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Irritability uniquely predicts prefrontal cortex activation during preschool inhibitory control among all temperament domains: A LASSO approach

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Abstract

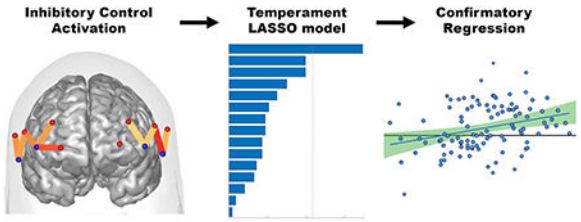
Temperament, defined as individual variation in the reactivity and regulation of emotional, motor, and attentional processes, has been shown to influence emotional and cognitive development during the preschool period (ages 4–5). While relationships between temperament and neural activity have been investigated previously, these have typically investigated individual temperament dimensions selected *ad hoc*. Since significant correlations exist between various temperament dimensions, it remains unclear whether these findings would replicate while analyzing all temperament dimensions simultaneously. Using functional near infrared spectroscopy (fNIRS), 4–5-year-old children (N=118) were administered a Go/No-Go task to assess prefrontal cortex activation during inhibitory control. The relationship between PFC activation and all 15 temperament domains defined by the Children's Behavior Questionnaire (CBQ) was assessed using automatic feature selection via LASSO regression. Results indicate that only the Anger/Frustration dimension was predictive of activation during the inhibitory control task. These findings support previous work showing relationships between irritability and prefrontal activation during executive function and extend those findings by demonstrating the specificity of the activation-irritability relationship among temperament dimensions.

Grahical abstract

[*]To whom correspondence regarding this article should be addressed: Frank Fishburn, University of Pittsburgh, Department of Psychiatry, The Loeffler Building, 121 Meyran Ave, Room 139, Pittsburgh, PA 15213, Ph: (412) 383-5280, fishburnf@upmc.edu, All stimuli and analysis code are available upon request through contact with the corresponding author (www.lcbd.pitt.edu). Author Note.

Ethics Statements

The authors are in full agreement that this paper be submitted to *NeuroImage*. We have no conflicts of interest, financial or otherwise, that would preclude a fair review or publication of this manuscript. This manuscript is not submitted for publication elsewhere, nor have any of the results been previously published or posted on any website. Approval to conduct this study was obtained from the University of Pittsburgh Institutional Review Board and informed consent was obtained from our subjects.



Keywords

Functional near-infrared spectroscopy (fNIRS); preschool; temperament, PFC; irritability; inhibitory control

1. Introduction

The preschool period (ages 4–5) is characterized by the rapid development and integration of emotional and cognitive systems. These maturational changes are hypothesized to be shaped by a child's temperament, defined as individual variation in the reactivity and regulation of emotional, motor, and attentional processes (Rothbart, 2007). Individual differences in temperament are observable from early infancy (Rothbart, 1981), are largely consistent across the lifespan (Caspi et al., 2003; Kopala-Sibley et al., 2018), and have a strong genetic basis (Posner et al., 2007). Although temperament has been widely studied, what remains unknown is how these emotional, motor, and attentional processes interact, which likely comprises both bottom-up reactive/affective and top-down regulatory processes.

Evidence has shown that affective and regulatory systems (e.g. cognitive control) are tightly coupled and interact through basic executive function (Blankson et al., 2013; Ferrier et al., 2016; Gray, 2004); a family of top-down mental processes required for effortful planning and execution of goal-directed behavior (Diamond, 2013). The construct of executive function is closely related to the temperamental construct of effortful control (Gagne, 2017; Zhou et al., 2011), though the latter is generally used in a more emotional context and with younger subjects. For consistency, we will use the term executive function throughout. The core processes of executive function are working memory, cognitive flexibility, and inhibitory control (Miyake et al., 2000). Importantly, executive functions are hypothesized to be tools by which individuals exert control over affective reactivity (Barkley, 2001). They emerge in nascent form in early infancy and reach a steep slope of development, with a large degree of individual variability, as they continue to mature throughout the preschool period (Diamond, 2006). Inhibitory control, specifically, involves the ability to selectively override natural impulses (both motor and affective) when appropriate, thus making it an important cognitive tool for affective regulation. This is particularly true in the transition from toddlerhood to preschool when greater emphasis is placed on the regulation of both positive (i.e. waiting until after dinner to eat dessert) and negative impulses (i.e. tolerating frustration without a tantrum). Inhibitory control begins development in infancy and matures rapidly throughout childhood (Diamond, 1990). Previous research notes the predictive value of toddlerhood and preschool age on inhibitory control across the lifespan. For example, inhibitory control abilities at toddlerhood predict early development of conscience

(Kochanska et al., 1997) and the internalizing of social norms (Bufferd et al., 2016; Kochanska et al., 1996). Further, low inhibitory control in toddlerhood has been noted to predict early school age emergence of externalizing problems (Kochanska and Knaack, 2003). Perhaps the most widely-known example of the stability and predictive nature of early childhood inhibitory control comes from a series of studies by Mischel and colleagues examining the related, higher-order, construct of delay of gratification (Mischel et al., 1972). Children who were able to wait during a 15-minute delay period to receive 2 marshmallows, rather than the immediate reward of 1 marshmallow, were demonstrated to have higher educational attainment (Ayduk et al., 2000; Mischel et al., 1972), lower body mass index (Schlam et al., 2013), and better self-regulatory competencies in later childhood (Shoda et al., 1990); all of which are instances of the application of inhibitory control to everyday life. A separate, 40-year longitudinal study confirmed some of the same results, showing that higher inhibitory control in childhood predicted better adult outcomes for health, wealth, incarceration, parenting, and substance abuse (Moffitt et al., 2013).

