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Abstract

The role of glucose in enhancing cognitive performance has been a subject of interest, with conflicting findings across various studies. Understanding the circumstances under which glucose administration yields benefits, harms or remains inconsequential for subsequent performance is of paramount importance, given its prominence as the dominant form of carbohydrate in our physiological energy supply. Even the neural processing of each and every word of this thesis will likely be powered by glucose, just as the thoughts that brought such words together. As the role of glucose in our physiology is of fundamental significance for both our body and mind, it also raises critical questions regarding the management of individuals with impaired glucose regulation, such as those with diabetes, spanning from infancy to old age. This doctoral thesis delves into the investigation of the cognitive effects resulting from glucose intake. Study A, B, and C represent the foundation of the overarching research project and are forming the basis of this thesis. Each of these contributions to the underlying body of research serves an empirical and a methodological purpose. Empirically, Study A investigated factors that influence interindividual differences in the magnitude of cognitive effects elicited by glucose administration, termed cognitive glucose sensitivity (CGS). Study B examined possible underlying physiological mechanisms of these cognitive effects. Study C explored CGS in a clinical context. Methodologically, the same studies represent the development of behavioral (Study A), physiological (Study B), and introspective (Study C) approaches to the study of glucose-related effects on cognition. This duality serves the purpose of answering key questions about the cognitive effects of glucose consumption, while at the same time overcoming the methodological limitations of our curiosity and encouraging the emergence of novel questions in the long term.

Research Articles

Study A Neukirchen, T., Radach, R., & Vorstius, C. (2022). Cognitive glucose sensitivity—proposing a link between cognitive performance and reliance on external glucose uptake. *Nutrition & Diabetes*, 12(1), 10.

Study B Neukirchen, T., Stork, M., Hoppe, M. W., & Vorstius, C. (2022). Spirometry has added value over electrodermal activity as a physiological marker of mental load in male subjects. *Scientific Reports*, 12(1), 4496.

Study C Neukirchen, T., Buitkamp, L. F., & Vorstius, C. (2023). Selbst eingeschätzte kognitive Glukosesensitivität: Zusammenhang mit Langzeitblutzuckerspiegel und diabetesbedingter Belastung bei Individuen mit Typ-1-Diabetes. *Prävention und Gesundheitsförderung*, 1-8.

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ATP	adenosine triphosphate
AUC	area-under-the-curve
BMI	Body Mass Index
CBT	Corsi-Block-Tapping-Task
CGS	Cognitive Glucose Sensitivity
EDA	electrodermal activity
HbA1c	glycated hemoglobin A1c
IGlu	Indicators of Glucose-Dependency
kGS	kognitive Glukosesensitivität
MV	Minute Volume
PAID	Problem Areas in Diabetes Scale
RER	Respiratory Exchange Rate
ROC	Receiver operating characteristic
RR	Respiratory Rate
SCL	Skin conductance level
ToS	Threat-of-Shock paradigm
VCO_2	carbon dioxide output
VO_2	oxygen uptake

1 General Introduction

On a neuronal level, glucose is a primary energy substrate. Interestingly, a plethora of research suggests that ingestion of glucose sources does not reliably increase cognitive performance. The main goal of this present doctoral thesis was to investigate this inconsistency of glucose induced effects on cognition.

My strategy to achieve this, was based on the theory that the magnitude of glucose induced effects are determined by differences between individuals as well as external factors. This allows to shift away from the question, whether glucose supplementation leads to increases in performance towards the answering under what circumstances, glucose supplementation will benefit cognition. Consistently, our workgroup labeled the individual performance gain in response to a glucose supplementation as *cognitive glucose sensitivity*[1] (*CGS*) and began with the investigation of factors that accounted for its variability between and within individuals.

Major steps of the research underlying this dissertation involved establishing CGS as a viable psychological construct. This was done by demonstrating the measurability of interindividual variance as well as its association with well-known, psychological parameters. Since the beginning of my dissertation project, the current state of research on CGS has diversified considerably, with follow-up studies branching out in a multitude of directions. Yet, this overarching research rests on three main studies (Study A, B, C), constituting its empirical and methodological foundation. Therefore, Study A, B, and C were selected to serve as the basis

[1] As a convenience to the reader of this dissertation, newly introduced technical terms, definitions, and major structural features are highlighted in italics.

for this doctoral thesis, semantically resembling the structure of the overarching body of research, to which it contributes. This fractal-like property emerges from the endeavor to conceive every study in a way that satisfies the principal of empirical and methodological duality.

Empirical and methodological progress constitute the dimensions that define the field of research on CGS. A field that neighbors and connects the empirical research on glucose-related cognitive effect and glucoregulation. The contributions presented in this dissertation are driven by the expectation that they may serve as a piece of the puzzle that helps to reveal a larger picture of the interplay between interindividual differences in energy metabolism and cognitive functioning.

The first study (Study A) contributes to the empirical investigation of factors influencing the extent of cognitive effects elicited by glucose administration, termed CGS. Secondly, possible underlying physiological mechanisms behind these cognitive effects are examined in Study B. Additionally, the thesis embarks also on a seminal exploration of the clinical relevance of CGS in Study C. In each of these three domains, this work provides initial answers, yet, importantly, it also gives rise to numerous uncharted research inquiries. Indeed, the three constituting studies of this thesis serve already as foundational stepping stones for consecutive research endeavors, which will be discussed in the final section. In line with the duality of purpose, from a methodological perspective, the presented studies constitute the development of behavioral (Study A), physiological (Study B) and introspective (Study C) approaches for the psychological investigation of glucose-related effects on cognition.

Therefore, the goal is to answer empirical questions regarding interindividual differences in cognitive effects of glucose ingestion, and secondly, developing the instruments necessary to answer the questions of the first aspect, overcoming the methodological limitations of our curiosity and encouraging the emergence of new questions in the long term. This thesis will present the outlined content in three sections, summarized below.

On a microlevel, Section 1 fulfills the following key functions. First, it explains what glucose is and its role in supplying energy to for our brains (Section 1.1). It outlines the mechanisms our bodies use to manage the energy supply with glucose (Section 1.2). Furthermore, it establishes that there are interindividual differences in the functional level of these mechanisms on a clinical, subclinical and non-clinical level, and why the body of research on glucose metabolism and cognition is therefore of fundamental relevance (Section 1.3). Evidence is provided for interindividual differences in the effect of glucose on cognitive performance and the extent to which this is related to task characteristics and interindividual differences in correlates of glucose regulation. Alongside, the historical growth of the body of research, to which the publications of this thesis contribute, is presented (Section 1.4). The same subsection will also explain and illustrate how this previous work has guided our contributions to research both in terms of empirical questions and methodological considerations. In Section 1.5, the goals and their logical foundations are briefly summarized.

On a macro level, this prelude (Section 1) allows to localize my empirical contributions (Section 2) in the overall scientific context and to ensure the comprehensibility of their underlying empirical questions and methods. The empirical and methodological implications of the overall picture (Section 1, Section 2) form the basis of the general discussion (Section 3), which

systematically uses the entire body of evidence presented to describe the updated state of knowledge, emerging branches of our current research, and directions for future exploration.

1.1 Glucose

Glucose, a simple carbohydrate, plays a pivotal role in both plant and animal physiology. It is produced through a complex biochemical process known as gluconeogenesis (Berg et al., 2013, p. 456). In plants and animals alike, glucose serves as storage for energy. Plants produce it from CO_2 and water by the process of photosynthesis, obtaining the required energy from light. During a process called cellular respiration, that energy, CO_2, and water is released (Berg et al., 2013, p. 503). This glucose-dependent release of CO_2 will play a fundamental role in Study B. Apart from the advantage of the abundance of its reactants, glucose features the benefit of being able to be stored in longer molecular chains, also known as complex carbohydrates (Berg et al., 2013, p. 329). For energy recovery, these complex carbohydrates can be broken down into the simple and reactive carbohydrate glucose, which is the energy substrate of a wide variety of cell types (Butterworth et al., 2011; Singh et al., 2010). The effects of glucose on the human body is relevant to the understanding of energy balance and the effects of nutrition as a whole, as carbohydrates constitute a major source of energy in human nutrition (Grigg, 1996).

When dietary intake fails to provide an adequate supply of carbohydrates, gluconeogenesis becomes paramount to provide a sufficient supply of carbohydrates. This occurs not only during periods of extreme starvation but also when the available food lacks digestible carbohydrates that can be metabolized into glucose (Rehner & Daniel, 2010). An intriguing aspect of glucose's importance lies in its fundamental role in providing energy to sustain brain function. This is because the adult human brain, with its intricate neural networks and cognitive processes,

operates as the most energy-demanding organ in the body. The majority of this energy demand stems from its neurons, which metabolize glucose to generate adenosine triphosphate (ATP). ATP serves as the primary energy source, facilitating the production of neurotransmitters and supporting the general maintenance of neuronal cells (Howarth et al., 2012; Mergenthaler et al., 2013).

Given the brain's reliance on glucose, maintaining optimal levels of blood glucose, known as euglycemia, becomes imperative for cognitive functioning. Abnormal fluctuations in blood glucose levels, whether too high (hyperglycemia) or too low (hypoglycemia), can profoundly affect an individual's cognitive abilities (Cox et al., 1993, 2005; De Feo et al., 1988; Holmes et al., 1984; Mcaulay et al., 2006; Taylor & Rachman, 1988). These findings emphasize the critical importance of *glucoregulatory capabilities*, which encompass all abilities to keep blood glucose levels within the optimal range, regardless of the nutritional context (Aronoff et al., 2004). Crucial components of the glucoregulatory capabilities are explained further in the following Section 1.2.

1.2 Glucoregulation

Maintaining glucose levels within the optimal range in healthy individuals is achieved through the interaction of various physiological mechanisms that are capable of *increasing, decreasing, and substituting glucose* as fuel in the blood. In this order, the following subsection briefly outlines selected examples of these mechanisms as they relate to this dissertation. Together, they describe the ability to respond and adapt to changes in metabolic or energy demands, also known as *metabolic flexibility*.

With regard *to increasing blood glucose* concentration during the absence of dietary sources of glucose, the processes of glycogenolysis and gluconeogenesis need to be considered. While the former involves converting glycogen, a storage form, back into glucose, the latter actually synthesizes glucose. In vertebrates such as humans, this occurs largely via pyruvate, which in turn is produced from alanine, glutamine, glycerol, and lactate (Gerich, 1993; Gerich et al., 2001). With the expenditure of energy, pyruvate can be used to produce glucose, which in turn can be used for energy production in the target tissue. In this process, pyruvate is generated again, which can ultimately be used again for the production of glucose. This cycle – the production of glucose from the waste of the energy production from glucose – is also known as the Cori cycle. One reason why the consumption of carbohydrates for the production of glucose is nevertheless useful lies in the fact that during the Cori cycle three times more ATP is consumed for the production of glucose than released during the metabolization of glucose. Accordingly, the proportion of glucose recycled in this way covaries with its necessity, for example, by the length of abstention from the intake of carbohydrate sources (Katz & Tayek, 1998).

When blood glucose concentrations fall, the human body responds by releasing various hormones to stimulate both, the body's own production and the utilization of stored glucose. The peptide hormone glucagon plays an essential role in this context, stimulating the processes of glycogenolysis and gluconeogenesis and thereby increasing blood glucose levels (Berg et al., 2013, p. 492). However, hormones commonly associated with emotional arousal, such as cortisol and adrenaline, may also raise blood glucose levels (Sharma et al., 2022). This is particularly relevant in Study B, that looked at possible reasons for changes in turnover of glucose in response to emotional stress.

Another hormone, that plays a crucial role in glucoregulation is insulin. Insulin is a peptide hormone secreted by the pancreas that *lowers blood glucose* by a combination of mechanisms. Insulin increases glucose uptake by tissues, especially muscles and fat, and suppresses glucose production by the liver (Wall et al., 1957). In addition, insulin reduces the breakdown of glycogen (Wall et al., 1957) and fat. Through this, the production of ketone bodies is reduced and fat storage is increased (Tamborlane et al., 1979).

Insulin acts on insulin receptors, which undergo a process called autophosphorylation upon insulin binding, leading to the activation of downstream signaling pathways (Virkamäki et al., 1999). This cascade can be affected by several factors, including nutrient excess, obesity, and inflammation, which can lead to a state of such low receptor sensitivity that it is referred to as insulin resistance (Schenk et al., 2008). In other words, insulin resistance can manifest as a severely decreased sensitivity or responsiveness of the receptor to insulin (Kahn, 1978). Interindividual differences in glucose uptake are often associated with differences in insulin sensitivity, which therefore plays an important role in glucoregulatory capacity, particularly with respect to glucose uptake and lowering of blood glucose levels (Hollenbeck & Reaven, 1987).

Substituting glucose with an alternative energy source – known as ketones or ketone bodies – is a strategy that becomes critical under conditions of limited glucose availability, such as during fasting, carbohydrate deprivation, or vigorous physical exertion. Ketone bodies, specifically acetone, acetoacetate, and beta-hydroxybutyrate, are molecules synthesized within the liver through the process of ketogenesis (Berg et al., 2013, p. 660). They emerge as an alternative energy reservoir when glucose levels in the bloodstream become suboptimal (Balasse & Neef, 1975). By facilitating the catabolism of stored fatty acids, the liver produces

ketone bodies. Subsequently, these molecules are transported via the bloodstream to target tissues, such as the brain and skeletal muscles, to meet their energy demands (Jensen et al., 2020; Mattson et al., 2018).

Ketone bodies play a crucial role in brain metabolism. Although glucose – if available – is the prioritized fuel for the brain, neuronal cells are able to efficiently metabolize ketone bodies, replacing up to 75% of glucose, when carbohydrate supply is scarce (Berg et al., 2013, p. 661; Jensen et al., 2020). This flexibility ensures that the brain continues to function properly even during periods of restricted carbohydrate intake.

An additional salient function of ketone bodies is the preservation of muscle protein (Thompson & Wu, 1991). During the earlier mentioned process of gluconeogenesis, amino acids are requisitioned from muscle tissue, a necessary step to produce alanine, an important precursor for production of glucose in humans (Berg et al., 2013, p. 494). Ketone bodies, such as acetoacetate and D-beta-hydroxybutyrate, have been found to inhibit glycolysis, reduce pyruvate availability, and inhibit protein degradation in skeletal muscle. This may serve as a survival mechanism during catabolic states (Thompson & Wu, 1991) thereby safeguarding lean muscle mass which is less expendable than the stored fat from which ketone bodies are produced. By functionally replacing glucose in various tissues, ketone bodies help maintaining blood glucose levels within physiological parameters for all tissues that cannot switch from glucose to ketone bodies for fuel. Thereby, ketone bodies help to ensure that vital cells reliant on glucose, such as erythrocytes, remain adequately fueled (Berg et al., 2013, p. 483).

The metabolism of glucose results in significantly higher CO_2 release than that of ketone bodies (Hanson, 1965; Lindsay & Setchell, 1976; Mallet et al., 1986; A. L. Miller et al., 1982; Prince et al., 2013). Within my dissertation, this is one of the fundamental principles behind the

methodological efforts to use spirometry to infer energy metabolism and individual differences in the use of glucose as an energy source to perform cognitive tasks (Study B). The reasoning behind this method is that an increasing proportion of ketone bodies and a decreasing proportion of glucose metabolized by the brain should be evident in the change in CO_2 release. People whose bodies are already accustomed to replacing glucose with ketone bodies should show smaller increases in CO_2 when the brain is stressed compared to people whose bodies rely less frequently on the replacement of glucose with ketone bodies.

The variety of processes that collectively result in a shift from the use of (external) glucose sources to the self-supply and the substitution of glucose with ketone bodies, is referred to as *metabolic switching*. *Metabolic switching is defined as the process by which the body switches from utilizing glucose as the primary source of energy to utilizing fatty acids and ketones instead* (Anton et al., 2018; Mattson et al., 2018). In other words, this concept simplifies the complex interaction of the various systems in the human body, which are forced into a constant struggle for balance through fluctuating energy supply and consumption. The ability to perform metabolic switching is therefore a key component of metabolic flexibility. Mattson and colleagues (2018) define and illustrate the concept of metabolic switching in the context that frequent, intermittent metabolic switching can improve cognitive function and have protective effects against adverse influences such as injury and disease (Mattson et al., 2018). The authors emphasize adaptations on the neuronal and behavioral level, which are predominantly proven in animal models (Cheng et al., 2003; Mattson et al., 2018; Wan et al., 2003).

The concept of metabolic switching resonates well with numerous empirical findings. Estrada and Isokawa (2009) demonstrated that fasting modulates signaling to the hippocampus, which is mediated by the so-called CREB signaling mechanism, that has been shown to be crucial in

the formation of mammalian long-term memory (Bourtchuladze et al., 1994). Other pathways, summarized by Mattson and colleagues (Mattson et al., 2018) as being health-promoting, include upregulation of antioxidants, neurotrophic factor signaling, DNA repair enzymes, protein deacetylases, and autophagy during bioenergetic challenges (when energy demand exceeds energy consumption), which protect neurons (Anton et al., 2018; Mattson et al., 2018). Mechanisms that stimulate mitochondrial biogenesis, cell growth, and plasticity are subsequently expressed to a particularly high degree in the recovery phase after the bioenergetic challenge - similar to a muscle that is stressed during exercise in order to supercompensate (recovering to a degree that is superior to its pre-exercise state) during recovery phases, whereas a training regimen in which either only exercising or only recovering is performed would lead to a less optimal adaptation of the muscle (Anton et al., 2018; Mattson et al., 2018; Wan et al., 2003). In the context of the benefits of metabolic switching, the alternation between bioenergetic challenge and recovery is therefore particularly important.

Considering the interindividual differences in the ability to accomplish metabolic switching – for reference, Landau et al. (1996) found that the contribution of gluconeogenesis to glucose production in healthy subjects, measured after an overnight fast, ranges from 25 to 70 % (while other sources state up to 75%; Berg et al., 2013, p. 661). Therefore, variability in metabolic switching struck me as a promising construct to explain vast interindividual differences in the effect of glucose ingestion on cognitive performance. Depending on how proficient a person is at autonomously compensating for the lack of external glucose sources by flipping their metabolic switch, the difference in performance between a baseline measurement without glucose administration and a measurement after glucose administration would vary. The underlying argument is that the studies cited on the effects of glucose on cognitive performance

abilities are predominantly based on a research design that compares a condition without metabolizable glucose sources after previous fasting to a condition in which glucose is provided (outlined in Section 1.4). Therefore, the bulk of the available evidence could also be described as examining the performance impairments caused by the lack of glucose sources (e.g., fasting in most cases), suggesting even more obviously the possibility of proximity to the concept of metabolic switching.

For the research question regarding the mechanisms underlying interindividual differences in the cognitive effects of glucose supplementation, metabolic switching is of particular interest. It describes a phenomenon that strongly resembles our research finding (see Section 2). People are differentially resilient to cognitive decline in the absence of glucose. Interestingly, those who are particularly vulnerable to these performance impairments are also those who tend to perform rather moderately even in the presence of glucose administration (Study A; Neukirchen, Radach, et al., 2022). In fact, it is the high-performers who barely increase their glucose turnover even during cognitive load at a level that is maximally challenging for them, whereas the low-performers sharply increase it – an observation that was independent of the emotional stress experienced by the task (Study B; Neukirchen, Stork, et al., 2022). These effects are severe enough – at least in people with clinically impaired glucose regulation – for them to be introspectively aware of them and to correlate with objective measures of elevated long-term blood glucose (Study C).

However, the use of a clinical sample in Study C should not detract from the fact that healthy people can have large differences in their glucoregulation. In order to substantiate this aspect, Section 1.3 provides an overview of selected non-clinical, preclinical and clinical factors that

constitute such differences, highlighting the scope and significance of the research to which this dissertation is intended to contribute.

1.3 Interindividual Differences in Glucoregulation

Evidence of clinically impaired glucoregulation is part of the growing body of research on interindividual differences in factors contributing to differential outcomes in response to glucose supplementation. This topic is gaining importance, especially in the face of the contemporary health challenges encountered worldwide.

The Neolithic period saw a shift towards a diet high in refined carbohydrates, particularly from cereals and dairy products (Cordain et al., 2005). This was a departure from the Paleolithic diet, which was lower in refined carbohydrates and higher in fiber and protein (Eaton & Eaton III, 2000). The Industrial Revolution further increased the availability of refined carbohydrates, leading to a significant increase in their intake (Konner & Eaton, 2010). These dietary changes have been linked to the emergence of chronic diseases in modern civilization (Cordain et al., 2005). The high prevalence of conditions impacting glucoregulation and their potential influence on cognition underscore not only the societal relevance of imbalances in glucose levels but also its importance for psychological research. In the following, the significance of interindividual differences in glucoregulatory abilities will be illustrated with high impact examples of the prevalence of *clinical, preclinical and non-clinical contributing factors*. This illustration is made against a background of overlapping cognitive deficiencies and serves two purposes. First, to substantiate the claim that the topic is of direct relevance to an immensely broad audience, both from a perspective of personal health interest and from a scientific,

psychological point of view. Secondly, it highlights the overlap between factors influencing both glucoregulation and cognitive functioning in both clinical and nonclinical contexts.

Arguably the most prominent *clinical impairment of glucoregulatory abilities*, diabetes, has experienced a sharp rise over the last decades. Recent epidemiological data indicate that the global prevalence of diabetes in 2021 was 529 million (Ong et al., 2023). Moreover, the prevalence of diabetes is increasing more rapidly in low- and middle-income countries than in high-income countries (Ong et al., 2023). The repercussions of uncontrolled diabetes are impacting communities and straining healthcare systems. Diabetes has become a major cause of various health complications, including blindness, kidney failure, heart attacks, stroke, and lower limb amputation (Brownlee, 2001; Ekoé, 2019). Less known but relevant in the context of this work is the fact that diabetes has also been linked to impairments in cognitive functioning (Moheet et al., 2015). Limiting the scope of inquiry to individuals with impaired glucoregulation, as defined by conventional clinical criteria, would fail to capture the full extent of the issue. This becomes particularly evident when we consider the prevalence of preclinical and non-clinical differences in glucoregulation.

The example of *prediabetes* highlights the importance of *preclinical variations in glucose metabolism*, which can be significant even in populations deemed healthy. Notably, the term prediabetes can be somewhat misleading, as not all individuals with prediabetes will progress to diabetes (Tabák et al., 2012). Prediabetes is generally defined based on elevated fasting glucose levels, typically measured in the morning, and glucose tolerance, assessed by the reduction of blood glucose levels following glucose administration (Hostalek, 2019; Tabák et al., 2012). The specific combinations of these criteria and cut-off values may vary. For example, the World Health Organization defines prediabetes as a state in which glucose tolerance is

normal, yet fasting glucose levels range between 6.1 and 7.0 mmol/L (Tabák et al., 2012). In contrast, the American Diabetes Association employs a lower cut-off value for fasting glucose (between 5.6 and 6.9 mmol/L) and also defines limits for the blood value of glycated hemoglobin A1c, also referred to as *HbA1c* (Tabák et al., 2012). The latter provides information about the average plasma glucose levels over the previous two to three months (Nathan et al., 2007), and is further discussed and used in Study C.

The prevalence of prediabetes is considerable, with an estimated 7.3% of the adult population affected in 2017. Projections indicate that this figure is likely to increase to 8.3% by 2045 (Hostalek, 2019). In conjunction with the prevalence of diabetes, clinical and preclinical factors in themselves could serve as the backdrop against which our investigation of the interplay of psychological and metabolic factors unfolds. However, these two states do not do justice to the holistic interindividual differences in glucoregulatory abilities, as a range of other factors are interacting with glucose regulation in healthy individuals. Given the substantial evidence indicating a close relationship between impaired glucoregulation and psychological processes (Bădescu et al., 2016; Frier, 2001; Geijselaers et al., 2017; Kalra et al., 2018; Van Bastelaar et al., 2010), including cognitive functioning (outlined in Section 1.4), it is evident that further research into this topic is both ethically and scientifically justified.

In other words, investigating interindividual differences in energy metabolism and their ties to the human psyche is relevant not only to clinically diagnosed diabetes, but also to prediabetes and possibly to a plethora of *non-clinical human conditions and factors*, that influence glucoregulation. Such include, but are not limited to age (Messier et al., 2003; Sellami et al., 2019; Zouhal et al., 2009), body weight (L. G. Nilsson & Nilsson, 2009; Smith et al., 2011; Wang et al., 2016), sex (Lapauw et al., 2010; Tramunt et al., 2020), physical activity (Balkau

et al., 2008; Borghouts & Keizer, 2000; Koivisto et al., 1986; Mikines et al., 1988), sleep (González-Ortiz & Martínez-Abundis, 2005; Leproult et al., 2015; Reutrakul & Van Cauter, 2018; Stamatakis & Punjabi, 2010), nutritional choices (Mattson, 2010; Nabb & Benton, 2006; Sünram-Lea & Owen, 2017), circadian rhythm (Coomans et al., 2013; Kitazawa, 2013; Qian et al., 2018; Stenvers et al., 2019), sun light exposure (Coomans et al., 2013; Gil-Lozano et al., 2016; Tai et al., 2008), stress (Avignon & Monnier, 2001; Seematter et al., 2000; Vranic et al., 1991), and genetic variation (Hart et al., 2004; Heni et al., 2010; Lamothe et al., 1998; Lindsten et al., 1976).

Age

Age has a significant impact on glucoregulatory capabilities, with older individuals experiencing alterations in plasma glucose and glucoregulatory hormones (Zouhal et al., 2009). These changes can lead to cognitive impairments, particularly in working memory and executive function (Messier et al., 2003). However, exercise has been shown to have a counteracting effect on such alterations, with some studies reporting an anti-aging effect of exercise training on glucoregulatory hormones (Sellami et al., 2019). This is coherent with our suggestions regarding the role of metabolic switching in CGS.

Body weight

Research consistently shows that *body weight* is associated with cognitive deficits, particularly in executive function, across all age groups (Smith et al., 2011). This relationship persists even after controlling for obesity-related diseases (Nilsson & Nilsson, 2009). There is evidence that the impact of obesity on cognition is mediated by factors such as hormonal dysregulation, which are crucial components of the glucoregulatory system (Wang et al., 2016). Furthermore, chronic

consumption of refined carbohydrates, a common feature of the Western diet, has been linked to neurocognitive deficits, independent of body weight (Hawkins et al., 2018). These findings are in line with our results regarding a relationship between BMI and CGS in Study A.

Sex

Sex has a significant impact on glucoregulatory capabilities, including insulin sensitivity. Studies have shown that short-term changes in sex steroids can affect postprandial triglyceride response, glucose-dependent insulinotropic polypeptide response, and insulin sensitivity (Lapauw et al., 2010). Women generally have higher insulin sensitivity and better glucoregulatory capabilities than men, which may be attributed to the protective effects of endogenous estrogens (Tramunt et al., 2020) and is congruent with our findings on sex differences regarding CGS in Study A.

Physical activity

As mentioned before in the context of metabolic switching (Section 1.2), physical activity has a significant impact on glucoregulatory capabilities. Acute exercise and chronic physical training both enhance insulin sensitivity, with the latter leading to multiple adaptations in glucose transport and metabolism (Borghouts & Keizer, 2000; Koivisto et al., 1986). Prolonged moderate exercise, for example, increases insulin action on glucose uptake (Mikines et al., 1988). Even more important for the majority of people in developed countries might be that total physical activity, including time spent sedentary and in light activity, is a major determinant of insulin sensitivity (Balkau et al., 2008).

Sleep

However, it is not activity alone but also our resting behavior, that influences our glucoregulatory capabilities. Sleep plays a crucial role in glucoregulatory capabilities, insulin sensitivity, and cognition. On the one hand, sleep deprivation has been linked to decreased insulin sensitivity and metabolic control (González-Ortiz & Martínez-Abundis, 2005). On the other hand, sleep extension has been shown to improve fasting insulin sensitivity in healthy adults with habitual sleep restriction (Leproult et al., 2015). Interestingly, also the duration of sleep intervals seems to matter. Sleep fragmentation has been associated with a decrease in insulin sensitivity and glucose uptake (Stamatakis & Punjabi, 2010). Adverse metabolic outcomes of sleep disturbances, like insulin resistance and increased diabetes risk, involve multiple mechanistic pathways, including increases in hunger and food intake (Reutrakul & Van Cauter, 2018). The effects of factors, that are relevant in vivo for interindividual differences in glucoregulation, can be mediated by complex psychological interactions. For example, the impact of sleep on glucoregulatory abilities could partially be mediated by nutritional choices, which in turn is a reaction on the effects of sleep –or the lack of it – on endocrine parameters (González-Ortiz & Martínez-Abundis, 2005).

Nutritional choices

Stable blood glucose levels, which can be achieved through a diet that minimizes fluctuations, are associated with better cognitive function and reduced risk of cognitive impairments (Sünram-Lea & Owen, 2017). This is in line with the hypothesis, that a high level of functioning in terms metabolic switching might be advantageous in minimizing nutrition related cognitive performance fluctuations. Excessive dietary energy intake and insulin resistance can have

adverse effects on cognition, while dietary energy restriction can enhance neural plasticity and reduce age-related dysfunction (Mattson, 2010). The relationship between breakfast macronutrient content and glucose tolerance can affect cognitive function (Nabb & Benton, 2006). Nabb and Benton (2006) demonstrated that higher memory performance is associated with better glucose tolerance and meals that release glucose into the blood more slowly. This supports the idea, proposed and supported in Study A, that glucose-induced cognitive benefits are due to the administration mitigating a lack of metabolic flexibility (Neukirchen, Radach, et al., 2022). In this context, it offers an explanation for the lack of benefits for people who already perform well in a fasted state.

Circadian rhythm

Qian and colleagues (2018) found that the circadian system and circadian misalignment affect glucose tolerance through different mechanisms, with the former reducing glucose tolerance in the evening and the latter lowering insulin sensitivity. Kitazawa (2013) further emphasized the interconnection between the circadian clock and metabolic pathways, including insulin sensitivity. Coomans (2013) demonstrated in an animal model that constant light exposure and a high-fat diet can disrupt circadian energy metabolism and insulin sensitivity, which is in line with the conclusions by Stenvers and colleagues (2019) who reviewed the physiological links between circadian clocks, glucose metabolism, and insulin sensitivity, highlighting the potential role of circadian disruption in insulin resistance.

Sun light exposure

Nonetheless, the role of light is also ambiguous. Sunlight exposure has been linked to improved insulin sensitivity and glucose metabolism, potentially due to its role in vitamin D synthesis

(Tai et al., 2008). In contrast, the aforementioned circadian disruptions, such as those caused by sleep deprivation and constant light exposure, can lead to insulin resistance and metabolic abnormalities, both in vitro and in vivo (Coomans et al., 2013; Gil-Lozano et al., 2016). While sunlight can have a positive impact on glucoregulatory capabilities, its effects can be negated by other factors such as the earlier mentioned sleep disturbances and circadian rhythm disruptions.

Stress

Nevertheless, in a complex biological system such as the human body, the role of sleep disturbance and disruption of circadian rhythms should not be considered in isolation, as they interact with other relevant factors such as psychological stress. Stress, such as hypoglycemia and epinephrine infusion, can lead to increased glucose production and decreased insulin sensitivity (Vranic et al., 1991). Seematter (2000) observed that mental stress can stimulate glucose uptake and energy expenditure in lean individuals, but these effects are blunted in individuals with obesity, which further highlights the importance of considering interindividual differences in the investigation of the effects of glucose supplementation in humans. Avignon and Monnier (2001) highlighted the role of stress hormones and cytokines in altering glucose homeostasis and inducing insulin resistance.

Genetic variation

Less modifiable but no less important, both for understanding differences and from a practical perspective of possible future individual prevention and intervention planning, is the significant influence of genetic variation on an individual's glucoregulation. Lamothe et al. (1998) demonstrated that alterations in key genes involved in insulin signaling and action can lead to

a range of phenotypes, from mild defects to severe diabetes. The impact of genetic variation in the G6PC2 gene on insulin secretion is influenced by glucose tolerance status, with hyperglycemia overriding the effects of genetic variation (Heni et al., 2010). Similarly, the plasma insulin response to glucose is genetically regulated, with a heritability (familial correlation) ranging from 0.38 to 0.72 (Lindsten et al., 1976). However, genetic variants of IGF-I and IGF-II genes do not appear to be associated with variations in glucose-stimulated insulin secretion (Hart et al., 2004). These findings collectively highlight the complex interplay between environmental, behavioral, and genetic factors that contribute to inter- and intraindividual variance in glucoregulatory capabilities, underpinning the necessity to consider less uniform and more individualized approaches to answering the question of glucose induced psychological effects in humans.

