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Higher locus coeruleus MRI contrast is associated with lower parasympathetic influence over heart rate variability

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ABSTRACT

The locus coeruleus (LC) is a key node of the sympathetic nervous system and suppresses parasympathetic activity that would otherwise increase heart rate variability. In the current study, we examined whether LC-MRI contrast reflecting neuromelanin accumulation in the LC was associated with high-frequency heart rate variability (HF-HRV), a measure reflecting parasympathetic influences on the heart. Recent evidence indicates that neuromelanin, a byproduct of catecholamine metabolism, accumulates in the LC through young and mid adulthood, suggesting that LC-MRI contrast may be a useful biomarker of individual differences in habitual LC activation. We found that, across younger and older adults, greater LC-MRI contrast was negatively associated with HF-HRV during fear conditioning and spatial detection tasks. This correlation was not accounted for by individual differences in age or anxiety. These findings indicate that individual differences in LC structure relate to key cardiovascular parameters.

Introduction

Despite having its own pacemaker cells, the heart does not usually beat at a steady rate. Sympathetic and parasympathetic inputs from the brain modulate the timing of the heart's sinoatrial node impulses and increase variability. These sympathetic and parasympathetic inputs have interacting and often opposing effects over heart rate variability (HRV), with parasympathetic input providing the dominant influence (Reyes del Paso, et al., 2013; Uijtdehaage and Thayer, 2000). Parasympathetic vagus nerve input influences both high- and low-frequency oscillations in heart rate, whereas sympathetic input directly influences only low-frequency oscillations (Berntson, et al., 1993; Laitio, et al., 2007), in part because sympathetic influences on the heart are slower due to different neurokinetics compared with parasympathetic influences (e.g., Saul, 1990).

HRV can be assessed in both the time and the frequency domains. Time domain indices of high-frequency variability such as the root mean square of successive differences (RMSSD) act as a high pass filter and thus reflect primarily parasympathetic influences. In the frequency domain, high-frequency HRV (HF-HRV) has been shown to correlate highly with activity of the vagus nerve and thus also reflects primarily parasympathetic influences on the heart (Kuo, et al., 2005). RMSSD and HF-HRV are highly correlated with each other and both can be used to index vagally-mediated HRV (Thayer, et al., 2010).

Recent neuroimaging work in humans has mapped out various ways in which individual differences in brain structure and function relate to HRV. A meta-analysis of this work showed that activations in the medial prefrontal cortex, anterior cingulate, putamen and amygdala were most consistently associated with HRV across studies (Thayer, et al., 2012). For instance, greater baseline RMSSD is associated with greater functional connectivity between amygdala and medial prefrontal cortex (Sakaki et al., 2016). Furthermore, across individuals, greater structural thickness in the anterior cingulate and prefrontal regions was associated with greater HF-HRV/RMSSD across several samples and among both younger and older adults (Winkelmann et al., 2016; Yoo et al., In preparation). These findings provide important insights into the cortical control of HF-HRV. However, evidence from patients and animal research indicate that various brainstem nuclei also exert key influences over HRV (George et al., 2004; Korpelainen, et al., 1996), and HRV has even been

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proposed as a way to assess brainstem function in order to discriminate between coma and brain death (Baillard et al., 2002; Schwarz, et al., 1987). Despite these linkages, little imaging work in healthy humans has addressed the relationships between brainstem and HRV, mainly due to the technical challenges of imaging small brainstem nuclei.

In the current study, we focus on the relationship between individual differences in HF-HRV and structure of the locus coeruleus, a brainstem nucleus that influences heart rate via multiple pathways. In addition to activating the sympathetic nervous system, LC activity inhibits parasympathetic cardiac vagal neurons (Wang, et al., 2014), including those in the dorsal motor nucleus of the vagus and the nucleus ambiguus, both vagal nuclei that influence heart rate (Samuels and Szabadi, 2008). Firing of these vagal nuclei reduces heart rate, whereas inhibiting them disrupts these reductions in heart rate (Samuels and Szabadi, 2008). Consistent with these LC noradrenergic suppressive influences over vagal nerve activity, administration of ß-adrenoceptor blocker drugs reduce heart rate and increase heart rate variability, effects that are attenuated when vagus nerve activity is blocked (Bittiner and Smith, 1986; for review see Grossman and Taylor, 2007).

In living humans, it has been difficult to obtain measures of LC structure, as it is small and has no visible markers on typical magnetic resonance imaging (MRI) scans. However, LC neurons contain neuromelanin, a pigmented polymer produced during oxidation of catecholamines, including norepinephrine in the LC (Wakamatsu et al., 2015). Recently developed MRI sequences optimize contrast for detecting neuromelanin and reveal the LC as bright white spots (Keren, et al., 2009; Shibata et al., 2006). Furthermore, by comparing the LC with a nearby control region, the neuromelanin signal intensity can be measured, and this LC-MRI contrast measure has been corroborated in post-mortem brains by comparing it to histological analyses of neuromelanin in LC brain tissue (Keren et al., 2015). In-vivo scans of a group of adults between ages 23 and 80 suggest that, during early and middle adulthood, neuromelanin builds up in the LC, presumably reflecting the accumulated effects of catecholamine metabolism over time, but then show a decreasing trend in the 70's (Shibata et al., 2006). The decreasing LC-MRI contrast values in late life are consistent with postmortem findings that the number of neuromelanin containing cells in the LC are lower in late life (German et al., 1988; Tomlinson, et al., 1981; Vijayashankar and Brody, 1979; Wree, et al., 1980). Thus, LC-MRI contrast provides a trait measure of LC structure that, based on hypothesized mechanisms of LC neuromelanin deposition (Wakamatsu et al., 2015), should be influenced by previous levels of LC activity through young and mid adulthood, as well as by late-life LC structural integrity.