Inhibitory control is linked to several brain regions, though most prominently the prefrontal cortex (PFC). Converging evidence across neuroimaging modalities has found PFC activation during inhibitory control tasks using magnetoencephalography (Sasaki et al., 1993), electroencephalography (Gemba and Sasaki, 1989), positron emission tomography (Kawashima et al., 1996), functional magnetic resonance imaging (Aron et al., 2004; Konishi et al., 1998; Ridderinkhof et al., 2004), and function near-infrared spectroscopy (Boecker et al., 2007) in adult populations. Specifically, inhibitory control has been linked to activation of the right inferior frontal gyrus (IFG) (Aron et al., 2004; Garavan et al., 1999; Rubia et al., 2003). Developmental functional neuroimaging research has also linked inhibitory control to PFC activation in children ages 6–10 (Durston et al., 2002), 7–12 (Casey et al., 1997), and 8–12 (Bunge et al., 2002). Specific to the preschool period, the often noted steep maturational slope of executive function coincides with major developmental changes within the PFC (Diamond, 2002). Notably, the preschool years are a time of rapid structural maturation of this region (Shaw et al., 2006). Further speaking to the temperamental stability of early childhood inhibitory control in relation to its neural substrates, one investigation contacted the adults who had originally participated in Mischel's 1972 marshmallow study (Mischel et al., 1972) as children and scanned their brains, using fMRI, during an inhibitory control, Go/No-Go task (Casey et al., 2011). Forty years after their preschool marshmallow test, it was found that individuals who were able to inhibit the desire for reward in early childhood were better able to inhibit a response during task performance. However, this effect was only present during an emotional version of the task (i.e., respond to fearful faces and inhibit response to happy faces), which points to the role of executive function in affect regulation. Neuroimaging revealed increased activation in the IFG for subjects who were able to inhibit in early childhood, along with increased striatal activation, a region important for reward processing in subjects unable to inhibit in preschool. These data suggest a neural substrate for inhibitory control, with a developmental timeline consistent with that of behavioral inhibition abilities and extending into adulthood in affective contexts, making inhibitory control an ideal target for investigating the neural bases of emotion dysregulation in early childhood.

One domain of temperament that encompasses low inhibitory control during increased negative affect is that of irritability. Irritability is defined as a relative dispositional tendency to respond with anger to blocked goal attainment, and includes both mood (trait) and behavioral (reactive state) dysregulation (Camacho et al., 2018; Wakschlag et al., 2017). Levels of irritable temperament have wide variability in children, ranging from low and easygoing to extremely high and, at the upper percentiles, clinically meaningful (Stringaris et al., 2010; Wakschlag et al., 2015). Notably, neuroimaging studies investigating frustration as a component of irritability have found overlapping circuitry with that of inhibitory control studies. Adult fMRI studies have found prefrontal activation during experimental induction of frustration (Cerqueira et al., 2010), which was found in a separate study to be even greater in chronically-frustrated individuals (Siegrist et al., 2005). Previous research from our group has shown that inducing frustration in typically-developing young children (3–5 years) activates the prefrontal cortex and correlates with irritable temperament in normative samples (Grabell et al., 2017; Perlman et al., 2014), though the relationship is reversed in children who were referred to clinical services for extreme impairment due to excessive temper loss and tantrums (Grabell et al., 2018). Further, activation of middle frontal gyrus and anterior cingulate cortex have been shown to be greater in clinicallyirritable children and adolescents during frustration than non-irritable controls (Rich et al., 2011). Importantly, links have also been established between irritability and executive function. Irritability has been shown to correlate with PFC activation during cognitive flexibility in preschoolers (Li et al., 2017), and inhibitory control-related event-related potentials have been shown to increase in magnitude after frustration induction (Lewis et al., 2006). In older youth, fMRI findings demonstrate deficits in IFG and striatal function during a cognitive flexibility task in children with clinically impairing irritability (Adleman et al., 2011). These data support the notion that irritability and executive function have a shared neural substrate in the prefrontal cortex and that maladaptive levels of irritability reflect a failure to engage the circuits necessary for the effective regulation of emotion.

Numerous previous studies have examined the relationship between brain activation and temperament. However, the specific temperament dimension to examine has generally been selected *ad hoc*, which presents clear challenges. First, temperament dimensions are not orthogonal, with some dimensions even being highly correlated with one another. The problematic aspect of this is that, while the pre-selected dimension may be a good predictor, there are potentially other dimensions that are better predictors. Moreover, once those other predictors are accounted for in the model, they may eclipse any correlation with the pre-selected predictor due to shared variance. Another issue with the pre-selection method is that the results are difficult to interpret without the full context of the other dimensions. For instance, the irritability dimension would have very different implications if paired with sadness than if it were paired with impulsivity (i.e., a negative affect interpretation versus a regulation interpretation). For these reasons, the common practice of analyzing individual temperament dimensions in isolation may be the most direct approach to answer a targeted question, but is inadvisable if a broader picture of the underlying constructs, in relation to each other is of interest. If one were interested in probing the broader picture, s/he might take the approach of independently calculating the correlation between activation and each temperament dimension in isolation. However, this approach introduces a multiple

comparisons problem due to the large number of correlations computed, which could either increase the likelihood of false discovery (type I error) if left uncorrected, or reduce sensitivity (type II error) if corrected. In this investigation, we instead used a model selection method for identifying predictive temperament dimensions, which can then be submitted to correlation analysis. We used the 'least absolute shrinkage and selection operator' (LASSO) method for variable selection (Tibshirani, 1996), which is a data-driven, multivariate model selection analysis that is rarely employed in neuroimaging. LASSO is an automated feature selection method allowing us to identify predictive variables without creating a multiple comparisons problem.

