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Hippocampal dependent neuropsychological tests and their relationship to measures of cardiac and self-report interoception

Richard J. Stevenson[a,*], Heather M. Francis[a], Megan J. Oaten[b], Rebecca Schilt[a]

[a] Department of Psychology, Macquarie University, Sydney, Australia
[b] School of Applied Psychology, Griffiths University, Gold Coast, Australia

ABSTRACT

The hippocampus is involved in interoceptive processing (i.e., perceiving internal bodily states), with much of this evidence relating to hunger and fullness. Here we examine whether cardiac and self-report measures of interoception are related to two measures of hippocampal dependent learning and memory (HDLM) – the Rey Auditory Verbal Learning Test (RAVLT) and Logical Memory. Healthy adults completed a neuropsychological test battery including all of these measures, along with assessments of intelligence and executive function. Biographical, medical and psychological-related data that might confound detecting an HDLM-interoception relationship was also collected. Both measures of HDLM were associated with cardiac interoception after controlling for confounding variables. More accurate cardiac interoception was linked to better HDLM performance. On the self-report measure of interoception, better performance on the RAVLT was associated with better-reported attention regulation, consistent with the hippocampus's known role in mindfulness. Overall, these findings suggest hippocampal involvement in cardiac and self-report interoceptive capacity. The broader functional role of the hippocampus in interoception is discussed.

1. Introduction

Interoception refers to the ability to perceive internal bodily states such as pain, hunger and arousal (Craig, 2002, 2003, 2009; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Harshaw, 2015; Wiens, 2005). A large body of human neuroimaging data implicates the anterior insular cortex (AIC) and the anterior cingulate cortex (ACC) as key structures in interoceptive processing (Craig, 2009; Critchley et al., 2004). However, a range of findings from animal lesions studies, human neuropsychology and more recently, functional connectivity studies, all suggest that the range of brain structures central to supporting interoceptive processing extends beyond the AIC and ACC. One structure identified by this body of literature as being important is the hippocampus, which has been closely tied to ingestion-related interoception. Here we test support for the idea of hippocampal involvement in interoceptive processing outside of the ingestive domain. We focus primarily on cardiac interoception (and also self-report interoceptive capacity), where evidence for hippocampal involvement has been less consistent.

Evidence favouring a role for the hippocampus in interoceptive processing derives from several sources. Animal data indicates that hippocampal lesions are associated with abnormal patterns of eating behavior, typified by small more frequent meals, which has been interpreted as an interoceptive deficit (Clifton, Vickers & Sommerville, 1998). A similar conclusion emerges from studies in which animals have to use or discriminate between interoceptive states, notably hunger and fullness, so as to obtain a food reward. Several reports have shown that hippocampal lesions are selectively effective at disrupting performance on these types of task (Davidson & Jarrard, 1993; Davidson et al., 2010; Hirsh, Leber & Gillman, 1978). Not surprisingly, given these behavioral data, the hippocampus receives all of the necessary information to serve as an interoceptive processor, including vagal afferent flow (e.g., Wang et al., 2006), hormonal inputs (e.g., relating to the bodies energy state; Lathe, 2001), and neural connections (e.g., AIC; Flynn, Benson & Ardila, 1999).

Somewhat independent of the animal literature, studies of patients with damage to the medial temporal lobe (MTL), and especially the hippocampus, have also suggested an interoceptive function. Starting with HM, who had a bilateral resection of the MTL for intractable epilepsy, not only did he rarely report being hungry, full or tired, but on formal testing he demonstrated impaired pain perception and diminished interoceptive sensitivity for hunger and fullness (Hebben, Corkin, Eichenbaum, & Shedlack, 1985). In the last mentioned case, after eating, HM showed little change in hunger/fullness and he willingly ate

* Corresponding author at: Department of Psychology, Macquarie University, Sydney, NSW 2109, Australia.
E-mail address: dick.stevenson@mq.edu.au (R.J. Stevenson).

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an identical second main meal almost immediately after finishing a first. While we do not know if the consumption of multiple meals in HM points to abnormal interoception, the failure to report changes in hunger/fullness certainly do. Since HM, a number of other patients with MTL damage have been similarly tested and they too show deficits in their ability to perceive hunger/fullness (Higgs, Williamson, Rotshtein, & Humphreys, 2008; Rozin, Dow, Moscovitch, & Rajaram, 1998). While we suggest that these interoceptive impairments in MTL patients arise from damage to the hippocampus (i.e., arguably paralleling the animal data above and related to the neuroimaging data reviewed below), this view is not universally shared. HMs interoceptive deficits have been ascribed to amygdala damage (Annese et al., 2014; Hebben et al., 1985).

Conventional fMRI has not generally detected hippocampal or MTL involvement across a range of interoceptive tasks, including widely used cardiac interoception measures (e.g., Craig, 2009; Pollatos, Schandry, Auer, & Kaufmann, 2007). Indeed the only fMRI evidence of MTL involvement has been in some (but not all) gastric fullness studies (Delparigi et al., 2004; Geeraerts et al., 2011). It is only more recently with the advent of network connectivity studies that this picture has begun to change. Using a network approach, neuroimaging has revealed a much larger set of structures that support interoceptive processing. In particular, bladder filling (Jarrahi et al., 2015), gastric discomfort/pain (Ploghaus et al., 2001) and most recently cardiac interoception (Kuehn, Mueller, Lohmann, & Schuetz-Bosbach, 2016), have all shown significant activity in the hippocampus, as well as in other structures more frequently associated with interoception, notably the AIC and ACC. These findings suggest that the hippocampus plays a broader role in interoceptive processing than indicated by the animal and neuropsychological studies reviewed earlier, which predominantly focussed on hunger and fullness.