At this point, consciously refraining from the risk of creating redundancy with the methodological sections of the following studies or prematurely delving into the content of the general discussion at the end of the thesis, direct methodological implications can be derived from the listed factors, which were decisive for the design of the following studies. On the one hand, the interindividual variance in the factors mentioned is large, which means that within-subject studies are generally advisable if the actual responsiveness to glucose is to be investigated with regard to its cognitive effects. On the other hand, there is also the challenge of considering aspects such as time of day, diabetes status, body mass and gender, which explains the experimental complexity of our studies and their follow-ups.

Our thoughts and ideas regarding the relationship between glucose supplementation and cognitive performance outcomes moderated by person and task characteristics did not emerge from a vacuum but are merely another chapter in a long line of research. In the following section

1.4, a historical overview of representative publications is presented, which contributed significantly to the current state of scientific knowledge and thus to the development of the empirical and methodological considerations of my dissertation. Accordingly, this overview is to be seen as a timeline of key inspirations and predecessors of our research contributions, whereby their description - by no means out of a lack of respect for the pioneers of the research field, but out of ample respect for the readership's time - is concise and in each case provided with the most relevant reference to our current research.

1.4 Glucose Effects on Cognitive Performance

Interestingly, not only are glucoregulatory abilities subject to large interindividual differences, but so are the effects of glucose administration on cognitive performance. The administration of glucose, typically in the form of simple carbohydrates, has been associated with both cognitive enhancement, impairment or even no behavioral effect at all, depending on various factors. Indeed, glucose supplementation has shown promise in improving cognitive task performance, particularly in memory-related tasks (e.g. Benton & Parker, 1998; L. Gonder-Frederick et al., 1987; Manning et al., 1998; Messier, 2004). It has even been linked to enhanced long-term verbal recall (Foster et al., 1998). However, the relationship between glucose administration and cognitive performance is far from straightforward, as will be outlined in greater detail below.

A retrospective review of the past decades shows trends and successive shifts in the perspective on the effects of glucose on cognitive processes and possible moderating variables. This path will be illustrated in the following text using key milestones of said research, up to my contribution to it, represented by the articles presented in Section 2. The path and its branches

will be further traced prospectively in the general discussion towards the end of the dissertation (Section 3). In view of the overarching relevance to the topic of this thesis, the following, historically structured overview begins with the first studies that investigated the effects of glucose on cognition in humans rather than with the studies on animal models, although these of course also represent essential pioneering work in this field. Should the reader desire to delve deeper into the origins of the foundations of my dissertation, they may find that publications such as the one by Gold (1986) constitute a useful starting point.

In a study published by Gonder-Frederick et al. (1987), the authors aimed to expand on previous research conducted on rats (e.g. Gold, 1986), which demonstrated that glucose injections improved memory in this specific animal model. To determine whether increased blood glucose levels could enhance memory performance in elderly humans, the researchers recruited eleven participants aged 58-76 years who underwent one of two test conditions. After an 9 hour long, overnight fast, participants consumed sweetened beverages, containing either 23.7 mg sodium saccharin (sweetener) or 50 g of glucose. Following the consumption of the beverages, the subjects completed four Wechsler Memory Scale tests. The results showed higher scores on narrative memory tests and the total Wechsler Scale after glucose consumption. These findings contributed to the understanding of the role of glucose metabolism in memory processes in humans and led to the discussion of the role of age and age-related cognitive decline in the context of glucose metabolism. On a methodological level, it also shows that the basic experimental design of testing cognitive glucose effects after and in contrast to an overnight fast is about as old as the documented, peer-reviewed research on this topic in humans, and this holds true up to my contribution to this body of research more than three decades later. This

circumstance is critical to the discussion of the role of glucoregulation and metabolic switching, and it is therefore advisable to keep it in mind.

Three years later, Benton (1990) published the results of two experiments, in which differential effects of glucose supplementation on different tasks were observed. While he found no evidence for improvement of hand-eye coordination, increasing blood glucose levels predicted performance increases on a sustained attention task (Benton, 1990). His results supported the notion that glucose-induced cognitive effects in humans are dependent on task characteristics, in this particular case it was interpreted as glucose being more beneficial for tasks requiring "low mental capacity" (Benton, 1990, p. 18).

Shortly after, Parsons and Gold (1992) used a more complex repeated-measures, counterbalanced, crossover design to examine the dose-response curve for glucose enhancement of memory in elderly humans (ages 60-82). The task used was the Wechsler Logical Memory Test, which was administered in four sessions (at least 1 week apart) following ingestion of a fruit drink sweetened with glucose in different dosages (0, 10, 25, and 50 g) and saccharin, the latter being a non-caloric sweetener used to match the sweetness of the drink in each session. The authors found that glucose enhanced performance in an inverted-U dose-response manner, with optimal enhancement obtained at the 25 g glucose dose.

The authors' interpretation of this observation is consistent with our proposed framework, as they noted that blood glucose levels in the 50 g condition were higher in this particular sample (225 mg/dL) than in their previous studies (160 and 175 mg/dL). Therefore, differences in blood glucose regulation between the samples seem likely and may have contributed to the different results. Parsons and Gold (1992) concluded that optimal performance enhancement by glucose

may be achieved by matching individual glucose regulation and dosage, an interpretation laying fundamental groundwork for more recent contributions to this particular body of research.

In the same year, Manning, Parsons, and Gold (1992) investigated the effect of glucose on anterograde and retrograde memory, similarly to the preceding studies, again in a sample of elderly individuals. They administered a dosage of 50 g of glucose before or after acquiring a narrative prose passage and found that it significantly improved recall 24 hours later compared to a control condition with saccharin. This suggested that glucose enhances memory storage processing retroactively in elderly humans, with the memory improvement extending beyond the transient increase in blood glucose levels after ingestion. The authors' contribution was also unique in that it addressed the question of whether glucose benefits on memory performance involve enhancement of encoding and/or retrieval processes.

By studying the effects of a glucose drink in comparison to a placebo on performance in a Rapid Information Processing and a Stroop Task, Benton and colleagues (1994) widened the scientific scope of tasks which might be susceptible to glucose supplementation. Reaction times on the Rapid Information Processing Task were improved by glucose both during the baseline period and after a glucose drink when blood glucose levels were high.

This is in line with a study by Owens and Benton that was published the same year (1994), showing that increasing blood glucose levels resulted in faster reaction times. For a Stroop task, performance was improved when blood glucose levels were rising prior to the start of the test. The authors concluded that performance was greater if a glucose drink had been consumed, arguing for a general benefit of higher glucose levels, interpreting their results as evidence that speed of processing is faster when the availability of glucose to the brain is increased. From a

retrospective perspective on the history of research on the effects of glucose on human cognition, these results also represent a significant contribution in that they examine specific physiological mechanisms as moderators of the effects of glucose and thus contrast with the body of research that is primarily concerned with glucose as a motivational variable. This distinction is important and will be emphasized for good reason in the concluding general discussion of this paper, especially in the context of hunger.

Foster, Lidder, and Sünram (1998) found significant glucose facilitation effects in long-term verbal free and cued recall tasks in a placebo-controlled experimental setup. The results remained significant after controlling for subjects' baseline blood glucose levels. They concluded that glucose may improve retrieval and/or retention in long-term verbal memory. The study's added value is that it confirms that glucose can significantly improve memory performance in normal, young, healthy participants. This finding is particularly noteworthy because, despite the young, healthy sample, delayed recall performance was shown to correlate significantly with blood glucose concentration in all participants. The evidence suggests that glucose supplementation can influence cognitive performance through physiological pathways, without the need for age or diabetes status to act as moderating variables. Implications for our work are, that glucose effects on cognition may be relevant to a much broader population than just the elderly or those with clinically impaired glucose metabolism. Furthermore, the correlation between blood glucose and delayed recall performance supports the notion that even within healthy individuals, interindividual differences in glucose metabolism (as outlined in Section 1.3) are sufficient to account for measurable variance in behavioral outcomes, which is a crucial precondition for our contributions to this body of research.

In the same year three individual experimental studies conducted by Benton and Parker (1998) were published, which ought to investigate the potential benefits of consuming sources of glucose at breakfast. Their findings further supported the notion of differential effects of glucose on tasks involving different cognitive domains. They reported a link between initial memory enhancement and blood glucose concentrations. Subsequent investigations revealed that an overnight fast and no breakfast had a negative impact on the recall of a word list and a narrated story, as well as recalling items while counting backward. However, no impact on intelligence test performance was noted. Within the same publication, Benton and Parker concluded that breakfast consumption has a preferential influence on memory-related tasks. The authors' finding that fasting-induced deficits in word list recall and backward counting memory performance were reversed by the consumption of a glucose-supplemented drink is consistent with our perception that glucose supplementation serves as a compensation for those who fail to perform in its absence (Study A). Nevertheless, the glucose drink did not counteract the decline in recall performance of a narrated story induced by morning fasting, underscoring the possible role of task characteristics in determining susceptibility to glucose-induced performance modulation.

Using a sample of young and middle-aged adults, Meikle, Riby, and Stollery (2004) studied the extent to which individual differences in age and glucoregulation mediate glucose effects on cognitive function in a double-blind, placebo-controlled study. Cognitive tests assessed episodic and semantic memory performance, attention, and visuospatial functioning. The authors found that at the highest level of difficulty, glucose augmented the reaction time performance of older adults to a level comparable to that of the younger participants. This evidence has been interpreted as indicating that glucose is beneficial only in tasks with high

cognitive demand and that there may be age effects of enhancement. Alternatively, in the context of our investigations, the same results could be interpreted as the weaker performing group (middle-aged adults) benefiting more from glucose (higher CGS) than the stronger performing group (young adults) within tasks testing a domain that has been shown to be most susceptible to CGS (memory). The results for the glucoregulation hypothesis fell just short of statistical significance, which, given a total sample size of 25, can elicit scientific curiosity rather than discouragement.

Five years later, Scholey and colleagues (2009) further underlined the relevance of task attributes to observe glucose-induced performance enhancement. Within their study, the authors demonstrated specific enhancements of cognitive performance in volunteers receiving glucose in comparison to a control group receiving a placebo. The experiment involved tracking a moving on-screen target and memorizing words during an auditory presentation. In different trials, both tasks were performed separately and also simultaneously, enabling the researchers to not only investigate glucose enhancement of tracking and word recall performance but also possible effects on the interference effects of the tasks. They found glucose enhancement effects only in terms of reduced costs of auditory word presentation on tracking performance and concluded that glucose might improve the allocation of attentional resources. These interesting results open up the possibility of shedding light on the mechanisms behind the higher susceptibility to the influence of glucose on memory performance, that has been repeatedly replicated up to this point. Such findings can be taken as an opportunity to suggest that attention – possibly also during the learning phase of memory tasks – may mediate task susceptibility to glucose effects. In fact, thought-provoking impulses such as these led to the decision to use

glucose to influence only the recall phase, rather than the learning phase, in our own experiments (Study A).

Research into the effect of glucose on attention was further promoted by authors like Gagnon, Greenwood, and Bherer (2011), who examined the relationship between glucose regulation and performance on attentional tasks in non-diabetic older adults who consumed a glucose solution. The experimental tasks included neuropsychological tests of attention (Trail Making Test, Modified Stroop Test) and a computerized dual task. Interindividual differences in glucoregulation predicted errors on the modified Stroop task, with poorer glucoregulation associated with worse performance. Similarly, participants with poorer glucoregulation tended to make more errors on the divided attention trials of the computerized dual task. Gagnon and colleagues suggested that glucose regulation may temporarily affect the performance of metabolically healthy older adults on tasks requiring divided attention. This is not only in line with the previously presented work by Scholey et al. (2009) but also underlines the notion of glucoregulation playing a vital role as moderator for the effects of glucose supplementation on cognitive performance outcomes, even in non-diabetic participants.

In the same line, Owen and colleagues (2013) made another fundamental contribution to further the investigation of response variability to glucose facilitation of cognitive enhancement – or, as we call it, CGS. Glucose regulation, body composition, and response of the hypothalamic-pituitary-adrenal axis were assessed in a sample of twenty-four participants in a double-blind, placebo-controlled, randomized, repeated-measures study. Similar to the study by Meikle et al. (2004), glucose was administered in two different doses (25 and 60 g). Glucose improved performance on tasks measuring numerical and spatial working memory, verbal declarative memory, and recognition speed. In contrast to the study by Meikle et al. (2004), Owen and

colleagues (2013) demonstrated that glucoregulation predicted CGS in immediate word recall accuracy and word recall accuracy, with participants with poorer glucoregulation benefiting more from supplementation, while good glucoregulation was actually associated with performance declines (25 g group only). Within this dissertation's framework, incorporating metabolic switching, this makes perfect sense as the administration of glucose would compensate for the low energy supply experienced by people with inferior metabolic switching abilities (see Section 1.2). The lower glucose dosage also provides a shorter lasting spike in blood glucose concentration, which would immediately decrease ketone body production and make it necessary again sooner than in those who regulate/absorb glucose poorly, necessitating a metabolic switching maneuver within the test session. The production of ketone bodies is interrupted quickly by glucose administration in humans, as circulating ketone bodies exert an inhibitory influence on the rate of ketogenesis (the production of ketone bodies) which means that once glucose is supplemented, ketone bodies are not further needed and production declines (Balasse & Neef, 1975). I suspect, that in the case of a low-dose glucose supplementation, the advantage of participants with well-functioning metabolic switching/ketone body production could actually be a disadvantage if just enough glucose is supplied to interrupt ketogenesis but not to sustain glucose-fueled performance throughout the tests. This line of thinking was key in our decision to use high doses of glucose in our experimental setups involving glucose administration (Study A).

Using an integrative multimodal neuroimaging approach, Zanchi and colleagues (2018) investigated the neural correlates of cognitive function in healthy subjects after acute administration of glucose, fructose, and placebo using a randomized, double-blind, crossover study design. The researchers used two different experimental setups. First, functional magnetic

resonance imaging (fMRI) sequences were obtained while working memory (N-back) and response inhibition (Go/No-Go) were assessed. A resting-state fMRI sequence was then used to examine the effects of glucose on the cognition-related fronto-parietal network and the salience network. Compared to placebo, glucose intake decreased activation in the anterior cingulate cortex during working memory processing. The same was true during the response inhibition task, resulting in decreased activity in the anterior cingulate cortex, insula, and visual cortex compared to placebo. Resting state fMRI revealed increased global connectivity strength of the fronto-parietal network and the salience network under the influence of glucose compared to placebo. Two main reasons made this study an especially valuable contribution to the growth of the body of research on the effects of glucose on cognition. First, it provided further evidence for the facilitative effects of glucose that are not mediated by the sensation of sweetness, as the substances were administered through a nasogastric tube. Second, it simultaneously observed changes at the cerebral level rather than relying on behavioral measures and was therefore substantiating prior notions on the physiological basis for the effects of glucose on cognitive performance.

Contributions, like the one mentioned above by Zanchi and colleagues (2018) are congruent with the findings of a number of neuroimaging studies investigating glucose enhancement of cognitive performance, which emerged in more recent years and were systematically reviewed by Peters et al. (2020). The authors found that glucose administration improved neurocognitive markers of episodic memory and attentional processes supported by medial temporal and frontal activation, sometimes even in the absence of measurable behavioral effects. In terms of my contributions to this body of research, it underscored the methodological need to monitor glucose metabolism in a way that goes beyond peripheral, low-time-resolution measurements

(e.g., blood glucose levels) and led us to explore the feasibility of monitoring metabolic byproducts of glucose turnover in respiratory gases (Study B).

In summary, from the studies presented in the context of this dissertation and its objectives, a number of implications for our research can be derived. The moderators that may affect the modulation of cognitive performance driven by glucose can be conceptualized in terms of *subject and task characteristics*. They are summarized below.

First, regarding the *properties of the subject*, it is worth noting that studies on the cognitive effects of glucose typically compare it to fasting subjects. Methodologically, it is reasonable to minimize confounding influences such as recently ingested food. However, due to this research design, acute cognitive deficits due to fasting could significantly contribute to the results, especially in those who are not adapted to it.

Second, this observation is consistent with the presented evidence, which repeatedly links glucoregulatory abilities to individual susceptibility to cognitive effects of glucose (referred to as CGS in our own work). The corresponding empirical literature has repeatedly mentioned two additional potential factors. Age has been suggested as a contributing factor to CGS, which is reasonable given the strong link between glucoregulation and age. Additionally, poor performance on tasks has been linked to more pronounced effects of glucose supplementation on cognitive performance outcomes.

Third, the magnitude of glucose-induced effects could be moderated by *task properties*. Task properties that may contribute to higher CGS include the involvement of memory and attentional processes. Memory augmentation might be mediated by the enhancement of both encoding and retrieval processes, in which the potential effects on attention might also play a

role. A review of neuroimaging studies supports the effect of glucose on the relevant brain regions at the neurophysiological level and substantiates the behavioral findings.

This raises questions and has implications and challenges for the methodological structure of future empirical studies. Our fundamental questions for replication and extension of the present research include the role of task and subject characteristics in the effect of glucose on cognitive performance.

Especially with regard to the duality of my research efforts, there are also methodological questions that have been and continue to be similarly formative for our contributions to this research. The question remains whether glucose administration compensates for a disadvantage or genuinely enhances cognitive function. Additionally, it is not certain whether glucose acts solely through the amount of fuel it can provide at the neuronal level, or through alternative pathways, for example, at the motivational level.

Furthermore, the question of glucose dosing in order to modulate cognitive performance is important and remains controversial. Evidence, such as that presented above, of differential glucose uptake depending on glucoregulatory characteristics, such as insulin sensitivity and metabolic switching, reinforces the impression that, once again, no simple yet satisfactory answer can be expected. From an experimenter's point of view, higher doses of glucose have the advantage of providing a greater probability of successfully raising blood glucose levels for a sustained period of time. However, there is evidence not only of diminishing returns, but also of an inverted u-shaped distribution of glucose augmentation, which must be considered.

1.5 Summary of Dissertation Outline and Goals

In the introductory sections of this thesis, the importance of glucose in cognitive function was highlighted. Glucose serves as the primary energy source for the human brain (Section 1.1), making glucoregulation (Section 1.2) and interindividual differences in glucoregulation (Section 1.3) relevant to cognitive performance outcomes. Glucose effects on cognitive performance result from a complex interplay of factors (Section 1.4), as evident from interindividual differences in sensitivity to externally supplemented glucose (Study A). Such differences might be mediated by interindividual variance in metabolism (Study B), glucoregulatory capabilities (Study C), as well as task properties (Study A). Understanding these dynamics is crucial for harnessing the potential benefits of glucose supplementation and shedding light on the complex relationship between glucose metabolism and cognition.

To summarize, the primary objective of this doctoral dissertation is to illuminate the intricate relationship between glucose intake and cognitive function. This endeavor has been pursued through a multifaceted approach involving a synergistic interplay of empirical research and field testing of methodological advances. On the *empirical* front, the research aims to

1) identify the determinants that influence the effects of glucose ingestion on cognitive performance (CGS; Study A).
2) Furthermore, it sought to elucidate the underlying physiological mechanisms governing these responses (Study B)
3) and probe into the potential clinical implications of CGS (Study C).

A summary of the relevant literature for each empirical objective can be found in Table I.

Methodologically, the dissertation project aimed to refine behavioral (Study A), physiological (Study B), and introspective (Study C) approaches for the psychological examination of glucose-related cognitive effects.

Table I

Empirical Objectives

Based on	Main Objective
Benton, 1990; Benton et al., 1994; Benton & Parker, 1998; Foster et al., 1998; Gagnon et al., 2011; Gonder-Frederick et al., 1987; Manning et al., 1992; Meikle et al., 2004; Owen et al., 2013; Owens & Benton, 1994; Parsons & Gold, 1992; Peters et al., 2020; Scholey et al., 2009; Zanchi et al., 2018	Identify determinants of CGS
Benton, 1990; Benton et al., 1994; Benton & Parker, 1998; Foster et al., 1998; Gagnon et al., 2011; Gonder-Frederick et al., 1987; Manning et al., 1992; Meikle et al., 2004; Owen et al., 2013; Owens & Benton, 1994; Parsons & Gold, 1992; Peters et al., 2020; Scholey et al., 2009; Zanchi et al., 2018	Elucidate physiological mechanisms of CGS
Benton et al., 1994; Gagnon et al., 2011; Gonder-Frederick et al., 1987; Manning et al., 1992; Meikle et al., 2004; Owen et al., 2013; Parsons & Gold, 1992; Peters et al., 2020	Probe potential clinical implications of CGS

Note. The literature on which the primary empirical objectives of this thesis are based.

2 Research Articles

2.1 Role of Study A

With Study A, we sought to examine individual responsiveness of cognitive performance to glucose supplementation (CGS). As a construct, CGS would need to correlate with other variables of interest. One such variable is baseline performance in the absence of glucose, as such a relationship would be consistent with our hypothesis that glucoregulatory abilities, such as metabolic switching, are relevant to CGS. The investigation of CGS in relation to BMI points in the same direction, since body mass is indeed related to glucoregulatory abilities (see section 1.3). For this purpose, tasks from cognitive domains that could be influenced by glucose administration in previous studies were used.

Due to a possible effect of sex on glucoregulatory abilities, men as well as women were studied. Other potentially relevant factors such as daytime of the experiment, previously consumed food, weight, age and diabetes status were also considered.

Methodologically, the aim was to test whether a within-subject design could be used to demonstrate variability of behavioral outcomes in cognitive performance tests as a function of glucose intake. Theoretically, this project could have ended the investigation of the CGS construct prematurely. For example, this would have been the case, if only minimal variance in the performance results had been observed (only tasks with high retest reliability were selected), as this variance could have been purely measurement error variance. This measurement error variance should by definition have been uncorrelated with the other variables investigated. Fortunately, the results were even more interesting than expected and led to new insights and further questions.

2.2 Study A

Title	Cognitive glucose sensitivity—proposing a link between cognitive performance and reliance on external glucose uptake
Authors and Affiliations	Tobias Neukirchen[a], Ralph Radach [a], Christian Vorstius[a] [a]General and Biological Psychology, Bergische Universität Wuppertal, Germany
Publication Outlet	Nutrition & Diabetes
Publisher	Springer Nature
Publication Type	Journal Article
Publication Year	2022
Publication Status	Published
License	Open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
DOI	https://doi.org/10.1038/s41387-022-00191-6
Abstract	Existing evidence on the effects of glucose supplementation on cognitive performance appears inconclusive. Metabolic switching offers an approach to explain such incoherent findings based on differences in cognitive functioning after fasting. We propose a new construct, cognitive glucose sensitivity (CGS), which quantifies individual performance gain due to glucose supplementation. We tested the hypothesis that the effects of glucose ingestion depend on CGS, cognitive task domain, and sex. In addition, the relationship between CGS and body mass index (BMI) was examined. Seventy-one participants (48 female) were tested in two conditions each (deprivation baseline vs. glucose supplementation), performing tasks from different cognitive domains (memory and executive functioning). We found significant evidence for a correlation of deprivation baseline performance and CGS across domains (Corsi-Block-Tapping Task: $r = -0.57$, $p < 0.001$; Go-No-Go Task: $r = 0.39$, $p = 0.001$; word list recall: $r = -0.50$, $p < 0.001$). Moreover, individual CGS differed significantly between tasks ($p = 0.018$). Only in men, BMI was significantly related to CGS in a word recall paradigm ($r = 0.49$, $p = 0.017$). Our findings support the notion that the effects of glucose depend on deprivation baseline performance, task domain, and sex. The effort to reduce performance impairment (short-term) might sacrifice independence from external glucose (long term), possibly via declining blood glucose regulation. Therefore, CGS could be regarded as a candidate to enhance our understanding of the etiology of unhealthy eating.

2.2.1 Introduction

The cognitive effects of glucose supplementation vary widely between individuals. This is reflected in a controversial discussion in the literature over the past decades. Reported findings in this debate have been contradictory (L. Gonder-Frederick et al., 1987; Hope et al., 2013; Macpherson et al., 2015; Meikle et al., 2004; Owen et al., 2013; Parsons & Gold, 1992; Andrew B. Scholey et al., 2009; Sünram-Lea et al., 2001) with some studies showing that glucose intake improves cognitive performance only under specific circumstances or can even have adverse effects (Hope et al., 2013; Meikle et al., 2004; Parsons & Gold, 1992). Such findings are in line with the assumption that a healthy human body is able to produce glucose in sufficient amounts by itself, therefore cognitive performance should be independent of external glucose intake. However, a number of studies also provide evidence that (external) glucose supplementation indeed does improve cognitive performance (L. Gonder-Frederick et al., 1987; Sünram-Lea et al., 2001).

Taking these finding into account, we suggest a new construct, namely an individual *cognitive glucose sensitivity* (CGS), which we define as the degree of glucose dependence of cognitive performance. This CGS corresponds to the individual increase in performance as a result of glucose intake, compared to baseline performance (without glucose intake).

Against this background, we hypothesize that a benefit of glucose supplementation on cognitive performance is moderated by individual variables (CGS, weight, sex) and performance domain (e.g. memory vs. executive functions). This idea is consistent with the findings of others (Meikle et al., 2004; Owen et al., 2013) and offers the opportunity to integrate recent findings on interindividual differences in glucose metabolism at the neurobiological level (Goyal et al.,

2019). The present study reflects the first attempt to quantify individual CGS, to lay the foundation for a useful descriptive performance parameter, exposing cognitive performance impairments that might result from weaknesses in metabolic switching (Mattson et al., 2018). The new construct, therefore, presents a potentially important factor in eating behavior and the development of diabetes, as it could impact individual food intake to prevent negative cognitive consequences that can be caused by hypoglycemia (M. Nilsson et al., 2019).

2.2.2 Method

2.2.2.1 *Study Design and Sample*

We implemented a within-subject design with randomized order of glucose supplementation (glucose vs. baseline) to observe interindividual cognitive performance differences. Each participant was tested on 2 consecutive days, with sessions differing only in terms of supplementation condition and (parallel) test versions of the cognitive paradigms. Testing was scheduled at the same time of day for both sessions after fasting for 12 hours (hydration with water was permitted). Participants were randomly assigned to predetermined, counterbalanced sequences of supplementation conditions and parallel test versions of cognitive tasks. On the day of glucose supplementation, a solution consisting of 200 ml water and 75 g glucose was ingested orally. The dosage was based on WHO recommendations for investigating glucose tolerance (Alberti & Zimmet, 1998). On baseline day, the same amount of water without glucose was consumed. To minimize confounding effects, participants and conducting research assistants were blind to which substance was consumed in each session (and were told only that one beverage was sweetened). Participants were informed at the end of the study about the nature of each drink by the supervising investigator.

All participants were native German speakers and participation was voluntary, although students could earn credit points for a research class. Participants with medical conditions (e.g., diabetes) or food/drug consumption within the last 12 hours were excluded. All aspects of the study design were approved by the university's internal review board (MS/BBL 191119) and the study was preregistered at the German clinical trial register (DRKS00019843). The sample consisted of 80 participants (27 men, 53 women). Nine data sets had to be excluded due to non-compliance with study requirements (prior food/drug consumption). The final sample included 71 participants with a mean age of 23.17 (*SD* = 6.75, range: 18-63 years) for analyzes.

2.2.2.2 ***Procedure and Materials***

On day one of testing, participant information was provided and informed consent was signed. The remainder of the study protocol was identical for both sessions, starting with beverage consumption (glucose solution or water). Participants were allowed three minutes for ingestion and, to ensure adequate absorption, spent the next 20min following a standardized protocol that preceded cognitive performance tests (learning phase of verbal recall test and anthropometric measures).

For anthropometric measurements, internationally standardized guidelines were applied (Stewart et al., 2011). BMI served as an indicator for participants' body composition, which was validated using caliper-measurements of four skinfold-thicknesses (triceps, suprailiac, subscapular, and thigh).

To assess cognitive performance, a selection of established standardized tasks for different domains was used. A computerized implementation of the Corsi-Block-Tapping-Task served as a measure for viso-spatial short-term memory performance (Corsi, 1973).

A Go-No-Go-Task (250 trials, 50% nogo) was used to measure inhibitory performance (Fillmore et al., 2006), with error rate and mean RT for correct responses as dependent variables.

The verbal recall was assessed using parallel versions of the German Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001). Depending on the time interval, retest reliability is stated to be between r_{tt} = .68 and r_{tt} = .87 (Helmstaedter et al., 2001). The three-minute recall phase concluded the experimental part of the first session. On the second day it was followed by a second, unannounced (long-time) recall phase of the word list from session one.

2.2.2.3 *Statistical Analysis*

Statistical analyzes were conducted using R (R Core Team, 2017). Scores for differences in performance between glucose and baseline condition were calculated for each participant and variable (CGS). Significance levels for all tests were set at $\alpha < 0.05$ and test assumptions were met unless specified otherwise.

2.2.3 Results

Descriptive statistics on physical and cognitive parameters are reported in Table s1. BMI did not differ significantly between sexes and was within the normal range (M_f=21.67, M_m=22.86; t=1.68, p=.097). The relationship between skinfold-thickness and BMI (r=.48, p<.001) did not imply any added benefit for including both. For this reason and for ease of replication, the actual hypothesis tests were carried out solely based on BMI.

Mean performance between baseline and glucose condition did not differ substantially across tasks, however, the mean of individual glucose-induced benefit values (expressed in percent of

baseline performance) reached considerable sizes (-70% to +233%, see Table s1). Especially for the Corsi-Block-Tapping-Task, the mean value of all individually computed glucose-induced benefit percentages exceeds the raw difference between the mean of baseline and glucose performance. This makes sense, given that low performers experienced greater glucose-induced benefit than higher performers, which is in line with the observed pattern displayed in Figure 1A.

Figure 1

Relation between deprivation baseline performance and glucose induced benefit across tasks by sex.

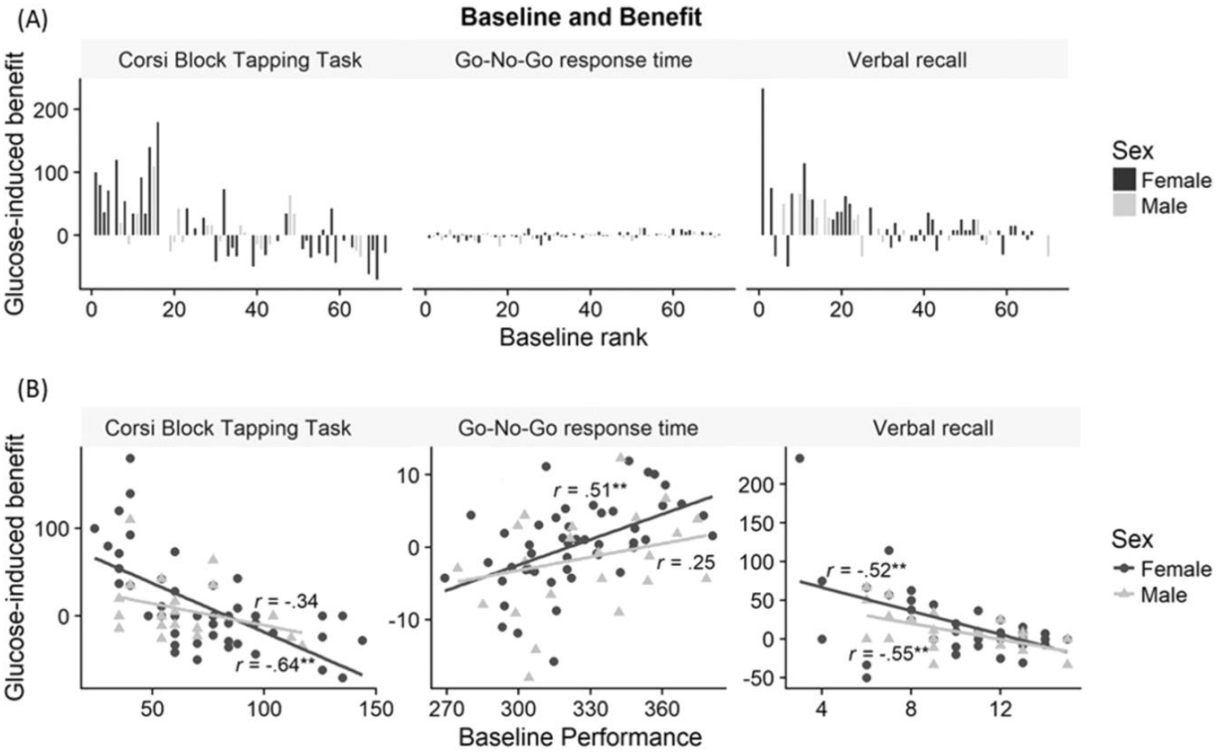

Figure 1. Each bar represents one participant's change in performance between glucose and baseline condition, expressed in percent of the baseline performance. Positive values indicate better performance (glucose-induced benefit). Baseline rank refers to the performance rank that each participant obtained in the corresponding task in the baseline condition. The lowest baseline performers are on the left while the highest baseline performers are on the right of each x axis. B Baseline performance and change in performance in response to glucose expressed in percent of performance in the baseline condition. Positive percentages indicate better performance in glucose condition (from left to right: higher score, faster response time, more words recalled). X axis represents absolute baseline performance (left to right: score, milliseconds, number of words recalled).

