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In a sweet mood? Effects of experimental modulation of blood glucose levels on mood-induction during fMRI

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ABSTRACT

Glucose is the primary source of energy for the human brain. Previous literature has shown that varying blood glucose levels may have a strong impact on behaviour, subjective mood, and the intensity of the BOLD signal measured in fMRI. Therefore, blood glucose levels varying even within the normal range may interact with cognitive and emotional processing as well as BOLD signal.

Here, in a placebo-controlled, double-blind crossover study on 20 healthy women, we show that overnight fasting, compared to an elevated glucose condition, influences brain activation and the affective state during mood induction. Results indicate that our brain may compensate for low glucose levels during fasting by stronger recruitment of the brain areas relevant to the task at hand. Additionally, we systematically tested the effect of prior cognitive effort on behavioural and neural patterns and found that elevated activation is only associated with maintained performance as long as no prior cognitively challenging task is administered. Prior cognitive effort leads to deteriorated performance and a further increase in emotion-associated brain activation in the pregenual anterior and posterior cingulate, the superior frontal gyrus, and the pre-SMA. These results are in line with the strength model of self-regulation.

Our results corroborate the strength model of self-regulation and extend it to affect regulation processes. Additionally, our observations suggest that experimentally controlling for fasting state or glucose levels may be beneficial, especially when studying processes that involve self-regulation.

Introduction

Hunger and mood are closely interconnected. This relationship has even led to a neologism, with the word 'hangry' purporting to describe a state in which the desire or need to eat causes frustration or anger. Hunger is triggered by a decrease in blood glucose levels (BGL) (Southgate, 1995). Low blood glucose has also a broad impact on cognitive functioning. In healthy adults, cognitive impairments may arise at levels of 46–55 mg/dl (Warren and Frier, 2005). Generally, complex tasks are more strongly impaired by hypoglycemia than simple tasks. Most prone to disruptions by hypoglycemia are (among others) memory performance, attention, and visual and auditory processing. These effects may persist even after the restoration of BGL, and very low levels or persistent hypoglycemia may lead to brain damage (Warren and Frier, 2005). Studies involving patients with diabetes, who may have treatment-related recurring periods of low to very low BGL and increased risk of depression, have helped reveal the effects of BGL on mood (Anderson et al., 2001). In a large cohort study, undiagnosed diabetes patients showed elevated levels of depressive symptoms, similar to those in diagnosed depressed patients (Holt et al., 2009), ruling out the possibility that chronicity of the disease might have led to depression. Furthermore, Gonder-Frederick and colleagues (Gonder-Frederick et al., 1989) found an association between subjective self-ratings of emotion and BGL in diabetes patients over a time interval of 40 days, relying on four ratings per day. Low BGL was associated with negative mood states, whereas high BGL correlated with positive mood states.

Although differences in methodology limit comparability of studies in healthy subjects with low normal BGL (after overnight fasting) and clinically relevant hypoglycemic states, these states have to be distinguished. Evidence points towards a significant interaction of blood glucose and affect even in low normal BGL in healthy adults. Low BGL

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after fasting is associated with aggression in men (Benton et al., 1982), and in women (Donohoe and Benton, 1999), it leads to more pronounced expression of anger (McCrimmon et al., 1999). In contrast, elevated BGL is associated with relief from tension (Benton and Owens, 1993). Intake of carbohydrates may increase subjective energy for a short time, while it may lead to a sedative effect after a long period, although this effect is inconsistent and may be mediated by psychological factors such as cognitive effort (Benton, 2002; Owens et al., 1997). Direct associations between self-reported mood and BGL are sporadic and effect sizes are small (Gailliot and Baumeister, 2007). Investigating the link between BGL and mood following cognitive demand, Owens and colleagues (Owens et al., 1997) found a significant positive correlation between self-reported energy and BGL. Gailliot and Baumeister (2007) summarise the findings and propose that BGL is closely linked to self-control. The 'strength model' the authors refer to states that self-control relies on one's limited resources, which may be depleted by acts of self-regulation. This depletion has been termed ego depletion. According to the authors, these acts of self-control or regulation rely upon glucose, which is a limited resource and may be depleted (Baumeister et al., 2007). This ego depletion may in turn lead to a decrease in the ability of self-regulation with decreased BGL (e.g. during fasting). The 'strength model' was evaluated in a recent meta-analysis (Hagger et al., 2010), in which the authors identified blood glucose as a possible mediator of ego depletion, which can be compensated by administration of glucose.

Neuronally, the interaction between blood glucose and mood regulation has not been studied so far. However, there are data that imply a strong influence of hypoglycaemia on the BOLD response (Anderson et al., 2006; Driesen et al., 2007), with up to 28% decreases in BOLD response. Investigations into the effects of BGL on BOLD response intensity during fMRI experiments have so far focused on BGL hypoglycaemic situations, mainly by employing insulin clamps (Anderson et al., 2006; Driesen et al., 2007; Schafer et al., 2012; Warren and Sommerfield, 2008), which lower BGL to a predefined level for a certain period of time. Peripheral BGL within the 'normal' range (approx. 80–100 mg/dl, Benton, 2002) may not have a similarly strong impact on BOLD signal as glucose proliferation in the brain is well regulated and is probably only disrupted by clinically relevant hypoglycaemia or long-lasting fasting states (Paulson et al., 2010). A recent study, investigating the influence of blood glucose after fasting and its modulation following glucose administration on reactivity to emotional stimuli, has reported modulation of hypothalamic activation in the hyperglycemic state. However, overall, no significant modulation of the neural correlates of emotional reactivity during low BGL after fasting (Schöpf et al., 2013) has been observed.

