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Juvenile onset depression alters cardiac autonomic balance in response to psychological and physical challenges

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ABSTRACT

Cardiac autonomic balance (CAB) indexes the ratio of parasympathetic to sympathetic activation (Berntson, Norman, Hawkley, & Cacioppo, 2008), and is believed to reflect overall autonomic flexibility in the face of environmental challenges. However, CAB has not been examined in depression. We examined changes in CAB and other physiological variables in 179 youth with a history of juvenile onset depression (JOD) and 161 healthy controls, in response to two psychological (unsolvable puzzle, sad film) and two physical (handgrip, and forehead cold pressor) challenges. In repeated measures analyses, controls showed expected reductions in CAB for both the handgrip and unsolvable puzzle, reflecting a shift to sympathetic relative to parasympathetic activation. By contrast, JOD youth showed increased CAB from baseline for both tasks (p's < .05). No effects were found for the forehead cold pressor or sad film tasks, suggesting that CAB differences may arise under conditions requiring greater attentional control or sustained effort.

Abnormalities in autonomic nervous system functioning have been associated with depression. More specifically, there is qualified support for an association between major depression in adults and low resting parasympathetic nervous system (PNS) activity, as indexed by resting levels of respiratory sinus arrhythmia, with mostly positive (RSA; Kemp et al., 2010; Kikuchi et al., 2009; Rottenberg, 2007; Udupa, Sathayaprabha, Thirthalli, Kishore, Lavekar, et al., 2007; Udupa, Sathayaprabha, Thirthalli, Kishore, Raju, et al., 2007) but some negative results (e.g., Lehofer et al., 1997; Licht et al., 2008; Yeragani et al., 1991). More consistent findings have been observed for RSA reactivity in response to laboratory tasks, with depressed adults exhibiting blunted RSA withdrawal to a laboratory speech stressor (Bylsma, Salomon, Taylor-Clift, Morris, & Rottenberg, 2014; Rottenberg, Clift, Bolden, & Salomon, 2007), as well as a handgrip task (Nugent, Bain, Thayer, Sollers, & Drevets, 2011). These patterns are postulated to relate to poorer self regulation. Elsewhere, we have found that atypical patterns of resting RSA and RSA reactivity in youths with a history of juvenile onset depressed predicted deficits in mood repair, where mood repair refers to behaviors that decrease feelings of sadness or dysphoria (e.g., Josephson, Singer, & Salovey, 1996), as assessed by both trait measures and laboratory probes (Yaroslavsky et al., 2015)). We have also found that atypical patterns of resting RSA and RSA reactivity are more highly concordant in siblings with a history of depression, suggesting that aspects of autonomic functioning may be heritable (Yaroslavsky, Rottenberg, & Kovacs, 2014).

To a lesser extent, abnormalities in sympathetic nervous system (SNS) activity have also been observed in depressed adults. For example, Saloman, Clift, Karlsdottir, and Rottenberg (2009) and Salomon, Bylsma, White, Panaite, and Rottenberg (2013) found blunted sympathetic nervous system (SNS) reactivity to a laboratory stressor task, as indexed by lengthened pre-ejection period (PEP), although others have found shorter PEP in individuals with depressive symptoms (Light, Kothandapani, & Allen, 1998). Overall, research thus far reveals mixed evidence of PNS and SNS deficits in depression.

To date, depression research has focused almost exclusively on individual parasympathetic or sympathetic indices. This exclusive focus is unfortunate in light of recent theory argues arguing for

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the critical importance of integrating sympathetic and parasympathetic control to provide a comprehensive understanding of behavioral and affective reactivity and regulation (Berntson, Cacioppo, & Quigley, 1991). In fact, the historical views of reciprocally determined activity in both branches of the autonomic nervous system (e.g., activity increases in one branch would be accompanied by invariable decreases in the other) have been largely overturned by new theory and data, which indicate that both autonomic branches can react either independently or together, resulting in complex physiological patterns, including co-activation and co-inhibition (Berntson et al., 1991, 2008). Importantly, theory and empirical evidence have indicated that reciprocal sympathetic activation (increases in sympathetic activity in conjunction with decreases in parasympathetic activity) during stress responses are ordinarily adaptive, whereas reciprocal parasympathetic activation would be most adaptive in calm and relaxed states (Berntson et al., 1994; El-Sheikh et al., 2009). Thus, examination of the balance of parasympathetic and sympathetic activity may lead to a more complete picture of regulatory functioning and risk for depression.

Berntson et al. (2008) has previously defined two useful indices for describing complex patterns in autonomic space: cardiac autonomic balance (CAB) and cardiac autonomic regulation (CAR). These indices are derived from a parasympathetic index, RSA, and a sympathetic index, PEP. RSA is a parasympathetically mediated variation in heart rate that is germane to individual differences in emotional functioning and regulation capacity in adults and youth (e.g., Beauchaine, 2001; Musser et al., 2011; Yaroslavsky, Bylsma, Rottenberg, & Kovacs, 2013; Yaroslavsky et al., 2014). PEP is a sympathetically mediated index that reflects the time between left ventricular depolarization and ejection of blood through the aorta, with smaller values indicating greater SNS activity (Berntson et al., 1994). PEP has been viewed as an index of effort mobilization needed to meet environmental demands (with decreases in PEP reflecting increased effort mobilization) required for behavioral approach (Gendolla, 2012; Kelsey, 2012; Richter & Gendolla, 2009; Richter, Friedrich, & Gendolla, 2008), and it has been validated as a SNS index in children and adolescents (e.g., Matthews, Salomon, Kenyon, & Allen, 2002; McGrath & O'Brien, 2001; Quigley & Stifter, 2006).