Results for hypothesis tests are presented in Table 1. We found significant correlations between baseline performance and magnitude of glucose-induced benefit for all three cognitive tasks. A one-way rmANOVA was conducted to compare the effect of task domain on individual glucose-induced benefit and indicated a significant effect of task domain, $F(2, 140)=4.08$, $p=.018$. Additional analyzes for sex differences revealed that female participants' results were mirroring overall results, whereas in the male sub-sample only the verbal recall paradigm showed a significant relationship between glucose-induced benefit and baseline performance (Figure 1B).

BMI was not significantly associated with greater glucose-induced benefit overall, but we found specific effects for sex. Specifically, for Go-No-Go response time, a relationship between women's BMI and individual glucose-induced benefit approached significance. More importantly, in word list recall, male BMI was significantly correlated to higher glucose-induced benefit. Notably, the direction of the correlation between BMI and glucose-induced benefit in verbal recall performance was opposite between the two sexes (Figure s1).

Table 1. Relationship between glucose-induced benefit and baseline performance/BMI

	Baseline performance			BMI		
	Pearson's *r*	*p* value	FDR	Pearson's *r*	*p* value	FDR
Corsi-Block-Tapping Task	−0.57	<0.001***	<0.001	−0.17	0.169	0.276
Women only	−0.64	<0.001***	<0.001	−0.17	0.261	0.357
Men only	−0.34	0.112	0.202	−0.18	0.405	0.455
Go-No-Go Task	0.39	0.001**	0.002	0.13	0.290	0.357
Women only	0.51	<0.001***	0.001	0.26	0.076	0.152
Men only	0.25	0.245	0.357	0.04	0.856	0.857
Word list recall	−0.50	<0.001***	<0.001	0.02	0.857	0.857
Women only	−0.52	<0.001***	0.001	−0.15	0.297	0.357
Men only	−0.55	0.006**	0.015	0.49	0.017*	0.037

Note. Go-No-Go Task performance was expressed as response time. Thus, the corresponding correlation coefficients' algebraic signs need to be interpreted in reverse. The total sample size was 71 (48 women, 23 men). Correlations were computed one-tailed. False discovery rate (FDR) is given for each tested hypothesis. *p < 0.05, **p < 0.01, ***p < 0.001.

2.2.4 Discussion

In the current study, we provided evidence for a significant relationship between individual cognitive performance in the baseline condition and individual performance gain under glucose supplementation. Furthermore, there was a significant effect of task domain on glucose-induced benefit. BMI effects occurred only for male participants with a higher performance increase under glucose supplementation in the short-term memory task.

This pattern of results provides support for our hypotheses that a benefit of glucose supplementation on cognitive performance is moderated by individual variables and performance domain. A closer look at Figure 1 suggests a compensatory effect, especially benefiting low performing individuals, rather than a general enhancement of performance, as high performing individuals were relatively unresponsive to glucose intake.

The observation of sex specific effects is in line with previous suggestions of a potential link between excess weight and cognitive decline in men (Elias et al., 2005) and notions about sex differences in brain metabolism (Goyal et al., 2019). This is also consistent with additional analyzes, indicating that performance in the unannounced verbal recall task was significantly negatively correlated to BMI in men but not in women. The absence of significant general performance differences between supplementation conditions may be an indicator of the high relevance of interindividual responsiveness, as operationalized by CGS.

On a general level, our results support the notion of a moderating role of cognitive and non-cognitive parameters in performance effects of glucose supplementation, while raising questions about the underlying mechanisms of the moderating parameters. Possible candidates here include factors that influence glucose homeostasis in relevant tissues, such as cerebral

insulin sensitivity or accommodation to the utilization of ketone bodies (Jensen et al., 2020; Kullmann et al., 2016b; M. Nilsson et al., 2019).

Overall, the present study can be regarded as a proof of concept for the CGS construct, as we did find reliable effects in the assumed direction, CGS and related effects seem to be a promising research avenue. Follow-up studies with larger sample sizes should attempt to employ direct measures of blood glucose regulation or manipulate it directly, e.g., as applied in research involving intranasal insulin applications (Reger et al., 2008). Overcoming the limitation posed by the lack of physiological measures in the presented study could also be key to investigating the role of metabolic switching in the context of CGS. In this context, the recruitment of appropriate samples could enable the investigation of the role of other glucose metabolism-related factors (e.g., age, diabetes status, activity level).

In addition, inclusion of a second control group with a sweet tasting placebo could help differentiate to what extent CGS is mediated by other psychological effects, e.g. reward motivation (Schmidt et al., 2012). Furthermore, expectancy effects should be regarded using appropriate questionnaires. The investigation of CGS in additional tasks could help to further disentangle the effects of task domain and difficulty. Considering the inverted u-shaped relationship between glucose-uptake and performance suggested by pioneers in the field (Parsons & Gold, 1992), CGS should also be studied in the context of different dosages.

We have presented evidence that individuals without diabetes may already show severe cognitive impairment in the absence of external glucose sources (operationalized as CGS). Behaviorally compensating for this in everyday life, leading to a progressive dependence on frequent glucose intake in the long term, could be one pathway for increased diabetes risk.

Owing to its potential behavioral influence, CGS could represent a facilitating and maintaining factor in the development of overweight. In addition, the relevance of the construct for performance optimization in non-clinical contexts, such as school nutrition, might also be explored.

Regarding the potential compensatory effects of glucose intake on low cognitive performance, we would like to encourage the investigation of CGS, its behavioral consequences, and their role in the development of - and interplay with - impaired blood glucose regulation and overweight, e.g. in a framework as proposed by Hargrave, Jones and Davidson (2016).

Conflict of Interest: We declare that there is no conflict of interest that could be perceived to bias our work.

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Contributions: TN and CV designed the research; TN ran the experiments, data acquisition, and data analysis; TN and CV contributed to data interpretation; TN wrote the manuscript; RR and CV have supervised the study. This research was done in partial fulfillment of the doctoral dissertation of TN. All authors read and approved the final manuscript.

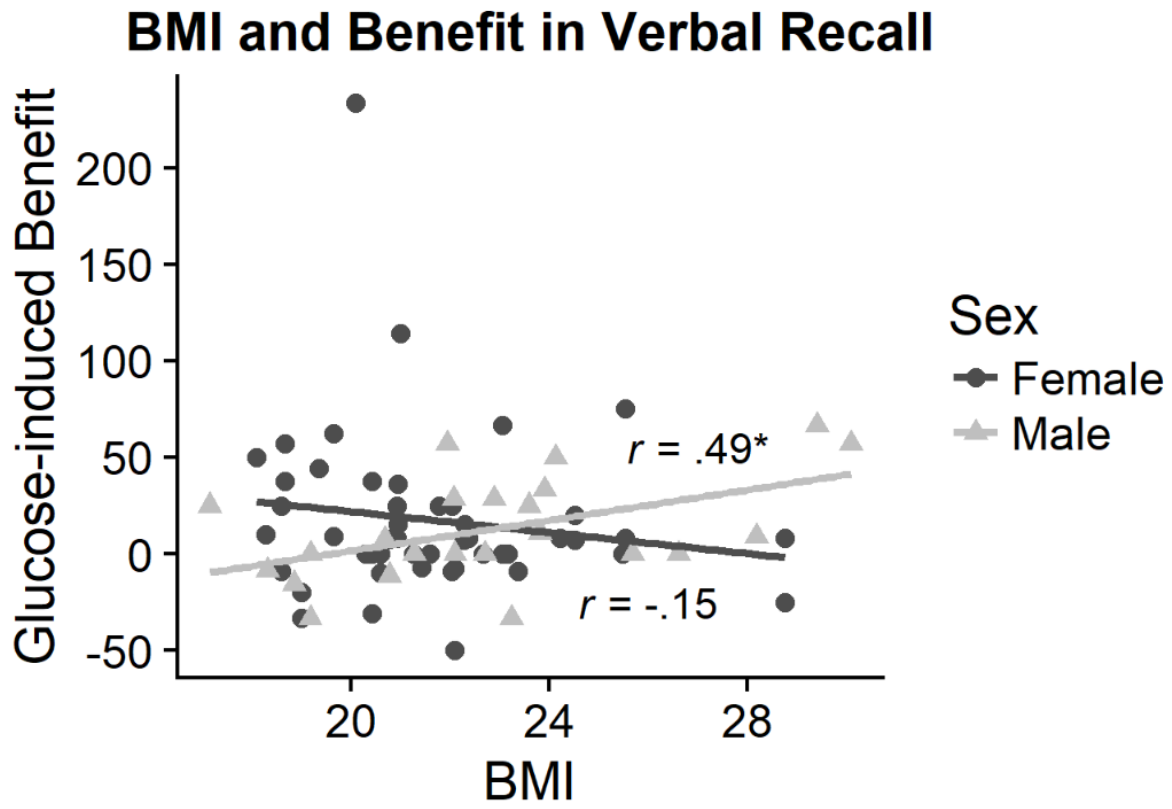
Appendix – Study A

Table s1. Mean, standard deviation, minimum and maximum for physical and cognitive variables of interest.

Variable	**Mean**	***(SD)***	**Min**	**Max**
Physical variables				
age	23.17	(-6.75)	18	63
height	171.75	(-9.16)	148	193
weight	65.90	(-11.52)	48.35	109.50
skinfold-thickness	58.93	(-16.76)	20.25	118.50
BMI	17.16	(-2.84)	17.15	30.08
Corsi Score				
baseline	69.46	(-28.31)	24	144
glucose	69.45	(-24.68)	30	135
glucose-induced benefit	10.78	(-47.2)	-70	180
Go-No-Go response time				
baseline	324.9	(-26.95)	269.07	381.02
glucose	325.09	(-26.53)	263.31	395.04
glucose-induced benefit	-0.26	(-6.38)	-18.03	12.27
Word list Recall				
baseline	10.14	(-3.01)	3	15
glucose	11.18	(-2.96)	3	15
glucose-induced benefit	15.98	(-38.86)	-50	233

Note. Age is stated in years; height in centimeters; weight in kilograms; skinfold-thickness in millimeters. All physical values are the mean of all in session measurements (day 1 and day 2). Reaction times are stated in milliseconds. word list recall scores are the number of words correctly recalled. Glucose-induced benefit was defined as the performance difference between glucose and the baseline session. Positive values indicate better performance when glucose was given. Benefit values are expressed in percent of the performance in the baseline condition. The mean value of all individually computed glucose-induced benefit percentages may exceed the raw difference between the mean of baseline and glucose performance when low performers experienced greater glucose-induced benefit than high performers (and vice versa).

Figure s1.



BMI and change in number of correctly recalled words in response to glucose, expressed in percent of the performance in the baseline condition. Positive percentages indicate that more words were recalled correctly in the glucose condition.

2.3 Role of Study B

After our initial work on CGS, I did not know whether the basis of the behaviorally measurable CGS effects was psychological or physical. For the former, hypotheses based on reward or motivational effects would be conceivable, whereas for the latter, hypotheses regarding neuronal energy supply were considered. For example, a theory such as the one on the relationship between glucose and ego-depletion by Baumeister and colleagues (Gailliot & Baumeister, 2007) could explain intra- and interindividual variance in CGS by arguing that, depending on one's depletion of the resource self-control, the intake of glucose might provide different levels of benefit. Originally linked to the actual blood glucose level, such a theory would be an example of a physiological approach to explain CGS. However, subsequent work has also demonstrated such effects by simply rinsing the mouth with glucose, arguably without increasing blood glucose levels (Sanders et al., 2012). Such work would suggest psychological mechanisms behind CGS rather than nutrition related explanations.

Therefore, if CGS was primarily a psychologically caused phenomenon (e.g. by the sweet sensation), the effects of glucose administration should have been independent of glucose metabolism, whereas the opposite would have been true for a hypothesis based on neuronal energy provision. This created the need to study glucose metabolism during the processing of a cognitive task in which a large interindividual variance in CGS had already been established. In this way, one would be able to determine whether and to what extent CGS and glucose metabolism correspond in such a task, i.e., whether CGS is fundamentally based on physical factors.

This would not have been evidence against effects of emotional arousal or stress during the processing of cognitive tasks. Therefore, a simultaneous, separate measurement and manipulation of emotional arousal and stress, respectively, was considered necessary. Skin conductivity was selected as an established and reliable method of choice (Christopoulos et al., 2019). Finally, I decided to conduct the experiment without external glucose administration, as such an intervention could affect both glucose levels and emotional state, rendering our results useless for distinguishing between psychological and physical mechanisms of CGS.

Taking advantage of the inherent duality of the work, I decided to focus the publication of Study B on the methodological advantage of using spirometry in a psychophysiological context. This decision was made, as I believed that the novel application of spirometry would have a bigger scientific value than additional insights into glucose supplementation. However, while the publication of Study B focused on the untapped potential of the investigated procedure application for psychophysiological research in general, for me the presented experiment was also a major step in our endeavor to deepen our understanding of the mechanisms of glucose-related cognitive effects.

2.4 Study B

Title	Spirometry has added value over electrodermal activity as a physiological marker of mental load in male subjects
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Publication Year	2022
Publication Status	Published
License	
DOI	https://doi.org/10.1038/s41598-022-08480-x
Abstract	The objective distinction of different types of mental demands as well as their intensity is relevant for research and practical application but poses a challenge for established physiological methods. We investigated whether respiratory gases (oxygen uptake and carbon dioxide output) are suitable to distinguish between emotional stress and cognitive load. To this end, we compared the application of spirometry with an established procedure, namely electrodermal activity (EDA). Our results indicate that electrodermal activity shows a strong responsivity to emotional stress induction, which was highly correlated with its responsivity to cognitive load. Respiratory gases were both sensitive and specific to cognitive load and had the advantage of being predictive for cognitive performance as well as self-reported emotional state. These results support the notion that respiratory gases are a valuable complement to common physiological procedures in the detection and discrimination of different mental demands.

2.4.1 Introduction

2.4.1.1 *Background*

Research on using spirometry and corresponding respiratory gases, such as oxygen uptake (VO_2) and carbon dioxide output (VCO_2), for measuring psychological parameters is limited. In contrast, measuring local metabolic activity and using self-report to learn about latent cognitive and emotional processes are common methods in psychological research. Imaging methods for metabolic processes within the brain (e.g., fMRI, NIRS, fPET) are established to investigate cognitive processes, whereas peripheral physiological measurement methods (e.g., measurement of skin conductivity and pulse rate) are commonplace in studying emotional processes (Shu et al., 2018).

Despite their established application in other scientific disciplines such as sport science and medicine (Hoppe et al., 2015), respiratory gas measures are sparsely used in psychological research. This fact could be highly disproportionate to its potential use, as indicated by a recent review (Grassmann et al., 2016). Yet, as Suess and colleagues (1980) pointed out over four decades ago, respiration rate alone seems to be an insufficient measure of respiratory reactivity to psychological stimuli and more sophisticated parameters are needed. Such parameters of respiratory gases, particularly VO_2 and VCO_2, seem to be more sensitive to cognitive load and might even allow conclusions about task-related physiological and psychological processes (Grassmann et al., 2016), making them promising candidates for the investigation of metabolic demands in cognitive task processing.

As psychological influences on respiration are far better understood in relation to emotional reactions, it might seem counterintuitive to utilize them in the context of cognitive load.

Especially, as it is well established that emotional processes can alter respiratory parameters such as depth and frequency (Boiten, 1998; Homma & Masaoka, 2008), which in turn might impact VO_2 and VCO_2 (Hoppe et al., 2015). From an evolutionary point of view, this supports the idea that emotions serve as means to enhance physical preparedness, e.g., to provide additional oxygen to fuel an imminent fight or flight response (Landis, 1930). In this case, the skeletal muscles can metabolize the additional oxygen as they work. In a similarly vein, the brain metabolizes oxygen to energize cognitive processing. In both cases, the metabolite carbon dioxide is produced (Wasserman et al., 2005) .

This raises the question, how emotional and task-related cognitive processing work can be measured and distinguished, when analyzing respiratory parameters that are influenced by both processes? Grasmann and colleagues (2016) suggested that a crucial distinction can be made, whether a respiratory response is *adaptive or maladaptive*. This is because an increased effort to upregulate VO_2 (e.g., by changing breathing patterns) is maladaptive if it is triggered in preparation for a redundant (emotion mediated) fight or flight response. An example of this is the induction of emotional stress in a physically resting participant. In this maladaptive case, the VCO_2 of exhaled gases is diminished, as metabolic processes are outpaced by respiration. An adaptively increased VO_2, as with increased cognitive effort in a physical resting participant, however, should show a matching rate of VCO_2. In other words, when using spirometry to measure cognitive load, it should be possible to detect emotion induced changes in respiration by observing an increased VO_2 without a matching increase in VCO_2, because emotional stress alone does not seem change metabolic demand and increase O_2 consumption (Masaoka & Homma, 2001).

Hence, in line with Grasmann and colleagues (2016), we promote the idea that it should be possible to distinguish between cognitive load and mental stress using spirometry. Furthermore, depending on the magnitude of the suggested effects, respiratory gas parameters could even provide insight into the effort exerted for a cognitive task. This is also in line with our work on cognitive glucose sensitivity, in which we demonstrated profound interindividual differences in the effects of carbohydrate ingestion and cognitive performance (Neukirchen, Radach, et al., 2022). It is reasonable to expect that VCO_2 corresponds to effort-related increases in glucose metabolism (Sue et al., 1989) .

Additionally, we are pioneering the combination of spirometry and classical peripheral psychophysiological measures in the context of cognitive and emotional processing. Therefore, we investigated whether VO_2, VCO_2 and their responsiveness are a suitable tool to enhance detection and better distinguish between periods of emotional stress and cognitive task related processing compared to EDA measures.

2.4.1.2 *Hypotheses*

It was not clear, whether an absolute difference between conditions was detectable (absolute perspective), or if the individual change from baseline to a specific condition had to be considered (relative perspective) as a better parameter. Therefore, we explored both (simple mean comparison and comparison of the individual change to baseline) in the hypotheses for our three research questions:

Firstly, we investigated whether respiratory gas parameters are sensitive to a change of demand condition on an individual level (baseline, cognitive load, emotional stress,). This should manifest in a task-dependent individual change in respiratory gases relative to the individual

baseline (hypothesis 1a). In addition to this relative statement, an absolute aspect was added, namely, to check whether specific load conditions can be reliably assigned to certain respiratory values on an interindividual bases (hypothesis 1b).

Secondly, we examined whether spirometry can differentiate between cognitive load and emotional stress, testing the hypothesis that Corsi-Block-Tapping-Task (CBT) and the Threat-of-Shock paradigm (ToS) can be distinguished based on VCO_2 rather than VO_2 (Grassmann et al., 2016) and comparing it to the established measure of electrodermal activity (hypothesis 2a).

Complementary, we explored the idea of differential adaptivity of a respiratory response to psychological stimuli in more depth by testing whether the use of Respiratory Exchange Rate (RER), as an individual index of the ratio between VCO_2 production and VO_2 consumption, can offer added diagnostic value (hypothesis 2b).

Finally, we investigated the external and discriminant validity of the spirometry in this unconventional application (hypothesis 3a and b). For the former, we tested whether variance in cognitive performance outcomes corresponds with VO_2 and VCO_2. Additionally, the external validity to detect self-reported levels of emotional stress of all physiological variables was tested (hypothesis 3a). For the discriminant validity, interrelations between parameter responsiveness to both cognitive load and emotional stress were examined (hypothesis 3b).

2.4.2 Method

All methods were approved by the universities internal review board (MS/BBL 191119) and in accordance with the current version of the Declaration of Helsinki. Furthermore, informed consent was obtained from all participants at the beginning of the experimental session.

2.4.2.1 *Study Design*

In a within-subject design, all participants successively went through relaxation, baseline and two types of experimental conditions (cognitive load, emotional stress). The whole experimental procedure was divided into a total of six episodes (e.g., relax, baseline, relax, emotional stress, relax, cognitive load). Cognitive load and emotional stress were induced in counterbalanced order across participants.

2.4.2.2 *Sample*

Due to gender effects and possible hormonal, respiratory, and metabolic changes during the menstrual cycle (Aitken et al., 1986; Schoene et al., 1981; White et al., 1983), only male participants were recruited. The original sample consisted of 34 healthy participants with an average age of 26.35 (*SD* = 8.75). Mean height was 180.85 cm (*SD* = 8.99) with a mean weight of 80.55 kg (*SD* = 11.56). Of the participants, 90.9% were right-handed and 78.8% were non-smokers. All participants with a cognitive performance value of zero had to be excluded from analysis, as their immediate failure in the first trial of the cognitive task did not allow for the collection of useful data for EDA and spirometry. In addition, it can be assumed that they did not understand or follow task instructions. Due to technical problems with EDA measurement, 2 participants had to be excluded, resulting in a final sample size of $N = 25$ for analyzes involving EDA and $N = 27$ for all others.

2.4.2.3 *Data Preparation and Statistical Analysis*

Part of the first hypothesis, concerning the relative perspective, referred to whether the change in respiratory parameters differs between going from baseline to a cognitive task versus going

from baseline to emotional stress induction. The respective change of going from baseline to either condition was expressed in percent of baseline values and we refer to this variable as the *responsiveness* of the parameter to a certain condition.

Expanding on the adaptivity hypothesis of Grasmann and colleagues (2016) we used the RER, computed as quotient of VCO_2 and VO_2 for our hypothesis 2b. The expression of this quotient should be indicative of the adaptivity of the respiratory response.

All analyzes were conducted using R (R Core Team, 2017) and figures were produced using the package ggplot2 (Wilkinson, 2011). For all reported correlations, Pearson's correlation coefficient was used. Mean comparisons were carried out using repeated measures t-test. The significance level for all tests was set at $\alpha = .05$. Although normal distribution was violated for some variables, we still report t-test results as the amount of data points can be regarded as sufficient to be robust against violations of normality. In addition, when testing with non-parametric tests, the result pattern remained the same. As multiple hypotheses were tested, the false discovery rate (FDR) was determined (Benjamini & Hochberg, 1995).

2.4.2.4 ***Procedure***

To minimize confounding variables, participants agreed in advance to consume only water 2 hours, no drugs (including alcohol, caffeine, and nicotine) 12 hours before the study, and to refrain from exercise for 24 hours prior to participation. On arrival, demographic data were collected, and body weight and height were measured. Participants were guided to an air-conditioned room with a temperature set to 22° Celsius. Next, equipment for physiological measurements (EDA, spirometry) was attached to the participants and calibrated according to the manufacturers. All physiological measurements were taken simultaneously. Afterwards,

participants were seated comfortably facing a computer screen (14-inch, resolution 1920 x 1080, 60 Hz) and the automated experimental protocol (Inquisit 5, Millisecond Software, Seattle, USA) started with a 4.5 min period for EDA electrode stabilization before the recording. A trackpad was used as input device to minimize participant movement during the experiment.

A relaxation episode, consisting of a slide show of neutral landscape images, constituted the beginning of the experimental protocol. A relaxation episode was included after each condition for 90 seconds. Baseline measurements were obtained during a minimally demanding vigilance task to prevent potential activation due to excitement or anticipation of the demands (Jennings et al., 1992). Next, again separated by an relaxation episode, cognitive load (Corsi-Block-Tapping-Task) (Kessels et al., 2000) and emotional stress (Threat-of-Shock Paradigm) (Suess et al., 1980) were induced. Finally, measures of subjective fear of shock, estimation of shock probability, and well-being were obtained using questionnaires. Emotional stress induction and baseline episode had a duration of 3 minutes. The duration (minutes) of the cognitive load episode varied with individual performance (M = 2.57, SD = 1.30). All other episodes lasted for 3min and the first and last 5 seconds of each episode were excluded from analyzes to account for artifacts and the delay between local metabolic activity and changes in respiratory gas parameters.

Participants were informed about the background and the subject of the study after the survey was conducted. However, former participants were instructed not to talk to any other potential participants about the test procedure, as the method of emotional stress induction (see below) relies on the illusive anticipation of electric shocks. Participation was voluntary and students

could receive partial course credit. All procedures were approved by the university's ethics committee.

2.4.2.5 *Physiological Measurements*

A Mindfield eSense Skin Response Sensor (Mindfield Biosystems, Gronau, Germany) was used to measure EDA. Dry electrodes, placed on volar surfaces of distal phalanges of index and middle finger of the non-dominant hand were attached using velcro strips. The portable sensor was connected to a computer via the headphone jack. EDA data were collected with DC and recorded with 5Hz. Skin conductance level (SCL) was calculated as the mean skin conductance value for each participant in each specified task. For additional analyzes, parameters distinguishing between phasic (p_mean) and tonic (t_mean) portions of the EDA-signal were calculated following the algorithm suggested by Greco and colleagues (Greco et al., 2016).

For the analysis of respiratory gases, we used a PowerCube Ergo respiratory gas analyzer (Ganshorn, Niederlauer, Germany). VO_2 and VCO_2 were measured by breath-by-breath technology and averaged over 10 seconds. The gas analyzing system was calibrated with a calibration gas (15.5% O_2, 5% CO_2 in N; Messner, Switzerland) and a precision 1-L syringe (Ganshorn, Germany) before each test. Data from the gas analyzer were processed using LF8 software (Ganshorn, Niederlauer, Germany).

2.4.2.6 *Emotional Stress Induction*

Using the Threat-of-Shock paradigm (ToS), the expectation of electric shocks was intended to induce emotional stress in the form of anxiety. We used a self-report item to obtain a measure

of fear of anticipated shock (4-point scale). The ToS setup was consistent with that of Suess et al (1980).

2.4.2.7 *Cognitive Load*

The Corsi-Block-Tapping-Task (CBT) served to induce progressive cognitive load. It serves as a measure of visuo-spatial short-term memory performance (Corsi, 1973). We used a computerized implementation of the task as described by Kessels, van Zandvoort, Postma, Kappelle, & de Haan (2000). Participants were instructed to correctly reproduce a sequence of highlighted blocks using a touch pad. Sequence length (difficulty) increased by one with every successful trial, up to a sequence of nine blocks. Parallel versions contained different random lighting sequences. Total score, computed from the longest, correctly reproduced span and the total errors made, served as index for proficiency.

2.4.3 Results

Descriptive results for the psychophysiological variables that were subject to subsequent hypothesis tests are summarized in Table 1. An overview of the analyses presented in the following section and their associated hypotheses can be found in Table 2. All mean comparisons refer to the averaged physiological values for the duration of the respective experimental condition.

Table 1

Descriptive statistics of the psychophysiological measurements across experimental conditions

	Initial Relax			Baseline			CBT			ToS		
	M	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
VO_2	0.31	0.05	0.20	0.27	0.05	0.21	0.33	0.06	0.26	0.30	0.07	0.25
VCO_2	0.30	0.06	0.23	0.27	0.06	0.24	0.30	0.06	0.27	0.28	0.07	0.27
SCL	5.26	2.70	11.97	6.51	2.97	13.33	6.55	2.98	13.58	7.29	3.14	14.05
RER	0.93	0.07	0.26	0.98	0.11	0.54	0.92	0.11	0.53	0.92	0.09	0.40
RR	12.90	3.22	13.06	13.22	3.04	13.50	16.24	3.67	13.97	13.70	3.23	15.47
MV	8.59	2.02	8.69	9.25	2.28	9.42	10.03	2.07	7.91	9.22	2.41	8.53

Note. EDA = Electrodermal activity (σ), VO_2 = Volume of oxygen uptake (l/min), VCO_2 = Volume of carbon dioxide output (l/min), RER = Respiratory Exchange Ratio (VCO_2/VO_2), RR = Respiratory Rate, MV = Minute Volume, CBT = Corsi Block-Tapping Task, N = 27 for every condition except EDA (N = 25).

Table 2

Inference statistical results sorted by hypotheses and relevant physiological variables/conditions.

Hypothesis	Variable	Condition	p-value	FDR
Task-dependent-difference to baseline—Relative Perspective: Mean difference between responsiveness to experimental conditions	relative increase in VO_2	cognitive load - emotional stress	**<.001**	**.018**
	relative increase in VCO_2	cognitive load - emotional stress	.104	.798
	relative increase EDA	cognitive load - emotional stress	**<.001**	**.019**
Task-dependent-difference to baseline—Absolute Perspective: Mean difference between experimental condition and baseline	VO_2	cognitive load - baseline	**.013**	.303
	VO_2	emotional stress - baseline	**.007**	.109
	VCO_2	cognitive load - baseline	**.019**	.271
	VCO_2	emotional stress - baseline	.388	1.000
	SCL	cognitive load - baseline	.772	1.000
	SCL	emotional stress - baseline	**.003**	.061
Difference between Cognitive Load and Emotional Stress Mean difference between experimental conditions	VO_2	cognitive load - emotional stress	**.006**	.105
	VCO_2	cognitive load - emotional stress	.100	.798
	SCL	cognitive load - emotional stress	**<.001**	**.007**
Adaptivity of Respiratory Response: Comparing quotient of gases between conditions	RER	cognitive load - emotional stress	.775	1.00
	RER	cognitive load - baseline	**.022**	.280
	RER	emotional stress - baseline	**.007**	.111
External Validity				
Cognitive Performance	VO_2—cognitive task performance	cognitive load	**.023**	.280
	VCO_2—cognitive task performance	cognitive load	**.037**	.369
	SCL—cognitive task performance	cognitive load	.292	1.000
Fear of Shock	VO_2—fear of shock	emotional stress	**.022**	.280
	VCO_2—fear of shock	emotional stress	**.003**	.059
	SCL—fear of shock	emotional stress	.317	1.000
Discriminant validity: Intercorrelation between responsivenesses in experimental conditions (within same parameter)	relative increase in VO_2	cognitive load - emotional stress	.456	1.000
	relative increase in VCO_2	cognitive load - emotional stress	**.048**	.434
	relative increase in SCL	cognitive load - emotional stress	**<.001**	**.002**

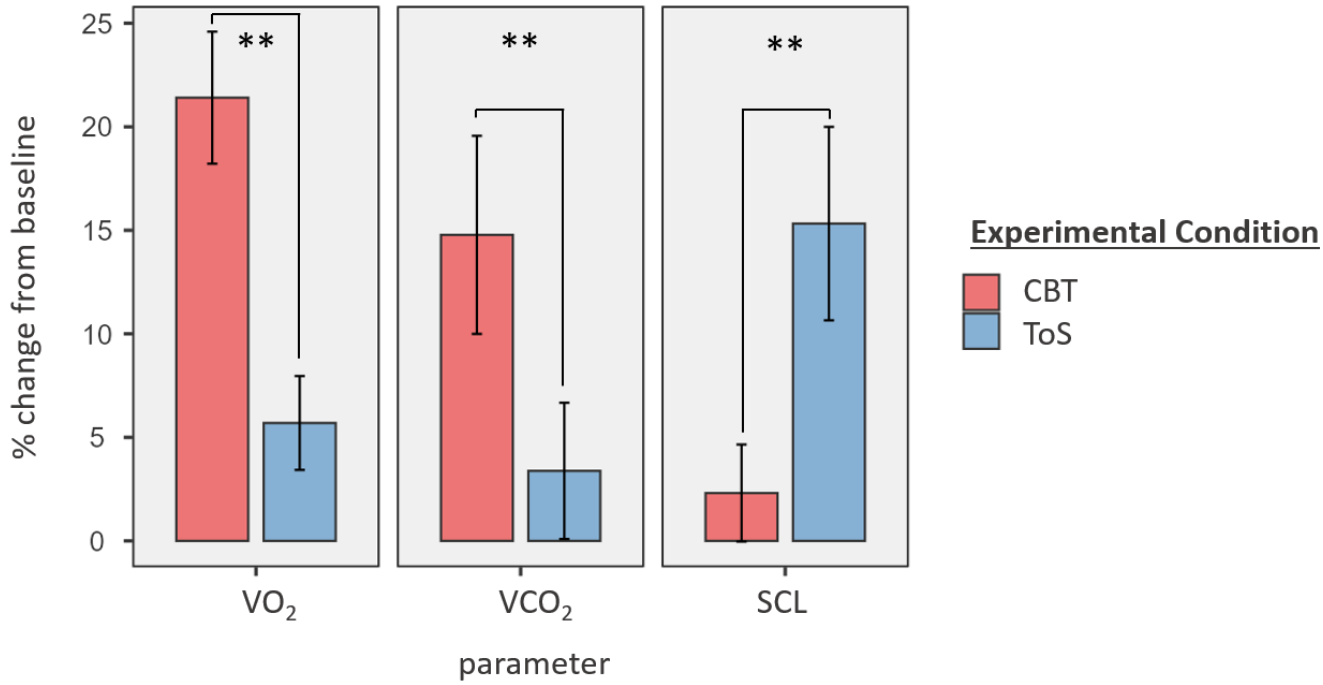
Note. Experimental conditions refer to emotional stress induction and cognitive load and are to be differentiated from baseline condition. We defined responsiveness of a physiological parameter to an experimental condition as the difference between its mean values in baseline and the corresponding experimental condition, expressed in percent of its baseline value. False discovery rate (FDR) is given for each tested hypothesis. Sample size for all tests was $N = 27$ except for EDA ($N = 25$). EDA: Electrodermal activity (σ), VO_2: Volume of oxygen uptake (l/min), VCO_2: Volume of carbon dioxide output (l/min), RER: Respiratory Exchange Ratio (VCO_2/VO_2).

