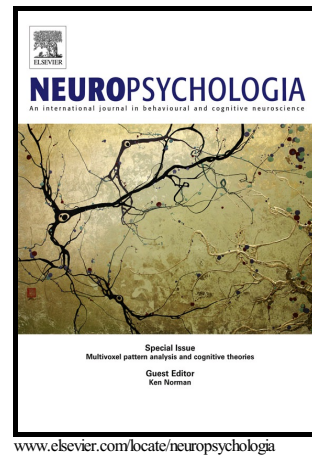


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Testing the importance of the Medial Temporal Lobes in human interoception: Does it matter if there is a memory component to the task?

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Abstract

Interoception is the ability to consciously perceive internal bodily states. Neuroimaging suggests that the insula (IC) and anterior cingulate cortex (ACC) mediate interoception, while studies involving patients/animals with brain lesions suggest the medial temporal lobe (MTL) is particularly important. One reason for these contrasting conclusions may lie in the types of interoceptive task used by these different approaches. Some tasks probably require integration of current physiological state with mnemonic information (e.g., how much one last ate), and these may be especially reliant upon MTL processing. We compared one task that probably requires integration - a water load task - with one that likely does not - a heart-rate tracking task - in two individuals with selective MTL damage (and with intact IC and ACC). A group

of matched healthy individuals served as controls. The main finding was that individuals with MTL damage, relative to controls, were *equally* and significantly impaired on both types of interoception task. This suggests that MTL structures are involved in mediating interoception even when using a task (heart rate tracking) that does not seemingly require memory and that in neuroimaging studies activates the IC and ACC. The reasons for this apparent inconsistency with neuroimaging findings and the functional role of the MTL in interoception are discussed.

Key Words: Bodily states, Heart-rate tracking, Hippocampus, Insular Cortex, Memory, Appetite

1. Introduction

Interoception is the ability to perceive internal bodily states such as heartbeat, hunger, pain and fullness (Craig, 2002; Pollatos et al., 2007a; Van Oudenhove et al., 2004). Human studies suggest that medial temporal lobe (MTL) lesions can generate interoceptive impairments (Hebben et al., 1985; Higgs et al., 2008; Rozin et al., 1998). Anatomically, the MTL includes three major parts: (1) the olfactory system; (2) the hippocampus, entorhinal, perirhinal and parahippocampal cortices; and (3) the amygdala - with the latter structures (notably (2)) supporting declarative memory (Squire, Stark & Clark, 2004). The MTL's putative role in interoception was first suggested by case HM. After his bilateral MTL resection HM rarely reported being hungry, thirsty or tired, and had a diminished capacity to feel pain (Hebben et al., 1985). What makes the results from HM and other MTL cases so puzzling, is that neuroimaging studies typically suggest that the insula cortex (IC) and the anterior cingulate cortex (ACC) are crucial for mediating interoception (Craig, 2002, 2003, 2009). Yet HM, whose brain has now been dissected, appears to have had no damage to his IC or ACC (Annese et al., 2014). In this study we explore one possible explanation for these divergent conclusions

and study the extent to which selective MTL lesions, sparing the IC and ACC, affect interoception.

Neuroimaging research, mainly using PET and fMRI, has employed a range of tasks to investigate the neural correlates of interoception. These have included: oesophageal stimulation (e.g., Pollatos et al., 2007a); gastric distension (e.g., Wang et al., 2008); respiratory tasks (Rosenkranz et al., 2005); rectal stimulation (Berman et al., 2008); sexual responses (Komisaruk et al., 2004); bladder filling (Mehnert et al., 2008); thirst (Denton, et al., 1999); and heart rate tracking (Pollatos et al., 2007b). In line with a theory advanced by Craig (2002, 2003, 2009), which states that the IC has a primary role (and to a lesser extent the ACC) in supporting introspection, every study examined across these various task-types reported activation of the IC, with around half also reporting activation of the ACC. MTL activation was only more rarely observed.

Neuropsychological studies of interoception started with HM, finding that he was unable to process information related to the sensations of hunger, thirst, fullness and pain (Hebben et al., 1985). As noted above, HM had an almost complete removal of the MTL (i.e., entorhinal cortex, anterior hippocampus, and most of the amygdala in both hemispheres) but with no lesions to his IC and ACC (Annese et al., 2013). The importance of the MTL in mediating interoception has been confirmed in two subsequent studies of patients with bilateral MTL lesions. All reported interoceptive deficits in hunger and fullness – the sole modalities explored in these studies (Higgs et al., 2008; Rozin et al., 1998). The importance of MTL structures in interoceptive processing is also suggested by two further sets of findings. The first concerns animal studies, with selective lesions of the hippocampus resulting in interoceptive deficits in hunger and satiety (Davidson and Jarrad, 1993; Davidson et al., 2009) and dysregulation of food intake (Clifton et al., 1998). The second concerns neuroimaging. While nearly all studies of gastric interoception demonstrate insula involvement, some also

reveal MTL activation as well (including the amygdala), a finding which *may* be particular to ingestion-related tasks (e.g., DelParigi et al., 2004; Geeraerts et al., 2011).