The present study was designed to investigate the relationship between PFC activation during inhibitory control and the entire set of temperamental dimensions. We did this by entering all 15 domains of temperament, as defined by Rothbart and colleagues (Rothbart et al., 2001), into a LASSO model in order to best predict prefrontal activation in 4 & 5 year-old children. Subjects were administered a child-friendly Go/No-Go task while activation was recorded from the prefrontal cortex using functional near-infrared spectroscopy (fNIRS). fNIRS has emerged in recent years as a non-invasive imaging modality well-suited for the study of cortical activity in infants and children (Aslin and Mehler, 2005; Gervain et al., 2011). The nonconfining nature of the apparatus and relative robustness to motion artifacts yield greater compliance and more reliable signal in young subjects than is achievable with fMRI. Based on the prior work associating activation during executive function with irritability, we hypothesized that activation during this inhibitory control task would be predicted by anger/frustration, the domain which best maps to the construct of irritability. Since previous studies have not examined all of the temperament dimensions, we were left to speculate which others might be associated with activation. We hypothesized that the temperament dimensions in which variability in executive function features prominently (i.e. inhibitory control, impulsivity, and attentional focusing) would also be associated with activation during this inhibitory control task.

2. Materials and Methods

2.1 Subjects

One hundred fifty-one typically-developing preschool-aged participants were recruited for the Emotional Growth (EmoGrow) Study. This study was designed to longitudinally assess variability in preschool irritability, and its neural components, as a predictor of childhood psychopathology. Specific focus is placed on the moderating role of the development of executive function in predicting the onset of symptomatology based on preschool temperament. Our goal was to characterize the role of normative levels of irritable temperament in later diagnosis prior to psychopathology onset, thus children were excluded from the study if their parents reported they were seeking clinical services, had any current or past psychiatric diagnosis, or had a first degree relative with a severe psychiatric diagnosis during the lifetime of the child. Data presented in this manuscript are from the first study visit, when 4–5-year-old children completed a battery of emotional and executive function tasks while their brain was monitored using functional near-infrared spectroscopy (fNIRS). Given the subject-compliance challenges of imaging participants in this age range, specific

tasks within the battery were presented to subjects in a random order to ensure a reasonable sample size for each task. From the 151 original subjects, 127 attempted the Go/No-Go task. Others became fatigued and ended testing before the Go/No-Go task could be presented to them. Of these 127 children, computer errors during data collection resulted in the loss of data for 9 subjects. Thus, the analytic sample reported in this manuscript included 118 children (63 male; 55 female) ages 4–5 years (mean=4.87; SD=0.62). Children were identified by their parent/guardian as 73% Caucasian, 19% African-American, 3% Asian, and 6% Biracial (97% Non-Hispanic and 3% Hispanic). There was a large spread in reported family annual incomes (15 earned $0–20,000; 19 earned $21,000–40,000; 14 earned $41,000–60,000; 16 earned $61,000–80,000; 16 earned $81,000–100,000; 16 earned $101,000–120,000; 0 earned $121,000–140,000; 6 earned $141,000–160,000; 16 earned $160,000+).

2.2 Temperament Assessment

The Children's Behavior Questionnaire (CBQ) was administered to the participant's parent or guardian (Rothbart et al., 2001). The CBQ is a questionnaire to survey 15 dimensions of temperament in children aged 3–7 years. The dimensions are: activity level, anger/frustration, approach, attentional focusing, discomfort, falling reactivity & soothability, fear, high intensity pleasure, impulsivity, inhibitory control, low intensity pleasure, perceptual sensitivity, sadness, shyness, and smiling & laughter. The CBQ data were checked for multivariate outliers by computing the Mahalanobis distance between each subject and all of the others (i.e., the leaveone-out method). The threshold for outlier detection was set by visual identification of the inflection point. We have noted correlations between dimensions of the CBQ and neural activation during emotional and executive function tasks in previous publications (Karim and Perlman, 2017; Perlman et al., 2015; Perlman and Pelphrey, 2010).

2.3 Task Procedure

Participants were asked to complete a custom-developed, computerized Go/No-Go task (Figure 1). Participants were told the story of a group of children who were playing outside when it starts to rain. The children would like to keep playing, so it is the participant's job to make the rain go away and the sun to come back. During the 'Inhibition' condition, subjects were presented with a string of sunshine illustrations; each stimulus presented for 1 second followed by a 500 ms ISI. Sunshine illustrations (the "go" stimulus) were interspersed with the occasional raincloud illustration (the "no-go" stimulus). Subjects were instructed to press a button every time they saw sunshine, but to inhibit their response when they saw a rain cloud. During the sensorimotor 'Control' condition, subjects were told that the rain storm had begun and that the children needed umbrellas. A series of umbrella photographs were presented (1 second duration, 500 ms ISI). Subjects were told to press the button every time they saw an umbrella and that there would not be other stimuli present. The task consisted of three blocks per condition with the sequence of blocks alternating between the two conditions; always starting with an 'Inhibition' block and ending with a 'Control' block. Each task block consisted of 20 trials. Within the 'Control' blocks, 100% of trials consisted of "go" stimuli (i.e. umbrellas), while within the 'Inhibition' blocks, 60% of trials consisted of "go" stimuli (i.e. sunshine) and 40% consisted of "no-go" stimuli (i.e. raincloud). Blocks were preceded by 2 seconds of the instructions that were read out loud by the experimenter

(e.g. “Oh no, the rain storm has started. Pick up all the umbrellas”). Blocks were interleaved with a rest period of 12–18 seconds to allow the hemodynamic response to return to baseline. The total task duration was 4 minutes and 27 seconds. Reaction time and accuracy data were collected for each trial. Performance data were lost for one subject, but since performance was at an acceptable level for all of the other subjects, this subject was included in all analyses except those involving task performance.