First, we tested the hypothesis that respiratory gases are sensitive to a change in demand condition on an individual level (baseline, CBT, ToS) from both, a relative and an absolute perspective (Figure 1 and 2).

Regarding the relative perspective (hypothesis 1a), paired samples t-tests indicated significant differences for the responsiveness of VO_2 with the CBT (M_O = 21.40 %) inducing a greater increase than the ToS (M_O = 5.69 %, $t(26) = 3.76$, $p < .001$), both relative to baseline.

Figure 1

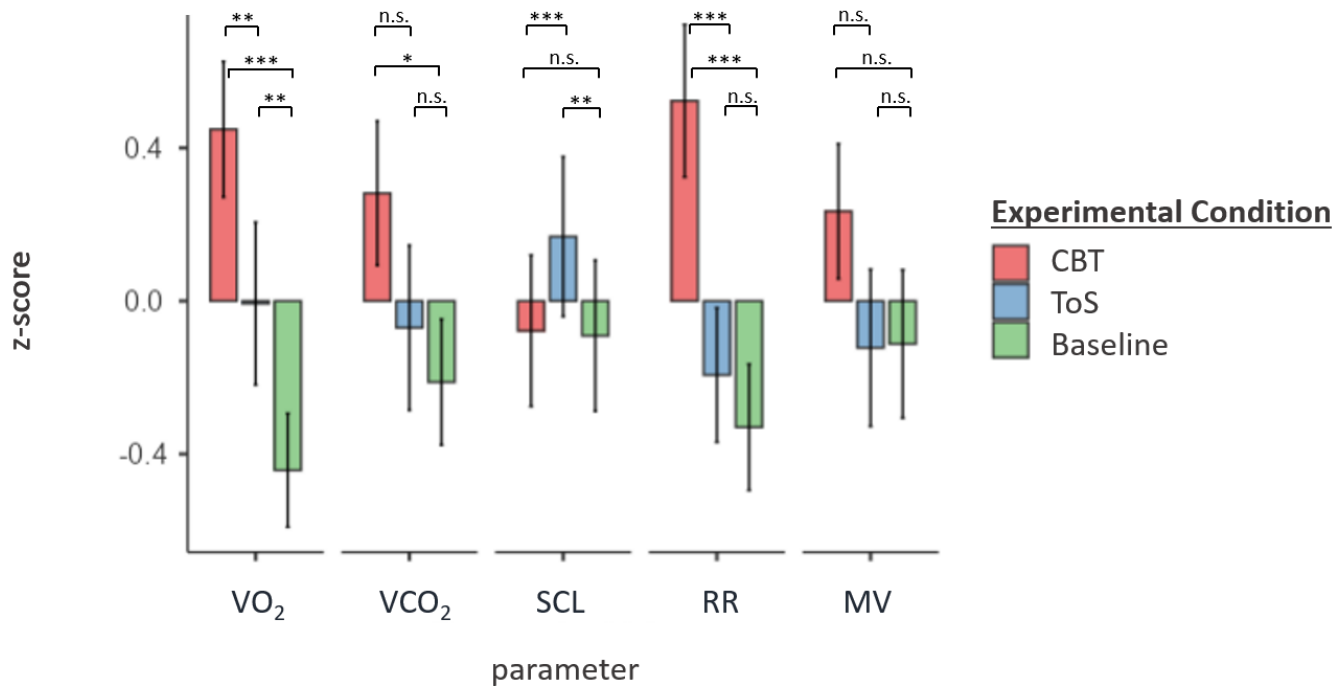
Responsiveness of physiological parameters (relative perspective)



Note. Responsiveness corresponds to the parameter value change in percent when shifting from the baseline to the respective experimental condition. Except for VCO_2, all mean comparisons between experimental conditions were significant. CBT = Corsi-Block-Tapping-Task; ToS = Threat-of-Shock; error bars indicate standard deviation.

Figure 2

Mean values of physiological measures across experimental conditions (absolute perspective)



Note. Due to scaling differences of EDA and gas parameters, mean values presented in this figure were z-standardized for each parameter. CBT = Corsi-Block-Tapping-Task, ToS = Threat-of-Shock; VO_2 = Volume of oxygen uptake, VCO_2 = Volume of carbon dioxide output, SCL = Skin conductance level, RR = Respiratory Rate, MV = Minute Volume; error bars indicate standard deviation. * $p < .05$, ** $p < .01$, *** $p < .001$

Results for the responsiveness in VCO_2 again showed a higher increase between baseline and CBT (M_C = 14.78 %) than for baseline and ToS (M_C = 3.38 %) although it failed to reach statistical significance ($t(26) = 1.68$, $p = .104$).

In contrast, SCL results showed a greater responsiveness to ToS (M = 15.32%) than to CBT (M = 2.31%), again in reference to the baseline ($t(24) = -3.76$, $p < .001$).

Next, hypothesis 1b tested the absolute perspective, comparing the mean respiratory gases of each testing condition (CBT, ToS) to baseline. Mean VO_2 during CBT (M_O = .33, t(26) = -7.18, p < .001) and ToS (M_O = .30, t(26) = -2.94, p = .007) differed significantly from baseline values (M_O = .27). For the mean VCO_2, only the difference between baseline (M_C = .27) and CBT condition reached significance (M_C = .30, t(26) = -2.49, p = .019).

For SCL, there was no significant mean difference between baseline and CBT (t(24) = -.29 p = .772), whereas mean SCL during ToS (M = 7.29) differed significantly from both baseline (M = 6.51, t(24) = -3.25, p = .003) and CBT (M = 6.55, t(24) = -3.94, p < .001).

Additional analyzes using paired sample t-tests revealed significant differences for respiratory rate between baseline (M = 13.22) and CBT (M = 16.24, t(24) = -7.31, p < .001), as well as between ToS (M =13.70) and CBT, (t(24) = 5.59, p < .001) but not for the comparison baseline vs. ToS. There were no significant differences for minute volume across experimental conditions.

The assumption that emotional and cognitive load can be distinguished based on VCO_2 rather than VO_2 (hypothesis 2a) was tested using paired samples t-tests. The difference between CBT and ToS reached significance for the VO_2 (t(26) = -2.69, p = .006) but fell short to do so for VCO_2 (p = .100). The difference between mean SCL during CBT and ToS was significant (t(24) = -3.93, p < .001).

Complementary, we explored whether there is evidence for the hypothetical maladaptive respiratory response to emotional stress using the quotient of VCO_2 and VO_2 - the RER (hypothesis 2b). Paired samples t-test indicated significant differences in the RER between baseline (M = .98) and CBT (M = .92, t(26) = 2.45, p = .022) and between baseline and ToS (M

= .92, $t(26) = -2.91$, $p = .007$). However, no significant differences between the RER of ToS and CBT were found ($p = .775$).

Regarding hypothesis 3a, external validity for cognitive performance, the spirometric parameters from the relative perspective showed the greatest diagnostic value of all investigated parameters: Pearson's bivariate correlations, which were computed for this purpose, were only significant for the increase of VO_2 ($r(25) = -.44$, $p = .023$) and VCO_2 ($r(25) = -.40$, $p = .037$) relative to individual baseline values (hypothesis 3a) but not for any of the other investigated absolute/relative parameters (neither EDA nor spirometry).

Further investigating external validity, analyzes of self-reported fear of actually receiving an electric shock during ToS, revealed that fear of shock was correlated significantly with both VO_2 ($r(25) = .44$, $p = .022$) and VCO_2 ($r(25) = .55$, $p = .003$). Such an association could not be demonstrated for any of the SCL values, nor the relative change measures of VO_2/VCO_2 in this study.

Moreover, for discriminant validity (hypothesis 3b) we noted that SCL responsiveness to CBT and ToS was significantly correlated ($r(23) = .70$, $p < .001$), indicating a lack of discrimination between cognitive load and emotional stress from the relative perspective. Looking at the responsiveness for respiratory parameters, however, we found evidence for a superior discriminating ability, with a significant negative correlation between increments in VCO_2 in response to the different mental conditions (*baseline-ToS* with *baseline-CBT*, $r(25) = -.38$, $p = .048$).

2.4.3.1 *Additional Analyzes*

To gain more in-depth insight into the specificity and sensitivity of the methods studied, ROC analyzes were conducted. Additionally, phasic and tonic portions of the EDA-signal were considered to broaden the picture. For ROC analyzes, area-under-the-curve (AUC) results mirrored those obtained by previously calculated t-tests. In a direct comparison of the AUCs between EDA measures (SCL, tonic, and phasic) and absolute values of VO_2/VCO_2, tonic EDA measures initially appear superior in discriminating between baseline and CBT (SCL: 0.485; tonic: 0.859; phasic: 0.685; VO_2: 0.778; VCO_2: 0.653) as well as baseline and ToS (SCL: 0.589; tonic: 0.866; phasic: 0.575; VO_2: 0.637; VCO_2: 0.590). However, when taking the relative perspective, VO_2/VCO_2 show a larger AUC in terms of discriminating a shift from baseline to ToS from a shift from baseline to CBT (SCL: 0.666; tonic: 0.459; phasic: 0.633; VO_2: 0.797; VCO_2: 0.701).

2.4.4 Discussion

In the present study, we used respiratory gases and electrodermal activity in an effort to objectively distinguish different demands (cognitive vs. emotional) in information processing. While EDA has been used extensively in research regarding emotional processing (Shu et al., 2018) and gas parameters have mostly been used in sport sciences and medicine (Hoppe et al., 2015), the combined use with respect to cognitive processing is innovative. Even in the context of this relatively simple feasibility study, basic spirometry measures were able to perform equally well or better compared to the diagnostic values of basic (SCL) and more sophisticated EDA measures (basic and tonic portions), as established and refined psychophysiological procedures. Spirometry in psychophysiological application could potentially benefit from more tailored data preparation methods for this purpose as well.

Nevertheless, our results indicate that respiratory gases are promising candidates for the detection and discrimination of different psychological demands. They also exhibit useful and arguably superior specificity and validity (external and discriminant) when compared to established psycho-physiological parameters, namely EDA.

In line with existing research (Setz et al., 2010), we demonstrated that EDA is capable of detecting emotional stress. With respect to cognitive load, however, our data indicate that EDA measures are mostly an indicator of the absence of emotional stress. Our results support the notion that respiratory gas parameters can enhance the detection of cognitive load and its discrimination from emotional stress (Fig. 1).

Specifically, VO_2 and VCO_2 were sensitive to changes in cognitive load (absolute and relative to baseline), whereas EDA measures were more sensitive to emotional stress than cognitive

load. The comparison of gas parameters across both experimental conditions (cognitive load and emotional stress) further supported the specificity of VO_2, differing significantly between emotional stress and cognitive load. However, we could not find significant evidence for the hypothetical maladaptive respiratory response to emotional stress as proposed by Grassmann et al. (2016). Potentially, a more elaborate approach, rather than simply using the quotient of VCO_2 and VO_2 (RER), is required to capture such an effect. Alternatively, a reduced discrimination capability of VCO_2 is based on greater susceptibility of this parameter to other (non-cognitive) influences (Hoppe et al., 2015).

Concerning discriminant validity, there was a strong intercorrelation of EDA responsiveness for cognitive load and emotional stress induction whereas the lack of such intercorrelation for gas parameters indicated their benefit beyond EDA. In addition, respiratory gas parameters showed superior external validity over EDA, as apparent in significant correlations with both non-physiological parameters (cognitive performance and self-reported fear of shock). In detail, cognitive performance outcomes were negatively related to VO_2 and VCO_2 responsiveness. As energy metabolism is arguably a primary mechanism behind variance in gas parameters (Wasserman et al., 2005), these results are in line with previous findings on interrelations of cognitive performance and responsiveness to glucose supplementation (Neukirchen, Radach, et al., 2022). The latter revealed a correlation between performance deficits and the degree of dependence of performance on the consumption of glucose. We suggest that the simultaneous investigation of respiratory gases under cognitive load with differing amounts of glucose supplementation and measures is a promising next step.

2.4.5 Conclusion

In summary, our experiments revealed different strengths and weaknesses of EDA and spirometry measures, which were most apparent (1) in terms of discriminating baseline activity from each of the two experimental conditions, and (2) with respect to external validity (fear of electric shock during ToS and cognitive performance during CBT). Thus, we think that the combination of spirometry and EDA indeed has added diagnostic value in the detection and discrimination of cognitive load and emotional stress.

Therefore, the study presented here provides an argument for further research into the analysis of respiratory gases in the context of psychological research. In doing so, it demonstrates partly superior, but primarily complementary strengths compared with the established psychophysiological EDA measures. Due to the relatively larger increases in VO_2 and VCO_2 compared to that of EDA parameters caused by cognitive load and the opposite relationship under emotional stress, future attempts could be made to identify the different conditions based on the aforementioned and more sophisticated parameters.

Taking into account that we also found changes in respiratory rate, one could argue that this mediates our findings regarding the sensitivity of gas parameters. However, this does not affect the basic ability of spirometry to discriminate episodes of cognitive vs. emotional load. The benefit of this novel use of spirometry is likely limited to physically resting individuals, as metabolic effort from physical activity is likely to override that from mental effort. Conversely, even when dealing with spirometry in the context of non-psychological research, attention should be paid to the possible variance elicited by psychological factors, as demonstrated in the presented experiment. In the present study the focus was to differentiate periods of cognitive

load and emotional stress rather than direct stimuli related responses. For future studies it would also be relevant to study spirometry as a psychophysiological method in an experiment with an event-related design (Bari et al., 2018).

From a practical point of view, spirometry is still limited by the usually large size of measuring devices and the associated restriction of mobility. A potential solution could be provided by measurement of gas concentrations in the subjects' periphery or portable devices. We hope that our presented work will spark interest in furthering the use of physiological measures, including spirometry, to obtain objective measures of mental processes.

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Contributions: T.N. and C.V. designed the research; M.S. performed experiments and data acquisition; T.N. and C.V. contributed to the data analysis; T.N., M.S. and C.V. contributed to the data interpretation; T.N. wrote the manuscript; C.V. and M.H. have supervised the study. All authors read and approved the final manuscript.

2.5 Role of Study C

In the third part of my research on the cognitive effects of glucose administration, I again pursued several objectives of both an empirical and methodological nature. To address the empirical question of the extent to which CGS is a useful psychological construct, I sought to test its association with variables of potential pathological significance in a clinically relevant sample of individuals with type 1 diabetes.

Methodologically, I tested a self-developed prototype of a questionnaire to determine introspectively accessible components of CGS. The development of a less invasive and more cost-effective method than those used in Studies A and B would greatly increase the practicality and reach of the CGS construct. Therefore, the methodological efforts, combined with the empirical questions above, resulted in a project that supports the feasibility of basic, introspective measures of psychological functioning in relation to the availability of glucose sources.

Moreover, it did so in a clinically relevant sample of people with type 1 diabetes, in which CGS was found to be related to an established psychological construct, diabetes-related distress. The significant relationship between introspectively measured CGS and an indicator of long-term blood glucose acts synergistically with previous efforts to establish a substantial portion of the interindividual variability of CGS as being physiologically determined.

2.6 Study C

Title	Self-reported cognitive glucose sensitivity: association with long-term blood-glucose-levels and diabetes-related distress in individuals with type 1 diabetes
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License	Open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
DOI	https://doi.org/10.1007/s11553-023-01017-8
Abstract	**Background:** Diabetes is often associated with a significant impact on psychological functioning and well-being. Effective prevention and health promotion of persons with diabetes requires a deeper understanding of this problem, which is based on the interaction of psychological and biological processes. **Objectives:** The study aims to contribute to the understanding of how subjective cognitive glucose sensitivity (cGS) is related to long-term blood glucose levels (HbA1c) and diabetes-related distress in people with type 1 diabetes. **Materials and methods:** As part of an online study, the relevant variables (kGS, latest measured HbA1c, diabetes-related distress) were recorded economically using self-report questionnaires. **Results:** In a sample of 354 adults with type 1 diabetes (283 female), we found significant correlations between kGS and HbA1c ($r(352) = .133$, $p = .006$) and diabetes-related distress ($r(352) = .242$, $p < .001$). HbA1c was also significantly correlated with diabetes-related distress($r(352) = .223$, $p < .001$). **Conclusion:** Our results indicate that cGS is physiologically determined and related to established diabetes-related measures (HbA1c and diabetes-related stress). Overall, the findings reaffirm a need for intensified research and development of comprehensive care for persons with diabetes integrating experience and behaviors of the affected person's mind as a substantial part. Ultimately, this could clarify the extent to which the treatment of cGS can have a preventive effect against negative impacts of diabetes on psychological well-being and would thus be beneficial to the health promotion of affected individuals.

2.6.1 Einleitung

2.6.1.1 *Hintergrund*

Diabetes beeinträchtigt nicht nur das körperliche, sondern auch das psychische Wohlbefinden betroffener Personen (Holt & Kalra, 2013; Kalra et al., 2018). Die Berücksichtigung psychischer, einschließlich kognitiver, emotionaler und verhaltensbezogener Aspekte, rückt vermehrt in den Fokus aktueller Forschung, da sie von entscheidender Bedeutung für das Patientenwohl sind (Bădescu et al., 2016; Gonzalez et al., 2016; Guénette et al., 2016; Holt & Kalra, 2013; Hunter et al., 2018; Kalra et al., 2018; Knutsson et al., 2020; Weinger & Lee, 2006).

Autoren wie Kalra und Kollegen argumentieren, dass die Vernachlässigung psychischer Aspekte eines Diabetes vorwiegend auf den Mangel an geschultem Personal, Zeit und Ressourcen zurückzuführen sei (Kalra et al., 2018). Mit Blick auf die mögliche Vermeidung psychischer Folgeerkrankungen (Griva et al., 2007; Guénette et al., 2016; Guerrero Fernández de Alba et al., 2020; Macrodimitris & Endler, 2001) und die – durch psychische Faktoren vermittelte (Gonzalez et al., 2016; Griva et al., 2007; Guénette et al., 2016; Macrodimitris & Endler, 2001) – Verbesserung der Therapieadhärenz erscheinen Investitionen in diese Bereiche jedoch ausgesprochen sinnvoll.

Konstrukte, wie die sogenannte diabetesbedingte Belastung, wurden eigens zum Zweck der Operationalisierung der Gesamtheit diabetesbedingter psychischer krankheits- und therapiebedingter Faktoren entwickelt. Sie umfassen die Besorgnis des Patienten hinsichtlich

des Krankheitsmanagements, sozialer Unterstützung, emotionaler Belastung sowie bezüglich des Zugangs zu medizinischer Versorgung (Polonsky et al., 1995). Mit Fragebögen wie der Problem Areas in Diabetes Scale (PAID-Skala) wurde Praxis und Forschung ein einfaches Instrument an die Hand gegeben, dass eben jene subjektiven Herausforderungen der Patientinnen/Patienten erfasst. Diabetesbedingte Belastung ist dabei mit entscheidenden Patientenvariablen, wie Adhärenz von Bewegungsvorgaben und Medikamenten (Alzubaidi et al., 2022; Nguyen et al., 2020), HbA1c-Wert und glykämischer Kontrolle (Hong et al., 2021; Nguyen et al., 2020) assoziiert.

Selbst im subklinischen Bereich sind die Zusammenhänge zwischen Variablen des glucoregulativen Systems und psychischen Aspekten evident. So gehen beispielsweise bei gesunden Personen höhere Blutzuckerspiegel im Normalbereich mit geringeren Volumina der grauen/weißen Substanz in den frontalen Kortizes einher, was sich auf behavioraler Ebene wiederum in schlechteren Ergebnissen in psychologischen Leistungstest äußert (Mortby et al., 2013; Razzak et al., 2018). Das Ausmaß dieser Effekte ist dabei zum Teil gravierend – Personen mit einem Blutzuckerspiegel im Prädiabetesbereich unterliefen in einer Inhibitionsaufgabe fast doppelt so viele Fehler wie Personen mit normalem Blutzuckerspiegel (Hawkins et al., 2016).

Mit dem Konstrukt der kognitiven Glukosesensitivität (kGS) wurde ein weiteres Instrument geschaffen, welches eine genauere Betrachtung des Wechselspiels von psychischen Prozessen und Glukosehaushalt ermöglichen soll. Es handelt sich dabei um die individuelle Responsivität mentaler Vorgänge auf die externe Zufuhr von Glukose (Neukirchen, Radach, et al., 2022). Diese wurde bisher experimentell gemessen, indem entsprechende Leistungsparameter individuell, jeweils mit und ohne externe Glukosezufuhr, erhoben wurden. Während eine niedrige kGS für eine geringe Veränderung psychischer Parameter infolge der Glukosezufuhr

steht, ist eine hohe kGS als eine starke, glukosebedingte Verbesserung dieser Parameter zu verstehen. Die im Experiment festgestellten Effekte der kGS sind dabei erheblich – Personen mit den schlechtesten Leistungen im Fastenzustand konnten ihre Leistung unter Glukosezufuhr teilweise mehr als verdoppeln (Neukirchen, Radach, et al., 2022). Bei den Personen mit den besten Leistungen im Fastenzustand konnte in derselben Studie hingegen keine große kGS nachgewiesen werden. Die kGS stellt also ein individuelles und situatives Leistungsdefizit dar, welches durch eine Glukosezufuhr kurzfristig teilkompensiert werden kann. Neuheitswert besitzen dabei vor allem zwei Aspekte. Erstens, die starke Vorhersagekraft der Leistung in Abwesenheit einer Glukosezufuhr auf die zu erwartende Leistungssteigerung durch eine Glukosezufuhr. Wenn eine Person ohne kurzfristig vorangegangene Glukosezufuhr schlechte kognitive Leistung erbringt, dann ist die Wahrscheinlichkeit groß, dass eine Glukosezufuhr die Leistung verbessern wird. Ein solcher Effekt, insbesondere dieser Größenordnung, ist alles andere als intuitiv, wenn man die Vielzahl an – oftmals dispositionalen und zeitlich stabilen – Determinanten interindividueller Unterschiede kognitiver Leistungen berücksichtigt. Der zweite Aspekt mit Neuheitswert liegt darin, dass es infolge einer Glukosegabe lediglich auf intraindividueller Ebene um eine Leistungszunahme handelte. Interindividuell betrachtet blieb in derselben Studie das Leistungsniveau von Personen mit hoher kGS stets unter dem von Personen mit niedriger kGS, die sowohl fastend als auch unter Glukosezufuhr die besten Leistungen erbrachten.

Die Größe des beschriebenen Effekts spricht für eine deutliche praktische Signifikanz der kGS. Eine Leistungsveränderung die mehr als 50% entsprach, fand sich in einem Drittel aller gesunden Versuchspersonen – dasselbe Drittel, dass auch das letzte Drittel der Ränge der kognitiven Leistungstests belegte (Neukirchen, Radach, et al., 2022). Beachtet man, dass die

Stichprobe verhältnismäßig jung war (M = 23.17, SD = 6.75), so ist eine praktische Relevanz eines solches Effekts im klinischen als auch im pädagogischen Kontext sowie im größeren Rahmen der Gesundheitsförderung denkbar.

Die durch die kGS quantifizierten individuellen Unterschiede in der kognitiven Sensitivität für die Einflüsse von Glukose stehen im Einklang mit Ergebnissen hinsichtlich der unter kognitiver Last verstoffwechselten Glukosemenge (gemessen über die Atemluft) (Neukirchen, Stork, et al., 2022), weshalb der individuelle Glukosehaushalt als mediierende Größe sehr plausibel erscheint.

Angesichts der Tatsache, dass die kGS bereits bei klinisch unauffälligen Personen erhebliche interindividuelle Varianz aufweist (Neukirchen, Radach, et al., 2022), ist die Untersuchung der kGS in Personen mit pathologisch verändertem Glukosehaushalt besonders interessant. Sowohl der Anwendung als auch der Forschung kommt dabei zugute, dass das Konstrukt der kGS nicht zwangsläufig mit dem relativ aufwendigen Verfahren – bestehend aus zwei Laborsitzungen mit und ohne externe Glukosezufuhr – erfasst werden muss. Ersten Erkenntnissen zufolge sind die Auswirkungen der kGS profund genug, um von den Betroffenen wahrgenommen und bewusst beschrieben werden zu können (Neukirchen, 2019). Grundsätzlich sind durch den Glukosehaushalt bedingte, psychische Effekte durchaus introspektiv zugänglich, wie es sowohl in der Praxis durch etablierte Fragebögen zur diabetesbedingten Belastung oder auch durch zahlreiche Publikationen belegt ist (L. A. Gonder-Frederick et al., 1989; Young & Benton, 2014). Auch unter Berücksichtigung der zuvor beschriebenen, individuellen glukosebedingten Leistungsunterschiede von bis zu über 200% ist es nicht sonderlich überraschend, dass Betroffene die kGS selbst an sich wahrnehmen können.

Somit liegt nahe, dass Einschränkungen des psychischen Funktionsniveaus, wenn kürzlich keine Glukosequellen konsumiert wurden, introspektiv operationalisierbar sind. Diesen Umstand macht sich der Fragebogen *Indicators of Glucose-Dependency* (IGlu) zu Nutze, der das Ausmaß oben beschriebener Effekte erfasst und somit die *subjektive* kGS misst. Mit der subjektiven kGS wird also der Grad der selbst wahrgenommenen Einschränkungen des psychischen Erlebens — insbesondere der kognitiven Verarbeitung — beschrieben, welche mit zunehmender Nahrungsdeprivation auftritt.

Diese Größe kovariiert mit ihrem experimentell gemessenen Gegenstück und beide lassen sich durch Interventionen, welche mit Gewichtsreduktionen einhergingen, positiv beeinflussen (Neukirchen, 2019). Diese Erkenntnis stimmt insofern optimistisch, als dass die kGS insbesondere bei Männern mit dem Körpergewicht assoziiert ist (Neukirchen, Radach, et al., 2022). Angesichts des etablierten Zusammenhangs zwischen Körpergewicht und Insulinsensitivität, sowie der Evidenz hinsichtlich der moderierenden Rolle des Geschlechts (Masharani et al., 2009; Sierra-Johnson et al., 2004; Yki Jarvinen & Koivisto, 1983), gelten Insulinsensitivität und Glukosehaushalt als die wahrscheinlichsten Mechanismen hinter der kGS (Neukirchen, Radach, et al., 2022). Die Erforschung der kGS bei Personen mit pathologischen Auffälligkeiten des Glukosehaushalts ist somit ein naheliegender nächster Schritt, welcher im Rahmen der hier vorgestellten Studie begangen wurde. Dabei bot sich zunächst die nähere Betrachtung der subjektiven kGS an, welche die kontaktfreie, onlinegestützte Untersuchung von Menschen mit Diabetes – einer Risikogruppe für Covid-19 (Targher et al., 2020) – während der Pandemie ermöglichte.

Das erste wesentliche Ziel der Studie ist die Untersuchung eines möglichen Zusammenhangs zwischen subjektiver kGS und einem etablierten Indikator des Langzeit-Blutzuckerspiegels, dem HbA1c-Wert. Ein solcher Zusammenhang wäre insofern bedeutsam, als dass er einen weiteren Hinweis für die enge Beziehung zwischen Blutglukoseregulation und psychischen Prozessen darstellen würde, welche ultimativ das Wohlbefinden des Patienten beeinflussen. Wenn das Patientenwohl priorisiert werden soll, dann müssen es ebenso jene Mechanismen, welche den Einfluss zwischen Soma und Psyche vermitteln. Der Grund dafür ist, dass eine hohe kGS per Definition ein situatives Leistungsdefizit darstellt, deren physiologischen Mechanismen wir im Glukosestoffwechsel und den mit ihm relatierten Faktoren vermuten. Beim Langzeitblutzuckerwert und der diabetesbedingten Belastung handelt es sich um eben solche. Daher erwarten wir jeweils positive, korrelative Zusammenhänge zwischen subjektiver kGS und den beiden unmittelbar diabetesrelatierten Konstrukten (diabetesbedingter Belastung und HbA1c-Wert). Die Annahme ist dabei, dass je schlechter die Glucoregulation ist (hoher HbA1c), desto störanfälliger ist das psychische Funktionsniveau, wenn keine externen Glukosequellen zugeführt werden. Ein solches Ergebnis stünde im Einklang mit etablierten Befunden hinsichtlich zerebraler Insulinsensitivität, individueller Anpassung an die Verwertung von Ketonkörpern sowie dem Zusammenhang zwischen Leistungsdefiziten und erhöhtem Glukoseumsatz unter kognitiver Belastung (Jensen et al., 2020; Kullmann et al., 2016a; Neukirchen, Stork, et al., 2022; M. Nilsson et al., 2019).

Zweitens sollte untersucht werden, inwiefern eine Beziehung zwischen subjektiver kGS und diabetesbedingter Belastung besteht. Da die subjektive kGS nach dem aktuellen Forschungsstand beeinflussbar ist, würde ein Zusammenhang zwischen den beiden

Konstrukten einen Ansatz zur Reduktion der diabetesbedingten Belastung durch Senkung der kGS darstellen. Im Gegensatz zur diabetesbedingten Belastung ist die kGS ein psychologisches Konstrukt, welches sich auch bei Personen ohne Diabetes einsetzen lässt. Die Erforschung der Beziehung zwischen beiden Konstrukten birgt somit langfristig auch das Potential, diabetesspezifische von diabetesunspezifischen Einflüssen auf das Erleben und Verhalten zu differenzieren oder auch psychische Effekte des Glukosehaushalts über das gesamte Kontinuum der Insulinresistenz (Levy-Marchal et al., 2010) zu erforschen.

