC activation can be successfully regulated with rt-fMRI neurofeedback in adults, adolescents, and children.[21,26-28] Importantly, down-regulation of aIC activation is associated with reduced anxiety in phobic participants at 3-month follow-up[28] and, in healthy adolescents, has effects on a network of regions associated with emotion regulation.[21] The aIC is thus a prime target for dnf with the goal of increasing emotion regulation in adolescents.

Figure 1



Parents and adolescent dyads display co-activation in the anterior insula.

APPROACH: This study will utilize a rigorous multi-method, multi-informant design to examine the effects of dnf on adolescent brain activation with fMRI hyperscanning (see **Table 1** for Project Timeline). Parents and adolescents will also report on emotion regulation, depressive symptoms, and parenting practices. Data collection procedures will take place at the Laureate Institute for Brain Research (LIBR), which is equipped with two identical scanners that have advanced real-time fMRI systems capable of conducting parallel fMRI hyperscanning, including the capacity for neurofeedback developed by Dr. Jerzy Bodurka, who is also Dr. Kerr’s mentor. IRB approval will be obtained from the Oklahoma State University Center for Health Sciences. Parents will complete a phone screen to determine initial eligibility (see Inclusion/Exclusion criteria in **Table 2**). If initial study criteria are met, a 2-hour in-person lab visit will be scheduled where mothers and daughters will complete consent/assent; diagnostic interviews (the Mini-International Neuropsychiatric Interview [parent MINI 7.0, adolescent MINI KID 7.0]); surveys on emotion regulation, parenting practices, depression, and anxiety (Table 3); and additional screening. Survey data will be used for preliminary exploratory analyses. Based on data collected from the screening visit, participants will be invited to participate in the full study: a 4-hour visit where mothers and daughters will complete emotion ratings, mock scanner training, and fMRI tasks individually and together using hyperscanning (scan time = 16 min resting-state [2 runs], 7 min structural MRI, 40 min fMRI tasks, 10 min clinical MRI scans).

Table 1: Project Timeline	Year 1			Year 2		
Task	3/15/2019 - 8/15/2019	8/16/2019 - 12/15/2019	12/16/2019- 4/14/2020	4/15/2020 - 8/15/2020	8/16/2020 - 12/15/2020	12/16/2020- 3/14/2021
General Project Activities						
Weekly meetings with mentors	x	x	x	x	x	x
Protocol development and testing	x					
Train and hire RA	x					
Recruitment and Data Collection						
Recruitment and screening	5 dyads		5 dyads			
Scan sessions	5 dyads			5 dyads		
Data Entry, Analysis, and Coding						
Data entry and cleaning	x			x		
fMRI data processing and QA	x	x		x		
Transcription and coding of tasks	x	x		x	x	
Hypothesis testing		x				
Conference presentation			x	x		
Manuscript preparation					x	x
Preparation for K99/R00 Application						
Preliminary data analysis	x					
Draft research plan/revisions		x				
Finalize proposal and submit		x				

Table 2: Inclusion/Exclusion Criteria

Criteria	**Moms**	**Girls**
Inclusion		
Eligible for fMRI	✓	✓
Sufficient English fluency to complete tasks	✓	✓
BMI	18.0-40.0	16.0-40.0
Right-handed	✓	✓
Biological female	✓	✓
Biological mother	✓	
Co-residing at least 4 days/week	✓	✓
Primary caregiver > 50% of child’s lifespan	✓	
Age 13-17		✓
Exclusion		
Current psychiatric diagnosis	X	X
Medications influencing fMRI	X	X
Medical conditions influencing fMRI	X	X
Alcohol or psychoactive drug on scan day	X	X
Neurodevelopmental delay		X
History of mood or psychotic disorder		X
History of OCD or ADHD		X

Participants. 10 adolescents (ages 13-17; all female) and their biological mothers, total N=20, recruited using electronic flyers distributed through local schools and from a previous lab project (Dyadic Inter-Brain Signaling study). Our sample will include ~40% from ethnic/racial minority groups.

Consideration of biological variables. This study will result in pilot data and a protocol for a future intervention study in depression. Scientific reasons to only include females are: (1) rates of depression are three times higher among females than males[29]; (2) during adolescence, female and male brains develop at different rates, with some studies indicating a gap in brain maturation due to the onset of puberty occurring two years earlier for girls[30]; (3) many adolescents do not have a consistent father figure in the home, with rates of 1 in 4 children living in single mother families[31]; and (4) mothers and fathers diverge in emotion socialization techniques and parenting styles that could impact results.[32]

fMRI hyperscanning. All hyperscanning experiments will be conducted on two MR750 3T MRI scanners with fMRI imaging protocols and parameters described elsewhere.[33,34] Prior to scanning, participants will complete a brief training session in the mock scanner to desensitize them to the MRI environment and to practice talking while remaining as still as possible. After this training, subjects will complete an 8-minute eyes-open resting-state scan followed by the dnf training and transfer runs. Subjects will then undergo a second resting-state scan and complete post-scan emotion rating scales.