2.4 fNIRS Data Collection

Non-invasive optical imaging was performed using a continuous-wave NIRScout fNIRS system (NIRx Medical Technologies LLC, Glen Head, NY). Light was emitted at 760 nm and 850 nm from a total of 8 LED light sources and measured from 4 photodiode light detectors, yielding 10 measurement channels per wavelength. The optical signals were collected at 15.625 Hz. Sensors were mounted onto a neoprene head cap, with a source-detector distance of 2.9–3.1 cm. For each participant, the fNIRS head cap was positioned according to the international 10–20 coordinate system with the dorsomedial sources over AF3/AF4, and the ventromedial sources over Fp1/Fp2. Hair was manually parted under the optodes to improve signal detection. The probe extended over middle frontal gyrus (MFG) and inferior frontal gyrus (IFG) of each hemisphere of the PFC (Figure 2). Once the fNIRS instrument was securely and comfortably placed upon the subject’s head, they were seated at a child-size desk. On the desk was a touchscreen computer, designed to present the task and record responses. One experimenter was seated at the desk next to the subject in order to guide him/her through the task. A second experimenter controlled the fNIRS instrument from a separate room with camera monitors. On average, the total fNIRS setup time to place the head cap was around 5 min.

2.5 fNIRS Preprocessing

Preprocessing and activation analyses were carried out using NIRS Brain AnalyzIR toolbox (Santosa et al., 2018). Raw fNIRS intensity signals were first converted to changes in optical density. The data were then corrected for motion artifacts by calculating the temporal derivative and iteratively reweighting the values using Tukey’s bisquare function until the observation weights stabilized. This effectively reduces the magnitude of large fluctuations (i.e., motion) in the signal, while leaving small fluctuations (i.e., hemodynamics) intact. A manuscript detailing this method is currently under review. Signals were then converted to oxygenated and deoxygenated hemoglobin concentrations using the modified Beer-Lambert relationship with a differential pathlength factor of 6 and a partial volume correction of 60 for both wavelengths.

2.6 Quantification of Task Activation

Task activation was quantified by convolving the boxcar function for each condition (‘Go’ and ‘No-Go’) with the canonical hemodynamic response function (HRF) and submitting to a general linear model. To account for slow drift in the signal, a 3rd-order Legendre polynomial regressor was included in the design matrix. Coefficients were estimated using the autoregressive iteratively-reweighted least squares approach (Barker et al., 2013), as it has been shown to account for the presence of serial correlations, including those from systemic physiological oscillations.

The estimated coefficients for both conditions were submitted to a robust weighted mixed effects model, with condition modeled as a fixed effect and subject as a random effect. The response variable and design matrices were weighted using the inverse of the 1st-level coefficient covariance matrices, effectively weighting observations by the reliability of the estimate. The activation of each condition was assessed using the t-contrasts corresponding to 1-sample t-tests. Inhibitory control-related activation was quantified by the 'Inhibition' versus 'Control' t-contrast. Multiple comparisons were controlled for by using the false discover rate (FDR) correction for the number of channels (Benjamini and Hochberg, 1995).

The global amount of activation was assessed for each subject by running within-subject linear mixed models, with 1st-level beta values as the dependent variable, task condition as a fixed effect, and channel ID as a random effect. Only those channels that were found to have significant ($p<.05$, FDR-corrected) activation for the inhibitory control contrast at the group level were included in the subject-level models. The 'Inhibition' versus 'Control' t-contrast was then applied, yielding a single t-statistic per subject quantifying the global amount of activation related to inhibitory control.

2.7 Activation-temperament LASSO model

In order to take a data driven approach to determine which dimensions of temperament were significant predictors of neural activation as a function of inhibitory control, a regression analysis was performed using the 'least absolute shrinkage and selection operator' (LASSO) method for variable selection (Tibshirani, 1996). Linear regression problems can be described by the equation

$$y = X\beta + \varepsilon \quad (1)$$

where X is the matrix of independent variables, β is the vector of coefficients for each independent variable, is the dependent variable, and y is the residual error of the model. The ordinary least squares solution to this regression problem is defined as that which minimizes the mean squared error:

$$\min_{\beta \in \mathbb{R}^p} \left\{ \frac{1}{N} \|y - X\beta\|_2^2 \right\} \quad (2)$$

LASSO regression extends ordinary least squares by adding a regularization term that adjusts by the L^1 norm of the coefficients,

$$\min_{\beta \in \mathbb{R}^p} \left\{ \frac{1}{N} \|y - X\beta\|_2^2 + \lambda \|\beta\|_1 \right\} \quad (3)$$

where λ is a tuning parameter that controls the amount of regularization. By taking the L^1 norm of the coefficient estimates, the LASSO objective function favors solutions with fewer nonzero coefficients, resulting in sparse models. In practice, the choice of the λ parameter is

determined via cross-validation, where the dataset is randomly split and trained on one subset while the prediction error is estimated on the other subset. The prediction error is estimated over a large number of partitions of the data and for a range of values of λ. The value of λ is then selected as the largest value (i.e., most sparse model) that still falls within an acceptable range of prediction error, often one standard error above the minimum (also known as the 'one standard error rule'). Using the LASSO, we determined which CBQ dimensions predicted activation during inhibitory control within a single model, obviating the need for multiple comparisons corrections, which may be overly conservative.

The global activation t-statistics and CBQ scores were first screened for univariate outliers using a robust variant of Chauvenet's criterion

$$\left| \frac{x_s - median(x)}{1.4826\ MAD(x)} \right| > 3 \quad (4)$$

where x is the raw activation or CBQ values, s is the index of a specific subject, MAD is the median absolute deviation, and 1.4826 is a constant scaling factor used to estimate standard deviation of a normal distribution from the MAD. Using this criterion, 9 subjects were excluded from the lasso model (N=109). The data were then checked for multivariate outliers using the Mahalanobis distance (Mahalanobis, 1936), which is defined as

$$d = \sqrt{(x - \mu)\Sigma^{-1}(x - \mu)^T} \quad (5)$$

where x is a vector containing all dimensions (i.e., global activation and CBQ scores) for a given subject, μ is the vector of means for each dimension, and Σ is the of inter-dimension covariance matrix. Since the values of μ and Σ are affected by outliers, the robust variants of these were estimated using minimum covariance determinant via the FAST-MCD algorithm (Rousseeuw, 1985; Rousseeuw and Driessen, 1999). The squared Mahalanobis distance follows a χ^2 distribution with degrees of freedom equal to the number of dimensions, thus the χ^2 inverse cumulative density function was used to generate the outlier detection threshold corresponding to p<.0001. Using this approach, 4 subjects with atypical patterns of relationships between CBQ dimensions or between CBQ dimensions and activation were excluded from the LASSO model (N=105). The robust Mahalanobis distances and threshold are shown in Supplementary Figure 1.