2.6.2 Methode

Alle Methoden standen im Einklang mit Richtlinien der Ethikkommission der Universität (Gutachtennummer MS/BBL 210329 Neukirchen Buitkamp) und der aktuellen Fassung der Deklaration von Helsinki. Zu Beginn der Datenerhebung wurde von allen Teilnehmenden das Einverständnis zur Teilnahme und Datenverarbeitung eingeholt.

2.6.2.1 *Stichprobe*

Die Rekrutierung der Probanden erfolgte über soziale Medien sowie über Aushänge in diabetologischen Schwerpunktpraxen. Die Erhebung der Daten fand zwischen April und Juni 2021 statt. Die Ad-hoc-Stichprobe bestand nach Datenbereinigung (siehe unten) aus n=354 erwachsenen Personen mit Typ 1 Diabetes (80% weiblich) im Alter von 18 bis 72 Jahren (M = 37.30, SD = 12.32). Die Körpergröße lag zwischen 150 und 198 cm (M = 170.35, SD = 8.25) und das Gewicht betrug zwischen 43 und 150 kg (M = 79.30, SD = 19.40). Der BMI lag damit im Mittel bei M = 27.27, SD = 6.21. Eine a-priori Poweranalyse, die auf der konservativen Erwartung kleiner

Effektstärken beruhte (Hagger et al., 2018; Van Bastelaar et al., 2010), ergab eine minimale Stichprobengröße von 320 Personen für eine angestrebte Power von .95 bei einem $\alpha = .05$.

2.6.2.2 *Fragebögen*

2.6.2.2.1 Demografischer Fragebogen

Der demografische Fragebogen erfasste anthropometrische und demografische Daten. Desweitern wurden Informationen bezüglich der Diabeteserkrankung erfragt, wobei in der hier vorgestellten Studie dem aktuellsten HbA1c-Wert (mit dazugehörigem Bestimmungsdatum) die größte Bedeutung zukommt. Der HbA1c-Wert wird als Indikator der durchschnittlichen Blutzuckerkonzentration verwendet. Er gibt Auskunft über die Bindung von Zucker an Hämoglobin über einen Zeitraum von sechs bis acht Wochen (Landgraf, 2006). Dabei bewegt sich ein HbA1c zwischen 4-6% laut der International Federation of Clincal Chemistry (IFCC) und dem National Glycohemoglobin Standardization Program (NGSP) im Normbereich (Group, 1993). Laut der American Diabetes Association gilt als grobes Therapieziel die Aufrechterhaltung eines HbA1c-Wertes von unter 7% (Association, 2011). Ist der HbA1c-Wert über einen längeren Zeitraum erhöht, so steigt das Risiko für Folgeerkrankungen (Selvin et al., 2006). In Deutschland wird bei Diabetikern die Bestimmung des HbA1c einmal pro Quartal empfohlen, da er Rückschlüsse über den Erfolg oder Misserfolg der Diabetestherapie und somit das Risiko für Folgeerkrankungen aufzeigt (Association, 2011; Group, 1993). Diesen Umstand machten wir uns in der vorliegenden Studie zu Nutze.

2.6.2.2.2 IGlu

Die oben eingeführte subjektive kGS wurde mit dem Selbstberichtsfragebogen „Indicators of Glucose-Dependency“ (IGlu) erfasst (Neukirchen, 2019). Hierbei handelt es sich um einen Selbstberichtsfragebogen mit 38 Items. Die Items enthalten Zustimmungen zu Aussagen über die subjektiv empfundene Abhängigkeit des emotionalen, kognitiven und physischen Funktionsniveaus von einer unmittelbaren Nahrungsaufnahme. Dabei liegt der Fokus auf den subjektiven Verschlechterungen besagter innerer Zustände und Prozesse, wie beispielsweise Unachtsamkeit, Vergesslichkeit und Gereiztheit in Abhängigkeit von der letzten Nahrungsaufnahme.

Der IGlu-Fragebogen erfasst das Ausmaß besagter Effekte über Items, welche sich auf Einschränkungen in gedächtnisbezogenen und problemlösenden kognitiven Prozessen, der Wahrnehmung und Regulation von Emotionen sowie der Wahrnehmung des eigenen Körpers beziehen. Ergänzt werden diese Aspekte um selbstsuggestive Überzeugungen, welche Einschränkungen der Leistungsfähigkeit in der Abwesenheit einer unmittelbaren Nahrungsaufnahme begünstigen könnten, sowie Items zur Erfassung potenziell relevanter Gesundheitsverhaltensweisen und Lebensumstände. Aufgrund der Art ihrer Operationalisierung mittels Fragebogen wird der individuelle Gesamttestwert auch als *subjektive* kGS bezeichnet. Der Gesamttestwert ist das arithmetische Mittel aller Items, die mithilfe eines Zustimmungsreglers mit einem Wert zwischen 0 (vollkommende Ablehnung) und 100 (vollkommende Zustimmung) bewertet werden, so dass dieser auch einen Wert zwischen 0 und 100 annimmt.

2.6.2.2.3 PAID

Der Selbstberichtsfragebogen „Problem Area in Diabetes“ (PAID) von Polonsky und Kollegen aus dem Jahr 1995 erfasst die diabetesbedingte Belastung. Das Messinstrument umfasst 20 Items, welche vier Subskalen (emotionale Probleme, therapiebezogene Probleme, ernährungsbezogene Probleme und Probleme, die die soziale Unterstützung betreffen) zugeordnet sind. Aus den Subskalenwerten kann ein Gesamttestwert aggregiert werden, welcher in der vorliegenden Studie zur Hypothesenprüfung herangezogen wurde. Der PAID-Testscore wurde gemäß den Vorgaben von Polonsky und Kollegen (Polonsky et al., 1995) berechnet, indem die einzelnen Rohwerte aufsummiert und dann mit dem Faktor 1,25 multipliziert wurden, so dass sich Werte zwischen 0 und 100 ergeben. Die interne Konsistenz des Instruments ist sowohl im englischsprachigen Original ($\alpha = .95$) als auch in der deutschen Version ($\alpha = .93$) belegt (Polonsky et al., 1995).

2.6.2.3 *Datenaufbereitung und statistische Analyse*

Die Daten wurden in R ausgewertet (R Core Team, 2017). Insgesamt begannen N=812 Personen mit der Bearbeitung der Fragebögen. Nachdem die Daten auf Stichprobenebene bereinigt wurden (Einwilligung der anonymisierten Datenerfassung erteilt, vollständige Bearbeitung aller Fragen, HbA1c > 0 und < 20, Dauer der Erkrankung < Lebensalter) verblieben 416 Versuchspersonen. Ausgehend von der mittleren Lebensdauer menschlicher Erythrozyten (Wick et al., 2002) wurde lediglich Fälle zur Analyse zugelassen, bei denen der HbA1c vor weniger als 121 Tagen vor Teilnahme an der Studie ermittelt wurde. Es verblieben damit n=354 Personen zur Analyse in der Stichprobe. Das Signifikanzniveau für alle statistischen Tests wurde auf $\alpha = .05$ festgelegt.

2.6.2.4 *Ablauf*

Die Datenerhebung erfolgte Online und anonymisiert über die Plattform Soscisurvey (Leiner, 2014). Nachdem die Versuchspersonen den Datenschutzerklärungen zugestimmt hatten, wurde ihnen der demographische Fragebogen vorgelegt. Im Anschluss wurde die diabetesbedingte Belastung mithilfe des Fragebogens „Problem Areas in Diabetes“ (Polonsky et al., 1995) und die subjektive kGS mit dem IGlu-Fragebogen (Neukirchen, 2019) erfasst.

2.6.3 Ergebnisse

In Tabelle 1 findet sich eine Übersicht der Ergebnisse der deskriptiven Analyse der physischen und hypothesenrelevanten Variablen aller Teilnehmenden, deren Datensätze den Selektionskriterien (vgl. Datenaufbereitung und statistische Analyse oben) entsprachen. Die Korrelation zwischen IGlu und HbA1c erreichte statistische Signifikanz, $r(352) = .133$, $p = .006$. Auch Prüfung des angenommenen Zusammenhangs zwischen den Testwerten des IGlu und PAID ergab eine hochsignifikante Korrelation mit $r(352) = .242$, $p < .001$. Zusätzlich wurde ein möglicher Zusammenhang zwischen HbA1c und PAID untersucht, welcher sich ebenfalls als statistisch hochsignifikant erwies, $r(352) = .223$, $p < .001$. Vertiefend wurde geprüft, inwiefern der Zusammenhang zwischen IGlu und HbA1c durch die diabetesbedingte Belastung bedingt sein könnte. Eine entsprechende partielle Korrelation zwischen IGlu und HbA1c, bei der der Einfluss der diabetesbedingten Belastung kontrolliert wurde, ergab eine tendenziell signifikante Assoziation zwischen IGlu und HbA1c, $r(352) = .084$, $p = .058$. Die beschriebenen Zusammenhänge blieben in der gleichen Stärke auch erhalten, wenn in den Analysen für Alter kontrolliert wurde.

Tabelle 1

Deskriptive Statistiken zu erhobenen Variablen innerhalb der untersuchten Stichprobe.

	M	SD	Range	Min	Max
Lebensalter	37,299	12,319	54	18	72
Jahre seit Diagnose	15,952	12,522	54	0	54
Körpergewicht	79,297	19,404	107,000	43,000	150,000
Körpergröße	170,345	8,248	48	150	198
BMI	27,267	6,209	35,207	15,605	50,811
HbA1c	7,094	1,641	12,000	4,900	16,900
Aktualität HbA1c	45,674	30,763	119,956	0	120,383
PAID-Testwert	58,129	20,734	91,250	25,000	116,250
IGlu-Testwert	44,831	11,869	66,868	15,684	82,553

Anmerkung. Lebensalter in Jahren, Körpergewicht in kg, Körpergröße in cm, BMI = Body Mass Index, HbA1c in %, Aktualität des HbA1c in Tagen (Differenz Teilnahmedatum - Datum der angegebenen HbA1c-Messung), $N = 354$.

In Zusatzanalysen wurden mögliche geschlechtsspezifische Effekte untersucht. Dazu wurden die Zusammenhänge von IGlu, HbA1c und PAID getrenntgeschlechtlich betrachtet für zwei der drei überprüften Zusammenhänge interessante Unterschiede zwischen den Geschlechtern entdeckt. Während der Zusammenhang zwischen IGlu und HbA1c für Männer und Frauen vergleichbar war (r(281) = .138, p = .020; r(69) = .124, p = 0.303)), zeigte sich für den Zusammenhang zwischen IGlu und PAID eine substantiell höhere Korrelation in der männlichen Substichprobe (r(69) = .517, p < .001) im Vergleich zur Weiblichen (r(281) = .170, p = .004). Auch für den Zusammenhang zwischen HbA1c und PAID fand sich eine wesentlich ausgeprägtere Korrelation für die männliche (r(69) = .409, p < .001) als die weibliche Substichprobe (r(281) = .180, p = .002). Analog zur Gesamtstichprobe, fand sich in der weiblichen Substichprobe ebenfalls eine wesentliche Reduktion des Zusammenhangs zwischen IGlu und HbA1c, wenn für PAID kontrolliert wurde (r(281) = .084, p = .117).

2.6.4 Diskussion

In der vorliegenden Studie überprüften wir mögliche Zusammenhänge zwischen der subjektive kGS und dem Langzeitblutzuckerspiegel sowie der diabetesbedingten Belastung in einer Stichprobe aus Personen mit Typ 1 Diabetes.

Weiterhin untersuchten wir innerhalb derselben Stichprobe die Beziehung zwischen diabetesbedingter Belastung und dem HbA1c.

Unserer Ergebnisse stützen die Hypothesen und zeigen Zusammenhänge zwischen den genannten Konstrukten und untermauern damit unsere ursprüngliche Annahme, dass eine

höhere Störanfälligkeit des psychischen Funktionsniveaus unter Nahrungsdeprivation (skGS) mit einer schlechteren Glucoregulation (hoher HbA1c) einhergeht. Die Beziehung zwischen skGS und diabetesbedingter Belastung ist Indiz für die Relevanz kognitiver Einschränkungen für die Folgen einer Diabeteserkrankung für das psychische Wohlbefinden.

Im Einzelnen gelang bei dieser erstmaligen Anwendung des IGlu-Fragebogens zur Messung der subjektiven kGS in einer klinisch relevanten Stichprobe der Nachweis einer Assoziation mit dem HbA1c. Die subjektive kGS stand zudem mit der diabetesbedingten Belastung im Zusammenhang. Darüber hinaus erfolgte die Replikation der etablierten Beziehung zwischen diabetesbedingter Belastung und HbA1c (Hagger et al., 2018; Van Bastelaar et al., 2010). Diese Ergebnisse stehen im Einklang mit der Annahme, dass das Konstrukt der kGS physiologisch bedingt ist (Neukirchen, Radach, et al., 2022; Neukirchen, Stork, et al., 2022) und sind damit für dessen weitere Erforschung richtungsweisend.

Die Erkenntnis, dass die diabetesbedingte Belastung wesentlich zu der Beziehung zwischen kGS und HbA1c beiträgt, ist in mehrerlei Hinsicht interessant. Die subjektive Eigenwahrnehmung der kGS bei Personen mit Typ 1 Diabetes scheint substantiell durch die emotionalen Folgen der Diabeteserkrankung beeinflusst zu werden. Dies hat zweierlei mögliche Implikationen. Einerseits könnte die Introspektion durch die Belastung negativ beeinflusst sein - Betroffene starker diabetesbedingter Belastung schätzen die Abhängigkeit ihrer kognitiven Fähigkeiten von externen Glukosequellen als größer ein als diese tatsächlich ist. Andererseits wäre es denkbar, dass die diabetesbedingte Belastung tatsächlich Auswirkungen auf die kGS hat und betroffene Personen vulnerabler für die kognitiven Folgen von Nahrungsdeprivation macht.

Darüber hinaus stellt sich die Frage, durch welche Konstrukte eine mögliche Assoziation zwischen HbA1c und kGS bei Personen ohne Diabetes vermittelt werden würde. Angesichts der bereits etablierten Mediatorrolle diabetesbedingter Belastung zwischen HbA1c und depressiver Symptomatik (Van Bastelaar et al., 2010) ist auch eine Effekt der kGS bei der Entwicklung depressiver Symptome denkbar. Die Assoziation depressiver Symptomatik mit Einschränkungen der kognitiven Verarbeitung emotionaler Stimuli gilt als etabliert (Jacobs et al., 2020; Rock et al., 2014). Unter Berücksichtigung der hohen Vulnerabilität von Personen mit Diabetes (Bădescu et al., 2016; Hong et al., 2021; Hunter et al., 2018), ist es naheliegend, zukünftig auch spezielle Einschränkung des kognitiven Funktionsniveaus – wie die kGS – im Kontext von Diabetes und Depressivität zu untersuchen.

Die etablierten Korrelate der diabetesbedingten Belastung, wie Adhärenz von Bewegungsvorgaben und Medikamenten (Alzubaidi et al., 2022; Nguyen et al., 2020) und glykämische Kontrolle (Hong et al., 2021; Nguyen et al., 2020) könnten ihrerseits den Zusammenhang mit der kGS beeinflussen. Beispielsweise könnten Variablen wie die Adhärenz protektive Faktoren darstellen, die determinieren, ob ein erhöhter HbA1c tatsächlich zu den situativen Einschränkungen des psychischen Funktionsniveaus führt, welche die kGS konstituieren. Entsprechend elaborierte, konsekutive Studien, welche sowohl über Methoden zur Erfassung weitere Konstrukte als auch angepasste Untersuchungsdesigns verfügen, könnten wesentlich zur Beantwortung dieser Fragen beitragen. Dabei gilt es, sowohl die wissenschaftlichen Erkenntnisse als auch die identifizierten Limitationen der vorgestellten Studie aufzugreifen, wie z.B. das auf Selbstauskunft des HbA1c basierende Design. Dies stellt einen Kompromiss dar, den bereits wesentliche Pionierarbeiten des Feldes eingehen mussten (Hagger et al., 2018) und den es in zukünftigen Projekten zu überwinden gilt. Eine mögliche

Lösung könnte durch die Verwendung von Krankenakten der Patienten erzielt werden, z. B. durch die unmittelbare Durchführung der Studie in Zusammenarbeit mit klinischen Einrichtungen und Behandlungszentren. Diesbezüglich sollten zukünftige Untersuchungen ebenfalls überprüfen, ob und inwiefern sich ähnliche Resultate bei Personen mit Typ 2 Diabetes replizieren lassen. Dabei ist zu beachten, dass viele Personen mit Typ 2 Diabetes älter als der Bevölkerungsdurchschnitt sind (Jacobs et al., 2020) und somit die Rekrutierung einer Stichprobe ausreichenden Umfangs im Rahmen einer internetbasierten Umfrage eine Herausforderung sein könnte.

Die dargestellten Daten machen deutlich, dass die Verwendung psychologischer Messgrößen, einschließlich der kognitiven Glukosesensitivität, wertvolle Hinweise und Erkenntnisse über mentale Prozesse darstellen. Dies können, zu einem besseren Verständnis der Verbindung von physiologischen Leiden und der Qualität des Erlebens und Verhaltens betroffener Personen beitragen und perspektivisch sinnvolle Ergänzungen in der Diabetestherapie bieten. Aus diagnostischer Sicht ist dabei die Tatsache interessant, dass mit dem IGlu-Fragebogen in erster Linie kognitive Einschränkungen operationalisiert werden während PAID überwiegend emotionale Aspekte des Erlebens erfasst. Somit ergibt sich in kombinierter Nutzung die Möglichkeit zur umfangreicheren Ermittlung des psychischen Funktionsniveaus unter Berücksichtigung der Einschränkungen im Glukosestoffwechsel. Die Involvierung höherer kognitiver Prozesse in der Konstituierung der selbsteingeschätzten kGS birgt Potential zur Interventionsbildung durch kognitive Verhaltenstherapie.

Erfolgen könnte dies beispielsweise durch die Bewusstmachung von Kognitionen, welche die subjektiven Einschränkungen des eigenen Funktionsniveaus im Zusammenhang mit Glukose betreffen. Die anschließende Prüfung der Angemessenheit solcher Kognitionen könnte sowohl

zur Verringerung von selbstsuggestiven Effekten als auch zur Identifikation von Symptomen suboptimaler Medikation oder Therapieadhärenz beitragen. Somit könnten entsprechende Denkmuster direkt modifiziert und negativen Effekten von Diabeteserkrankungen auf die Psyche entgegengewirkt werden. Dass sich die kGS bereits in Personen ohne Diabeteserkrankungen als valides psychologisches Konstrukt erwies, weckt Hoffnungen auf einen Mehrwert im Bereich der Prävention psychischer Negativfolgen, lange bevor die Einschränkungen des Glukosehaushalts den subklinischen Bereich verlassen.

2.6.5 Limitationen

Aufgrund des verwendeten Untersuchungsdesigns lassen sich keine eindeutigen Kausalitäten aus den festgestellten Zusammenhängen ableiten. Denkbar wären transaktionale Zusammenhänge zwischen den psychischen Konstrukten und dem HbA1c, welche durch behaviorale Aspekte (z.B. niedrigere Adhärenz, emotionales Essen) vermittelt werden könnten. Weiterhin basieren die ausgewerteten Daten auf anonymen Selbstberichten von freiwilligen, interessierten Personen mit Internetzugang, weshalb introspektive Fähigkeiten, Validität der Angabe des letzten HbA1c und Teilnahmebereitschaft als potentiell bei der Ergebnisinterpretation berücksichtigt werden sollten. Insbesondere die Geschlechterverteilung der Ad-hoc-Stichprobe entspricht nicht der Gesamtpopulation und birgt – nebst der Tatsache, dass weniger als die Hälfte aller teilnehmenden Personen den Fragebogen vollständig bearbeiteten – Verbesserungspotential für zukünftige Untersuchungen.

2.6.6 Schlussfolgerung

Die Beziehung zwischen den Testwerten der beiden psychometrischen Instrumenten sowie deren Assoziation mit dem HbA1c bekräftigten, dass psychische Auswirkungen einer Diabeteserkrankung vielfältig, hoch-prävalent und ökonomisch nachweisbar sind. Erwähnenswert dabei ist, dass die Korrelation zwischen kGS und diabetesbedingter Belastung lediglich von moderater Größe ist. Das spricht dafür, dass beide psychometrischen Verfahren tatsächlich unterschiedliche, Konstrukte operationalisieren, wenngleich bei vorliegender Diabeteserkrankung die diabetesbedingte Belastung wesentlich zur subjektiven Bewertung der eigenen kGS beiträgt.

Weiterhin liefern die gewonnenen Ergebnisse zusätzliche Evidenz für geschlechtsspezifische Unterschiede im Kontext der kGS. Die in der Einleitung erwähnte Interaktion von Geschlecht und Körpergewicht auf die objektiv gemessene kGS (Neukirchen, Radach, et al., 2022) wirft im Zusammenspiel mit den hier vorgestellten Befunden die zukünftig zu beantwortende Frage auf, ob die kGS bei Männern allgemein stärker mit komorbiden Begleiterscheinungen (nebst höherer diabetesbedingter Belastung) einhergeht.

2.6.7 Fazit für die Praxis

Für die Praxis bedeuten unsere Ergebnisse, dass die Verwendung von psychometrischen Instrumenten, wie dem PAID oder IGlu, lohnenswerte Optionen darstellen, um das Patientenwohl bei vorliegendem Diabetes standardisiert und differenziert zu erfassen.

Entsprechende Instrumente können bei der Erkennung von mit der Erkrankung assoziierten Einschränkungen des psychischen Erlebens helfen und zur konkreten und zeitökonomischen Evaluation eines möglichen Handlungsbedarfs von ärztlicher / therapeutischer Seite beitragen.

Die – insbesondere bei männlichen Patienten – ausgeprägte Assoziation zwischen HbA1c und den hier erforschten psychologischen Konstrukten sollte bei der Anamnese im diabetologischen als auch im psychiatrischen Bereich berücksichtigt werden.

3 General Discussion

3.1 Summary of the Key Findings

The overarching purpose of this dissertation is to elucidate the nuanced effects of glucose intake on cognition. This was pursued through three complementing empirical and methodological objectives, which worked in synergy with each other in their pursuit.

Empirically, the objectives of this thesis were to identify factors that influence cognitive effects following glucose administration, termed cognitive glucose sensitivity (CGS; Study A); to investigate the underlying physiological mechanisms governing these effects (Study B); and to explore the potential clinical utility of CGS (Study C).

Methodologically, the studies aimed to refine behavioral (Study A), physiological (Study B), and introspective (Study C) approaches to the psychological study of glucose-related cognitive effects.

Of course, this highly simplified separation of the different study aims does not fully reflect the reality of the overall research endeavor. For example, the goal of investigating possible underlying mechanisms of CGS, is primarily assigned to Study B in the context of this dissertation. Yet, investigating BMI in Study A served as a proxy for glucoregulation; while Study C contributed to the same goal by investigating participants with diabetes and considering their long-term blood glucose levels. In other words, even if the individual studies have different emphases in the pursuit of the above-mentioned goals, the individual studies are intertwined with one another and, in their emergence, contribute to the semantic thread of the overall work.

Study A investigated the behaviorally measurable individual cognitive performance change following glucose administration. One key finding of Study A was that both domain and

individual performance deficits in the absence of glucose administration were highly predictive of the effects of glucose, the magnitude of which we termed CGS. Thereby, the individual performance change as a result of glucose administration turned out to be more of a compensation for low-performers, while at high performance levels, CGS was low. The data supports the idea that glucose-induced performance advantages are due to the inability to fulfill one's performance potential in the absence of dietary glucose sources; an observation that fits harmoniously within the concept of interindividual differences in metabolic switching (Section 1.2).

However, on the basis of Study A, I was unable to determine the extent to which psychological effects (e.g. due to the sweetness of glucose and the affect that might be associated with it) played a role in the observed effects. Although, in one of our unpublished studies, all results were obtained in similar magnitude in a placebo-controlled manner. This suggests that ingestion of an equally sweet placebo solution (erythritol) at baseline does not induce the same performance modulating effects as glucose administration. Therefore, the evidence was in favor of prioritizing the exploration of glucose metabolism in the context of cognitive effort, leading to Study B.

Study B addressed a method for noninvasively measuring glucose turnover under cognitive load. It also examined the extent to which the hypothesized relationship between glucose metabolism and cognitive performance is confounded by effects of fear-induced physiological arousal as measured by electrodermal activity. Indeed, an increase in glucose turnover, measured via metabolized O_2 and exhaled CO_2, could be reliably attributed to the cognitive performance condition.

For this purpose, we used the task that produced the largest CGS effects in Study A without necessitating an oral response format. Speaking likely would have interfered with the measurement of respiratory gases. Consistent with the results of Study A, we were able to show that the better the subjects' performance, the lower was their increase in glucose turnover compared to the baseline measurement. Thereby, Study B suggests that key findings of Study A, regarding the relationship between being a low-performer and having a pronounced CGS, may in fact possess a physiological basis. This evidence is congruent with the hypothesis of interindividual differences in metabolic switching contributing to CGS.

Study C demonstrated that introspectively assessed CGS is related to long-term blood glucose levels (HbA1c) as well as diabetes-related distress in individuals with type 1 diabetes. On the one hand, this allowed to gather evidence for the introspective accessibility of one's dependence on external sources of glucose for cognitive performance. On the other hand, it demonstrated the basic applicability of the construct in individuals with pathologically impaired glucose homeostasis. In synergy with the findings of Study A and B, we extended the current state of research by providing complementary evidence regarding the contributions of physiological processes to the manifestation of CGS.

In the following section, the key findings of the studies are discussed in more detail in terms of their relevance to the research question of this dissertation, as well as the resulting implications for current and future research. Table II provides an overview and extends Table I with the results of Studies A, B, C, and the findings from the general discussion of my thesis.

Table II

Empirical Objectives, Findings, and Implications

Based on	Main Objective	Corresponding Main Finding	Relevant Study	Implications for Further Research
Benton, 1990; Benton et al., 1994; Benton & Parker, 1998; Foster et al., 1998; Gagnon et al., 2011; Gonder-Frederick et al., 1987; Manning et al., 1992; Meikle et al., 2004; Owen et al., 2013; Owens & Benton, 1994; Parsons & Gold, 1992; Peters et al., 2020; Scholey et al., 2009; Zanchi et al., 2018	Identify determinants of CGS	Relevance of task properties	A	attentional processes [1,2,3], demand [1,2,3], difficulty [1,2,3], metacognitive strategies [2,3], performance domain [1,2,3]
		Relevance of participant properties (baseline performance; BMI in men)		age [2,3], androgens [3], dosage [2,3], energy demand [1,2,3], estrogens [3], food cue processing [1,2,3], genetic variation [3], hunger [1,2,3], ketones [2,3], metabolic switching [1,2,3], nutritional choices [2,3], physical activity [2,3], sleep and circadian rhythm [1,2,3], stress [3], sun light exposure [3], weight change [1,2,3]
Benton, 1990; Benton et al., 1994; Benton & Parker, 1998; Foster et al., 1998; Gagnon et al., 2011; Gonder-Frederick et al., 1987; Manning et al., 1992; Meikle et al., 2004; Owen et al., 2013; Owens & Benton, 1994; Parsons & Gold, 1992; Peters et al., 2020; Scholey et al., 2009; Zanchi et al., 2018	Elucidate physiological mechanisms of CGS	Performance negatively related to increase in glucose turnover	B	
		Increase in glucose turnover in cognitive performance condition		
Benton et al., 1994; Gagnon et al., 2011; Gonder-Frederick et al., 1987; Manning et al., 1992; Meikle et al., 2004; Owen et al., 2013; Parsons & Gold, 1992; Peters et al., 2020	Probe potential clinical implications of CGS	Introspectively assessed CGS is associated with: HbA1c diabetes-related distress	C	model of the vicious cycle of CGS and metabolic inflexibility [1,2,3] emotional intelligence [1,2,3] interoceptive ability [1,2,3] introspectively/experimentally measured CGS [1,2,3] cognitive-behavioral interventions [3] emergence and maintenance of pathological eating behaviors [3]

Note. The columns, arranged from left to right, represent the following: literature on which the primary empirical objectives of this thesis are based; main findings corresponding to the main objectives; own study that contributed the corresponding main finding; implications and directions for further research derived from the combination of all former columns. Superscript digits: under current investigation[1], planned investigation[2], future direction[3].

3.2 Discussion of the Key Findings

Our contribution to the main objectives is discussed below, based on the results of Studies A, B, and C. The following section acts as a complement to the introduction, mapping the findings to questions presented earlier. Some of these lead to new questions that motivated additional studies. Here the findings of Studies A, B, and C are combined with the relevant core statements derived from the literature presented in Section 1.4. The implications of these results for the research objectives of the dissertation, as well as potential follow-up studies will be discussed as well.

3.2.1 Study A

Out of the three studies, Study A arguably contributed the most to my goal of identifying factors that influence cognitive effects after glucose administration. Methodologically, it used a straightforward within-subject design, inspired by landmark study designs established in this area of research, to measure the individual sensitivity to glucose effects on cognitive performance.

The findings obtained in Study A, using a randomized repeated measures design and a sample of 71 individuals without a history of metabolic disease, were able to support the hypotheses, that the benefits of glucose supplementation on cognitive performance are moderated by the performance domain addressed, baseline performance and physical variables related to differences in glucose metabolism, namely BMI and sex.

Study A answered the objective of *the investigation of factors influencing the extent of cognitive effects elicited by glucose administration*. In line with several authors (e.g. Meikle et al., 2004;

Owen et al., 2013), this objective addressed inconsistencies in findings on the cognitive benefits of glucose. Such inconsistencies may be related to heterogeneity in participant and task characteristics (see Section 1.4). Accordingly, our main findings regarding the factors influencing the magnitude of CGS will be discussed in two clusters. The first cluster reflects factors related to *task properties*, while the second cluster represents factors related to *characteristics of the person* performing the tasks. For the first cluster, the aforementioned effects were strongest for the two tasks that predominantly rely on memory, especially the verbal recall task, but the other cognitive tasks also showed significant coherent effects. The second cluster of findings includes the role of baseline performance, BMI, and sex.

Task properties

Arguably the most controversial claim that emerges from the first cluster of main findings regards the effect of the *performance domain*. On a first glance, it is clearly in line with the literature outlined in Section 1.4, indicating that tasks with memory components seem to be especially susceptible to performance modulation by glucose supplementation (Benton et al., 1994; Benton & Parker, 1998; Foster et al., 1998; L. Gonder-Frederick et al., 1987; Manning et al., 1992; Meikle et al., 2004; Owen et al., 2013; Parsons & Gold, 1992).

The results are consistent with the general statement that glucose effects may be task-dependent. Nevertheless, it does not fit neatly with Benton's (1990) statement that glucose is beneficial in the performance of tasks requiring low mental capacity. It is challenging to operationalize required mental capacity identically across different tasks. Here, the novel application of spirometry, as explored in Study B, can provide a feasible solution. In one of our ongoing follow-up studies, we are investigating the extent to which respiratory gases are affected by the

difficulty of a cognitive task and how they differ between tasks from different domains. Therefore, mental capacity is measured relative to maximum glucose turnover under cognitive load. This may seem unorthodox at first, but could hopefully establish comparability via a common energetic currency across neurocognitive subsystems. Measuring global mental capacity by behavioral changes, such as the degree of deterioration in task-specific performance, is likely to introduce unwanted confounds such as domain specificity, task switching ability, and their interaction effects. As such, the objective recording of task- and difficulty-dependent changes in energy metabolism could contribute to answering the question raised by Benton over 30 years ago.

So far, however, we cannot claim to know exactly whether CGS is more likely to be observed in specific tasks, domains, or any other factors often confounded with tasks. Such factors include, for example, the *difficulty* and *demand* of the task, the *role of attention*, or the use of *metacognitive strategies*.