CAB is computed as the difference between standardized values of parasympathetic control (RSA) and sympathetic control (PEP) along a bipolar model of autonomic balance. Therefore, higher CAB values reflect greater parasympathetic relative to sympathetic activation. CAR reflects the coactivation or coinhibition of PNS and SNS activity and is computed as the normalized sum of RSA and PEP. Autonomic dysregulation is often described as overactive SNS and hypoactive PNS (i.e., lower CAB), which has been associated with coronary artery disease, increased mortality (for a review, see Thayer, Yamamoto, & Brosschot, 2010), increased risk of metabolic syndrome (Licht, de Gues, & Penninx, 2013), diabetes (Berntson, Norman, Hawkley, & Cacioppo, 2008) and chronic stress states (Lampert, Ickovics, Horwitz, & Lee, 2005), and may serve as a link between negative affect and disease states (Thayer et al., 2010). High CAR (high PNS and CNS coactivation) has also been associated with increased risk for metabolic syndrome (Licht et al., 2013) and prior occurrence of myocardial infarction (Berntson et al., 2008).

While CAB and CAR represent potentially useful indices of autonomic system functioning that reflect autonomic flexibility, they have not yet been examined in the context of depression or depression risk. Prior depression-related work with joint autonomic indices used metrics that have limited interpretability, such as LF/HF ratio (the ratio of low to high frequency heart rate variability; Malliani, 2005; Malliani & Montano, 2002). While depressed and depression-vulnerable persons have been found to have a higher LF/HF ratio (Chang et al., 2012; Nugent et al., 2011; Udupa, Sathayaprabha, Thirthalli, Kishore, Lavekar, et al., 2007; Udupa, Sathayaprabha, Thirthalli, Kishore, Raju, et al., 2007), LF is an ambiguous sympathetic index because, as it is currently defined, LF is contaminated by parasympathetic activity (Berntson et al., 1997; Eckburg, 1997; Reyes del Paso, Langewitz, Mulder, van Roon, & Duschek, 2013). Further, as Heathers (2014) explains, there is no sound mathematical basis to directly compare LF and HF power, as these measures are only internally consistent (i.e., examining changes over time within an individual), so that comparing their relative proportions is questionable. In addition, possible co-activations in the sympathetic and parasympathetic branches are also not taken into account for the LF/HF ratio (Pagani, Lucini, & Porta, 2012).

CAB has been studied once in a depression-relevant sample: Miller, Wood, Lim, Ballow, and Hsu (2009) found that children with asthma who were high on depression symptoms showed greater increases in CAB in response to films depicting distressing scenes of loss, death, and dying (greater increases in PNS relative to SNS activity). In contrast, asthmatic children low on depressive symptoms showed the normative pattern of response to stress (greater decreases in CAB—greater increase in sympathetic relative to parasympathetic activity), which the authors indicated would be most adaptive for airway functioning in these patients. CAR, which reflects the co-activation of sympathetic and parasympathetic activity, has yet to be studied in depression.

The present study focused on cardiac autonomic balance (CAB) in youths with histories of early onset depression and healthy controls with no history of depression. We examined CAB during baseline (viewing a neutral film) and across two physical and two psychological stressor tasks. We expected that the tasks (unsolvable puzzles, handgrip, sad film, and forehead cold pressor) would uncover group differences in psychophysiological reactivity. In studies with healthy individuals, the typical normative response to most laboratory stressors is a decrease in RSA accompanied by an increase in sympathetic relative to parasympathetic activity (Key, Campbell, Bacon, & Gerin, 2008; Lackschewitz, Hüther, & Kröner-Herwig, 2008; O'Donnell, Brydon, Wright, & Steptoe, 2008). However, since the forehead cold pressor task elicits a "dive reflex", which is typically accompanied by activation of the PNS system (Heath & Downey, 1990), we would expect increases in RSA (and likely increases in CAB) in response to this task. Since previous findings have suggested that abnormalities in PNS and SNS activation are associated with depression, we predicted that youth with such a history will fail to show appropriate changes in CAB in response to the stressor tasks. In other words, we expected that healthy controls would show decreases in CAB for the sad film, puzzle, and handgrip tasks or increases in CAB for the forehead cold pressor, while youth with a history of depression would fail to show these changes. As a point of comparison, we also examined effects for the LF/HF ratio, which has been considered another index of autonomic balance. Finally, we included Cardiac Autonomic Regulation (CAR) as a secondary, exploratory measure, given the lack of prior empirical literature.

1. Methods

1.1. Subjects

This study included 216 probands whose histories of childhood onset major depressive disorder (MDD) were previously established (e.g., Baji et al., 2009; Kiss et al., 2007). The probands are a subset of a larger sample, which were gathered in Hungary from approximately 1997–2006 for a prior genetic and clinical study (e.g., Baji et al., 2009; Dempster et al., 2009; Tamás et al., 2007). Probands for the original study were recruited at 23 child mental health and guidance facilities across Hungary and met several study entry criteria, including having current or recent DSM-IV (American Psychiatric Association, 2000) depressive disorder, being 7–14 years old at initial screen, and not mentally retarded. Six probands who came from families with a history of mania were excluded from analyses. Mean age of the