Table 3: Survey Measures

Parenting
Child Report of Parent Behavior Inventory
Alabama Parenting Questionnaire
Emotion Socialization and Regulation
Emotion as a Child Scales
Difficulties in Emotion Regulation Scale
Mental Health – Adolescent
Mood and Feelings Questionnaire
Screen for Child Anxiety Related Disorders
Depression, Anxiety, and Stress Scale-21
Achenbach's Child Behavior Checklist (parent report)
Mental Health – Parent
Quick Inventory of Depressive Symptomatology – Self Report
Beck Anxiety Inventory
Depression, Anxiety, and Stress Scale-21

Emotion Discussion with Dyadic Neurofeedback Task. This task will be completed in the scanner using simultaneous hyperscanning data collection. Prior to the fMRI, adolescents (without the parent present) will be asked to think of recent situations when they were feeling strong negative emotions, such as anger, sadness, and/or anxiety. They will be informed that they will be talking to their mother about each situation during the scan. The mother (without the daughter present) will be provided with task instructions and informed that while talking to her daughter she will be receiving neurofeedback from a region in her daughter's brain. The mother will be told that her goal is to decrease activation in that region by calming her daughter and decreasing the intensity of her daughter's emotional response. The emotion discussion task will consist of four types of trials, each lasting 40s: Rest trials, Count trials, Discussion trials, and Reflection trials. During the first Discussion trial, the adolescent will describe the emotional situation. This will be followed by a second Discussion trial during which the mother will respond to the adolescent while receiving neurofeedback from the adolescent's aIC. This will be followed by a Count trial during which participants will mentally count backward from 300 by a number specified on the screen (for example, by 6: 300, 294, 288…) in order to bring aIC activation back to baseline. This will be followed by a 40s Rest period. Following the Rest trial, the adolescent will be provided 40s to respond to her mother (no neurofeedback presented), and the mother will subsequently respond again to the adolescent while receiving neurofeedback from her daughter's aIC. This will again be followed by a Count and Rest trial. Finally, both the adolescent and her mother will be asked to mentally (i.e., silently) reflect on the discussion while receiving neurofeedback representing the synchrony between both participants' aIC activation. This will be followed by another 40s Count trial and 40s Rest trial, for a total runtime of 8 minutes. Participants will complete three runs of the emotion discussion task with dnf, followed by a fourth transfer run in order to determine if the effects of the training persist. During the transfer run, the task will be exactly the same except no neurofeedback will be presented.

Audio Collection and Coding. Although collection of valid fMRI data during free speech requires extra care,[35] we can correct for speech-related signal artifacts. In addition to standard pre-processing including volume registration and inclusion of motion parameters as covariates in regression analyses, we will use a continuous-speech 'de-noising' procedure developed by Xu et al.[36] that employs a dual-mask spatial independent component analysis (ICA) method to identify noise components based on spatial origins. We will use active noise-cancelling microphones and headphones (OptoActive II NC Microphones and ANC Headphones, Opto acoustics Ltd.) and an intercom link between the scanners that produces voice/audio quality equivalent to most mobile phone calls. To avoid motion artifact interfering with the neurofeedback signal, neurofeedback will not occur when the subject of the neurofeedback is talking. The audio during the emotion discussion task will be recorded and later transcribed. The parents' responses will be coded for specific types of statements using the parent-child validation/invalidation behavior coding scales.[37] Validating statements are supportive of the adolescent's emotional experience and show empathic understanding, while invalidating statements minimize, dismiss, or criticize the adolescent and/or her expressed emotions. In the proposed study, all transcriptions will be double-checked, and at least 2 of the 5 conversations will be double-coded. PI Kerr will oversee coding, transcription, and reliability checks (80% agreement or higher).

fMRI Data Acquisition Parameters. fMRI data will be collected on two GE MR750 3 Tesla MRI scanners (scan time = 1hr 30m). Functional images will be acquired as echoplanar imaging (EPI, optimized to minimize signal dropout and image distortions; 46 contiguous 2.9-mm thick slices collected in the axial plane, ensuring whole-brain coverage [TR/TE = 2000/30 ms, SENSE acceleration R=2, flip angle = 90°, voxel size = $2.5\times2.5\times2.9$ mm^3]). Both LIBR scanners are equipped with advance real-time fMRI systems, allowing for EPI image quality examination and artifact troubleshooting before the subject begins the task scans, as well motion tracking during the scans. T1-weighted MRI anatomical MPRAGE high resolution (voxel size = $1\times1\times1$ mm^3) images will be acquired. All imaging parameters, synchronization, audio, and visual coupling among the scanners have been, and will be, determined in consultation with LIBR's physicist, Dr. Jerzy Bodurka, who has developed and has experience with fMRI hyperscanning and will also serve as a mentor on the project.