In fact, several authors (see Section 1.4) suggest that the effect of glucose on cognitive performance may be moderated by *difficulty* and *task demand*. This includes Benton, Owens, and Parker (1994), that linked blood glucose levels with improved performance on the Stroop task. They explicitly considered it to be the most cognitively demanding subtest of their experiment, possibly because it was contrasting the above discussed notion on low-capacity tasks being more susceptible to glucose, made by Benton four years earlier (1990). This statement aligns with Meikle, Riby, and Stollery's (2004) interpretation, who identified task demand as a factor contributing to the magnitude of glucose-induced memory enhancement. However, the authors specified that the influence of cognitive demand was only observable within a word recognition task and not in a tracking task (Meikle et al., 2004). In fact, the

authors did not explicitly define their concept of cognitive demand, but used it as a synonym for the number of words to be memorized (Meikle et al., 2004). In the context of our work, I use the term difficulty in the sense familiar from item response theory concepts, that is, the probability of answering an item correctly. The close relationship between the difficulty of a memory task and the amount of information to be remembered may make this discrepancy seem irrelevant from a practical point of view. Nevertheless, it makes a decisive difference whether we consider task difficulty to be a general moderator of glucose effects or whether low-demand tasks are generally inappropriate to detect neuroenhancement of any substance, e.g. due to ceiling effects. The above cited pioneers of glucose research investigated cognitive demand in the sense of quantity of information or even as an inherent task property, with the latter being in line with the work of Scholey, Harper, and Kennedy (2001). In this context, cognitive demand has been defined through subjective ratings and peripheral physiological arousal (Kennedy & Scholey, 2000). It is important to note that the relationship between the quantity of information and difficulty may not be the same for every task. For instance, this relationship would likely differ for a simple feature search compared to a mnemonic task. The results of the follow-up study of Study B, which examines the CGS and energy expenditure during the processing of tasks with increasing and decreasing difficulty, might provide further insights (discussed in Section 3.2.2). We see the implication to address the heterogenous concepts of cognitive demand and difficulty in the investigation of glucose effects on cognitive functioning. As mentioned above, we are probing to approach the investigation of task demand and mental capacity relative to an individual's cerebral energy demand, and difficulty in the sense of the probability of solving a task. This would allow for an easier comparison between different tasks, or even combined tasks. The indicated follow up-study could improve our understanding of

either an inherent susceptibility of a task to glucose supplementation that becomes apparent at a certain level of difficulty, or even a global difficulty factor that may make any task susceptible to glucose effects.

Alternatively, difficulty might be a necessary but not sufficient condition for certain tasks to reveal CGS. The latter would imply that CGS is indeed task-specific, with the caveat that susceptible tasks must also be sufficiently difficult. In other words, it needs to be clarified whether underlying main effects of task and difficulty, or their interaction, allow CGS effects to occur. This need arises from the potential confounding of task domain and difficulty (see above). The follow-up studies to my dissertation project address this challenge methodologically by using objective demands (glucose turnover) to establish comparability across tasks in terms of their difficulty (solution probability). The follow-up studies of Study B will be outlined further below, when implications of Study B are discussed in detail (Section 3.2.2).

Similar to the ambiguity of the possible role of difficulty, a parallel challenge is posed by the findings of several authors listed in Section 1.4 regarding the *role of attention* in the processing of tasks that tend to reveal CGS. In fact, a subset of the seminal papers listed, refer to the influence of glucose on attentional processes (Benton et al., 1994; Gagnon et al., 2011; Peters et al., 2020; Andrew B. Scholey et al., 2009). Therefore, considering the presented empirical literature alongside our results, the question arises whether the susceptibility of performance in memory tasks could also be explained by a modulation of attentional processes. Central to this is the idea that glucose may affect the learning or encoding phase of tasks involving a pronounced memory component. Using the classification by Petersen and Posner (2012), this

is conceivable in several ways. The classification includes three networks of the attention system, consisting of *alerting*, *orienting*, and *executive* networks.

Norepinephrine seems to play a crucial role within the *alerting* network, thought to be responsible for the enhancement of reaction speed by prior warning signals (Petersen & Posner, 2012). One of the main arguments for this is that manipulating norepinephrine release modulates the effects of warning signals on reaction time (Marrocco et al., 1998; Petersen & Posner, 2012). Therefore, we see possible clues to glucose effects in evidence linking both glucose and insulin to effects on norepinephrine. Marette and Bukowiecki (1989) found that norepinephrine can increase glucose transport and also potentiate the effects of insulin on glucose transport. Ebner and colleagues (1987) provided evidence that norepinephrine increases glucose oxidation by as much as the factor seven. In addition, Figlewicz et al. (1993) found that insulin can inhibit norepinephrine reuptake, potentially increasing its synaptic concentration. Nevertheless, this evidence has not been obtained in human neurons. We encourage further research into the possible role of norepinephrine and glucose on the neuronal substrates of the alerting network, as implicated by this combined evidence.

Petersen and Posner (2012) attribute two brain systems that focus attention on stimuli to the *orienting* network, based on findings, for example, by Corbetta and Shulman (2002). On the one hand, a dorsal system consisting of certain parietal and frontal regions, particularly the frontal eye fields, which are considered to play a direct role in the strategic control of attention. On the other hand, the second orienting subsystem is thought to play a role in interrupting the focus of attention on cued locations and shifting the focus to a new target location. The shift appears to involve the temporoparietal junction and the ventral frontal cortex. Interestingly, these regions overlap with brain areas that appear to be affected by glucose administration, as

reviewed by Peters and colleagues (2020). In addition, cholinergic systems, originating in the basal forebrain, appear to play a critical role in orienting. In this context, the influence of glucose on cholinergic systems may be of interest. Indeed, the findings of Stone et al. (1988) support the view that circulating glucose levels can modulate central cholinergic function. Earlier, Malaisse (1967) found that cholinergic agents could stimulate insulin secretion, while Sharp (1974) demonstrated that cholinergic agents could alter the pattern of insulin release. Lévesque (2006) contributed to this line of reasoning by showing that cholinergic blockade reduces insulin sensitivity and inhibits insulin-mediated glucose uptake and vasodilation. Lundquist (1982) added that cholinergic stimulation may promote insulin secretion through muscarinic receptors and that this effect may be influenced by nutritional status. Taken together, these studies suggest a complex interplay between glucose and cholinergic signaling, which is also discussed in greater detail in the literature cited above (Benton & Parker, 1998; Messier, 2004; Owens & Benton, 1994). These findings are relevant to the present dissertation. On the one hand, due to the relationship between glucose administration and insulin secretion as outlined in Section 1.3. On the other hand, they are relevant to our research, which includes manipulating the nutritional state (Study A), operationalizing glucose metabolism (Study B and Study C), and studying individuals with pathologically altered insulin and glucose balance (Study C). Combined, they suggest that modulation of attentional processes may play a role in the emergence of CGS effects and warrants further exploration of the biochemical and neural basis of glucose effects on cognitive function, including attention.

Petersen and Posner (2012) also argued for two separate networks in terms of the neural basis of *executive* control. A frontoparietal network and a cingulo-opercular network, which act relatively independently to achieve top-down control. The former, the frontoparietal system, is

thought to be involved in task switching and initiation, as well as transient within-trial adjustments. The second subnetwork, the cingulo-opercular control system, is involved in maintaining attention during task performance. Top-down control is particularly interesting in the context of the presented work. This is because it offers scope for confounding the putative effects of glucose on memory and attention, even at a conscious, motivational level – a circumstance with potential relevance to the IGlu questionnaire discussed later. It is conceivable that attention is influenced by nutritional status. For example, if a person is particularly dependent on finding sources of glucose, as would be the case with a poor metabolic switcher, it would make sense to adjust attentional control to detect more food cues. In other words, a top-down redirection of attention towards food cues and away from non-food cues would be adaptive. This simple assumption also fits a generalized view of signal detection theory in terms of an increasing response bias, in this case toward greater sensitivity to potential food cues at the expense of attentional focus (Peterson et al., 1954). In fact, hunger modulates attention, particularly in relation to food stimuli (Mogg et al., 1998; Sänger, 2019).

Historically, a motivational and attentional shift in favor of food-related cues at the expense of other domains (e.g., social interaction) as a result of prolonged fasting was described as early as 1945 in participants of the infamous Minnesota Starvation Experiment (Kalm & Semba, 2005). However, this argument again highlights a methodological limitation in much of the glucose research literature. Namely, the possible confounding of potential psychological effects of glucose supplementation with the effects of satisfying hunger in a fasting control condition. Conversely, in the context of our findings, evidence for a possible mediation of CGS effects in memory tasks via attentional modulation should be taken with caution. More specifically, the previously postulated direct effects of glucose on attention and its possible role in the learning

phase of memory tasks may be at odds with our findings in Study A. This is because the word list learning phase occurred immediately after glucose consumption, whereas blood glucose levels are likely to peak approximately 15 minutes after glucose administration (Bryant et al., 2014). Therefore, either small increases in blood glucose levels are sufficient to promote the learning phase - possibly by improving attention - or glucose is particularly facilitative to recall. In the latter case, a mediation of memory effects via attention seems less straightforward. If enhancement of recall is indeed the primary driver, the argument of top-down modulated control of attentional processes (*executive*) would be more appropriate than the previously mentioned alternatives (*alerting*, *orienting*).

One of our lines of research, also an offshoot of the CGS research presented here, addresses some of the issues and limitations that arise. One pilot study investigated the visual processing of food cues of different caloric density as a function of individual CGS, extending Potthoff and Schienle's research (2020). Gaze behavior was recorded, using eye tracking technology (EyeLink1000) during the presentation of stimulus pairs consisting of high-caloric (HC), low-caloric (LC), and non-food (NF) items in three combinations (HC-LC; HC-NF; LC-NF). CGS was assessed with the updated version of the IGlu questionnaire, familiar from Study C. Hunger and appetite were also assessed with the intention of distinguishing their effects from CGS. The complete analysis of the eye-tracking data is ongoing; however, preliminary results suggest high CGS manifests itself in gaze behavior, e.g., a pronounced processing of foods high in carbohydrates (i.e., potential sources of glucose). This supports the idea of control visual attentional as a possible underlying mechanism in the short-term compensatory strategy to avoid an imminent decline in performance. This pilot study, for the first time, addresses the confounding of hunger and CGS in the context of attentional gaze. Based on the results, the

exact design of future work investigating attention in terms of Peterson and Posner's classification can be considered.

Moving away from the possible mediation of CGS effects via attention, we now turn to the previously announced discussion of a similar possible role of *metacognitive strategies*. This hypothesis is based on two main arguments.

First, the applicability of metacognitive strategies varies across tasks. For example, metacognitive strategies have been shown to particularly impact memory tasks, especially in older people (Carretti et al., 2011; Drigas et al., 2022) who, perhaps not coincidentally, are also susceptible to CGS effects (see Section 1.3 - 1.4). In addition, memory tasks are highly prone to being influenced by semantic associations (Howard et al., 2007; Poirier & Saint-Aubin, 1995; Tse, 2009) and cognitive strategies such as chunking (G. A. Miller, 1956). From a physiological perspective, in-depth study of these notions may also seem interesting, since the glucoregulatory system interacts with the endocannabinoid system (Di Marzo et al., 2009), which in turn has been linked to associative thinking (Ioannidou et al., 2021).

Second, the use of metacognitive strategies depends on various state variables, including hunger. For example, Swieten (2021) showed that hunger increases reliance on primitive reinforcement learning rather than planned action. Again, this points to the previously discussed question on the exact relationship between hunger and CGS.

In a similar vein, the flexible use of strategies can be considered to be a metacognitive skill alongside or interacting with task difficulty. For example, the ability to switch between cognitive strategies, has been demonstrated to be a relevant factor in explaining interindividual cognitive performance outcomes (Barulli et al., 2023). Sünram-Lea and colleagues (2002) found that glucose ingestion prior to a memory task can improve retrieval, especially when a

secondary task is present (see Section 1.4). Examining the effects of glucose on cognitive flexibility and strategy use is promising enough for it to be examined in consecutive studies. They could include the paradigm used by Barulli and colleagues (2023) in conjunction with the multifaceted examination of CGS as developed by Studies A, B, and C.

In addition to possible effects of attention or metacognitive strategy use, the *role of dosage* plays an important role for the second cluster of main findings from Study A. These will conclude the discussion on this part. In a strict sense, the role of dosage could either be dependent or relatively independent on the subject's characteristics. This is due to two reasonable positions, emerging from the presented evidence.

The first position is that general effects of glucose on certain tasks are elicited above a certain dose, in susceptible persons. From this position, if a person has a sensitivity to a substance (glucose), a certain dosage will cause specific effects. A person without this sensitivity will not experience such effects, regardless of the dosage. In this case, Study A provides evidence that a dosage of 75 g of glucose was sufficient to produce effects in a significant number of sensitive participants.

The second position is that there could be interindividual differences at what dosage CGS effects are observed. In an extreme case, this could imply equal potential for CGS effects across every person, if glucose dosage were tailored to each person. In this case, the methodological limitations of glucose studies using a fixed dosage would result in pseudo-variance in CGS between individuals. Research by Parsons and Gold (1992) suggests that glucose dosage may be an important moderator of its effects on performance on the Wechsler Logical Memory Test. They found evidence in their data for an inverted u-shaped distribution of the dose-response relationship between glucose and performance improvement. Interestingly, the dosage used in

Study A (75 g) exceeded the largest one used by Parsons and Gold (1992) by 25 g and should have been, according to their proposed distribution of the dose-response relationship, rather ineffective. Given that dosage, subject characteristics, sample size, and tasks have all differed between the above-mentioned study by Parsons and Gold (1992), we see a need for further research. Addressing this need, we planned a subsequent study on the influence of dosage effects on CGS. Participants will receive five glucose dosages, accumulating to a total of 75g of glucose. Each dosage will be administered, blood glucose concentration will be measured, and cognitive performance will be assessed, before the next dose is administered. This method allows us to determine the dose (and blood glucose concentration) at which CGS effects become detectable. By measuring respiratory gases in parallel, as in Study B, we can then also examine the change in actual glucose turnover.

On the one hand, we consider it likely that there are interindividual differences in the dose-response relationship between glucose and cognitive performance. This would be consistent with the overall evidence presented above for interindividual differences in glucose regulation (Section 1.3) and glucose effects on cognitive performance (Section 1.4), particularly in light of the hypothesized role of metabolic switching. On the other hand, we also believe that the moderating role of dose is relatively limited. Based on the evidence presented, we hypothesize that a change in performance should generally be observed if the ingested dose is high enough to compensate for a performance deficit in the fasting state and/or to interrupt the fasting state.

The investigation of dose-response relationships is also relevant from a methodological point of view. For example, an ideal glucose dose, that produces cognitive effects in appropriately sensitive individuals, could both facilitate future research and be used to compensate for short-

term performance deficits, while minimizing the disadvantages of excessive glucose (and thus energy) intake.

Characteristics of the person

For the second cluster of the main results of Study A – which concern the characteristics of the person displaying high CGS – *baseline performance*, *BMI*, and *biological sex* are of particular importance.

Baseline performance (performance in the absence of glucose supplementation) was strongly correlated with CGS. In other words, for all tasks, the data showed that the worse the performance of participants without an external glucose supply, the more they benefited when glucose was supplied. This result is strikingly similar in both direction and magnitude to that demonstrated by Kaplan and colleagues (2000) in a sample of elderly people, in other words, I was able to replicate this effect in our sample of young participants.

There could be several reasons for this effect. On the one hand, it could be argued that people who happen to show a bad performance on one day will perform better the next time (regression toward the mean). In this case, we would observe an effect whereby these outlier scores approach their true scores over repeated measures. If this were the case, we would see in Figure 1 that the resulting scatter is evenly distributed around the y-axis intercept of 0. This is because, in the absence of a substance effect, there would be no reason for a shift toward increased glucose-induced performance. Nevertheless, such a shift is particularly clear in the verbal recall in Figure 1 of Study A. In other words, if the effect was merely a matter of measurement error, it should not be correlated with any of the substance conditions, as measurement errors are by definition uncorrelated. Given that this is not the case, at the very least there is a bias towards

better performance in the glucose condition. Considering the randomized assignment of subjects to counterbalanced substance sequences, this is equivalent to a true effect of glucose, which is particularly strong in subjects with performance deficits in the baseline condition. Therefore, the discussion of a true effect of baseline performance on the glucose effect remains reasonable. As derived in Section 1, it is hypothesized that this is primarily due to differences in glucoregulation, more specifically metabolic switching. In addition, the effects of hunger, as previously discussed, cannot be ruled out. Overall, several implications can be drawn from the reviewed literature and this work.

Firstly, one could validate whether the observed effects are indeed due to differences in metabolism, in particular glucoregulation. The combination of the methodologies of studies A, B, and C is suitable for this purpose, as it is already underway in the further course of the research series on study B (to be discussed in Section 3.2.2).

Secondly, the exact role of metabolic switching in this context can be examined in various ways. Three different possible experimental design strategies appear appropriate here: reliable induction of endogenous ketone body production, supply of exogenous ketone bodies, and operationalization of the natural variance of ketone body production.

Consequently, the first two strategies involve manipulation of the factor that might mediate the effect of metabolic switching on CGS. As previously discussed, the standard baseline for glucose effects is usually obtained after an overnight fast. This risks confounding the induction of impairment by fasting and the true glucose effects on cognitive performance. However, I believe that this effect can be exploited. Landau and colleagues (1996) showed that after an overnight fast, gluconeogenesis accounts for approximately 50% of energy supply. This fits well with the presented data and the hypothesis about the role of metabolic switching in the

development of its variance. Even the simple visualization of Figure 1 of Study A shows a split in the middle of the baseline ranks, with the largest effects in the memory demanding tasks. Landau and colleagues showed that after 42 hours of fasting, the metabolic switch was almost complete in all healthy subjects. Applying this insight to future studies could allow to test whether the effects of CGS would be leveled out if prolonged fasting induced metabolic switching in all subjects. This approach is limited by the feasibility of a 42-hour fast and the increased confounding effects of hunger and CGS.

Alternatively, exogenous ketone bodies could be administered to bypass the endogenous adaptation of the metabolic switch. Similar to the research on glucose, the evidence on the effects of exogenous ketones on cognitive performance is mixed. Dong (2020) demonstrated that exogenous administration of ketones improved attentional accuracy in healthy adults, but not in three other tasks relying on memory. Evans and Egan (2018) found effects of ketone administration on attenuating the decline in executive function following strenuous exercise. Waldman (2020) reported no improvement in performance on a dual-stress challenge following exogenous ketone administration. These findings suggest that the effects of exogenous ketones on cognitive performance – similar to those of glucose – may be influenced by various factors, such as the type of cognitive task being performed.

The third strategy, the measurement of ketone bodies, has several potential advantages. It can be combined with our previous methods of Studies A, B and C, as well as the strategies for manipulating ketone bodies. It is therefore methodologically suitable both for testing a correlation between CGS and ketone body formation, and as a manipulation check when manipulating ketone body levels. The use of the method developed by Landau and colleagues (1996) for ketone body production via radioisotopes would also be interesting here.

Alternatively, ketone bodies can also be determined via the blood and urine. In each case, the balance of invasiveness, temporal resolution, and measurement accuracy should be considered and selected according to the circumstances of future study designs. The further development of spirometry for the direct measurement of ketone body metabolism, instead of the more indirect approximation via the by-products of glucose metabolism (Study B), also represents a potential prospect. Combined, this implies that it might be reasonable to extend the research in this thesis to include the administration and measurement of ketone bodies.

Overall, the relationship between *BMI* and glucose dependence of cognitive performance was significant only in male participants. This is consistent with research suggesting a link between higher bodyweight and cognitive decline in men (e.g. Elias et al., 2005) as well as sex differences in brain metabolism (Goyal et al., 2019; see also Section 1.3).

The potential role of BMI in the context of Study A and our overall research is multifaceted (Section 1.3, Study A, Study C). BMI is often used in studies instead of body weight, as the former considers body weight in relation to height. To complement the information provided, rather than create unnecessary redundancy, the duality of the role of BMI in the findings of my dissertation and our overall work is outlined below. First, BMI can serve as an indicator of long-term behavioral trends in exercise and dietary patterns, selected aspects of the endocrine system, and an individual's energy balance over a long period of time. Second, BMI can serve as a target for studies to modify some of the above aspects because it is highly correlated with body fat. Adipose tissue is an endocrine organ and affects hormone balance, so the above relationships are often transactional in nature (Kershaw and Flier 2004). This is consistent with the idea of a vicious cycle of CGS leading to short-term compensation of cognitive deficits by carbohydrate intake, long-term deterioration of glucoregulation, increasing BMI, changes in endocrine and

motivational parameters, and ultimately further increases in CGS. This idea will be revisited later in the discussion (Section 3.2.2). Overall, the interaction of gender and BMI on CGS is consistent with the literature. It should be noted, that the sub-sample of men was smaller and had a wider range of BMI. Therefore, despite results being consistent with the presented literature and the hypothesized role of metabolic switching, they warrant further investigation. This has already been achieved in part by a yet unpublished diet study (discussed in a more appropriate context in Section 3.2.2), in which BMI was reduced and the effects on CGS were investigated.

An important implication of this finding is that further research is needed. Specifically, a longitudinal study of CGS has already been planned, particularly in the clinical context of people with obesity. This will be done with the intention of investigating the role of a hypothetical vicious circle in which CGS plays a transactional role with BMI. Possible implications include the treatment of individuals with pathological alterations in eating behavior and the improvement of adherence to treatment after bariatric surgery.

In the light of our results from Study A, the relevance of biological sex must be evaluated in an additional direction that complements the literature described in Section 1.3. The interaction effect found for BMI and sex are of particular interest because of the role of sex hormones, particularly estrogens and androgens.

On the one hand, these hormones themselves have an influence at the neuronal level and on glucoregulation (Gillies & McArthur, 2010; Hammond et al., 2001; Lapauw et al., 2010; Tramunt et al., 2020). The sex differences in insulin sensitivity and glucoregulatory capacity mentioned in Section 1.3 may be due, at least in part, to the protective effects of endogenous estrogens (Tramunt et al., 2020). This protective effect may account for the interaction between

BMI and sex in Study A.

On the other hand, the ratio of estrogens to androgens in the human body also shifts with body composition. The enzyme aromatase, largely expressed in fat cells, converts androgens into estrogens (Lapauw et al., 2010). This can be so significant that a pathological deficiency of testosterone, the primary androgen in men, can be caused by obesity, as the excess estrogens exert a strong negative feedback on gonadotropin release (Fernandez et al., 2019). Therefore, the results are also indicative of the role of sex hormones in the effect of glucose on cognition. Consistent with the hypothesis on the role of metabolic switching, androgens and estrogens significantly influence ketone body production and energy balance. Synonymous with the transactional relationship between BMI and glucoregulation, an interplay between sex hormones and body composition has been established (Carrageta et al., 2019; Fernandez et al., 2019; Pasquali et al., 1991; Zouras et al., 2017). This suggests the utility of future investigations into the role of sex hormones in the context of CGS. In the long term, this has the potential to inform clinical assessment and treatment of gonadal hypofunction, age-related changes in cognitive ability, endocrine milieu, and body composition.

Taken together, the results of Study A contribute to a conceivable and coherent explanation reconciling the heterogeneous evidence from more than three decades of research on the cognitive effects of glucose supplementation in humans. This explanation involves the assumption that people differ in their ability to cope with performance deficits due to low or no external supply of glucose sources. Consistent with the majority of the literature presented, CGS effects were also shown to be particularly pronounced on tasks with a high proportion of memory components. It should be noted, however, that based on the overall evidence, it is not yet possible to say with certainty that the causes are fully understood.

Study A was also a success from a *methodological* perspective, as we were able to demonstrate that using the typical dose for medical glucose tolerance testing in a within-subject design reliably induced CGS effects across multiple tasks. Further refinements, especially of substance application, the inclusion of a sweet placebo, and refined dosing, are likely achievable.

3.2.2 Study B

Study B contributed in particular to two of the main empirical objectives of the present dissertation. First, the investigation of possible underlying physiological mechanisms of CGS. This was accomplished by demonstrating that the increase in glucose turnover, as measured by metabolized O_2 and exhaled CO_2, can be reliably attributed to the cognitive performance condition. The second objective was to investigate factors that influence the magnitude of cognitive effects induced by glucose administration. The corresponding main finding was that the better the performance of the subjects, the lower the increase in glucose turnover compared to baseline.

Methodologically, it contributed to the main objective of developing physiological approaches to the study of CGS, but also to the study of energy demand in relation to cognitive performance in general. In fact, the methodological aspect was the main focus of the publication of Study B and was discussed in detail in the article. This is why the main empirical findings are discussed here against the background of the overall aims of the dissertation.

The first major finding of Study B within this dissertation supports the idea that the examined task indeed produced measurable changes in glucose metabolism. Alongside several pivotal publications, described in more detail in Section 1.4 (Benton et al., 1994; Foster et al., 1998;

Gagnon et al., 2011; Owen et al., 2013; Owens & Benton, 1994; Peters et al., 2020; Zanchi et al., 2018), this strengthens the assumption of physiological mechanisms of action behind CGS.

The clarification of this matter is crucial for the direction of consecutive research and potential practical applications of CGS. As such, Study B was instrumental in the development of Study C. If it had not found a relationship between glucose metabolism and the performance of the potentially glucose-sensitive task identified in Study A, Study C would not have been conducted. Instead, I would have focused on self-suggestive beliefs about the effect of glucose and motivational aspects. This is also relevant from a future application perspective, such as reducing CGS and thereby establishing greater autonomy of acute food intake for psychological functioning. In another study to be published, I found that the level of CGS (assessed by both the IGlu questionnaire and experimentally, placebo-controlled) predicts weight loss before a diet. Impaired cognitive performance due to restricted food intake is an understandable obstacle to weight loss. Fortunately, the study was able to show that CGS is reduced by the diet. This further supports the hypothesis that improving glucoregulation, especially metabolic switching, is a key mechanism of CGS. In synergy with the investigation of CGS and visual processing of food cues discussed in the context of Study A, an enormous potential for applications emerges. An empirical examination of a vicious cycle of short-term compensation of cognitive deficits by carbohydrate intake, long-term deterioration of glucoregulation, weight gain, and exacerbation of CGS is now within reach.

The second main finding of Study B was that improved performance was negatively associated with increased glucose turnover. This is not only consistent with the hypothesized relationship to metabolic switching. It is also coherent with the idea that performance enhancement by glucose uptake generally compensates for fasting-induced performance deficits, as observed by

Benton and Parker (1998). Furthermore, it fits well with the glucoregulation-related response variability to glucose in terms of cognitive enhancement described by Owen and colleagues (2013). The second main finding also suggests that metabolic switching is likely to be the major component of metabolic flexibility accounting for CGS effects. If other aspects of metabolic flexibility, such as gluconeogenesis, played a more dominant role, the interindividual difference in the increase in CO_2 release would have looked different. This is because gluconeogenesis provides glucose (a higher energy demand would increase CO_2) while ketone body utilization results in smaller increases in CO_2 release (see Section 1.2). The fact that Study B has indeed succeeded in demonstrating the unconventional use of spirometry in the context of the psychological investigation of the relationship between peripherally measured energy expenditure and cognitive performance opens up new possibilities and questions. The most obvious of these questions in the context of this dissertation is probably the extent to which CGS, as measured experimentally in Study A, has an effect on glucose metabolism, as measured in Study B. To this end, the methods of Study A and B need to be combined in a meaningful way. This is currently part of an ongoing follow-up study of Study B.

As briefly mentioned in the discussion of the main results and their implications of Study A, a substantial follow-up study to Study B examines CGS and energy expenditure during the performance of tasks of increasing and decreasing difficulty. CGS will be measured using both the IGlu questionnaire and a more refined methodology derived from Study A. Two measurement sessions will be scheduled per subject, one after ingestion of glucose and one after ingestion of a sweetener with no effect on glucose metabolism (aspartame). The ascending and descending difficulty of the various tasks in the experiment allows for a variety of measurements. For example, we can test the relationship between glucose turnover and the

factors of task, difficulty, and introspective and behavioral CGS. By defining task difficulty as the probability of a correct response, we can test whether CGS effects are indeed task-specific or always occur above a certain level of difficulty. From a methodological point of view, this also allows us to further refine the procedure and to determine the reliability of the measurements within an individual. The results of the IGlu questionnaire, the behavioral CGS, and the physiological examination of glucose turnover also make it possible to test convergent validity. Summarizing, the described follow-up study corresponds to the fusion of the three constituting studies of this thesis. As such, it is one of the most immediately recognizable and potentially impactful implications, addressing the methodological limitations of each presented study through the strengths of the others.

3.2.3 Study C

In Study C, significant correlations were found between introspectively assessed CGS (IGlu-Questionnaire) and HbA1c and diabetes-related distress in an online questionnaire study with a sample of 354 adults with type 1 diabetes (283 women). HbA1c also correlated significantly with diabetes-related distress. Therefore, Study C addressed both empirical and methodological primary objectives.

Empirically, it contributed to the investigation of possible underlying physiological mechanisms behind the cognitive effects of glucose supplementation. It did so by including an established, valid indicator of glucoregulation (HbA1c) and thus works in conjunction with Studies A and B, as well as the literature in Sections 1.3 and 1.4.

Study C pioneered the exploration of the potential clinical relevance of self-reported CGS by using a sample of individuals with clinically proven impaired glucoregulation. Here, it provided

the key finding of the basic applicability of the CGS construct in individuals with pathologically impaired glucose homeostasis. This result is limited by the lack of data from experimentally assessed CGS. This is mainly due to ethical and methodological aspects. On the one hand, it is problematic to administer large doses of glucose to individuals with pathologically impaired glucose homeostasis, especially before adequate evidence is available to justify the appropriateness of such an approach. On the other hand, a blinded approach is not feasible here, as the corresponding population with type 1 diabetes must apply appropriate insulin doses after carbohydrate ingestion. In this context, the correlation between CGS and glucoregulation should be interpreted with caution. This is likely to be an indication of worsening CGS symptoms as a result of suboptimal medication or treatment adherence. An interpretation in terms of a possible vicious circle of CGS, compensation and further deterioration of glucoregulation would be somewhat premature, as endogenous glucoregulation is replaced by exogenous insulin administration. Thus, one implication is that future studies should directly examine glucoregulation in relation to CGS in people without diabetes, rather than indirectly using BMI as a rough indicator, as we did in Study A. Recruitment of people with type 2 diabetes who are insulin resistant and not insulin deficient should also be considered.

Regarding the main methodological objectives, Study C contributed to the development of introspective approaches to the accessibility of one's dependence on external sources of glucose for cognitive performance. The IGlu questionnaire used for this purpose is a prototype, the main features of which have already been used in the dietary study mentioned above, which is yet to be published. From a practical point of view, this questionnaire has the advantage that it can be administered quickly, is cost- and time-efficient, and can even be completed online. This allows the recruitment of much larger samples compared to the methods of studies A and B. The ethical

challenges are also marginal, which in principle also allows testing of people who cannot be administered large amounts of glucose, for example, for the reasons discussed above.

According to another unpublished follow-up study, one of the main limiting factors of the questionnaire is the interoceptive ability of the person filling it out. This is reasonable, because in order to make valid statements in a measurement procedure based on introspection, knowledge of one's own bodily states must be available. In a similar vein, a significant positive correlation between emotional intelligence and IGlu scores was observed in the same follow-up study. Since the IGlu questionnaire includes items related to processing information in social and emotional contexts, the most likely explanation is analogous to the previous point. A certain level of emotional intelligence may be a prerequisite for gaining knowledge about one's own processing of social and emotional information under certain circumstances, in this case, when abstaining from glucose sources. Introspectively, only information that the person has access to can be assessed directly. Ultimately, the data from the follow-up studies will provide an opportunity to further examine both the psychometric properties and possible measurement error invariance across different populations.

Study C, in combination with its follow-up studies, thus led to the methodological insight that CGS should be measured by different methods whenever possible if an accurate global assessment is desired. The dietary study mentioned above also found that although experimental and interoceptively measured CGS were similarly altered by diet, there was only a limited cross-sectional relationship between them. This allows for several interpretations. One possible explanation for this is the aforementioned limitation of interoception. Alternatively, CGS may represent two potentially complementary constructs that together would be particularly predictive of the vicious cycle model mentioned above.