All fifteen temperament dimensions from the CBQ were decorrelated using the 'ZCA-cor' whitening procedure, which orthogonalizes the variables with respect to one another while maximizing the correlation between the original and whitened versions of each variable (Kessy et al., 2017). These decorrelated CBQ scores were entered into the LASSO model as the independent variables and the global inhibitory control activation t-statistic for each subject was entered as the dependent variable. Cross-validation was performed for 10,000 iterations, using the holdout method with a 90/10 split of training and testing data. The value of λ was chosen by selecting the largest lambda (i.e., most regularization, fewest non-zero coefficients) that yields a cross-validation error within 1 standard error of the minimum.

As described in Eqn. (3), the LASSO model penalizes the L^1 norm of the coefficients, assessed at varying levels of regularization, λ. Based on this, highly predictive regressors will be present in the model even at large values of λ, while nonpredictive regressors will be excluded at lower values of λ. For this reason we have visualized the results of the lasso model by showing for each regressor the maximal value of λ that was achieved before it was excluded from the model. Thus, the more predictive values regressors will have a higher max(λ) than less predictive.

Follow-up correlation analysis of the LASSO-selected temperament dimensions was performed by regressing the inhibitory control activation t-statistic onto the whitened CBQ dimensions that were selected by the LASSO model. Robust regression was employed for this analysis, using Tukey's bisquare weighting function and a tuning constant of 4.685, which yields 95% efficiency compared to ordinary least squares. All analyses were carried out using both oxygenated and deoxygenated hemoglobin signals. However, since the LASSO model only yielded significant results for the oxygenated signal, only the data from the oxygenated signal are presented.

3. Results

3.1 Temperament

The range, means, standard deviations, LASSO support, and correlation with neural activation are shown for each CBQ dimension in Table 1. The CBQ scores showed wide variability as one would expect from a normative sample. The correlations between CBQ dimensions are shown in Supplementary Figure 2.

3.2 Task performance

Task accuracy was high for both the 'Inhibition' (mean=80.66%; SD=13.06%) and 'Control' conditions (mean=90.97%; SD=9.26%). As expected, accuracy was lower during the 'Inhibition' condition than 'Control' ($t(116)=8.93$, $p<10^{-14}$). Reaction time was reasonably fast for both 'Inhibition' (mean=597 ms; SD=132 ms) and 'Control' conditions (mean=459 ms; SD=125 ms). Reaction time was greater for the 'Inhibition' condition than 'Control' ($t(116)=12.96$, $p<10^{-23}$).

3.3 PFC activation during inhibitory control

The activation images for both the 'Inhibition' and 'Control' conditions, as well as the 'Inhibition'-'Control' contrast are shown in Figure 3. The 'Inhibition' condition elicited significantly greater activation than 'Control' in 9 out of 10 channels ($p<.05$; FDR-corrected).

3.4 Association between performance and inhibitory control-related PFC activation

The change in reaction time increases associated with the addition of inhibitory control (i.e., 'Inhibition'–'Control') correlated positively ($r(115)=.190$, $p<.05$) with the mean increase in PFC activation (Figure 4).

3.5 Association between temperament and inhibitory control-related PFC activation

The LASSO model selection procedure yielded only the Anger/Frustration dimension of the CBQ as a significant predictor of mean task activation for the 'Inhibition'–'Control' contrast (Figure 5). Follow-up robust regression analysis revealed a positive correlation between Anger/Frustration score and inhibitory control-related PFC activation ($r(103)=.282$, $p<.01$; Figure 6). For transparency and validation purposes, the Pearson correlations between the global activation t-statistic and the raw scores for each of the CBQ dimensions are presented alongside the results of the LASSO model (Table 1). Only Anger/Frustration had a significant correlation with activation at an uncorrected threshold of $p<.05$.

4. Discussion

4.1 General Discussion

The current study examined the relationship between inhibitory control-related activation and temperament in a cross-sectional study of 4–5-year-old children. Using a data-driven approach to multivariate feature selection, we assessed the relative contribution of all 15 temperament domains to predicting activation during an inhibitory control task. The results showed that the Anger/Frustration subscale was uniquely predictive among temperament domains of the amount of activation related to inhibitory control. To our knowledge, this is the first developmental study to rigorously test linkages between the full range of temperament dimensions and PFC activation, generating novel data on the specificity of these patterns.

Our first finding demonstrated a relationship between the behavioral and neural correlates of inhibitory control. We found that the more participants slowed down to respond to no-go trials, compared to their speed on go trials, the greater their PFC activation. Thus, children who were more impulsive and less able to inhibit their prepotent response also engaged their PFC to a lesser extent. This increase in reaction time, correlating with the increase in PFC activation, falls in line with existing research finding that the cognitive demands of inhibitory control yield greater engagement of the prefrontal cortex in children (Bunge et al., 2002; Casey et al., 1997; Durston et al., 2002; Inoue et al., 2012). Our study, however, is amongst the first to demonstrate this pattern in preschool age children (4–5 years). Much like our previous study which discovered that the neural correlates of working memory have developed by the age of three (Perlman et al., 2016), in this study we have found early childhood PFC engagement during a second domain of executive function, i.e., inhibitory control. Here, we demonstrate that the neural correlates of inhibitory control are in place by late preschool age, but may continue to specialize and increase throughout development. This will surely be an important question to investigate as the study continues its longitudinal progress.