In healthy individuals, mood induction procedures (MI) have been widely applied to study neural correlates of feeling states. Various forms of MIs have been reported in the literature (Westermann et al., 1996). In general, one can distinguish between MIs ranging from mostly automatic mood induction (like music) to highly cognitive, strategic induction procedures (like imagination) and different combinations of these MIs with differing effectiveness and validity (for reviews see Gerrards-Hesse et al., 1994; Westermann et al., 1996). In general these procedures aim at changing the overall, background affective experience. Thus in analogy to the emotion regulation literature (e.g. up- or down-regulation of emotional reactivity to a valenced stimulus; Gross, 2007), mood induction procedures can be seen as an operationalization of mood regulation (Larsen, 2000). Nevertheless, mood and emotion regulation have to be distinguished, although both can be viewed as affect regulation.

Different approaches have been applied to study the neural correlates of MI, with some by directly instructing participants to change their mood voluntarily (Habel et al., 2005; Hofer et al., 2006; Kohn et al., 2013; Pelletier et al., 2003; Reske et al., 2007), while others by inducing mood changes more passively (e.g. Goldin et al., 2005; Hutcherson et al., 2005; Mitterschiffthaler et al., 2007). Both positive and negative mood states elicit activity in the amygdala–hippocampal area, the prefrontal and temporal areas, the anterior cingulate cortex (ACC) and the precuneus (Habel et al., 2005; Mitterschiffthaler et al., 2007; Pelletier et al., 2003).

In this study, we aimed to investigate the effects of BGL after overnight fasting on mood regulation and its underlying neural network. To that end, we applied a well-validated MI during fMRI measurements. The procedure involves presenting happy or sad faces to the participant, respectively. Additionally, the participant is instructed to try and get into a happy or sad mood and is encouraged to use autobiographical material as support.

Our placebo-controlled double-blind design assesses blood glucose levels that occur naturally in healthy individuals after overnight fasting and may also be present in subjects participating in fMRI studies (in cases, for instance, where subjects have not eaten for several hours, e.g. having skipped breakfast). However, this is normally not controlled for in experiments. We therefore instructed our participants to fast overnight for approximately 14 h prior to the fMRI measurements in order that this influence could be analysed. Every participant had a BGL lower than 80 mg/dl at the beginning of the fMRI measurements. Participants were scanned in an elevated BGL condition after prolonged fasting (EC), in which the BGL was elevated via infusion of glucagon and a non-modulated fasting BGL condition (FC), in which participants received sodium chloride and remained in a prolonged fasting-induced low normal BGL state. We started with a resting state measurement, continued with either MI or a working memory paradigm (CPT, described in Methods) in counterbalanced order. These paradigms were followed by a basal visual stimulation paradigm (checkerboard). The scanning session was ended with a final resting state scan. The results from the basal visual stimulation have been published before and point to an influence of prolonged fasting on higher order visual processing areas, which may be related to attention and is associated to decreased brain activation in prolonged fasting compared to an experimental re-feeding condition (Kohn et al., 2014). In the working memory paradigm we found no behavioural differences between an elevated glucose condition compared to a fasting condition, nevertheless, brain activation in bilateral dorsal midline thalamus and the bilateral basal ganglia was reduced in prolonged fasting suggesting high sensitivity of these task relevant regions to minimal changes in blood glucose levels (Chechko et al., 2014). The present analysis of the mood induction paradigm may add important information on the influence of prolonged fasting on mood regulation, adding to the previous manuscripts on basal visual stimulation and working memory.

Additionally, our design enabled us to test the strength model proposed by Gailliot and Baumeister (2007), which postulates that every act of self-regulation consumes glucose. Thus, a cognitively demanding task (CPT) prior to the mood induction paradigm may induce stronger differences between elevated and low blood glucose conditions.

We hypothesized, therefore, that (A) prolonged fasting results in decreased task-related brain activation (lateral prefrontal cortex, superior frontal gyrus, anterior and posterior cingulate, basal ganglia, and amygdala). Additionally, decreased BOLD signal strength has been observed in low BGL in previous fMRI studies (Anderson et al., 2006; Driesen et al., 2007). In contrast to the study by Schöpf et al. (2013), we Q6 conducted a demanding mood regulation task, which may arguably lead to stronger effort-related changes in brain activation and subjective affect. Regarding the subjective affective state, we hypothesized that (B) a reduced ability to regulate one's own mood state is indicated by lower increases in the happy/sad mood in the fasting state compared to the elevated BGL condition. This pattern is contingent on the arousal differences in these conditions and would additionally support the concept of glucose as an essential agent of self-regulation (Gailliot and Baumeister, 2007).

Furthermore, in line with the strength model, we expected to see (C) more pronounced differences neuronally as well as behaviourally

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