ANALYSES: Data will be analyzed in real-time with LIBR software.[33,34] An automated script will generate an anatomically-defined spherical region-of-interest (5mm radius) centered at the aIC (locus: [38, 16, 4], MNI space).[38] The dnf, updated every 2s and shown as a bar with moving height, will be measured as % signal change relative to baseline (obtained by averaging the fMRI signal for the preceding 40s rest block). To reduce bar fluctuations due to noise in the fMRI signal, bar height will be computed at every time point as the mean of the current and two preceding fMRI signal change values. All offline fMRI data preprocessing and analyses will be conducted as described elsewhere.[33,34] General Linear Models (GLM) will be used to analyze individual subjects' data with predictors in the model. Regressors of non-interest will be included in all models to account for each run's signal mean, linear, quadratic, and cubic signal trends, as well as motion parameters. Regressors will also include the block stimulus conditions (daughter: Describe/Respond, Listen, Count, Rest, Reflect; mother: Respond [dnf], Listen, Count, Rest, Reflect) and five polynomial terms for modeling the baseline. The GLM β coefficients will be computed for each voxel and converted to % signal change for contrasts of interest (e.g., Listen versus Count, Listen versus Rest, Count versus Rest, Reflect versus Rest, and Reflect versus Count). Statistical contrast maps for exploratory whole-brain analyses will include corrections for multiple comparisons.

Hypothesis 1A. Mothers will perceive that they are able to influence their daughters' aIC activation using the daughter's fMRI neurofeedback signal (e.g., dnf), based on rating scales presented at the end of each run (i.e., average rating of ability to move bar ≥ 5/10). We will ask the mother to rate how effective she felt she was at changing her daughter's brain activity on a Likert scale from 0-10. For this analysis, we will simply take the mean of all parent participants' responses over all runs and determine if it is at least 5, providing evidence that mothers perceived they were able to effectively regulate their daughter's brain activity.

Hypothesis 1B. Mothers and daughters will be able to establish and maintain temporal synchronous aIC activation while reflecting on their interaction. Correlations will be calculated between mothers' and daughters' aIC timecourses (Reflect vs Rest contrast).

Hypothesis 2A. Mothers' own aIC activation while listening to their daughters will be positively correlated with that of their daughters' during the mothers' response. The correlation between the mothers' and daughters' average beta weights for aIC activation during each participant's Listen trials will be calculated.

Hypothesis 2B. Stronger temporal synchrony and coupling between mothers' and daughters' aIC activation during the reflection condition will be associated with more coded validation statements during the task and lower self-report ratings of negative emotions in both participants. a) Coupling will be measured as the correlation between timecourses for aIC activation as described in Hypothesis 1B, transformed to *z*-scores (Fisher's *r*-to-*z* transformation). b) Participants will be asked to rate the intensity of various emotions they felt during the scan (0-10 Likert scale). Correlations will be calculated between the *z*-scores (a) and 1) the number of validating statements made by the mother across the scan and 2) ratings of negative emotions (b).

Hypothesis 3A (Exploratory). Mothers' and daughters' neural activation of resting-state networks will be more temporally synchronous at the end of the hyperscanning session (following neurofeedback), as compared to their first resting-state fMRI scans in the hyperscanning session. Similarity of resting-state networks will be evaluated as described in Lee et al. (2017).[18] ICA will identify intrinsic resting-state networks at the group level. On the individual level, a matrix of correlation coefficients for all possible pairs of resting-state networks will be created and transformed to Fisher's *z*, then vectorized and correlated between each pair of mother-daughter dyads to determine the level of synchrony within the dyad. A paired *t*-test will be conducted to determine if there is a significant difference between resting-state synchrony at the beginning versus end of the scanning session.

Hypothesis 3B. Ratings of positive emotions will be higher following the hyperscanning session as compared to ratings taken before the scan. Paired *t*-tests will be conducted separately for mothers and daughters to determine if ratings of positive emotions (e.g., "happy," "calm") made on a 0-10 Likert scale before the scan differ significantly from those made after the scan.