Our data-driven feature selection method led to partial confirmation of our hypotheses. Specifically, only the Anger/Frustration temperament dimension, among all 15 temperament dimensions, predicted inhibitory control-related activation. The specific directionality of this relationship, however, is a challenge to predict *a priori*. On the one hand, children high in irritability could have decreased PFC activation during executive function, which could

underlie their low tolerance to emotional distress. On the other hand, children who are high in irritable temperament, but also within a normative range of functioning, may have excellent executive functioning, which allows them to recruit the PFC at an increased rate during emotional and cognitive challenges and prevent impairment. This heightened neural component of executive function may serve as a buffer against the development of psychopathology at middle childhood. The present study found that the higher the preschool-age child was in irritability, the more PFC activation increased during inhibitory control (a positive correlation), supporting the second possibility. Thus, this finding represents a replication and extension of our previous research. In the domain of executive function, we have previously found that lateral PFC activation positively correlates with irritability in 3–5 year-olds during a cognitive flexibility task (Li et al., 2017). In the domain of affective regulation, we have previously demonstrated that irritable temperament is predictive of lateral PFC activation during a child-friendly frustration induction in typicallydeveloping children (Perlman et al., 2014), but that children who fall within the clinically severe range of irritability demonstrate decreased PFC activation during the same frustration induction in both preschool (Grabell et al., 2018) and middle childhood (Perlman et al., 2015). Of note, temperamental measures are not optimized to capture the full normal-abnormal spectrum of irritability, particularly in terms of differentiating those children at the more severe end of the spectrum. Taken together, the results of this investigation and those of our previous research might indicate that within the irritable domain of temperament, children who are rated high by their parents, but are within the normative range of functioning, might be particularly adept at exerting neural executive function, both in a basic cognitive context, but also in a context in which executive function is needed to regulate affect.

Our hypotheses that additional temperament domains theorized to link the neural underpinnings of inhibitory control (i.e., Impulsivity, Inhibitory Control, Attentional Focusing), however, were not confirmed. Specifically, no other domains of temperament were selected by the LASSO model. One possible explanation for this finding is that the Go/No-Go task and temperament domains of the CBQ are probing different applications of the same construct. Our simple Go/No-Go task tests the most basic component of the inhibitory control construct by inducing a prepotent response, then infrequently deviating from the established pattern, requiring the *participant* to monitor and suppress the established response. In contrast, the CBQ questions the *parent* about general behavioral regulation within the social context in which they observe their child. It may be the case that this temperament questionnaire encompasses a much broader and applied definition of inhibitory control, which is influenced by other factors such relationships, the social environment of the child, and parent disciplinary strategies. Indeed recent research replicating and extending Mischel's original marshmallow task (Mischel et al., 1972; Shoda et al., 1990) finds that children from disadvantaged backgrounds are less likely to control impulses and delay the consumption of a desired treat (Watts et al., 2018). This discrepancy in findings may point to influences from the social environment, in which, disadvantage children may be overwhelmed by the scarcity of resources in their home or be less able to trust unfamiliar experimenters. A second explanation for the lack of findings in the cognitive temperament domains may be related to additional demands of the task. The Go/No-Go task

represents additional attentional, motor control, and working memory demands that may not be well-represented in any single domain of the temperament questionnaire. This explanation is supported by studies indicating that there are multiple dissociable forms of inhibitory control (Diamond, 2013). Indeed, these executive components may be better amalgamated in an affective construct, such as irritability, that encompasses a mixture of emotional response and control. The use of multi-method approaches to temperament (e.g., the LAB-TAB) may further elucidate this question.

4.2 Limitations

Although this study makes important contributions to the neurodevelopmental literature, some limitations must be noted. First, we limited our investigation to the prefrontal cortex, as it has a well-defined role in inhibitory control and is known to yield high quality signal using fNIRS, which can only measure regions located in the superficial cerebral cortex. Thus, our study only measured activation within a limited portion of the brain, while additional regions such as parietal cortex and the frontro-striatal pathway (Clare et al., 2004; Durston et al., 2002) are known to be relevant for inhibitory control, especially within an affective context (Jarcho et al., 2013; Leibenluft et al., 2007; Perlman et al., 2015). A second limitation of this study is that we only included children within the normative range of developmental functioning. Previous work from our group has shown an inverted U-shaped association for irritability and activation during a frustration task, wherein activation was high for those with moderate/normative irritability and low for those with low or clinically-high irritability (Grabell et al., 2018). From the present study it is unclear whether a similar non-linear association would be found if we extended the sample to children with impairing levels of irritability. An additional limitation is that significant results were only achieved using the oxygenated hemoglobin signal. While oxygenated and deoxygenated hemoglobin concentrations are negatively correlated, it is widely known that the deoxygenated signal has a poorer signal-to-noise ratio than the oxygenated signal (Maki et al., 1995; Strangman et al., 2002). It may be the case that similar results would be obtained from the deoxygenated signal if the signal-to-noise ratio were higher, which is especially difficult to achieve in a sample of young subjects who are prone to movement. One final limitation is that the cross-sectional nature of this study does not allow within-subject investigation of irritability as a function of developmental changes in executive function. However, this dataset is drawn from the first time point of an ongoing longitudinal study. Thus, future directions include charting these maturational changes as children age into middle childhood. An additional priority for further work in this domain is to extend these findings to functional connectivity, to determine the relevance of functional integration of the prefrontal cortex in mediating the link between irritability and executive function.

