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Obesity and insulin resistance are associated with reduced activity in core memory regions of the brain

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ABSTRACT

Increasing research in animals and humans suggests that obesity may be associated with learning and memory deficits, and in particular with reductions in episodic memory. Rodent models have implicated the hippocampus in obesity-related memory impairments, but the neural mechanisms underlying episodic memory deficits in obese humans remain undetermined. In the present study, lean and obese human participants were scanned using fMRI while completing a What-Where-When episodic memory test (the "Treasure-Hunt Task") that assessed the ability to remember integrated item, spatial, and temporal details of previously encoded complex events. In lean participants, the Treasure-Hunt task elicited significant activity in regions of the brain known to be important for recollecting episodic memories, such as the hippocampus, angular gyrus, and dorsolateral prefrontal cortex. Both obesity and insulin resistance were associated with significantly reduced functional activity throughout the core recollection network. These findings indicate that obesity is associated with reduced functional activity in core brain areas supporting episodic memory and that insulin resistance may be a key player in this association.

1. Introduction

Obesity is a major risk factor for premature mortality (Kopelman, 2000) and carries an enormous financial burden for health care providers worldwide (Gorsky et al., 1996). With nearly half of the US population currently overweight or obese (World Health Organization, 2010), and prevalence rising, understanding the neurobiological correlates of this condition is becoming increasingly important.

There is a growing literature exploring the association between obesity and cognitive health (Prickett et al., 2015). A number of studies have demonstrated a negative association between anthropometric measures of obesity, such as body weight, body mass index (BMI), or waist circumference (WC), and cognitive performance (Elias et al., 2012), in particular worse executive function (Barkin, 2013; Gunstad et al., 2007). However, other studies have found no such association (van Boxtel et al., 2007) or even small positive associations with cognition (Kuo et al., 2006). One particular cognitive domain which has been suggested as displaying an impairment in obesity is episodic memory. There is considerable evidence for reduced memory performance in rodent models of obesity (Jurdak et al., 2008; Popovic et al., 2001). Obesity in humans has been associated with poor performance on measures of verbal learning such as delayed recall and recognition (Cournot et al., 2006; Gunstad et al., 2006) as well as visual what-where-when episodic memory tasks (Cheke et al., 2016). However, again this association with memory is not seen in all studies (Conforto and Gershman, 1985; Nilsson and Nilsson, 2009).

The mixed results in the behavioural literature are reflected in imaging investigations. Willette and Kapogiannis (2015) reviewed articles that directly or indirectly addressed the association between adiposity (most commonly defined by BMI) and brain volume. A general trend towards lower global gray-matter volume was found in individuals of all ages. In particular, a negative association between BMI and volume in the prefrontal cortex was found in 17/23 studies assessing that area (Maayan et al., 2011; Pannacciulli et al., 2006; Smucny et al., 2012; Ursache et al., 2012; Weise et al., 2013) although 1 study showed an association in the other direction (Taki et al., 2008). Results from the temporal lobe were more mixed; 14/22 studies to investigate temporal lobe volume found increased atrophy with adiposity (Brain Development Cooperative Group, 2012; Pannacciulli et al., 2006; Weise et al., 2013) while others did not, and only 11/28 of the studies specifically investigating hippocampal volume found a negative association with obesity (Anan et al., 2010; Bruehl et al., 2011; Debette et al., 2010; Ho et al., 2010a,b, 2011; Jagust et al., 2005; Kurth et al., 2013; Taki et al., 2008) with two studies reporting associations in the other direction (Kurth et al., 2013; Widya et al., 2011).

There has, to date, been only one functional imaging investigation

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of episodic memory in obesity. Boraxbekk et al. (2015) assigned 20 overweight middle-aged women to either a modified Palaeolithic diet or a standard healthy diet for 6 months. The authors assessed episodic memory with a face-name recognition paradigm while using functional magnetic resonance imaging to examine brain activity before and after the dietary intervention. Memory performance improved significantly after the dietary interventions (with no difference between the two groups), and decreases in waist circumferences correlated significantly with increased brain activity in the superior temporal gyrus and insula. However, the results of this study are difficult to interpret for a number of reasons. First, a recognition face-name paradigm may rely on a number of mnemonic processes and cannot be said to be specifically assessing episodic memory. Second, due to the lack of a control group, and because the same memory stimuli were used at the beginning and end of the intervention, it is problematic to determine what degree of change in performance and brain activity one might expect without dietary intervention during this time period.

A major issue in the investigating the association between obesity and cognition is the heterogeneity of the obese population. While "obesity" is defined in terms of excess adiposity, individuals matched for body mass index may vary considerably in comorbid conditions such as hypertension and insulin resistance, and it may be these factors that are mediating the association between obesity and cognition. For example, Gonzales et al. (2010) assessed the impact on obesity on functional activity during a 2-back working memory task in 32 cognitively normal middle aged adults with BMI's ranging from the healthy range to obese. In addition, the authors examined insulin sensitivity as a potential factor mediating the association between BMI and brain activity. It was found that the obese group displayed significantly lower task-related activity in the right parietal cortex (BA 40/7) than either the normal or overweight group; an effect that was found to be fully mediated by insulin sensitivity.

It has been well established that obesity increases the risk of insulin resistance and type 2 diabetes mellitus (Bonadonna et al., 1990; Matsuzawa et al., 2011). Diabetes currently affects around 250 million people worldwide (Cole et al., 2007) and is particularly prevalent in older adults (Wild et al., 2004). While the systemic damage caused by diabetes is well described (Zhao et al., 2010), only recently have researchers began to recognise the significance of insulin and insulin resistance for brain and cognitive health.