Our contention is that certain types of interoceptive task may draw more heavily on MTL structures than others. In particular, a key difference may lie in whether the task requires integration of information, namely between current physiological state and past behaviour (e.g., for fullness – what is felt *now* with *recollection* of what was eaten before). The literature on effects of MTL lesions on interoception in humans and animals has focussed mainly on eating related variables. This type of variable may be just the sort of task that is influenced by both current visceral state (e.g., feelings of hunger) and by the memory of past events (e.g., food ingested), requiring the integration of these two pieces of information – a task well suited to the MTL, and especially the hippocampus. One reason to suggest this possibility comes from a study by Brunstrom et al., (2012), where *both* how much food participants actually ate and how much they *thought* they ate, were manipulated. They found that fullness ratings shortly after ingestion (i.e., current physiological state) were primarily influenced by what had *actually* been eaten, but with time, what the participants *thought* they had eaten became the more dominant influence (i.e., integration of memories of food intake with physiological state data). While the latter task may require MTL involvement, it is possible that tasks that are reliant upon just *current* physiological state alone, would not. Thus, in this case, we would expect MTL lesions to have no effect.

In the current study we therefore included two types of interoceptive task, one that we thought would involve the MTL and one that would not – respectively - The Water Load Task (WLT) and the Heart-Rate Tracking (HRT) task. The WLT involves rating sensations of fullness prior to drinking water until feeling comfortably full, and then making further fullness ratings at two later time points (based upon, Herbert et al., 2012). The HRT task requires participants to count their heartbeat and is a good example of a task that probably does *not*

involve any memory integration – just monitoring of current physiological state. Indeed, the HRT task is the most suitable measure for *just* assessing cardiac interoception, as its main alternative the heart beat detection task assesses multisensory integration of interoceptive and exteroceptive information (Michal et al., 2014; Schulz et al., 2013). One potential concern with the HRT task is that participants who may be unable to discern their heart beat could then try to use explicit knowledge of their heart rate and use this to mentally calculate a response (see Ring et al., 2015). To forestall this possibility, we instructed participants that if they were completely unable to discern their heart beat they were to report being unable to do so on that trial. Consistent with many other interoceptive tasks, HRT has been shown to activate the IC and ACC in fMRI studies, but not MTL structures (Pollatos et al., 2007b).

As we planned to test patients with MTL lesions - relative to healthy matched controls - and as MTL structures (especially the hippocampus) are critical for episodic memory (e.g., Jenson & Squire, 2012), measures of immediate and delayed memory (Logical Memory; WAIS-IV, Wechsler, 2008) were administered to confirm the expected pattern of deficit. Measures of working memory (Digit Span; WAIS-IV, Wechsler, 2008) were also included, as this variable was not expected to differ between patients and controls, as working memory is not dependent upon the MTL (e.g., Canavan et al., 1989). Two control tasks (The Water Level test and the Tone Counting task) were also included. These mirrored the non-interoceptive aspects of the HRT task and WLT involving making judgements and counts, so as to look for any such underlying task-specific deficits. Finally, variability in interoceptive performance is associated with anxiety (Pollatos et al., 2007a), fitness (Vaitl, 1996), physical symptom reporting (Duddu et al., 2003), depression (Pollatos et al., 2009), obesity (Herbert & Pollatos, 2014), and sleep deprivation (Greer et al., 2013). All of these variables were measured in order to identify any relevant confounds between patients and controls.

In sum, we hypothesised that individuals with selective damage to the MTL and with no damage to the IC or ACC, would demonstrate interoceptive deficits on the WLT, as this likely involves the integration of gastric visceral sensations with memory of prior water intake. In contrast, it was hypothesised that there would be no difference between the patients and controls on the HRT task, as this does not require integration. Thus, we predicted an interaction between task type and ‘group’ (i.e., patients vs. healthy controls).

2. Material and Methods

2.1 Participants

Two patients were recruited from the Neuropsychology Unit, Royal Prince Alfred Hospital (RPAH), Sydney. PT, was a 40 year old right-handed female, currently employed as a bank loan-manager, who underwent a right temporal lobectomy in 2002 for intractable epilepsy. PT reported memory problems, with a neuropsychological assessment conducted at RPAH (one year prior to testing here) indicating deficits in memory for both visual and verbal material. PT reported feeling no sensations of hunger but experienced feelings of fullness after eating. She reported that she often forgot to drink, did not experience thirst, and would only remember to drink if she developed a headache due to dehydration.

An MRI conducted six months prior to testing confirmed a partial right temporal lobectomy with resection of the head and body of the right hippocampus as well as encephalomalacia in the residual temporal lobe involving the superior temporal gyrus on the right (see Fig.1a). No other abnormalities were reported.

The second patient, JW, was a 62 year old left-handed female retired book-keeper, who presented with a six month history of memory loss. Neuropsychological assessment conducted

at RPAH (3 months prior to testing for this project) detected marked impairments on tests of verbal and visual anterograde memory. JW also reported recent weight loss (1-2 kg in the last two weeks), which was associated with a lack of appetite, and forgetting to eat. This was of concern to her carer, who had taken to reminding her to eat throughout the day. JW reported drinking regularly without reminders.

Magnetic resonance imaging (MRI) was conducted three months prior to the study (see Fig.1b). The imaging revealed symmetrical, bilateral atrophy of both hippocampi with enlargement of the temporal horns, suggestive of mesial temporal sclerosis. Volume loss was also evident in the right amygdala. In addition, there was a small lacune in the white matter of the right parietal lobe lying just above the occipital horn of the right lateral ventricle. Elsewhere, there was evidence of white matter hyperintensities in cerebral hemispheric white matter consistent with lesions due to small vessel ischaemia.