References

1 Breslau, J. *et al.* Sex differences in recent first-onset depression in an epidemiological sample of adolescents. *Transl Psychiatry* **7**, e1139, doi:10.1038/tp.2017.105 (2017).
2 Malik, S., Wells, A. & Wittkowski, A. Emotion regulation as a mediator in the relationship between attachment and depressive symptomatology: A systematic review. *J Affect Disord* **172**, 428-444, doi:10.1016/j.jad.2014.10.007 (2015).
3 Mojtabai, R., Olfson, M. & Han, B. National trends in the prevalence and treatment of depression in adolescents and young adults. *Pediatrics*, e20161878 (2016).
4 Hankin, B. L. *et al.* Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology* **107**, 128-140 (1998).
5 Wade, T. J., Cairney, J. & Pevalin, D. J. Emergence of gender differences in depression during adolescence: National panel results from three countries. *Journal of the American Academy of Child & Adolescent Psychiatry* **41**, 190-198 (2002).
6 Patton, G. C. *et al.* Predicting female depression across puberty: a two-nation longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry* **47**, 1424-1432 (2008).
7 Malik, S., Wells, A. & Wittkowski, A. Emotion regulation as a mediator in the relationship between attachment and depressive symptomatology: A systematic review. *Journal of affective disorders* **172**, 428-444 (2015).
8 Yap, M. B. H., Schwartz, O. S., Byrne, M. L., Simmons, J. G. & Allen, N. B. Maternal Positive and Negative Interaction Behaviors and Early Adolescents' Depressive Symptoms: Adolescent Emotion Regulation as a Mediator. *Journal of Research on Adolescence* **20**, 1014-1043, doi:10.1111/j.1532-7795.2010.00665.x (2010).
9 Silk, J. S., Steinberg, L. & Morris, A. S. Adolescents' emotion regulation in daily life: links to depressive symptoms and problem behavior. *Child Dev* **74**, 1869-1880 (2003).
10 Fowler, C. H., Miernicki, M. E., Rudolph, K. D. & Telzer, E. H. Disrupted amygdala-prefrontal connectivity during emotion regulation links stress-reactive rumination and adolescent depressive symptoms. *Developmental cognitive neuroscience* **27**, 99-106 (2017).
11 Gottman, J. M., Katz, L. F. & Hooven, C. Parental meta-emotion philosophy and the emotional life of families: Theoretical models and preliminary data. *Journal of Family Psychology* **10**, 243-268, doi:Doi 10.1037/0893-3200.10.3.243 (1996).
12 Yap, M. B., Allen, N. B. & Ladouceur, C. D. Maternal socialization of positive affect: the impact of invalidation on adolescent emotion regulation and depressive symptomatology. *Child Dev* **79**, 1415-1431, doi:10.1111/j.1467-8624.2008.01196.x (2008).
13 Morris, A. S., Silk, J. S., Steinberg, L., Myers, S. S. & Robinson, L. R. The Role of the Family Context in the Development of Emotion Regulation. *Soc Dev* **16**, 361-388, doi:10.1111/j.1467-9507.2007.00389.x (2007).
14 Morris, A. S., Squeglia, L. M., Jacobus, J. & Silk, J. S. Adolescent Brain Development: Implications for Understanding Risk and Resilience Processes Through Neuroimaging Research. *J Res Adolesc* **28**, 4-9, doi:10.1111/jora.12379 (2018).
15 Whittle, S. *et al.* Positive parenting predicts the development of adolescent brain structure: a longitudinal study. *Dev Cogn Neurosci* **8**, 7-17, doi:10.1016/j.dcn.2013.10.006 (2014).
16 Romund, L. *et al.* Maternal parenting behavior and emotion processing in adolescents-An fMRI study. *Biol Psychol* **120**, 120-125, doi:10.1016/j.biopsycho.2016.09.003 (2016).
17 Whittle, S. *et al.* Adolescents' depressive symptoms moderate neural responses to their mothers' positive behavior. *Social cognitive and affective neuroscience* **7**, 23-34 (2011).
18 Lee, T. H., Miernicki, M. E. & Telzer, E. H. Families that fire together smile together: Resting state connectome similarity and daily emotional synchrony in parent-child dyads. *Neuroimage* **152**, 31-37, doi:10.1016/j.neuroimage.2017.02.078 (2017).