The second interpretation would be consistent insofar as internalized beliefs about the necessity of dietary carbohydrates for one's own cognitive functioning could also influence behavior. In combination with the actually demonstrable physiological dependence on sources of glucose, it would be conceivable that a more precise prediction of the eating behavior becomes feasible. With the ongoing and planned follow-up studies described so far, it should be possible to elucidate these questions. In the long run, the treatment of pathological eating behavior could be addressed on several levels, including the promotion of glucoregulation, cognitive-behavioral interventions, and psychoeducation. Corresponding collaborative projects with clinics in Germany and abroad are therefore preparing to test the IGlu questionnaire in patients with obesity as well as in senior citizens. In combination with the literature on age and body weight related differences in glucoregulation (Sections 1.3 and 1.4). This would allow to translate the results of the presented research into clinical practice for vulnerable key populations.

3.3 Brief Outlook and Concluding Remarks

In summary, the present thesis adds a novel theoretical construct and several new empirical methods to the field of psychophysiological research on effects of glucose intake. Building on and refining approaches from decades of research by pioneers of glucose research, the present work contributes to the understanding of the determinants that influence the effects of glucose ingestion on cognitive performance. Compared to prior research, this work was grounded in a shift of perspective, viewing differences in behavioral outcomes of glucose intake as the result of interindividual differences. Based on the current state of empirical research, including my own contribution to it, I tentatively assume these differences to be based on physiological variations in glucoregulation, in particular metabolic switching.

Addressing both empirical and methodological challenges, my work facilitated a connection between the biomedical study of metabolic flexibility and psychological research on the neurocognitive level. In doing so, it strengthens the basic understanding of the intricate relationship between mind and body and underscore the potential of psychological research in the prevention and remediation of a major group of diseases.

Without doubt, empirical findings are not beyond the inevitable limitations that arise when complex organic systems interact with their infinitely complex environment. A number of these limitation have been addressed in some detail during the discussion of key findings. Thanks to the broad thematic and methodological positioning of its constituent studies, my dissertation as a whole was able to partially compensate for some limitations of its elements. Nevertheless, it leaves an enormous potential for optimization in future projects.

It is perhaps the wealth of questions raised by the research that is more meaningful than the limited answers it provided. The roles of tasks and participant characteristics have been addressed in the studies presented here, as well as in follow-up projects. In terms of task properties, the roles of performance domain, difficulty, task demand, attentional processes and metacognitive strategies are currently being examined. Further exploration of sex hormones, weight changes, hunger, glucose dosing, metabolic switching, ketones, energy demand, food cue processing, physical activity, age, sleep and circadian rhythm, sun light exposure and genes are further important waypoints on the road towards fully understanding the role of participant properties.

In a more long-term perspective, our future theoretical model will hopefully provide a way to fully understand the vicious cycle of CGS and metabolic inflexibility that likely plays a major role in the development and maintenance of metabolic diseases and their complications. I expect that this future research will show that such a cycle can be intervened, e.g. via specific weight interventions, interoceptive skills training, cognitive-behavioral interventions, and hormone replacement therapy. In this way, this line of research could provide solutions for some of the greatest health challenges in modern society.

References

Aitken, M. L., Franklin, J. L., Pierson, D. J., & Schoene, R. B. (1986). Influence of body size and gender on control of ventilation. *Journal of Applied Physiology*, *60*(6), 1894–1899. https://doi.org/10.1152/jappl.1986.60.6.1894

Alberti, K. G. M. M., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabetic Medicine*, *15*(7), 539–553. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S

Alzubaidi, H., Sulieman, H., Mc Namara, K., Samorinha, C., & Browning, C. (2022). The relationship between diabetes distress, medication taking, glycaemic control and self-management. *International Journal of Clinical Pharmacy*, *44*(1), 127–137. https://doi.org/10.1007/S11096-021-01322-2

Anton, S. D., Moehl, K., Donahoo, W. T., Marosi, K., Lee, S. A., Mainous, A. G. 3rd, Leeuwenburgh, C., & Mattson, M. P. (2018). Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. *Obesity (Silver Spring, Md.)*, *26*(2), 254–268. https://doi.org/10.1002/oby.22065

Aronoff, S. L., Berkowitz, K., Shreiner, B., & Want, L. (2004). Glucose Metabolism and Regulation: Beyond Insulin and Glucagon. *Diabetes Spectrum*, *17*(3). http://spectrum.diabetesjournals.org/content/17/3/183

Association, A. D. (2011). Standards of Medical Care in Diabetes—2011. *Diabetes Care*, *34*(Supplement_1), S11–S61. https://doi.org/10.2337/DC11-S011

Avignon, A., & Monnier, L. (2001). [Insulin sensitivity and stress]. *Diabetes & metabolism*, *27*(2 Pt 2), 233–238.

Bădescu, S. V., Tătaru, C., Kobylinska, L., Georgescu, E. L., Zahiu, D. M., Zăgrean, A. M., & Zăgrean, L. (2016). The association between Diabetes mellitus and Depression. In *Journal of medicine and life* (Vol. 9, Issue 2, pp. 120–125). Carol Davila - University Press. /pmc/articles/PMC4863499/

Balasse, E. O., & Neef, M. A. (1975). Inhibition of ketogenesis by ketone bodies in fasting humans. *Metabolism: Clinical and Experimental*, *24*(9), 999–1007. https://doi.org/10.1016/0026-0495(75)90092-x

Balkau, B., Mhamdi, L., Oppert, J.-M., Nolan, J., Golay, A., Porcellati, F., Laakso, M., & Ferrannini, E. (2008). Physical activity and insulin sensitivity: the RISC study. *Diabetes*, *57*(10), 2613–2618. https://doi.org/10.2337/db07-1605

Bari, D. S., Aldosky, H. Y. Y., Tronstad, C., Kalvøy, H., & Martinsen, G. (2018). Electrodermal responses to discrete stimuli measured by skin conductance, skin potential, and skin susceptance. *Skin Research and Technology*, *24*(1), 108–116. https://doi.org/10.1111/srt.12397

Barulli, D., Habeck, C., & Stern, Y. (2023). Assessing Flexibility of Solution Strategy: Strategy Shifting as a Measure of Cognitive Reserve. *The Journals of Gerontology: Series B*, *78*(6), 977–986. https://doi.org/10.1093/geronb/gbad024

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. In *Journal of the Royal Statistical Society. Series B (Methodological)* (Vol. 57, pp. 289–300). WileyRoyal Statistical Society. https://doi.org/10.2307/2346101

Benton, D. (1990). The impact of increasing blood glucose on psychological functioning. *Biological Psychology*, *30*(1), 13–19. https://doi.org/10.1016/0301-0511(90)90087-D

Benton, D., Owens, D. S., & Parker, P. Y. (1994). Blood glucose influences memory and attention in young adults. *Neuropsychologia*, *32*(5), 595–607. https://doi.org/10.1016/0028-3932(94)90147-3

Benton, D., & Parker, P. Y. (1998). Breakfast, blood glucose, and cognition. *American Journal of Clinical Nutrition*, *67*(4), 8. https://doi.org/10.1093/ajcn/67.4.772S

Berg, J. M., Tymoczko, J. L., & Stryer, L. (2013). *Stryer Biochemie*. Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-8274-2989-6

Boiten, F. A. (1998). The effects of emotional behaviour on components of the respiratory cycle. *Biological Psychology*, *49*(1–2), 29–51. https://doi.org/10.1016/S0301-0511(98)00025-8

Borghouts, L. B., & Keizer, H. A. (2000). Exercise and insulin sensitivity: a review. *International Journal of Sports Medicine*, *21*(1), 1–12. https://doi.org/10.1055/s-2000-8847

Bourtchuladze, R., Frenguelli, B., Blendy, J., Cioffi, D., Schutz, G., & Silva, A. J. (1994). Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell*, *79*(1), 59–68. https://doi.org/10.1016/0092-8674(94)90400-6

Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*, *414*(6865), 813–820. https://doi.org/10.1038/414813a

Bryant, C. E., Wasse, L. K., Astbury, N., Nandra, G., & McLaughlin, J. T. (2014). Non-nutritive sweeteners: no class effect on the glycaemic or appetite responses to ingested glucose. *European Journal of Clinical Nutrition*, *68*(5), 629–631. https://doi.org/10.1038/ejcn.2014.19

Butterworth, P. J., Warren, F. J., & Ellis, P. R. (2011). Human α-amylase and starch digestion: An interesting marriage. *Starch - Stärke*, *63*(7), 395–405. https://doi.org/10.1002/star.201000150

Carrageta, D. F., Oliveira, P. F., Alves, M. G., & Monteiro, M. P. (2019). Obesity and male hypogonadism: Tales of a vicious cycle. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity*, *20*(8), 1148–1158. https://doi.org/10.1111/obr.12863

Carretti, B., Borella, E., Zavagnin, M., & De Beni, R. (2011). Impact of metacognition and motivation on the efficacy of strategic memory training in older adults: analysis of specific, transfer and maintenance effects. *Archives of Gerontology and Geriatrics*, *52*(3), e192-7. https://doi.org/10.1016/j.archger.2010.11.004

Cheng, C. M., Kelley, B., Wang, J., Strauss, D., Eagles, D. A., & Bondy, C. A. (2003). A ketogenic diet increases brain insulin-like growth factor receptor and glucose transporter gene expression. *Endocrinology*, *144*(6), 2676–2682. https://doi.org/10.1210/en.2002-0057

Christopoulos, G. I., Uy, M. A., & Yap, W. J. (2019). The Body and the Brain: Measuring Skin Conductance Responses to Understand the Emotional Experience. *Organizational Research Methods*, *22*(1), 394–420. https://doi.org/10.1177/1094428116681073

Coomans, C. P., van den Berg, S. A. A., Houben, T., van Klinken, J.-B., van den Berg, R., Pronk, A. C. M., Havekes, L. M., Romijn, J. A., van Dijk, K. W., Biermasz, N. R., & Meijer, J. H. (2013). Detrimental effects of constant light exposure and high-fat diet on circadian energy metabolism and insulin sensitivity. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology*, *27*(4), 1721–1732. https://doi.org/10.1096/fj.12-210898

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews. Neuroscience*, *3*(3), 201–215. https://doi.org/10.1038/nrn755

Cordain, L., Eaton, S. B., Sebastian, A., Mann, N., Lindeberg, S., Watkins, B. a, & Keefe, J. H. O. (2005). *Origins and evolution of the Western diet: health implications for the 21st century*. https://doi.org/10.1093/ajcn.81.2.341

Corsi, P. M. (1973). Human memory and the medial temporal region of the brain. In *Dissertatopm Abstracts International* (Vol. 34, p. 891).

Cox, D. J., Gonder-Frederick, L. A., Schroeder, D. B., Cryer, P. E., & Clarke, W. L. (1993). Disruptive effects of acute hypoglycemia on speed of cognitive and motor performance. *Diabetes Care*, *16*(10), 1391–1392. https://doi.org/10.2337/diacare.16.10.1391

Cox, D. J., Kovatchev, B. P., Gonder-Frederick, L. A., Summers, K. H., McCall, A., Grimm, K. J., & Clarke, W. L. (2005). Relationships between hyperglycemia and cognitive performance among adults with type 1 and type 2 diabetes. *Diabetes Care*, *28*(1), 71–77. https://doi.org/10.2337/diacare.28.1.71

De Feo, P., Gallai, V., Mazzotta, G., Crispino, G., Torlone, E., Perriello, G., Ventura, M. M., Santeusanio, F., Brunetti, P., & Bolli, G. B. (1988). Modest decrements in plasma glucose concentration cause early impairment in cognitive function and later activation of glucose counterregulation in the absence of hypoglycemic symptoms in normal man. *Journal of Clinical Investigation*, *82*(2), 436–444. https://doi.org/10.1172/JCI113616

Di Marzo, V., Verrijken, A., Hakkarainen, A., Petrosino, S., Mertens, I., Lundbom, N., Piscitelli, F., Westerbacka, J., Soro-Paavonen, A., Matias, I., Van Gaal, L., & Taskinen, M.-R. (2009). Role of insulin as a negative regulator of plasma endocannabinoid levels in obese and nonobese subjects. *European Journal of Endocrinology*, *161*(5), 715–722. https://doi.org/10.1530/EJE-09-0643

Dong Y, H., Patrick, G. S., Sandro, P., William, D. W., & Amanda C, G. (2020). Neurocognitive Effects of Exogenously Administered Beta-Hydroxybutyrate In Adults: A Proof of Concept Study. In *Neurology and Neurobiology*. http://dx.doi.org/10.31487/j.NNB.2020.03.13

Drigas, A., Mitsea, E., & Skianis, C. (2022). Metamemory: Metacognitive Strategies for Improved Memory Operations and the Role of VR and Mobiles. *Behavioral Sciences (Basel, Switzerland)*, *12*(11). https://doi.org/10.3390/bs12110450

Eaton, S. B., & Eaton III, S. B. (2000). Paleolithic vs. modern diets - selected pathophysiological implications. *European Journal of Nutrition*, *39*(2), 67–70. https://doi.org/10.1007/s003940070032

Ebner, S., Burnol, A. F., Ferre, P., de Saintaurin, M. A., & Girard, J. (1987). Effects of insulin and norepinephrine on glucose transport and metabolism in rat brown adipocytes. Potentiation by insulin of norepinephrine-induced glucose oxidation. *European Journal of Biochemistry*, *170*(1–2), 469–474. https://doi.org/10.1111/j.1432-1033.1987.tb13723.x

Ekoé, J.-M. (2019). Diagnosis and Classification of Diabetes Mellitus. In I. Huhtaniemi & L. Martini (Eds.), *Encyclopedia of Endocrine Diseases (Second Edition)* (Second Edi, pp. 105–109). Academic Press. https://doi.org/10.1016/B978-0-12-801238-3.65822-1

Elias, M. F., Elias, P. K., Sullivan, L. M., Wolf, P. A., & D'Agostino, R. B. (2005). Obesity, diabetes and cognitive deficit: The Framingham Heart Study. *Neurobiology of Aging*, *26*(1), 11–16. https://doi.org/10.1016/j.neurobiolaging.2005.08.019

Estrada, N. M., & Isokawa, M. (2009). Metabolic Demand Stimulates CREB Signaling in the Limbic Cortex: Implication for the Induction of Hippocampal Synaptic Plasticity by Intrinsic Stimulus for Survival. *Frontiers in Systems Neuroscience*, *3*, 5. https://doi.org/10.3389/neuro.06.005.2009

Evans, M., & Egan, B. (2018). Intermittent Running and Cognitive Performance after Ketone Ester Ingestion. *Medicine & Science in Sports & Exercise*, *50*(11), 2330–2338. https://doi.org/10.1249/MSS.0000000000001700

Fernandez, C. J., Chacko, E. C., & Pappachan, J. M. (2019). Male Obesity-related Secondary Hypogonadism – Pathophysiology, Clinical Implications and Management. *European Endocrinology*, *15*(2), 83. https://doi.org/10.17925/EE.2019.15.2.83

Figlewicz, D. P., Bentson, K., & Ocrant, I. (1993). The effect of insulin on norepinephrine uptake by PC12 cells. *Brain Research Bulletin*, *32*(4), 425–431. https://doi.org/10.1016/0361-9230(93)90210-3

Fillmore, M. T., Rush, C. R., & Hays, L. (2006). Acute effects of cocaine in two models of inhibitory control: implications of non-linear dose effects. *Addiction*, *101*(9), 1323–1332. https://doi.org/10.1111/j.1360-0443.2006.01522.x

Foster, J., Lidder, P. G., & Sünram-Lea, S. (1998). Glucose and memory: Fractionation of enhancement effects? *Psychopharmacology*, *137*(3), 259–270. https://doi.org/10.1007/s002130050619

Frier, B. M. (2001). Hypoglycaemia and cognitive function in diabetes. *International Journal of Clinical Practice. Supplement*, *123*, 30–37. http://www.ncbi.nlm.nih.gov/pubmed/11594296

Gagnon, C., Greenwood, C. E., & Bherer, L. (2011). Glucose regulation is associated with attentional control performances in nondiabetic older adults. *Journal of Clinical and Experimental Neuropsychology*, *33*(9), 972–981. https://doi.org/10.1080/13803395.2011.589372

Gailliot, M. T., & Baumeister, R. F. (2007). The Physiology of Willpower: Linking Blood Glucose to Self-Control. *Personality and Social Psychology Review*, *11*(4), 303–327. https://doi.org/10.1177/1088868307303030

Geijselaers, S. L. C., Sep, S. J. S., Schram, M. T., van Boxtel, M. P. J., Henry, R. M. A., Verhey, F. R. J., Kroon, A. A., Schaper, N. C., Dagnelie, P. C., van der Kallen, C. J. H., Stehouwer, C. D. A., & Biessels, G. J. (2017). Insulin resistance and cognitive performance in type 2 diabetes — The Maastricht study. *Journal of Diabetes and Its Complications*, *31*(5), 824–830. https://doi.org/10.1016/j.jdiacomp.2017.01.020

Gerich, J. E. (1993). Control of glycaemia. *Baillière's Clinical Endocrinology and Metabolism*, *7*(3), 551–586. https://doi.org/10.1016/S0950-351X(05)80207-1

Gerich, J. E., Meyer, C., Woerle, H. J., & Stumvoll, M. (2001). Renal Gluconeogenesis: Its importance in human glucose homeostasis. *Diabetes Care*, *24*(2), 382–391. https://doi.org/10.2337/diacare.24.2.382

Gil-Lozano, M., Hunter, P. M., Behan, L.-A., Gladanac, B., Casper, R. F., & Brubaker, P. L. (2016). Short-term sleep deprivation with nocturnal light exposure alters time-dependent glucagon-like peptide-1 and insulin secretion in male volunteers. *American Journal of Physiology. Endocrinology and Metabolism*, *310*(1), E41-50. https://doi.org/10.1152/ajpendo.00298.2015

Gillies, G. E., & McArthur, S. (2010). Estrogen actions in the brain and the basis for differential action in men and women: a case for sex-specific medicines. *Pharmacological Reviews*, *62*(2), 155–198. https://doi.org/10.1124/pr.109.002071

Gold, P. E. (1986). Glucose modulation of memory storage processing. *Behavioral and Neural Biology*, *45*(3), 342–349. https://doi.org/10.1016/S0163-1047(86)80022-X

Gonder-Frederick, L. A., Cox, D. J., Bobbitt, S. A., & Pennebaker, J. W. (1989). Mood changes associated with blood glucose fluctuations in insulin-dependent diabetes mellitus. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *8*(1), 45–59. https://doi.org/10.1037//0278-6133.8.1.45

Gonder-Frederick, L., Hall, J. L., Vogt, J., Cox, D. J., Green, J., & Gold, P. E. (1987). Memory enhancement in elderly humans: Effects of glucose ingestion. *Physiology and Behavior*, *41*(5), 503–504. https://doi.org/10.1016/0031-9384(87)90087-4

González-Ortiz, M., & Martínez-Abundis, E. (2005). Impact of Sleep Deprivation on Insulin Secretion, Insulin Sensitivity, and Other Hormonal Regulations. *Metabolic Syndrome and Related Disorders*, *3*(1), 3–7. https://doi.org/10.1089/met.2005.3.3

Gonzalez, J. S., Tanenbaum, M. L., & Commissariat, P. V. (2016). Psychosocial Factors in Medication Adherence and Diabetes Self-Management: Implications for Research and Practice. *The American Psychologist*, *71*(7), 539. https://doi.org/10.1037/A0040388

Goyal, M. S., Blazey, T. M., Su, Y., Couture, L. E., Durbin, T. J., Bateman, R. J., Benzinger, T. L. S., Morris, J. C., Raichle, M. E., & Vlassenko, A. G. (2019). Persistent metabolic youth in the aging female brain. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(8), 3251–3255. https://doi.org/10.1073/pnas.1815917116

Grassmann, M., Vlemincx, E., von Leupoldt, A., Mittelstädt, J. M., & Van den Bergh, O. (2016). Respiratory changes in response to cognitive load: A systematic review. *Neural Plasticity*, *2016*. https://doi.org/10.1155/2016/8146809

Greco, A., Valenza, G., Lanata, A., Scilingo, E. P., & Citi, L. (2016). cvxEDA: A Convex Optimization Approach to Electrodermal Activity Processing. *IEEE Transactions on Biomedical Engineering*, *63*(4), 797–804. https://doi.org/10.1109/TBME.2015.2474131

Grigg, D. (1996). The Starchy Staples in World Food Consumption. *Annals of the Association of American Geographers*, *86*(3), 412–431. https://doi.org/10.1111/j.1467-8306.1996.tb01760.x

Griva, K., Myers, L. B., & Newman, S. (2007). Illness perceptions and self efficacy beliefs in adolescents and young adults with insulin dependent diabetes mellitus. *Psychology & Health*, *15*(6), 733–750. https://doi.org/10.1080/08870440008405578

Group, T. D. C. and C. T. R. (1993). The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *The New England Journal of Medicine*, *329*(14), 977–986. https://doi.org/10.1056/NEJM199309303291401

Guénette, L., Breton, M. C., Guillaumie, L., Lauzier, S., Grégoire, J. P., & Moisan, J. (2016). Psychosocial factors associated with adherence to non-insulin antidiabetes treatments. *Journal of Diabetes and Its Complications*, *30*(2), 335–342. https://doi.org/10.1016/J.JDIACOMP.2015.10.016

Guerrero Fernández de Alba, I., Gimeno-Miguel, A., Poblador-Plou, B., Gimeno-Feliu, L. A., Ioakeim-Skoufa, I., Rojo-Martínez, G., Forjaz, M. J., & Prados-Torres, A. (2020). Association between mental health comorbidity and health outcomes in type 2 diabetes mellitus patients. *Scientific Reports*, *10*(1). https://doi.org/10.1038/S41598-020-76546-9

Hagger, V., Hendrieckx, C., Cameron, F., Pouwer, F., Skinner, T. C., & Speight, J. (2018). Diabetes distress is more strongly associated with HbA1c than depressive symptoms in adolescents with type 1 diabetes: Results from Diabetes MILES Youth—Australia. *Pediatric Diabetes*, *19*(4), 840–847. https://doi.org/10.1111/PEDI.12641

Hammond, J., Le, Q., Goodyer, C., Gelfand, M., Trifiro, M., & LeBlanc, A. (2001). Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons. *Journal of Neurochemistry*, *77*(5), 1319–1326. https://doi.org/10.1046/j.1471-4159.2001.00345.x

Hanson, R. W. (1965). Interrelationship of ketone body metabolism and glucose utilization by adipose tissue in vitro. *Archives of Biochemistry and Biophysics*, *109*(1), 98–103. https://doi.org/10.1016/0003-9861(65)90292-4

Hargrave, S. L., Jones, S., & Davidson, T. L. (2016). The Outward Spiral: A vicious cycle model of obesity and cognitive dysfunction. *Current Opinion in Behavioral Sciences*, *9*, 40–46. https://doi.org/10.1016/j.cobeha.2015.12.001

Hart, L. M., Fritsche, A., Rietveld, I., Dekker, J. M., Nijpels, G., Machicao, F., Stumvoll, M., van Duijn, C. M., Häring, H. U., Heine, R. J., Maassen, J. A., & van Haeften, T. W. (2004). Genetic Factors and Insulin Secretion: Gene Variants in the IGF Genes. *Diabetes*, *53*(suppl_1), S26–S30. https://doi.org/10.2337/diabetes.53.2007.S26

Hawkins, M. A. W., Gunstad, J., Calvo, D., & Spitznagel, M. B. (2016). Higher Fasting Glucose Is Associated With Poorer Cognition Among Healthy Young Adults. *Health Psychology*, *35*(2), 199–202. https://doi.org/10.1037/HEA0000248

Hawkins, M. A. W., Keirns, N. G., & Helms, Z. (2018). Carbohydrates and cognitive function. *Current Opinion in Clinical Nutrition and Metabolic Care*, *21*(4), 302–307. https://doi.org/10.1097/MCO.0000000000000471

Helmstaedter, C., Lendt, M., & Lux, S. (2001). VLMT - Verbaler Lern-und Merkfähigkeitstest. In *Manual*.

Heni, M., Ketterer, C., Hart, L. M. 't, Ranta, F., van Haeften, T. W., Eekhoff, E. M., Dekker, J. M., Boomsma, D. I., Nijpels, G., Kramer, M. H., Diamant, M., Simonis-Bik, A. M., Heine, R. J., de Geus, E. J., Schäfer, S. A., Machicao, F., Ullrich, S., Thamer, C., Stefan, N., … Fritsche, A. (2010). The Impact of Genetic Variation in the G6PC2 Gene on Insulin Secretion Depends on Glycemia. *The Journal of Clinical Endocrinology & Metabolism*, *95*(12), E479–E484. https://doi.org/10.1210/jc.2010-0860

Hollenbeck, C., & Reaven, G. M. (1987). Variations in Insulin-Stimulated Glucose Uptake in Healthy Individuals with Normal Glucose Tolerance*. *The Journal of Clinical Endocrinology & Metabolism*, *64*(6), 1169–1173. https://doi.org/10.1210/jcem-64-6-1169

Holmes, C. S., Koepke, K. M., Thompson, R. G., Gyves, P. W., & Weydert, J. A. (1984). Verbal fluency and naming performance in type I diabetes at different blood glucose concentrations. *Diabetes Care*, *7*(5), 454–459. https://doi.org/10.2337/diacare.7.5.454

Holt, R. G., & Kalra, S. (2013). A new DAWN: Improving the psychosocial management of diabetes. *Indian Journal of Endocrinology and Metabolism*, *17*(Suppl 1), 95. https://doi.org/10.4103/2230-8210.119515

Homma, I., & Masaoka, Y. (2008). Breathing rhythms and emotions. In *Experimental Physiology* (Vol. 93, Issue 9, pp. 1011–1021). Blackwell Publishing Ltd. https://doi.org/10.1113/expphysiol.2008.042424

Hong, K. M. C., Glick, B. A., Kamboj, M. K., & Hoffman, R. P. (2021). Glycemic control, depression, diabetes distress among adolescents with type 1 diabetes: effects of sex, race, insurance, and obesity. *Acta Diabetologica*, *58*(12), 1627–1635. https://doi.org/10.1007/S00592-021-01768-W

Hope, C., Seiss, E., Dean, P. J. A., Williams, K. E. M., & Sterr, A. (2013). Consumption of glucose drinks slows sensorimotor processing: double-blind placebo-controlled studies with the Eriksen flanker task. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00651

Hoppe, M. W., Sperlich, B., Baumgart, C., Janssen, M., & Freiwald, J. (2015). Reliability of Selected Parameters of Cycling Ergospirometry from the PowerCube-Ergo Respiratory Gas Analyser. *Sportverletzung-Sportschaden*, *29*(3), 173–179. https://doi.org/10.1055/s-0034-1399096

Hostalek, U. (2019). Global epidemiology of prediabetes - present and future perspectives. *Clinical Diabetes and Endocrinology*, *5*(1). https://doi.org/10.1186/s40842-019-0080-0

Howard, M. W., Jing, B., Addis, K. M., & Kahana, M. J. (2007). *Handbook of latent semantic analysis* (T. K. Landauer, D. S. McNamara, S. Dennis, & W. Kintsch (eds.); pp. 121–141). Lawrence Erlbaum Associates Publishers.

Howarth, C., Gleeson, P., & Attwell, D. (2012). Updated energy budgets for neural computation in the neocortex and cerebellum. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *32*(7), 1222–1232. https://doi.org/10.1038/jcbfm.2012.35

Hunter, J. C., DeVellis, B. M., Jordan, J. M., Sue Kirkman, M., Linnan, L. A., Rini, C., & Fisher, E. B. (2018). The association of depression and diabetes across methods, measures, and study contexts. *Clinical Diabetes and Endocrinology 2018 4:1*, *4*(1), 1–8. https://doi.org/10.1186/S40842-017-0052-1

Ioannidou, C., Busquets-Garcia, A., Ferreira, G., & Marsicano, G. (2021). Neural Substrates of Incidental Associations and Mediated Learning: The Role of Cannabinoid Receptors. *Frontiers in Behavioral Neuroscience*, *15*, 722796. https://doi.org/10.3389/fnbeh.2021.722796

Jacobs, E., Rathmann, W., Tönnies, T., Arendt, D., Marchowez, M., Veith, L., Kuss, O., Brinks, R., & Hoyer, A. (2020). Age at diagnosis of Type 2 diabetes in Germany: a nationwide analysis based on claims data from 69 million people. *Diabetic Medicine : A Journal of the British Diabetic Association*, *37*(10), 1723–1727. https://doi.org/10.1111/DME.14100

Jennings, J. R., Kamarck, T., Stewart, C., Eddy, M., & Johnson, P. (1992). Alternate Cardiovascular Baseline Assessment Techniques: Vanilla or Resting Baseline. *Psychophysiology*, *29*(6), 742–750. https://doi.org/10.1111/j.1469-8986.1992.tb02052.x

Jensen, N. J., Wodschow, H. Z., Nilsson, M., & Rungby, J. (2020). Effects of Ketone Bodies on Brain Metabolism and Function in Neurodegenerative Diseases. *International Journal of Molecular Sciences 2020, Vol. 21, Page 8767*, *21*(22), 8767. https://doi.org/10.3390/IJMS21228767

Kahn, C. R. (1978). Insulin resistance, insulin insensitivity, and insulin unresponsiveness: A necessary distinction. *Metabolism*, *27*(12), 1893–1902. https://doi.org/10.1016/S0026-0495(78)80007-9

Kalm, L. M., & Semba, R. D. (2005). They Starved So That Others Be Better Fed: Remembering Ancel Keys and the Minnesota Experiment. *The Journal of Nutrition*, *135*(6), 1347–1352. https://doi.org/10.1093/jn/135.6.1347

Kalra, S., Jena, B. N., & Yeravdekar, R. (2018). Emotional and psychological needs of people with diabetes. *Indian Journal of Endocrinology and Metabolism*, *22*(5), 696–704. https://doi.org/10.4103/ijem.IJEM_579_17

Kaplan, R. J., Greenwood, C. E., Winocur, G., & Wolever, T. M. S. (2000). Cognitive performance is associated with glucose regulation in healthy elderly persons and can be enhanced with glucose and dietary carbohydrates. *American Journal of Clinical Nutrition*, *72*(3), 825–836. https://doi.org/10.1093/ajcn/72.3.825

Katz, J., & Tayek, J. A. (1998). Gluconeogenesis and the Cori cycle in 12-, 20-, and 40-h-fasted humans. *American Journal of Physiology-Endocrinology and Metabolism*, *275*(3), E537–E542. https://doi.org/10.1152/ajpendo.1998.275.3.E537

Kennedy, D. O., & Scholey, A. B. (2000). Glucose administration, heart rate and cognitive performance: effects of increasing mental effort. *Psychopharmacology*, *149*(1), 63–71. https://doi.org/10.1007/s002139900335

Kessels, R. P. C., van Zandvoort, M. J. E., Postma, A., Kappelle, L. J., & de Haan, E. H. F. (2000). The Corsi Block-Tapping Task: Standardization and Normative Data. *Applied Neuropsychology*, *7*(4), 252–258. https://doi.org/10.1207/S15324826AN0704_8

Kitazawa, M. (2013). Circadian Rhythms, Metabolism, and Insulin Sensitivity: Transcriptional Networks in Animal Models. *Current Diabetes Reports*, *13*(2), 223–228. https://doi.org/10.1007/s11892-012-0354-8

Knutsson, J., Nilsson, J.-E., Eriksson, Å., & Järild, L. (2020). Imagery Rescripting and Exposure in Social Anxiety: A Randomized Trial Comparing Treatment Techniques. *Journal of Contemporary Psychotherapy*, *50*(3), 233–240. https://doi.org/10.1007/s10879-019-09448-1

Koivisto, V. A., Yki-Järvinen, H., & DeFronzo, R. A. (1986). Physical training and insulin sensitivity. *Diabetes/Metabolism Reviews*, *1*(4), 445–481. https://doi.org/10.1002/dmr.5610010407

Konner, M., & Eaton, S. B. (2010). Paleolithic Nutrition. *Nutrition in Clinical Practice*, *25*(6), 594–602. https://doi.org/10.1177/0884533610385702

Kullmann, S., Heni, M., Hallschmid, M., Fritsche, A., Preissl, H., & Häring, H.-U. (2016a). Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. *Physiological Reviews*, *96*(4). https://doi.org/10.1152/physrev.00032.2015

Kullmann, S., Heni, M., Hallschmid, M., Fritsche, A., Preissl, H., & Häring, H. U. (2016b). Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. *Physiological Reviews*, *96*(4), 1169–1209. https://doi.org/10.1152/PHYSREV.00032.2015

Lamothe, B., Baudry, A., Desbois, P., Lamotte, L., Bucchini, D., De Meyts, P., & Joshi, R. L. (1998). Genetic engineering in mice: impact on insulin signalling and action. *The Biochemical Journal*, *335 (Pt 2*(Pt 2), 193–204. https://doi.org/10.1042/bj3350193

Landau, B. R., Wahren, J., Chandramouli, V., Schumann, W. C., Ekberg, K., & Kalhan, S. C. (1996). Contributions of gluconeogenesis to glucose production in the fasted state. *The Journal of Clinical Investigation*, *98*(2), 378–385. https://doi.org/10.1172/JCI118803

Landgraf, R. (2006). HbA1c - Goldstandard in der Beurteilung der Therapie des Diabetes? *DMW - Deutsche Medizinische Wochenschrift*, *131*(S 8), S243–S246. https://doi.org/10.1055/S-2006-956282

Landis, C. (1930). Walter B. Cannon. Bodily Changes in Pain, Hunger, Fear and Rage. (2nd ed., revised and enlarged.) New York: Appleton, 1929. Pp. xvi+404. *The Pedagogical Seminary and Journal of Genetic Psychology*, *38*(1–4), 527–531. https://doi.org/10.1080/08856559.1930.10532290

Lapauw, B., Ouwens, M., 't Hart, L. M., Wuyts, B., Holst, J. J., T'Sjoen, G., Kaufman, J.-M., & Ruige, J. B. (2010). Sex steroids affect triglyceride handling, glucose-dependent insulinotropic polypeptide, and insulin sensitivity: a 1-week randomized clinical trial in healthy young men. *Diabetes Care*, *33*(8), 1831–1833. https://doi.org/10.2337/dc10-0515

Leiner, D. J. (2014). *SoSci survey (version 2.4. 00-i)[computer software]*.