Thirty healthy controls participated in the study - 5 males (17%) and 25 females (83%). These included mature-aged students recruited from Macquarie University ($n = 13$) and people from the local community ($n = 17$). Inclusion criteria were: (1) age range of 30 to 65 years, and (2) English as a first language. Exclusion criteria were based upon factors that could affect task performance, influence interoception or affect neuropsychological testing: (1) hospitalization within the last six months; (2) a history of any brain disease or trauma which could potentially impair memory; (3) medical conditions (e.g., diabetes) and/or substance abuse that could impair cognitive functioning; (4) psychiatric illness; (5) bladder or kidney dysfunction; (6) prescription medications that affect attention/concentration; and (7) a history of eating disorders.

The study was approved by Macquarie University Human Research Ethics Committee and by the RPAH Ethics Committee. Informed consent was provided by all participants.

2.2 Materials

2.2.1. Biographical and background questionnaire data

Biographical and medical history was obtained from each participant, as well as measuring their weight and height so as to calculate Body Mass Index (BMI; weight in kg divided by height in M squared). Three questionnaires, with established reliability and validity, were also completed: (1) The Pittsburgh Insomnia Rating Scale (PIRS-2; Moul et al., 2002); (2) The International Physical Activity Questionnaire – short form (IPAQ; Craig et al., 2003); and (3) The Depression Anxiety Stress Scale (DASS-21; Lovibond & Lovibond, 1995). Respectively, higher scores on these three scales indicate poorer sleep, higher physical activity levels, and greater depression, stress and anxiety.

2.2.2 Interoception tasks

Interoceptive sensitivity was assessed with a version of the heart rate tracking (HRT) task (Herbert et al., 2007, 2010; Schandry, 1981). After an initial rest period of 60 seconds, participants were asked to concentrate on their heart, and to count their heartbeats over four counterbalanced time intervals of 25, 35, 45, and 55 seconds. Each counting period was separated by a standard resting period of 30 seconds, and a start and stop cue was given at the beginning and end of the counting period. At the end of each period participants were asked to verbally report the number of heartbeats counted, unless they were completely unable to discern their own heart beating. Participants were instructed to abstain from manually taking their pulse or any similar direct means of assessing heart rate. Participants were blind to the length of the counting phase and were not provided with feedback on their performance. During each trial, participants' heart rate was monitored with a Pulse Oximeter (Crucial Medical Systems). This test was conducted twice to confirm its reliability. After the conclusion of the second test, participants were asked to report how they went about the task.

An absolute difference was obtained by subtracting the estimated heart rate from the actual heart rate for each of the four time periods on the first and then the repeat test. In line with

Schandry (1981), each absolute difference score was then divided by actual heart rate, and the value subtracted from one. A score of 1 indicates perfect interoceptive ability on the HRT task, with scores approaching 0 indicating poor performance. Group means were calculated on these values for each of the two HRT tasks, providing two absolute value scores. These were collapsed into a single value (control range 0.04 to 0.93) after reliability (for patients and controls) was verified using the Intraclass Correlation Coefficient, $r = .95$. Two controls were excluded from this analysis. One was unable to sense their heart rate on any trial and one managed to do so on only one trial. Of the remaining controls, four were unable to sense their heart rate on certain trials - two on three trials and two on one trial. Both, patients reported being unable to sense their heart rate on particular trials, JW failed to provide a response on one occasion and PT provided responses on just two trials. In these cases of missing trials, the overall score was based on the remaining trials.

The water load task (WLT) was based upon Herbert et al., (2012). Participants were presented with a clear, five litre canister containing three litres of room temperature, non-carbonated water. They were asked to drink as much as they required over a five min period until they felt comfortably full. Identical 150 ml cups were used for each participant. The amount of water was measured prior to the participant arriving and after they had departed so as to calculate the volume consumed during the drinking phase. A key component of the WLT involved each participant measuring their subjective feelings of fullness on a 15cm visual analogue (VA) scale (anchors: 'Not at all' to 'Very') over three time periods: 15 minutes prior to drinking, immediately after drinking, and 30 minutes later. So as not to focus attention solely on fullness, participants' also rated hunger and thirst using similar scales.

Linear and quadratic slope coefficients were calculated for the three fullness ratings (i.e., across the three time periods) on the WLT. Positive linear slopes indicated increasing fullness over time, negative values, decreasing. Positive quadratic coefficients indicated falling and

then rising fullness over time, negative quadratic coefficients indicated increasing and then decreasing fullness over time.

We also included a self-report measure that assesses habitual attentiveness to bodily sensations – the Pennebaker Inventory of Limbic Languidness ([PILL] Pennebaker, 1982). On the PILL participants were asked to report the frequency with which they had experienced 54 common physical symptoms and sensations (e.g., ‘eyes water’) on a five-point scale ranging from 0 (*Have never or almost never experienced the symptom*) to 4 (*More than once every week*). Higher scores indicate greater levels of bodily sensation reporting.