4.3 Concluding Remarks

While previous studies have examined correlations between brain activation and individual temperament domains that were selected *ad hoc*, few have simultaneously examined the contribution of all temperamental domains. Notably, Karalunas and colleagues (2014) used the entire CBQ to derive distinct subtypes of ADHD using community detection techniques. To our knowledge, the present study is the first to employ a data-driven feature selection strategy to simultaneously assess the relationship between all temperament dimensions and

neural activation. Thus, for the first time, we have evidence that temperamental irritability predicts activation during executive function above and beyond any other temperamental traits, including those that are notionally related to executive processes. This study adds to the growing literature supporting a shared neural resource for executive function and irritability, but also lays the foundation for future longitudinal work investigating the developmental trajectory of neurodevelopment of the prefrontal cortex within the broader context of temperament.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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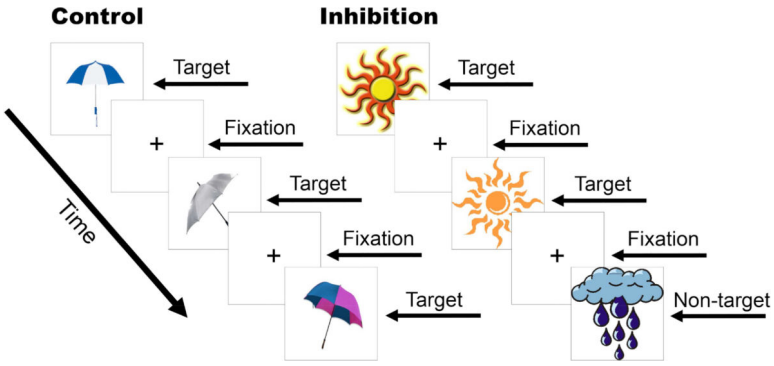

Figure 1. Go/No-go task design

Stimuli in the 'Control' blocks were umbrellas, which were all targets ('go'). In the 'Inhibition' block sun images served as targets ('go') and infrequent rain images were non-targets ('no-go').

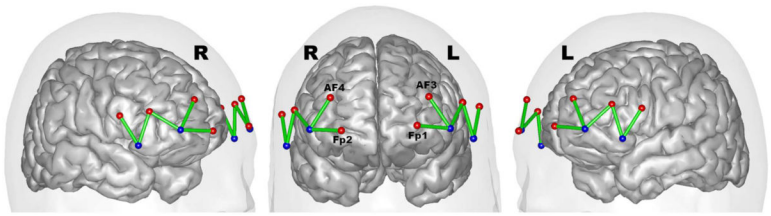

Figure 2. Probe configuration

The probe is visualized on the surface of the scalp after registration to the Colin27 atlas. Red spheres are optical sources, blue spheres are detectors, and green connections are measurement channels. The probe covered the anterior portion of bilateral inferior frontal gyrus (IFG), and middle frontal gyrus (MFG). Positioning was performed using the 10–20 coordinate system by placing the dorsomedial sources over AF3/AF4, and the ventromedial sources over Fp1/Fp2.

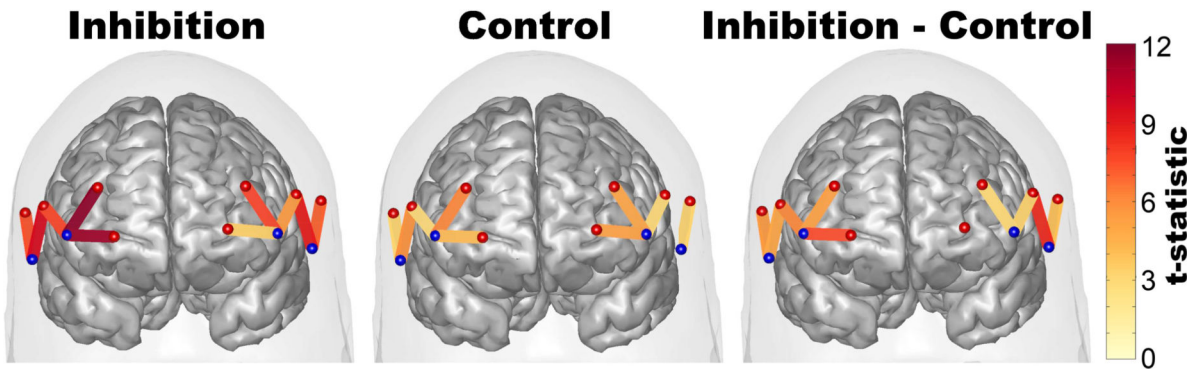

Figure 3. Go/No-go activation

Activation is shown for the ‘Inhibition’ and ‘Control’ conditions, as well as the ‘Inhibition’-’Control’ contrast. All images are thresholded at $p<.05$, with Benjamini-Hochberg FDR correction for the number of channels.

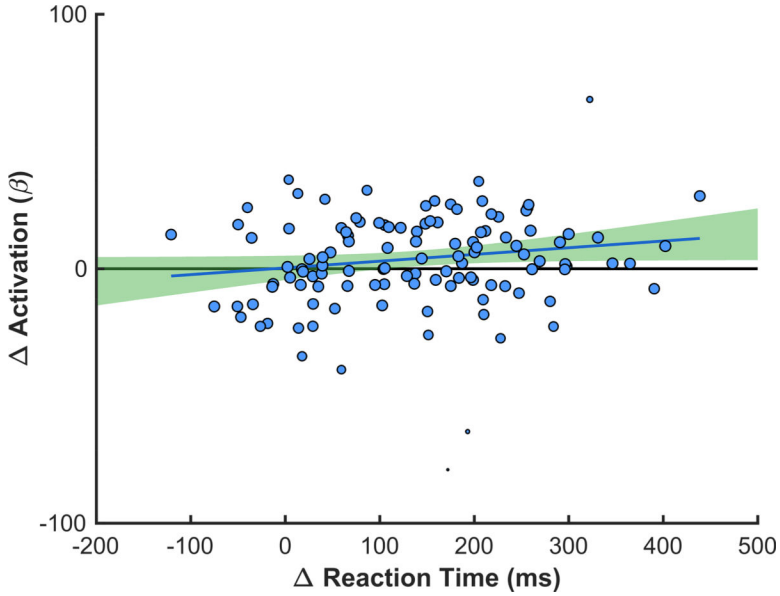

Figure 4. IC-related reaction time predicts activation

The change in reaction time during the Go/No-go (i.e., 'Inhibition'-'Control') predicted the change in PFC activation during inhibitory control ($r(115)=.190$, $p<.05$). Size of points reflects the robust regression weights (i.e., from extreme low or high activation levels). Green shaded area reflects the 95% prediction confidence interval.