In two previous studies we sought neuropsychological evidence of more general hippocampal involvement in interoceptive processing, by again studying cardiac interoception. In the first (Berriman et al., 2016), we examined two patients with bilateral damage principally confined to the hippocampus, on measures of cardiac interoception, gastric fullness, and self-report interoceptive capacity. Both patients were significantly impaired, relative to healthy matched controls, on the measures of cardiac and gastric interoception, but not on the self-report measure. In the second study (Dudley & Stevenson, 2016), we tested whether individual differences in performance on an established measure of hippocampal dependent learning and memory (HDLM) was associated with individual differences in performance on measures of cardiac interoception, gastric fullness and self-report interoceptive capacity. In this case we found significant associations with the fullness and self-report measure, but not with cardiac interoception.

In the current study, we were primarily interested in detecting a relationship between cardiac interoception and measures of HDLM. One reason why this is important is because much of the prior human and animal literature has focussed on ingestion-related interoception and it may be the case that hippocampal involvement is especially pronounced within this domain. Indeed, Parent (2016) noted that if we did not know that the hippocampus supported declarative learning and memory its suite of metabolic-related receptor types and ingestion-related afferent inputs would suggest a structure specialised in regulating food intake. Alternatively, and as we suspect, it may be that hippocampal involvement in interoception is more general - as network fMRI data would seem to suggest. The ability to perceive the beating of one's heart presents a good non-ingestion related test case in which to explore hippocampal involvement. Cardiac interoception is a widely used and investigated task (e.g., Azevedo, Aglioti, & Lenggenhager, 2016; Khalsa, Rudrauf, Feinstein, & Tranel, 2009; Pollatos et al., 2007; Ronchi et al., 2015; Vaitl, 1996) and its relationship with the hippocampus remains unclear.

To explore the role of the hippocampus in cardiac interoception we adopted a similar approach to Dudley and Stevenson (2016) examining whether individual differences on HDLM in healthy participants is associated with individual differences in cardiac interoception. To measure HDLM we included two measures (Logical Memory from the WMS; Wechsler, 2008a; and Rey Auditory Verbal Learning Test [RAVLT]; Rey, 1958) so as to improve reliability. Both of these tests have been linked via neuroimaging (Trenerry, Westerveld, & Meador, 1995; Wang et al., 2010; Yassa, Mattfeld, Stark, & Stark, 2011) and lesion-studies (Kramer et al., 2004: Martin et al., 1999; Rempel-Clower, Zola, Squire, & Amaral, 1996; Saling et al., 1993: Sass et al., 1992) to the hippocampus. Thus they represent indirect but relatively selective measures of hippocampal integrity (Griffith, Pyzalski, Seidenberg, & Hermann, 2004; Saury & Emanuelson, 2017).

The same measure of cardiac interoception was employed as in both of our prior studies (Berriman et al., 2016; Dudley & Stevenson, 2016), namely a version of the Schandry (1981) task. In addition, we obtained a self-report measure of interoceptive awareness (Multidimensional Assessment of Interoceptive Awareness [MAIA]; Mehling et al., 2012), with the same question in mind (i.e., association with HDLM). Finally, we also included a range of demographic (age, gender), lifestyle (activity levels, sleep, diet, BMI, depression, anxiety, stress) and neuropsychological control measures (executive function - digit span [forward and backward]; and intelligence). This was to ensure that any observed relationship between interoception and HDLM could not be readily attributed to some other cause (e.g., poor sleep, low activity levels, stress, etc.) known to influence interoception, HDLM or general test performance.

2. Method

2.1. Overview

The participants in this study took part in an unrelated experiment on ingestive behavior (see Francis et al., 2017), which involved two eating phases (a snack and lunch) separated by a one-hour interval. During this one-hour interval participants completed two neuropsychological tests of hippocampal dependent learning and memory (HDLM), tests of executive function and intelligence, and two interoceptive measures – a version of the Schandry heart rate task and the Multi-Dimensional Assessment of Interoceptive Awareness (MAIA) – all described further below. Participants also completed various measures to assess general health and functioning (e.g., sleep, exercise, mental health, BMI, etc.), which might act to confound the relationship between interoceptive performance and HDLM.

2.2. Participants

One hundred and sixty participants took part in this study (see Table 1 for details). All of these participants came from the ingestive behavior study as described above (see Francis et al., 2017) – for which they had to meet two sets of entry criteria. First, they needed to be in good health (i.e., no history of mental-related illness, no prescription medications, no physical illnesses likely to affect interoception or

Table 1
Demographic and questionnaire data.

Variable	Mean (SD)/number	Range
Gender	95 Women, 58 men	–
Age	19.7 (2.9)	17–32
Activity (higher score is more)	4.2 (2.9)	0–13
Sleep (higher score is poorer)	4.7 (1.3)	2–8
Diet (higher score is poorer)	61.8 (13.4)	35–99
BMI	22.4 (3.1)	15.4–34.1
DASS – depression	3.4 (3.4)	0–16
DASS – anxiety	3.1 (2.9)	0–16
DASS – stress	5.0 (4.1)	0–20