Insofar as LC activity suppresses parasympathetic influences that increase HF-HRV (Wang et al., 2014) and leads to catecholamine activity with neuromelanin as a byproduct (Wakamatsu et al., 2015), people with higher levels of LC activity on a daily basis should have both higher levels of neuromelanin and lower HF-HRV. In turn, in late life, loss of LC neuromelanin neurons should reduce LC suppression of parasympathetic influences. However, to our knowledge, no previous studies have examined the relationship between LC-MRI contrast and HRV. In the current study, we tested the prediction that higher levels of LC neuromelanin are associated with lower HF-HRV using electrocardiogram (ECG) derived measures of heart rate in both younger and older adults while they completed a couple of different tasks. These participants also completed structural MRI scans that included one targeting LC neuromelanin.

In this study we also examined and accounted for the role of age and trait anxiety in contributing to the relationship between LC-MRI contrast and HRV, as both aging and anxiety have been linked with the LC-NE system and HRV. For instance, in aging, LC structure changes (for review see Mather and Harley, 2016), and HRV declines (Bonnemeier et al., 2003; Lipsitz, et al., 1990; De Meersman and Stein, 2007; Umetani, et al., 1998). Likewise, anxiety has been linked with the LC-norepinephrine system (Redmond and Huang, 1979; Sullivan, et al., 1999; Tanaka, et al., 2000; Weiss et al., 1994) and is associated with lower HRV (for reviews see, Chalmers, et al., 2014; Friedman, 2007). We predicted that higher levels of LC-MRI neuromelanin contrast would be associated with lower HF-HRV even when controlling for age and trait anxiety. We used HF-HRV as our primary measure of vagally-mediated HRV. RMSSD and LF-HRV are included in the analyses to provide convergent and discriminant validity as RMSSD reflects primarily parasympathetic influences and so should yield similar results as HF-HRV, whereas LF-HRV reflects both sympathetic and parasympathetic influences and so is likely to show different results (Thayer et al., 2010).

Methods

Participants

Participants in this study were drawn from a larger set of participants recruited to complete a study with both MRI and HRV measures (see Clewett et al., 2016). For the current study, we included all those who had both an LC-MRI contrast measure and measures of heart rate variability during the experimental task runs. This yielded 27 younger adults (M_{age}=23.63 years, *SD*=4.79, age range=18–34; 10 female) and 18 older adults (M_{age}=67.89 years, *SD*=4.84, age range=60–75; 8 female). All participants were healthy, had normal or corrected-to-normal visual acuity, and were either students or community dwelling. Older adults were screened for dementia using the Telephone Instrument for Cognitive Status (TICS) over the phone before being scheduled (Brandt, et al., 1988), with a score of 31 or above required to participate. There were no significant differences between the two age groups in years of education ($M_{younger}$=16.3; M_{older}=16.5) or Wechsler Test of Adult Reading scores ($M_{younger}$=42.3; M_{older}=41.3). Participants provided written informed consent approved by the University of Southern California (USC) Institutional Review Board and were paid for their participation.

Procedure

Participants completed a series of structural and functional MRI scans acquired with a 3-T Siemans Magnetrom Trio scanner at the USC Dana & David Dornsife Cognitive Neuroscience Imaging Center. As part of this, a neuromelanin-sensitive-weighted MRI (LC-MRI) scan was conducted using a T1-weighted fast spin-echo sequence (repetition time=750 ms, echo time=12 ms, flip angle=120°, 11 axial slices, field of view=220 mm, bandwidth=220 Hz/Px, slice thickness=2.5 mm, slice gap=3.5 mm, in-plane resolution=0.429×0.429 mm^2, and scan duration=1 min and 53 s).

Heart rate was measured using ECG during an initial fear-conditioning learning task (about 6 min) and five task blocks of a spatial detection task (about 5 min for each block). For our main analyses, we averaged across the six different measurement occasions for each person, as aggregating across different measurement occasions increases the proportion of variance accounted for by trait rather than situation effects (Bertsch, et al., 2012). During the fear-conditioning task, either a low- or high-pitched tone was paired with mild electric shock. Participants were presented with one of the CS tones for 0.7 s. A shock was delivered for 0.5 s on half of the trials for the tone assigned to the CS+ condition. On the CS- tone trials there was no shock. During the spatial detection task, the CS+ or CS- tone played for 0.7 s, and then a place-object image pair appeared and participants were asked to identify the location of the salient image by pressing a left or right button. In each block, 16 CS+ trials and 16 CS- trials (all 32 without associated shock) were randomly intermixed during this phase with three additional “booster” CS+ trials with shock.