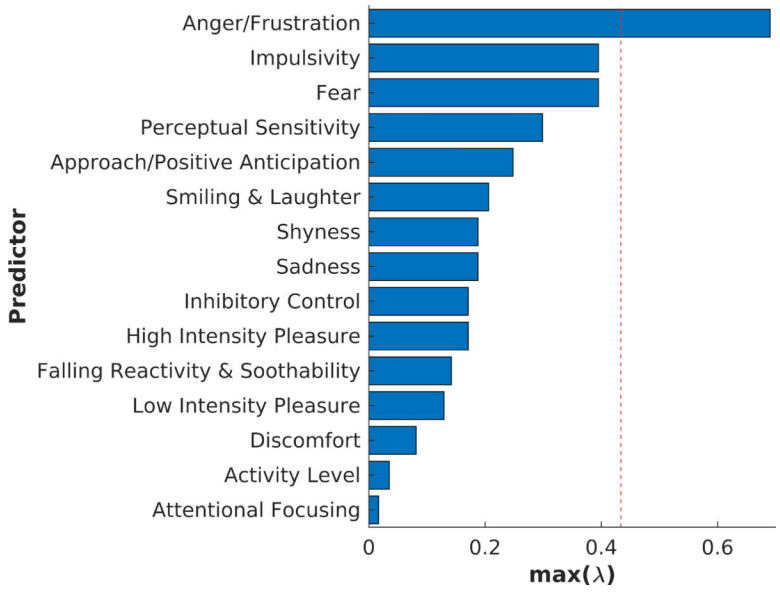

Figure 5. Model selection using LASSO

Bar plot showing the maximum value of lambda for each of the whitened temperament domains in the LASSO model. The red dashed line reflects the cross-validation-derived threshold for variable inclusion. The LASSO model selected only the Anger/Frustration dimension.

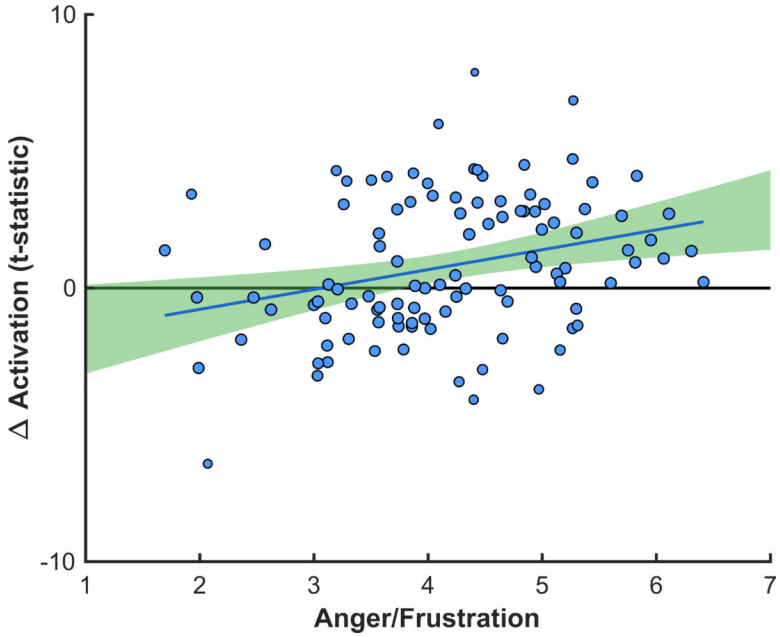

Figure 6. Anger/Frustration predicts inhibitory control activation

Follow-up robust regression analysis of the dimensions selected by the LASSO model revealed a significant positive relationship between Anger/Frustration and activation ($r(103)=.282$; $p<.01$). Size of points reflects the robust regression weights. Green shaded area reflects the 95% prediction confidence interval.

Table 1.
CBQ descriptive statistics and relationship with activation.

The range, mean, standard deviation, maximum λ in the LASSO model, and Pearson correlation with activation are presented for each of the 15 CBQ dimensions.

Dimension	Range	Mean (SD)	max. λ	Correlation
Activity Level	2.57 – 6.57	4.85 (0.75)	.035	−.035
Anger/Frustration	1.50 – 6.67	4.21 (1.06)	.691 *	.255 †
Approach/Positive Anticipation	3.00 – 6.50	5.04 (0.70)	.248	−.094
Attentional Focusing	1.67 – 6.83	4.97 (0.94)	.017	−.016
Discomfort	1.17 – 7.00	4.35 (1.08)	.081	.008
Falling Reactivity & Soothability	2.17 – 7.00	5.01 (0.86)	.142	−.071
Fear	1.67 – 6.83	3.80 (1.13)	.395	.162
High Intensity Pleasure	2.50 – 7.00	4.78 (0.93)	.171	.063
Impulsivity	1.83 – 6.83	4.27 (0.89)	.395	−.129
Inhibitory Control	2.00 – 6.83	4.81 (0.93)	.171	.047
Low Intensity Pleasure	1.75 – 7.00	6.11 (0.78)	.129	.064
Perceptual Sensitivity	2.67 – 7.00	5.37 (0.87)	.299	.124
Sadness	1.86 – 6.29	4.09 (0.82)	.188	−.013
Shyness	1.00 – 6.67	3.58 (1.20)	.188	.013
Smiling & Laughter	2.83 – 6.50	5.55 (0.52)	.206	.070

*indicates inclusion in the LASSO model (max. λ>.434).

†indicates a significant correlation with inhibitory control-related activation (p<.05).