Leproult, R., Deliens, G., Gilson, M., & Peigneux, P. (2015). Beneficial impact of sleep extension on fasting insulin sensitivity in adults with habitual sleep restriction. *Sleep*, *38*(5), 707–715. https://doi.org/10.5665/sleep.4660

Lévesque, M., Santuré, M., Pitre, M., Nadeau, A., & Bachelard, H. (2006). Cholinergic involvement in vascular and glucoregulatory actions of insulin in rats. *Diabetes*, *55*(2), 398–404. https://doi.org/10.2337/diabetes.55.02.06.db05-0684

Levy-Marchal, C., Arslanian, S., Cutfield, W., Sinaiko, A., Druet, C., Marcovecchio, M. L., Chiarelli, F., Amemiyia, S., Berenson, G., Caprio, S., Charles, M. A., Cook, S., Davis, E., Dolan, L., Dunger, D., Fagot-Campagna, A., Flodmark, C. E., Ford, E., Gautier, J. F., … Yajnik, C. (2010). Insulin Resistance in Children: Consensus, Perspective, and Future Directions. *The Journal of Clinical Endocrinology and Metabolism*, *95*(12), 5189. https://doi.org/10.1210/JC.2010-1047

Lindsay, D. B., & Setchell, B. P. (1976). The oxidation of glucose, ketone bodies and acetate by the brain of normal and ketonaemic sheep. *The Journal of Physiology*, *259*(3), 801–823. https://doi.org/10.1113/jphysiol.1976.sp011496

Lindsten, J., Cerasi, E., Luft, R., Morton, N., & Ryman, N. (1976). Significance of genetic factors for the plasma insulin response to glucose in healthy subjects. *Clinical Genetics*, *10*(3), 125–134. https://doi.org/10.1111/j.1399-0004.1976.tb00024.x

Lundquist, I. (1982). Cholinergic muscarinic effects on insulin release in mice. *Pharmacology*, *25*(6), 338–347. https://doi.org/10.1159/000137760

Macpherson, H., Roberstson, B., Sünram-Lea, S., Stough, C., Kennedy, D., & Scholey, A. B. (2015). Glucose administration and cognitive function: Differential effects of age and effort during a dual task paradigm in younger and older adults. *Psychopharmacology*, *232*(6). https://doi.org/10.1007/s00213-014-3750-8

Macrodimitris, S. D., & Endler, N. S. (2001). Coping, control, and adjustment in type 2 diabetes. *Health Psychology*, *20*(3), 208–216. https://doi.org/10.1037/0278-6133.20.3.208

Malaisse, W., Malaisse-Lagae, F., Wright, P. H., & Ashmore, J. (1967). Effects of Adrenergic and Cholinergic Agents Upon Insulin Secretion in Vitro. *Endocrinology*, *80*(5), 975–978. https://doi.org/10.1210/endo-80-5-975

Mallet, R. T., Kelleher, J. K., & Jackson, M. J. (1986). Substrate metabolism of isolated jejunal epithelium: conservation of three-carbon units. *American Journal of Physiology-Cell Physiology*, *250*(2), C191–C198. https://doi.org/10.1152/ajpcell.1986.250.2.C191

Manning, C. A., Parsons, M. W., & Gold, P. E. (1992). Anterograde and retrograde enhancement of 24-h memory by glucose in elderly humans. *Behavioral and Neural Biology*, *58*(2), 125–130. https://doi.org/10.1016/0163-1047(92)90351-4

Manning, C. A., Stone, W. S., Korol, D. L., & Gold, P. E. (1998). Glucose enhancement of 24-h memory retrieval in healthy elderly humans. *Behavioural Brain Research*, *93*(1–2), 71–76. https://doi.org/10.1016/S0166-4328(97)00136-8

Marette, A., & Bukowiecki, L. J. (1989). Stimulation of glucose transport by insulin and norepinephrine in isolated rat brown adipocytes. *American Journal of Physiology-Cell Physiology*, *257*(4), C714–C721. https://doi.org/10.1152/ajpcell.1989.257.4.C714

Marrocco, R. T., Davidson, M. C., & Parasuraman, R. (1998). *The attentive brain*.

Masaoka, Y., & Homma, I. (2001). The effect of anticipatory anxiety on breathing and metabolism in humans. *Respiration Physiology*, *128*(2), 171–177. https://doi.org/10.1016/S0034-5687(01)00278-X

Masharani, U., Goldfine, I. D., & Youngren, J. F. (2009). Influence of gender on the relationship between insulin sensitivity, adiposity, and plasma lipids in lean nondiabetic subjects. *Metabolism: Clinical and Experimental*, *58*(11), 1602–1608. https://doi.org/10.1016/j.metabol.2009.05.012

Mattson, M. P. (2010). The impact of dietary energy intake on cognitive aging. *Frontiers in Aging Neuroscience*, *2*, 5. https://doi.org/10.3389/neuro.24.005.2010

Mattson, M. P., Moehl, K., Ghena, N., Schmaedick, M., & Cheng, A. (2018). Intermittent metabolic switching, neuroplasticity and brain health. *Nature Reviews Neuroscience*, *19*(2). https://doi.org/10.1038/nrn.2017.156

Mcaulay, V., Deary, I. J., Sommerfield, A. J., Matthews, G., & Frier, B. M. (2006). Effects of Acute Hypoglycemia on Motivation and Cognitive Interference in People with Type 1 Diabetes. *Journal of Clinical Psychopharmacology*, *26*(2), 143–151. https://doi.org/10.1097/01.jcp.0000203202.41947.6d

Meikle, A., Riby, L. M., & Stollery, B. (2004). The impact of glucose ingestion and gluco-regulatory control on cognitive performance: A comparison of younger and middle aged adults. *Human Psychopharmacology*, *19*(8), 523–535. https://doi.org/10.1002/hup.643

Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends in Neurosciences*, *36*(10), 587–597. https://doi.org/10.1016/j.tins.2013.07.001

Messier, C. (2004). Glucose improvement of memory: a review. *European Journal of Pharmacology*, *490*(1–3), 33–57. https://doi.org/10.1016/j.ejphar.2004.02.043

Messier, C., Tsiakas, M., Gagnon, M., Desrochers, A., & Awad, N. (2003). Effect of age and glucoregulation on cognitive performance. *Neurobiology of Aging*, *24*(7), 985–1003. https://doi.org/10.1016/S0197-4580(03)00004-6

Mikines, K. J., Sonne, B., Farrell, P. A., Tronier, B., & Galbo, H. (1988). Effect of physical exercise on sensitivity and responsiveness to insulin in humans. *The American Journal of Physiology*, *254*(3 Pt 1), E248-59. https://doi.org/10.1152/ajpendo.1988.254.3.E248

Miller, A. L., Kiney, C. A., Corddry, D. H., Staton, D. M., Kiney, C. A., Corddry, D. H., & Staton, D. M. (1982). Interactions between glucose and ketone body use by developing brain. *Brain Research, 256 4*(4), 443–450. https://doi.org/10.1016/0165-3806(82)90188-2

Miller, G. A. (1956). The magical number seven, plus or minus two: Some limits on our capacity for processing information. In *Psychological Review* (Vol. 63, Issue 2, pp. 81–97). American Psychological Association. https://doi.org/10.1037/h0043158

Mogg, K., Bradley, B. P., Hyare, H., & Lee, S. (1998). Selective attention to food-related stimuli in hunger: are attentional biases specific to emotional and psychopathological states, or are they also found in normal drive states? *Behaviour Research and Therapy*, *36*(2), 227–237. https://doi.org/10.1016/s0005-7967(97)00062-4

Moheet, A., Mangia, S., & Seaquist, E. R. (2015). Impact of diabetes on cognitive function and brain structure. *Annals of the New York Academy of Sciences*, *1353*(1), 60–71. https://doi.org/10.1111/nyas.12807

Mortby, M. E., Janke, A. L., Anstey, K. J., Sachdev, P. S., & Cherbuin, N. (2013). High "Normal" Blood Glucose Is Associated with Decreased Brain Volume and Cognitive Performance in the 60s: The PATH through Life Study. *PLoS ONE*, *8*(9), e73697. https://doi.org/10.1371/journal.pone.0073697

Nabb, S., & Benton, D. (2006). The influence on cognition of the interaction between the macro-nutrient content of breakfast and glucose tolerance. *Physiology & Behavior*, *87*(1), 16–23. https://doi.org/10.1016/j.physbeh.2005.08.034

Nathan, D. M., Turgeon, H., & Regan, S. (2007). Relationship between glycated haemoglobin levels and mean glucose levels over time. *Diabetologia*, *50*(11), 2239–2244. https://doi.org/10.1007/s00125-007-0803-0

Neukirchen, T. (2019). *Thinking big: Do changes in body composition moderate the relationship between glucose ingestion and cognitive performance?* Masterarbeit, Maastricht University, Maastricht, NL.

Neukirchen, T., Radach, R., & Vorstius, C. (2022). Cognitive glucose sensitivity—proposing a link between cognitive performance and reliance on external glucose uptake. *Nutrition and Diabetes*, *12*(1). https://doi.org/10.1038/s41387-022-00191-6

Neukirchen, T., Stork, M., Hoppe, M. W., & Vorstius, C. (2022). Spirometry has added value over electrodermal activity as a physiological marker of mental load in male subjects. *Scientific Reports*, *12*(1), 4496. https://doi.org/10.1038/s41598-022-08480-x

Nguyen, V. B., Tran, T. T., Dang, T. L., Nguyen, V. V. H., Tran, B. T., Van Le, C., & Toan, N. D. (2020). Diabetes-Related Distress and Its Associated Factors Among Patients with Diabetes in Vietnam. *Psychology Research and Behavior Management*, *13*, 1181–1189. https://doi.org/10.2147/PRBM.S285291

Nilsson, L. G., & Nilsson, E. (2009). Overweight and cognition. *Scandinavian Journal of Psychology*, *50*(6), 660–667. https://doi.org/10.1111/j.1467-9450.2009.00777.x

Nilsson, M., Jensen, N., Gejl, M., Bergmann, M. L., Storgaard, H., Zander, M., Miskowiak, K., & Rungby, J. (2019). Experimental non-severe hypoglycaemia substantially impairs cognitive function in type 2 diabetes: a randomised crossover trial. *Diabetologia*, *62*(10), 1948–1958. https://doi.org/10.1007/S00125-019-4964-4

Ong, K. L., Stafford, L. K., McLaughlin, S. A., Boyko, E. J., Vollset, S. E., Smith, A. E., Dalton, B. E., Duprey, J., Cruz, J. A., Hagins, H., Lindstedt, P. A., Aali, A., Abate, Y. H., Abate, M. D., Abbasian, M., Abbasi-Kangevari, Z., Abbasi-Kangevari, M., Abd ElHafeez, S., Abd-Rabu, R., … Vos, T. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*, *402*(10397), 203–234. https://doi.org/10.1016/S0140-6736(23)01301-6

Owen, L., Scholey, A. B., Finnegan, Y., & Sünram-Lea, S. (2013). Response variability to glucose facilitation of cognitive enhancement. *British Journal of Nutrition*, *110*(10), 1873–1884. https://doi.org/10.1017/S0007114513001141

Owens, D. S., & Benton, D. (1994). The Impact of Raising Blood Glucose on Reaction Times. *Neuropsychobiology*, *30*(2–3), 106–113. https://doi.org/10.1159/000119146

Parsons, M. W., & Gold, P. E. (1992). Glucose enhancement of memory in elderly humans: An inverted-U dose-response curve. *Neurobiology of Aging*, *13*(3), 401–404. https://doi.org/10.1016/0197-4580(92)90114-D

Pasquali, R., Casimirri, F., Cantobelli, S., Melchionda, N., Morselli Labate, A. M., Fabbri, R., Capelli, M., & Bortoluzzi, L. (1991). Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism: Clinical and Experimental*, *40*(1), 101–104. https://doi.org/10.1016/0026-0495(91)90199-7

Peters, R., White, D., Cleeland, C., & Scholey, A. (2020). Fuel for Thought? A Systematic Review of Neuroimaging Studies into Glucose Enhancement of Cognitive Performance. *Neuropsychology Review*, *30*(2), 234–250. https://doi.org/10.1007/s11065-020-09431-x

Petersen, S. E., & Posner, M. I. (2012). The Attention System of the Human Brain: 20 Years After. *Annual Review of Neuroscience*, *35*(1), 73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Peterson, W., Birdsall, T., & Fox, W. (1954). The theory of signal detectability. *Transactions of the IRE Professional Group on Information Theory*, *4*(4), 171–212. https://doi.org/10.1109/TIT.1954.1057460

Poirier, M., & Saint-Aubin, J. (1995). Memory for Related and Unrelated Words: Further Evidence on the Influence of Semantic Factors in Immediate Serial Recall. *The Quarterly Journal of Experimental Psychology Section A*, *48*(2), 384–404. https://doi.org/10.1080/14640749508401396

Polonsky, W. H., Anderson, B. J., Lohrer, P. A., Welch, G., Jacobson, A. M., Aponte, J. E., & Schwartz, C. E. (1995). Assessment of diabetes-related distress. *Diabetes Care*, *18*(6), 754–760. https://doi.org/10.2337/DIACARE.18.6.754

Prince, A., Zhang, Y., Croniger, C., & Puchowicz, M. (2013). Oxidative metabolism: glucose versus ketones. *Advances in Experimental Medicine and Biology*, *789*, 323–328. https://doi.org/10.1007/978-1-4614-7411-1_43

Qian, J., Dalla Man, C., Morris, C. J., Cobelli, C., & Scheer, F. A. J. L. (2018). Differential effects of the circadian system and circadian misalignment on insulin sensitivity and insulin secretion in humans. *Diabetes, Obesity & Metabolism*, *20*(10), 2481–2485. https://doi.org/10.1111/dom.13391

R Core Team. (2017). R: A language and environment for statistical computing. *R Foundation for Statistical Computing, Vienna, Austria.* https://doi.org//S0103-64402004000300015

Razzak, R. A., Alshaiji, A. F., Qareeballa, A. A., Mohamed, M. W., Bagust, J., & Docherty, S. (2018). High-normal blood glucose levels may be associated with decreased spatial perception in young healthy adults. *PLOS ONE*, *13*(6), e0199051. https://doi.org/10.1371/journal.pone.0199051

Reger, M. A., Watson, G. S., Green, P. S., Baker, L. D., Cholerton, B., Fishel, M. A., Plymate, S. R., Cherrier, M. M., Schellenberg, G. D., Frey II, W. H., & Craft, S. (2008). Intranasal Insulin Administration Dose-Dependently Modulates Verbal Memory and Plasma Amyloid-β in Memory-Impaired Older Adults. *Journal of Alzheimer's Disease*, *13*(3), 323–331. https://doi.org/10.3233/JAD-2008-13309

Rehner, G., & Daniel, H. (2010). *Biochemie der Ernährung*. Spektrum Akademischer Verlag. https://doi.org/10.1007/978-3-8274-2217-0

Reutrakul, S., & Van Cauter, E. (2018). Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism: Clinical and Experimental*, *84*, 56–66. https://doi.org/10.1016/j.metabol.2018.02.010

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029–2040. https://doi.org/10.1017/S0033291713002535

Sanders, M. A., Shirk, S. D., Burgin, C. J., & Martin, L. L. (2012). The Gargle Effect: Rinsing the Mouth With Glucose Enhances Self-Control. *Psychological Science*, *23*(12), 1470–1472. https://doi.org/10.1177/0956797612450034

Sänger, J. (2019). Can't take my eyes off you - How task irrelevant pictures of food influence attentional selection. *Appetite*, *133*, 313–323. https://doi.org/10.1016/j.appet.2018.11.030

Schenk, S., Saberi, M., & Olefsky, J. M. (2008). Insulin sensitivity: modulation by nutrients and inflammation. *Journal of Clinical Investigation*, *118*(9), 2992–3002. https://doi.org/10.1172/JCI34260

Schmidt, L., Lebreton, M., Cléry-Melin, M. L., Daunizeau, J., & Pessiglione, M. (2012). Neural mechanisms underlying motivation of mental versus physical effort. *PLoS Biology*, *10*(2), e1001266. https://doi.org/10.1371/journal.pbio.1001266

Schoene, R. B., Robertson, H. T., & Pierson, D. J. (1981). Respiratory drives and exercise in menstrual cycles of athletic and nonathletic women. *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, *50*(6), 1300–1305. https://doi.org/10.1152/jappl.1981.50.6.1300

Scholey, A B, Harper, S., & Kennedy, D. O. (2001). Cognitive demand and blood glucose. *Physiology & Behavior*, *73*(4), 585–592. https://doi.org/10.1016/s0031-9384(01)00476-0

Scholey, Andrew B., Sünram-Lea, S., Greer, J., Elliott, J., & Kennedy, D. O. (2009). Glucose administration prior to a divided attention task improves tracking performance but not word recognition: Evidence against differential memory enhancement? *Psychopharmacology*, *202*(1–3), 549–558. https://doi.org/10.1007/s00213-008-1387-1

Seematter, G., Guenat, E., Schneiter, P., Cayeux, C., Jéquier, E., & Tappy, L. (2000). Effects of mental stress on insulin-mediated glucose metabolism and energy expenditure in lean and obese women. *American Journal of Physiology. Endocrinology and Metabolism*, *279*(4), E799-805. https://doi.org/10.1152/ajpendo.2000.279.4.E799

Sellami, M., Bragazzi, N. L., Slimani, M., Hayes, L., Jabbour, G., De Giorgio, A., & Dugué, B. (2019). The Effect of Exercise on Glucoregulatory Hormones: A Countermeasure to Human Aging: Insights from a Comprehensive Review of the Literature. *International Journal of Environmental Research and Public Health 2019, Vol. 16, Page 1709*, *16*(10), 1709. https://doi.org/10.3390/IJERPH16101709

Selvin, E., Wattanakit, K., Steffes, M. W., Coresh, J., & Sharrett, A. R. (2006). HbA1c and Peripheral Arterial Disease in DiabetesThe Atherosclerosis Risk in Communities study. *Diabetes Care*, *29*(4), 877–882. https://doi.org/10.2337/DIACARE.29.04.06.DC05-2018

Setz, C., Arnrich, B., Schumm, J., La Marca, R., Tröster, G., & Ehlert, U. (2010). Discriminating Stress From Cognitive Load Using a Wearable EDA Device. *IEEE Transactions on Information Technology in Biomedicine*, *14*(2), 410–417. https://doi.org/10.1109/TITB.2009.2036164

Sharma, K., Akre, S., Chakole, S., & Wanjari, M. B. (2022). Stress-Induced Diabetes: A Review. *Cureus*, *14*(9), e29142. https://doi.org/10.7759/cureus.29142

Sharp, R., Culbert, S., Cook, J., Jennings, A., & Burr, I. M. (1974). Cholinergic modification of glucose-induced biphasic insulin release in vitro. *The Journal of Clinical Investigation*, *53*(3), 710–716. https://doi.org/10.1172/JCI107609

Shu, L., Xie, J., Yang, M., Li, Z., Li, Z., Liao, D., Xu, X., & Yang, X. (2018). A review of emotion recognition using physiological signals. In *Sensors (Switzerland)* (Vol. 18, Issue 7). MDPI AG. https://doi.org/10.3390/s18072074

Sierra-Johnson, J., Johnson, B. D., Bailey, K. R., & Turner, S. T. (2004). Relationships between Insulin Sensitivity and Measures of Body Fat in Asymptomatic Men and Women. *Obesity Research*, *12*(12), 2070–2077. https://doi.org/10.1038/oby.2004.258

Singh, J., Dartois, A., & Kaur, L. (2010). Starch digestibility in food matrix: a review. *Trends in Food Science & Technology*, *21*(4), 168–180. https://doi.org/10.1016/j.tifs.2009.12.001

Smith, E., Hay, P., Campbell, L., & Trollor, J. N. (2011). A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obesity Reviews*, *12*(9), 740–755. https://doi.org/10.1111/J.1467-789X.2011.00920.X

Stamatakis, K. A., & Punjabi, N. M. (2010). Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest*, *137*(1), 95–101. https://doi.org/10.1378/chest.09-0791

Stenvers, D. J., Scheer, F. A. J. L., Schrauwen, P., la Fleur, S. E., & Kalsbeek, A. (2019). Circadian clocks and insulin resistance. *Nature Reviews Endocrinology*, *15*(2), 75–89. https://doi.org/10.1038/s41574-018-0122-1

Stewart, A., Marfell-Jones, M., Olds, T., & Ridder, de H. (2011). *International standards for anthropometric assessment.* (2011 ed.). International Society for Advancement of Kinanthropometry.

Stone, W. S., Cottrill, K. L., Walker, D. L., & Gold, P. E. (1988). Blood glucose and brain function: interactions with CNS cholinergic systems. *Behavioral and Neural Biology*, *50*(3), 325–334. https://doi.org/10.1016/S0163-1047(88)91018-7

Sue, D. Y., Chung, M. M., Grosvenor, M., & Wasserman, K. (1989). Effect of altering the proportion of dietary fat and carbohydrate on exercise gas exchange in normal subjects. *American Review of Respiratory Disease*, *139*(6), 1430–1434. https://doi.org/10.1164/ajrccm/139.6.1430

Suess, W. M., Alexander, A. B., Smith, D. D., Sweeney, H. W., & Marion, R. J. (1980). The Effects of Psychological Stress on Respiration: A Preliminary Study of Anxiety and Hyperventilation. *Psychophysiology*, *17*(6), 535–540. https://doi.org/10.1111/j.1469-8986.1980.tb02293.x

Sünram-Lea, S., Foster, J., Durlach, P., & Perez, C. (2001). Glucose facilitation of cognitive performance in healthy young adults: examination of the influence of fast-duration, time of day and pre-consumption plasma glucose levels. *Psychopharmacology*, *157*(1), 46–54. https://doi.org/10.1007/s002130100771

Sünram-Lea, S., Foster, J. K., Durlach, P., & Perez, C. (2002). Investigation into the significance of task difficulty and divided allocation of resources on the glucose memory facilitation effect. *Psychopharmacology*, *160*(4), 387–397. https://doi.org/10.1007/s00213-001-0987-9

Sünram-Lea, S., & Owen, L. (2017). The impact of diet-based glycaemic response and glucose regulation on cognition: evidence across the lifespan. *Proceedings of the Nutrition Society*, *76*(4), 466–477. https://doi.org/10.1017/S0029665117000829

Swieten, M. M. H. van, Bogacz, R., & Manohar, S. G. (2021). Hunger improves reinforcement-driven but not planned action. *BioRxiv*, 2021.03.24.436435. https://doi.org/10.1101/2021.03.24.436435

Tabák, A. G., Herder, C., Rathmann, W., Brunner, E. J., & Kivimäki, M. (2012). Prediabetes: A high-risk state for developingdiabetes. *Lancet*, *379*(9833), 2279. https://doi.org/10.1016/S0140-6736(12)60283-9

Tai, K., Need, A. G., Horowitz, M., & Chapman, I. M. (2008). Vitamin D, glucose, insulin, and insulin sensitivity. *Nutrition*, *24*(3), 279–285. https://doi.org/10.1016/j.nut.2007.11.006

Tamborlane, W. V, Sherwin, R. S., Genel, M., & Felig, P. (1979). Reduction to Normal of Plasma Glucose in Juvenile Diabetes by Subcutaneous Administration of Insulin with a Portable Infusion Pump. *New England Journal of Medicine*, *300*(11), 573–578. https://doi.org/10.1056/NEJM197903153001101

Targher, G., Mantovani, A., Wang, X. B., Yan, H. D., Sun, Q. F., Pan, K. H., Byrne, C. D., Zheng, K. I., Chen, Y. P., Eslam, M., George, J., & Zheng, M. H. (2020). Patients with diabetes are at higher risk for severe illness from COVID-19. *Diabetes & Metabolism*, *46*(4), 335. https://doi.org/10.1016/J.DIABET.2020.05.001

Taylor, L. A., & Rachman, S. J. (1988). The effects of blood sugar level changes on cognitive function, affective state, and somatic symptoms. *Journal of Behavioral Medicine*, *11*(3), 279–291. https://doi.org/10.1007/BF00844433

Thompson, J. R., & Wu, G. (1991). The effect of ketone bodies on nitrogen metabolism in skeletal muscle. *Comparative Biochemistry and Physiology Part B: Comparative Biochemistry*, *100*(2), 209–216. https://doi.org/10.1016/0305-0491(91)90363-I

Tramunt, B., Smati, S., Grandgeorge, N., Lenfant, F., Arnal, J.-F., Montagner, A., & Gourdy, P. (2020). Sex differences in metabolic regulation and diabetes susceptibility. *Diabetologia*, *63*(3), 453–461. https://doi.org/10.1007/s00125-019-05040-3

Tse, C.-S. (2009). The role of associative strength in the semantic relatedness effect on immediate serial recall. *Memory*, *17*(8), 874–891. https://doi.org/10.1080/09658210903376250

Van Bastelaar, K. M. P., Pouwer, F., Geelhoed-Duijvestijn, P. H. L. M., Tack, C. J., Bazelmans, E., Beekman, A. T., Heine, R. J., & Snoek, F. J. (2010). Diabetes-specific emotional distress mediates the association between depressive symptoms and glycaemic control in Type 1 and Type 2 diabetes. *Diabetic Medicine : A Journal of the British Diabetic Association*, *27*(7), 798–803. https://doi.org/10.1111/J.1464-5491.2010.03025.X

Virkamäki, A., Ueki, K., & Kahn, C. R. (1999). Protein–protein interaction in insulin signaling and the molecular mechanisms of insulin resistance. *Journal of Clinical Investigation*, *103*(7), 931–943. https://doi.org/10.1172/JCI6609

Vranic, M., Miles, P., Rastogi, K., Yamatani, K., Shi, Z., Lickley, L., & Hetenyi, G. (1991). *Effect of Stress on Glucoregulation in Physiology and Diabetes BT - Fuel Homeostasis and the Nervous System* (Mladen Vranic, S. Efendic, & C. H. Hollenberg (eds.); pp. 161–183). Springer US. https://doi.org/10.1007/978-1-4684-5931-9_13

Waldman, H. S., Shepherd, B. D., Egan, B., & McAllister, M. J. (2020). Exogenous Ketone Salts Do Not Improve Cognitive Performance During a Dual-Stress Challenge. *International Journal of Sport Nutrition and Exercise Metabolism*, *30*(2), 120–127. https://doi.org/10.1123/ijsnem.2019-0122

Wall, J. S., Steele, R., Bodo, R. C. De, Altszuler, N., Kimg, S. P., Med, C., York., N., Natl, B., Lab, Upton, N. Y., & Uj, E. (1957). Effect of insulin on utilization and production of circulating glucose. *The American Journal of Physiology*, *189 1*, 43–50. https://doi.org/10.1152/ajplegacy.1957.189.1.43

Wan, R., Camandola, S., & Mattson, M. P. (2003). Intermittent food deprivation improves cardiovascular and neuroendocrine responses to stress in rats. *The Journal of Nutrition*, *133*(6), 1921–1929. https://doi.org/10.1093/jn/133.6.1921

Wang, C., Chan, J. S. Y., Ren, L., & Yan, J. H. (2016). Obesity Reduces Cognitive and Motor Functions across the Lifespan. *Neural Plasticity*, *2016*, 2473081. https://doi.org/10.1155/2016/2473081

Wasserman, K., Hansen, J. E., Sue, D. Y., Stringer, W. W., & Whipp, B. J. (2005). Principles of exercise testing and interpretation: including pathophysiology and clinical applications. In *Medicine & Science in Sports & Exercise* (Vol. 37, Issue 7). LWW.

Weinger, K., & Lee, J. (2006). Psychosocial and Psychiatric Challenges of Diabetes Mellitus. *Nursing Clinics of North America*, *41*(4), 667–680. https://doi.org/10.1016/j.cnur.2006.07.002

White, D. P., Douglas, N. J., Pickett, C. K., Weil, J. V., & Zwillich, C. W. (1983). Sexual influence on the control of breathing. *Journal of Applied Physiology Respiratory Environmental and Exercise Physiology*, *54*(4), 874–879. https://doi.org/10.1152/jappl.1983.54.4.874

Wick, M., Pinggera, W., & Lehmann, P. (2002). *Erythropoese BT - Klinik und Labor Eisenstoffwechsel und Anämien* (M. Wick, W. Pinggera, & P. Lehmann (eds.); pp. 17–22). Springer Vienna.

Wilkinson, L. (2011). ggplot2: Elegant Graphics for Data Analysis by WICKHAM, H. *Biometrics*, *67*(2), 678–679. https://doi.org/10.1111/j.1541-0420.2011.01616.x

Yki Jarvinen, H., & Koivisto, V. A. (1983). Effects of body composition on insulin sensitivity. *Diabetes*, *32*(10), 965–969. https://doi.org/10.2337/diab.32.10.965

Young, H., & Benton, D. (2014). The nature of the control of blood glucose in those with poorer glucose tolerance influences mood and cognition. *Metabolic Brain Disease*, *29*(3). https://doi.org/10.1007/s11011-014-9519-2

Zanchi, D., Meyer-Gerspach, A. C., Schmidt, A., Suenderhauf, C., Depoorter, A., Drewe, J., Beglinger, C., Wölnerhanssen, B. K., & Borgwardt, S. (2018). Acute effects of glucose and fructose administration on the neural correlates of cognitive functioning in healthy subjects: A pilot study. *Frontiers in Psychiatry*, *9*(MAR). https://doi.org/10.3389/fpsyt.2018.00071

Zouhal, H., Vincent, S., Moussa, E., Botcazou, M., Delamarche, P., & Gratas-Delamarche, A. (2009). Early advancing age alters plasma glucose and glucoregulatory hormones in response to supramaximal exercise. *Journal of Science and Medicine in Sport*, *12*(6), 652–656. https://doi.org/10.1016/j.jsams.2008.03.003

Zouras, S., Stephens, J. W., & Price, D. (2017). Obesity-related hypogonadism: a reversible condition. *BMJ Case Reports*, *2017*, bcr-2017-220416. https://doi.org/10.1136/bcr-2017-220416