Insulin is a peptide released by pancreatic cells, which has multiple functions both in the periphery and in the central nervous system. Whether insulin is synthesized in the adult brain is a topic of controversy, however it is known to readily cross the blood brain barrier and perform many important functions within the brain (Abbott et al., 1999; Banks et al., 1997; Baskin et al., 1987; Baura et al., 1993; Chiu et al., 2008; Zhao and Townsend, 2009). Insulin receptors appear in high concentrations in the cerebral cortex and hippocampus (Baskin et al., 1987; Havrankova et al., 1978a, b; Lathe, 2001; Unger et al., 1991), and there is substantial co-localisation for insulin-containing neurons, insulin receptors and glucose transporter isoforms in the hippocampus and medial temporal lobe (Grillo et al., 2009). There are many proposed mechanisms by which insulin may modulate learning and memory: Examples include stimulating glucose uptake in key regions (Grillo et al., 2009), modulating expression of NMDA in the cell membrane, affecting the induction of long-term potentiation (LTP; Skeberdis, Lan, Zheng, Zukin, and Bennett, 2001) and modulating CNS levels of acetylcholine and norepinephrine (Figlewicz et al., 1993; Kopf and Baratti, 1996).

While the exact mechanisms by which insulin influences learning and memory remain to be fully elucidated, a number of lines of evidence suggest that changes in insulin levels and/or regulation can have significant consequences for cognition. The impact of insulin administration on declarative memory has been investigated in human and animal models and reliably shows a beneficial effect. In rats, intracerebroventricular administration of insulin improves performance on passive avoidance tasks (Park et al., 2000), while intranasal insulin administration has resulted in improved performance on water maze and radial arm tasks (Francis et al., 2008). In humans, intravenous infusion of insulin (while keeping glucose levels stable) has been found to improve hippocampal-dependant (word-list) memory (Kern et al., 1999), and such findings have been reflected in trials using intranasal infusions of insulin (Benedict et al., 2004, 2008; Hallschmid et al., 2008; Stockhorst et al., 2004). For example, Benedict and colleagues demonstrated that declarative memory (as measured by word list paradigms) could be improved in young healthy adult subjects by means of an 8-week course of intranasal insulin administration.

Insulin resistance (IR) can be broadly defined as a reduced cellular responsiveness to insulin (Goldstein, 2002), characterized by higher insulin levels needed to maintain glucose levels in the periphery and brain. Growing evidence has linked insulin resistance to cognitive decline and neurodegeneration (e.g. Craft et al., 2013). Higher IR in middle aged adults is a mediator for worse memory performance and greater reduction in GM volume over a 4-year period (Willette et al., 2013) supporting a suggested 7–13% increase in dementia in the presence of type 2 diabetes (Biessels and Kappelle, 2005; Craft et al., 2013; Craft and Watson, 2004; Roriz-Filho et al., 2009; Schrijvers et al., 2010). Indeed, higher levels of insulin resistance markers in MCI and AD patients are associated with worse performance on tests of working and episodic memory independent of plaque and tangle load. These findings suggest that disturbances in insulin signalling has a direct association with cognitive status in older adults (Talbot et al., 2012) rather than acting via increases in beta- amyloid and tangles, although there is also evidence for this route (Cole and Frautschy, 2007). Furthermore, pilot data suggests that intranasal infusions of insulin can be used to improve verbal memory both acutely and chronically in these patients without affecting insulin or glucose in the periphery (Reger and Craft, 2006; Reger et al., 2008a, b).

Long term insulin resistance is a key diagnostic criterion for diabetes mellitus. Both Type 1 and Type 2 diabetes are associated with reduced memory and executive functions (Awad et al., 2004; Grodstein et al., 2001; Kodl and Seaquist, 2008; Messier, 2005; Munshi et al., 2006; Perlmuter et al., 1984; Weinger et al., 2008). Children with type 1 diabetes demonstrate worse school performance and IQ scores than their nondiabetic peers (Dahlquist et al., 2007; Fox et al., 2003; Northam et al., 2001; Schoenle et al., 2002) and these impairments appear to persist into adulthood (Ryan, 2006). Structural neuroimaging studies suggest that individuals with type 1 and type 2 diabetes demonstrate cortical and subcortical atrophy, including the hippocampus and amygdala, related with impaired cognitive performance (Akisaki et al., 2006; Dejgaard et al., 1991; den Heijer et al., 2003; Longstreth et al., 1998; Perantie et al., 2007). These findings were significant even after controlling for cardiovascular health. Indeed, there was a strong interaction between diabetes and hypertension such that individuals exhibiting both conditions were at several times greater risk than those with either condition alone (Lobnig et al., 2006). Finally, cognitive decline and neurodegeneration has been shown to be increased not only in diabetes itself, but in pre-diabetes (Luchsinger et al., 2004), in which there is insulin resistance but enough insulin is still produced to prevent overt diabetes (Cole et al., 2007; Luchsinger et al., 2004; Yaffe et al., 2004).

To date, the vast majority of studies in this area have been conducted on older or middle aged adults and as such the association between obesity, insulin resistance and cognitive and neural function in otherwise healthy young adults remains unclear. Furthermore, while a number of studies have examined the impact of obesity and insulin levels on brain areas that previous research indicates to be involved in memory, or a change in brain activity after dietary intervention, none have compared functional activity in these areas during episodic memory task performance in lean and obese individuals. As such, it is currently difficult to assess the relevance of previous neuroscientific findings for understanding memory function in obesity. A direct