NeuroImage 184 (2019) 68–77

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

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

Frank A. Fishburn[a,*], Christina O. Hlutkowsky[a], Lisa M. Bemis[a], Theodore J. Huppert[b], Lauren S. Wakschlag[c,d], Susan B. Perlman[a]

[a] University of Pittsburgh, Department of Psychiatry, United States
[b] University of Pittsburgh, Department of Radiology, United States
[c] Northwestern University, Institute for Innovations in Developmental Sciences, United States
[d] Northwestern University Feinberg School of Medicine, Department of Medical Social Sciences, United States

ARTICLE INFO

Keywords:
Functional near-infrared spectroscopy (fNIRS)
Preschool
Temperament
PFC
Irritability
Inhibitory control

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.

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

* Corresponding author. University of Pittsburgh, Department of Psychiatry, The Loeffler Building, 121 Meyran Ave, Room 139, Pittsburgh, PA, 15213, United States.

E-mail address: fishburnf@upmc.edu (F.A. Fishburn).

https://doi.org/10.1016/j.neuroimage.2018.09.023
Received 9 July 2018; Received in revised form 31 August 2018; Accepted 7 September 2018
Available online 11 September 2018
1053-8119/

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-min 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 clinically-irritable 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.