2.2.3 Interoception control tasks

The Water Quantity Estimation test was designed to match the WLT and required participants to estimate the amount of water contained in three identical, but unusually contoured bottles (See Fig. 2), at three separate time periods similar to those used in the WLT. Each 150 ml bottle contained a different amount of water: Time one: 75mls; Time two: 37.5 mls; and Time three: 100 mls. Without touching the bottles, participants were asked to estimate the absolute fullness level in the bottles on a 15cm VA scale (anchors: ‘Empty’ to ‘Full’). At Times Two and Three, participants were also asked to estimate the volume change in the bottle, relative to the previous bottle on a 15cm VA scale (anchors: ‘A lot less’ to ‘A lot more’). Data for test here were the relative and absolute volume values generated by participants.

The second interoceptive control task was the Tone Counting task, which was matched to the HRT task methodology. This involved the participants silently counting a regular metronome tone over four counterbalanced time periods of 25, 35, 45, and 55 seconds. After initially identifying a level at which the tone could be comfortably heard, participants completed a 20-second practice session in order to familiarise with the task. The tone was set

at 72 beats per minute, and after completing each time interval, the participants reported the number of tones heard to the researcher. Each counting interval was separated by a 30 second resting period during which the participants were instructed to sit quietly without conversing. The metronome tone was computer generated (TempoPerfect Metronome v 3.08 NCH Software) and participants listened via headphones. Finally, a single absolute deviation value was calculated for the Tone Counting task in the same manner as for the HRT.

2.2.4 Neuropsychological tests

Logical Memory (LM), a subtest of the *Wechsler Memory Scale – Fourth Edition* (WMS-IV; Wechsler, 2009), is a measure of immediate and delayed memory for structured verbal information (two stories) and is sensitive to MTL damage (e.g., Griffith et al., 2004). In order to minimise the well-documented practice effects, which can occur with repeated exposure to LM (e.g., Schnabel 2012), an alternate form (Sullivan, 2005) was administered. This was particularly important for JW and PT, who had had recent prior exposure to the Wechsler LM stories. Both alternate stories had similar characteristics to the WMS-IV LM passages (e.g., number of words, characters, sentences; Sullivan, 2012) and were administered using the WMS-IV standardised instructions.

The Digit Span subtest (Forward, Backwards, and Sequencing) of the *Wechsler Adult Intelligence Scale – Fourth Edition* (WAIS-IV; Wechsler, 2008) was included as a measure of attention, concentration and working memory to ensure that these constructs were intact in all participants. This test was administered as per the manual and the Digit Span Total Scaled Score (SS) is reported.

The Test of Pre-Morbid Functioning (TOPF) was used to estimate patient and control IQ (Wechsler, 2011) and was administered and scored as per standardised instructions.

2.3 Procedure

All participants were asked to abstain from eating and drinking for two hours prior to testing. All reported complying with this request. After completing the information and consent form, the test battery was administered. Test ordering for the study was fixed (see Table 1) as some tests had to precede others as they had multiple parts.

2.4 Analysis

Data were analysed using Modified Crawford's t-tests (Crawford & Howell, 1998), with alpha set at .05. For the key test of whether any impairment on the HRT task is *less* than any impairment on the WLT fullness ratings, scores on the HRT task and the WLT (linear and quadratic coefficients for fullness ratings) were all converted to Z-scores (relative to controls). The difference in performance between the standardised HRT task and the standardised linear (and quadratic) coefficient fullness scores for WLT were calculated for each patient, and for the controls, to test for any differential deficit across test type.

3. Results

3.1 Biographical and background questionnaire data

There were no significant differences between JW and PT and controls in age, education, BMI, DASS scores, exercise (hours/week; IPAQ), or sleep quality (PIRS) – see Table 2.

3.2 Neuropsychological testing

As expected, both JW and PT scored significantly below the control mean in the LM delayed recall (see Table 3). PT also showed significant impairment in the immediate recall

condition. On Digit Span (see Table 3), there were no significant differences between JW and PT, and the controls. There were also no differences in estimated premorbid IQ (see Table 3).

3.3 Interoception tasks

No difference was expected between patients and controls on the HRT task. However, while JW performed somewhat less accurately than controls, PT's HRT score was very poor and significantly worse than controls (see Table 4). No participant reported using any calculation based strategy to generate a response rather all reported trying to focus on their heart rate. We note that across the whole sample (including both patients and excluding the one control who provided no responses on this task) the greater the number of trials on which a response was provided the more accurate the heart rate estimation ($r = 0.49, p < 0.01$).

We predicted that patient reports of fullness would differ from controls on the WLT, noting that we found no difference in water intakes (see Table 4). For the linear coefficient data, PT's fullness ratings decreased significantly more over time than controls (see Fig. 3a), but JW's did not differ from controls (see Fig. 3b). Turning to the quadratic coefficients, JW's score was significantly different from controls, with far more dynamic changes in fullness across time (See Fig. 3b). No significant difference was seen between PT's quadratic coefficient and that of controls (see Fig. 3a).

The key test is whether any impairment on the HRT task is *less* than any impairment on the WLT fullness ratings. Crucially, patients' degree of impairment did not differ between the two interoception tasks: for JW, HRT task vs. WLT linear coefficient, $t = 1.63$, HRT task vs. WLT quadratic coefficient, $t = 0.6$; for PT, HRT task vs. WLT linear coefficient, $t = 0.18$, HRT

task vs. WLT quadratic coefficient, $t = 1.41$. Thus, contrary to predictions, there was no evidence of any differential deficit in performance between the HRT task and the WLT fullness ratings in our two patients.