19 Lee, K. H., Siegle, G. J., Dahl, R. E., Hooley, J. M. & Silk, J. S. Neural responses to maternal criticism in healthy youth. *Soc Cogn Affect Neurosci* **10**, 902-912, doi:10.1093/scan/nsu133 (2015).
20 Aupperle, R. L. *et al.* Neural responses to maternal praise and criticism: Relationship to depression and anxiety symptoms in high-risk adolescent girls. *NeuroImage: Clinical* **11**, 548-554, doi:https://doi.org/10.1016/j.nicl.2016.03.009 (2016).
21 Cohen Kadosh, K. *et al.* Using real-time fMRI to influence effective connectivity in the developing emotion regulation network. *Neuroimage* **125**, 616-626, doi:10.1016/j.neuroimage.2015.09.070 (2016).
22 Miller, C. H., Hamilton, J. P., Sacchet, M. D. & Gotlib, I. H. Meta-analysis of Functional Neuroimaging of Major Depressive Disorder in Youth. *JAMA Psychiatry* **72**, 1045-1053, doi:10.1001/jamapsychiatry.2015.1376 (2015).
23 McLaughlin, K. A., Peverill, M., Gold, A. L., Alves, S. & Sheridan, M. A. Child Maltreatment and Neural Systems Underlying Emotion Regulation. *J Am Acad Child Adolesc Psychiatry* **54**, 753-762, doi:10.1016/j.jaac.2015.06.010 (2015).
24 Shipman, K. L. *et al.* Maternal Emotion Socialization in Maltreating and Non-maltreating Families: Implications for Children's Emotion Regulation. *Social Development* **16**, 268-285, doi:10.1111/j.1467-9507.2007.00384.x (2007).
25 Cui, L. *et al.* Adolescent RSA responses during an anger discussion task: Relations to emotion regulation and adjustment. *Emotion* **15**, 360-372, doi:10.1037/emo0000040 (2015).
26 Caria, A. *et al.* Regulation of anterior insular cortex activity using real-time fMRI. *Neuroimage* **35**, 1238-1246, doi:10.1016/j.neuroimage.2007.01.018 (2007).
27 Lawrence, E. J. *et al.* Self-regulation of the anterior insula: Reinforcement learning using real-time fMRI neurofeedback. *Neuroimage* **88**, 113-124, doi:10.1016/j.neuroimage.2013.10.069 (2014).
28 Zilverstand, A., Sorger, B., Sarkheil, P. & Goebel, R. fMRI neurofeedback facilitates anxiety regulation in females with spider phobia. *Front Behav Neurosci* **9**, 148, doi:10.3389/fnbeh.2015.00148 (2015).
29 Breslau, J. *et al.* Sex differences in recent first-onset depression in an epidemiological sample of adolescents. *Translational psychiatry* **7**, e1139 (2017).
30 Steinberg, L. *et al. Developmental psychopathology: Vol. 2. Developmental neuroscience*. (Wiley New York, NY, 2006).
31 U.S. Census Bureau Current Population Survey Annual Social and Economic Supplement (2016).
32 Zeman, J., Shipman, K. & Suveg, C. Anger and sadness regulation: predictions to internalizing and externalizing symptoms in children. *J Clin Child Adolesc Psychol* **31**, 393-398, doi:10.1207/S15374424JCCP3103_11 (2002).
33 Young, K. D. *et al.* Real-Time Functional Magnetic Resonance Imaging Amygdala Neurofeedback Changes Positive Information Processing in Major Depressive Disorder. *Biol Psychiatry* **82**, 578-586, doi:10.1016/j.biopsych.2017.03.013 (2017).
34 Kerr, K. L. *et al.* in *Annual Meeting of the Society for Neuroscience* (San Diego, CA, 2018).
35 Mehta, S., Grabowski, T. J., Razavi, M., Eaton, B. & Bolinger, L. Analysis of speech-related variance in rapid event-related fMRI using a time-aware acquisition system. *Neuroimage* **29**, 1278-1293, doi:10.1016/j.neuroimage.2005.03.039 (2006).
36 Xu, Y. *et al.* Denoising the speaking brain: toward a robust technique for correcting artifact-contaminated fMRI data under severe motion. *Neuroimage* **103**, 33-47, doi:10.1016/j.neuroimage.2014.09.013 (2014).
37 Schneider, R. & Fruzzetti, A. The parent-child validation/invalidation coding scales. Unpublished manuscript. (2002).
38 Morawetz, C., Bode, S., Derntl, B. & Heekeren, H. R. The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies. *Neurosci Biobehav Rev* **72**, 111-128, doi:10.1016/j.neubiorev.2016.11.014 (2017).