As there was no differential deficit between the HRT task and the WLT (fullness ratings), two overall deficit scores were computed. One was the average of the HRT task Z score and the WLT linear coefficient Z score, and the other was the average of the HRT task Z score and the WLT quadratic coefficient Z score. These were calculated for each patient, with these scores then compared to scores calculated for the controls.

For JW, there was a significant overall impairment for the joint HRT/WLT quadratic coefficient score, $t(27) = 2.49$, $p < 0.01$, but not for the HRT/WLT linear coefficient score ($t < 1$). PT was abnormal on both comparisons, for the HRT/WLT linear and quadratic scores, respectively, $t(27) = 4.64$, $p < 0.01$ and $t(27) = 2.37$, $p < 0.01$.

Finally, we tested whether there was any difference on the questionnaire measure of bodily sensations (PILL). No significant differences in symptom reporting were found between JW and PT, relative to controls (see Table 4).

3.3 Interoception control tasks

No significant differences were found between patients and controls on the ability to detect the absolute amounts of fluid contained in the bottles over the three time periods (JW all t 's < 0.6 ; PT all t 's < 1.78). There were also no differences between patients and controls in their capacity to estimate the relative volume change between the bottles at T1 vs T2 and T2 vs T3 (JW both t 's < 0.32 ; PT both t 's < 0.96).

There were no significant differences between JW and PT, and the control group on the number of tones counted during each time period (t 's < 0.88).

4. Discussion

The current study investigated whether two individuals with selective damage to MTL structures, but an intact IC and ACC, would demonstrate differential impairments across two types of interoceptive task. The WLT was hypothesised to involve the integration of current physiological state (i.e., gastric distension) with mnemonic information (i.e., fluid consumed). We predicted that performance on this interoception task would be impaired in individuals with MTL lesions. In contrast, the HRT task was hypothesised not to require integration, and prior fMRI research suggested that the IC and ACC would mediate performance on this task, not MTL structures. Thus, no impairment was expected in the MTL patients here. Overall, the two patients, JW and PT were poor at estimating their heart-rate, with PT's result being significantly worse than controls. As expected, both PT and JW demonstrated abnormal patterns in their fullness ratings over time, even though their water intake did not differ significantly from the control group's. Crucially, there was no evidence of a differential deficit between JW and PTs performance on the WLT relative to the HRT task. Rather, there was a general impairment across both tasks - relative to controls. These results suggest that task differences are unlikely to explain the divergent findings that emerge between lesion studies in patients and animals on the one hand, and neuroimaging in healthy subjects on the other.

Looking more specifically at the patients' interoceptive data, we note that their general pattern of performance was abnormal. Both JW and especially PT were inaccurate when it came to tracking their own heart rates. On the WLT, both PT and JW reported significantly different fullness responses relative to controls, although the differences identified for each patient were not the same. PT's ratings started high (i.e., full) and then decreased across the study – *even after drinking* (see Fig. 2). In contrast, JW's ratings started low (i.e., empty) and increased very rapidly after drinking (from almost the bottom to almost the top of the scale) after drinking only a modest amount (150ml) of water. These differences in pattern between PT and JW are not readily explained unless both are just reflective of guessing due to some

degree of interoceptive agnosia. When compared to HM (Hebben et al., 1985) and the other MTL cases (Higgs et al., 2008; Rozin et al., 1998), where ratings of hunger and fullness were obtained, these were characterised by an unresponsiveness to food intake (i.e., hunger and fullness ratings remained static). Some evidence of this can also be seen in PT, but even her ratings decrease at the final time point. Such differences could be attributed to the degree of MTL damage. This is far more limited in our two patients, relative to the severe form (with dense anterograde amnesia) in the other studied patients (Hebben et al., 1985; Higgs et al., 2008; Rozin et al., 1998). Finally, while on the topic of lesion extent, it is noteworthy that the unilateral lesion in PT appeared to be as effective as the bilateral lesion in JW at generating interoceptive impairments. Interestingly, Craig (2009) suggests a right-sided dominance (albeit for insula activation) for mediating particular types of interoception that are arousing, including heart beat awareness and gastric distension.

A number of other tests were also conducted. JW and PT's reports of attentiveness to a range of internal bodily sensations (e.g., indigestion, constipation, nausea) did not differ significantly to that of controls, which was perhaps surprising given their performance on the WLT and HRT task. One possibility is that responses to the PILL could be based on the patients' experiences *prior* to MTL damage, rather than on current interoceptive ability as presumably measured by the WLT and the HRT task. No differences were observed between patients and controls on either of the two interoceptive control tasks, suggesting that general task-related deficits (e.g., counting or volume estimation) were unlikely to explain the interoception findings. In regards to memory - and as would be expected - no differences were observed in working memory performance, but both JW and PT's immediate and delayed verbal memory scores were poorer than those of the controls.

The essential idea motivating this research was that the brain areas identified as being responsible for interoception may differ according to the type of task. Studies using patients or

animals with brain lesions have often used tasks that involve integrating current feeling states with mnemonic processes, while neuroimaging research with healthy people has often used tasks that do not. As both JW and PT were, overall, impaired on *both* types of interoceptive task (relative to the controls), this suggests that task type may not be a promising explanation for the contrasting findings that come from lesion and neuroimaging studies. Below, we briefly consider three further possible explanations of this difference.

A first and obvious starting point is to reconsider our assumption that the HRT task does not involve a task-specific mnemonic component. As we noted in the introduction, it is possible that under certain circumstances participants may feel forced to rely upon some form of explicit calculation, utilising memory of their past heart rate (e.g., Ring et al., 2015). We attempted to forestall this possibility by modifying the HRT task, so that when participants felt utterly unable to generate a response there was no pressure to provide one. Using this procedure we found that failures to report a tracking response were significantly associated with poorer cardiac interoceptive accuracy on reported trials, suggesting that those unable to consciously perceive their heart beating were indeed those with the lowest score on this task. In addition, no participant indicated using any form of recollection/calculation approach, not surprisingly when there was no pressure to do so.

A related possibility is that participants draw upon some form of implicit memory of cardiac output to inform their judgment (see Azevedo et al., 2016). For example, estimating ones heartbeat may be difficult as interoception may be intermittent, and so people may rely upon some form of implicit memory of their heart's rhythm so that they can keep counting over periods when they cannot consciously perceive their heartbeat. While traditionally it was thought that MTL structures played little role in implicit memory processes, more recent data suggests they do, and so it is plausible that an intact MTL may be necessary for this task-specific process to occur (Hannula & Greene, 2012). Importantly, however, this rests upon

two untested assumptions: (1) that participants do use some form of implicit memory to generate an estimate of their own heart rate on the HRT task; and (2) that the task-specific implicit memory process is MTL dependent. Notwithstanding these caveats, we return later to the more general idea that the brain may form models of interoceptive state that are memory dependent.

A second explanation for the divergent outcomes between much of the interoception-related fMRI data and the lesion data (human and animal) derives from a network view of interoceptive processing. Several authors (e.g., Phillips et al., 2003a & b; Schoenbaum, et al., 2002) have suggested that the limbic system is composed of two parts: The ventral system (amygdala, anterior IC, caudal orbital cortex and ventral parts of the ACC), which identifies the emotional significance of a stimulus and the resultant affective state, and the dorsal system (dorsal cingulate gyrus, hippocampus and PFC), which regulates these states. This division could suggest why MTL lesions may impair interoception in the absence of generally finding MTL activity. While these two systems are separate, it is plausible that together they form part of a multidimensional map of current interoceptive state, which then guides goal-directed behaviors. It may be that the MTL, and especially the hippocampus, reflects a unique point of vulnerability for this whole network, even if MTL structures are not always active.

A third possibility concerns the way in which much of the interoception neuroimaging research has been conducted. One pertinent example of this concerns the only fMRI study of the HRT task (Pollatos et al., 2007b), which found no MTL activations – in contrast to the conclusion from this study. One reason for this type of result may be the insensitivity of fMRI to temporal changes between the functionally connected brain networks active during interoceptive tasks (Jarrahi et al., 2015). Using deconstructed fMRI data and multivariate approaches Jarrahi et al., (2015) studied the temporal activation of neural networks in response to bladder stimulation. Bladder fullness engaged multiple structures, including the IC, ACC,

amygdalo-hippocampi and parahippocampal gyri, with interactions between the different areas changing across time. Indeed, when this type of technique is applied to cardiac interoception, a similar picture emerges, and one that is far more consistent with the data from this and other lesion studies. Kuehn et al., (2016) grouped participants into accurate or inaccurate cardiac interoceptors based upon the HRT task. Participants were then imaged and asked to *just* focus on their heart (i.e., not to count or do anything else). Here significant alterations were observed in functional connectivity between the insula and hippocampus, which differed between accurate and inaccurate cardiac interoceptors. It may be then, that it is the type of imaging paradigm that is responsible for the difference in findings/conclusions between fMRI and lesion studies, rather than the type of interoceptive task.

Finally, it is important to consider what functional role MTL structures play in interoception. This manuscript was initially motivated by the idea that MTL involvement might be restricted to certain tasks that required participants to integrate a memory of prior events (e.g., amount of food consumed or fluid drunk) with judgments of current state. We suggested that the Water Loading Task involved integration while the cardiac interoception task did not. The finding here of impaired cardiac interoception in MTL patients argues against this type of account. A second possibility is that MTL structures and especially the hippocampus, record interoceptive experience across time in a context-dependent manner, which then forms a crucial part of the input into the type of comparator model of interoception advanced by Barrett and Simmons (2015). In the comparator model, the brain constantly predicts interoceptive state, based upon past state information, and then compares this with current input. Feedback about the success or failure of the current model is then returned to the inputting system(s). Barrett and Simmons (2015) model utilises structures identified by existing interoceptive models (i.e., Craig, 2009), notably the anterior cingulate cortex and IC, but does not include roles for other structures that have been identified from lesion and

functional connectivity studies (i.e., MTL). Including MTL structures as an input of past state information would be an important extension of the comparator model. In particular, it would allow context to modulate input to the model, so that previous interoceptive experience at a particular place, time, mood etc was used to make current state predictions. In addition, we would suggest that a comparator model could not function properly in the absence of such context dependent input, which may be why MTL damage results in such significant impairment to interoception.

In conclusion, this study demonstrates that selective damage to MTL structures - with intact IC and ACC - can impair interoception, irrespective of the type of task. These findings challenge the view derived from neuroimaging literature, which suggests that the IC and ACC mediate interoceptive processing. Rather, we suggest, the MTL or an MTL centred network, is intimately involved in supporting interoception possibly via its involvement in some form of comparator model.

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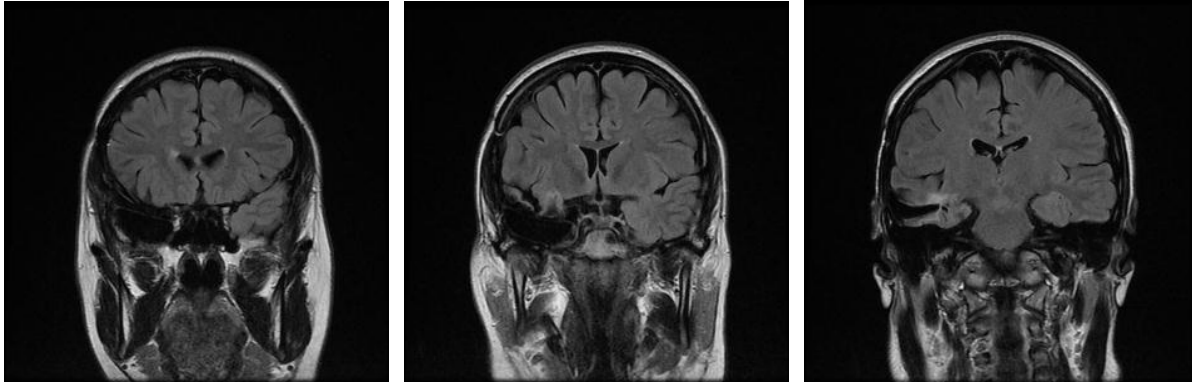
Fig.1: MRI Coronal T2 Flair images of (a) Case PT and (b) Case JW. From left to right, images move more posteriorly.

Fig.2: Bottles used in the Water Quantity Estimation Task

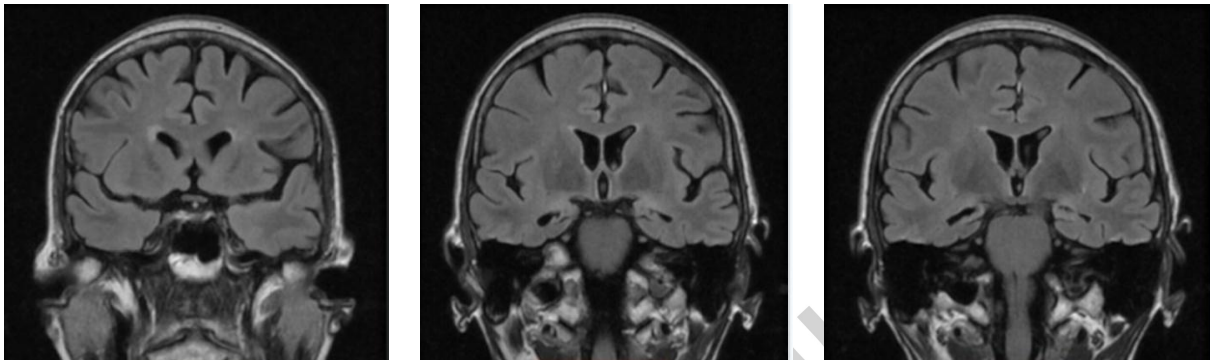
Fig.3: (a) Fullness ratings for PT and controls (mean) from T1-T3 and (b) Fullness ratings for JW and controls (mean) from T1-T3

Fig.1

(a)



(b)



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Fig.2

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Fig.3a & b

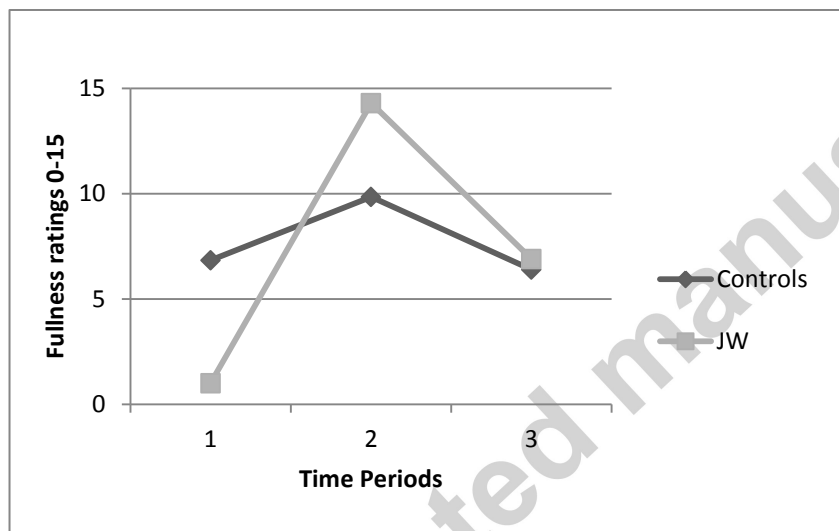
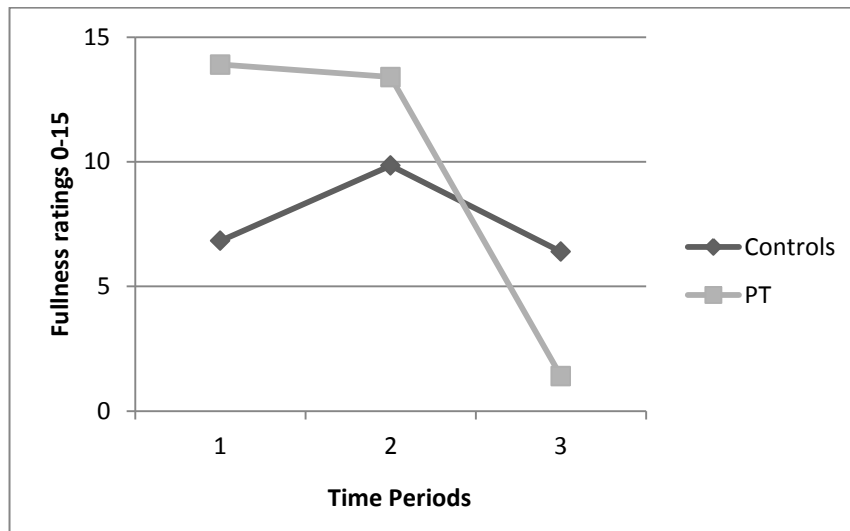


Table 1: Order of task administration

| Order | Task |
|-------|--|
| 1 | Biographical and Background Questionnaire data |

| | |
|----|---|
| 2 | Water Load Test (WLT) - Hunger, Thirst, Fullness Ratings #1 |
| 3 | Water Quantity Estimation test #1 |
| 4 | Heart Rate Tracking (HRT) Task #1 |
| 5 | Logical Memory Immediate Recall |
| 6 | WLT – Drinking phase |
| 7 | WLT - Hunger, Thirst, Fullness Ratings #2 |
| 8 | Test of Premorbid Functioning |
| 9 | Water Quantity Estimation test #2 |
| 10 | Depression, Anxiety, Stress Scale–21 (DASS-21) |
| 11 | Digit Span (Forward, Backwards, Sequencing) |
| 12 | Logical Memory Delayed Recall |
| 13 | HRT Task repeat #2 |
| 14 | Pennebaker Inventory of Limbic Languidness (PILL) |
| 15 | Water Quantity Estimation test #3 |
| 16 | Tone Counting task |
| 17 | WLT - Hunger, Thirst, Fullness Ratings #3 |

Table 2: Biographical and background questionnaire data for MTL patients and controls, and comparison of patients to controls

| Variable | Patient data | | Control data | Crawford t-test | |
|----------|--------------|----|--------------|-----------------|------|
| | JW | PT | M (SD) | JW | PT |
| Age | 61 | 39 | 47 (10.9) | 1.30 | 0.74 |

| | | | | | |
|-----------------|------|------|-------------|------|------|
| BMI | 18.5 | 29.8 | 25.3 (5.2) | 1.34 | 0.87 |
| Education | 3 | 3 | 4.8 (0.8) | 0.95 | 0.95 |
| DASS-21 | | | | | |
| Depression | 6 | 2 | 4.5 (5.4) | 0.28 | 0.48 |
| Anxiety | 0 | 0 | 4.5 (5.0) | 0.92 | 0.92 |
| Stress | 4 | 2 | 9.4 (7.3) | 0.76 | 1.04 |
| Exercise (IPAQ) | | | | | |
| | 5.5 | 5.3 | 11.3 (15.2) | 0.39 | 0.40 |
| Sleep (PIRS) | 0 | 2 | 2.1 (1.4) | 1.60 | 0.10 |

Table 3: Neuropsychological data for MTL patients and controls, and comparison of patients to controls

| Variable | Patient data | | Control data M (SD) | Crawford t-test | |
|--------------------|--------------|----|------------------------|-----------------|-------|
| | JW | PT | | JW | PT |
| Logical Memory | | | | | |
| Immediate | 5 | 3 | 9.2 (2.2) | 1.95 | 2.89* |
| Delayed | 5 | 2 | 10.3 (2.4) | 2.06* | 2.90* |
| Digit span (total) | | | | | |
| Scaled score | 12 | 11 | 11.6 (2.9) | 0.14 | 0.21 |
| TOPF | | | | | |
| IQ estimate | 124 | 94 | 109.7 (10.3) | 1.42 | 1.55 |

* $p < 0.05$

Table 4: Interoceptive task data for MTL patients and controls, and comparison of patients to controls

| Task | Patient data | | Control data | Crawford t-test | |
|--|--------------|------|---------------|-----------------|-------|
| | JW | PT | M (SD) | JW | PT |
| Heart rate tracking (HRT) task | | | | | |
| HRT score | 0.42 | 0.08 | 0.67 (0.21) | 1.29 | 2.44* |
| Water loading task (WLT) | | | | | |
| Linear coefficient (fullness ratings) | | | | | |
| | 3.0 | -6.3 | -0.2 (2.4) | 1.32 | 2.51* |
| Quadratic coefficient (fullness ratings) | | | | | |
| | -10.4 | -5.8 | -3.3 (3.1) | 2.31* | 0.82 |
| Water intake (ml) | | | | | |
| | 150 | 350 | 464.0 (202.6) | 1.58 | 0.57 |
| Pennebaker Inventory of Limbic Languidness (PILL) | | | | | |
| PILL Score | 20 | 12 | 13.2 (7.9) | 0.87 | 0.03 |

* $p < 0.05$

Highlights

- fMRI and lesion studies suggest different brain regions support interoception
- We tested whether this arises from the type of interoceptive task used

- Medial temporal lobe (MTL) lesion patients were compared to controls on two tasks
- Patients were equally impaired on both tasks, irrespective of its need for memory
- The role of the MTL in interoception and the contrast with fMRI data are discussed

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