**Mind your body: Could attention differentially regulate real-time biological processes   
of basic physiological actions?**

Research into the placebo effect has demonstrated that our minds can trigger neurobiological pathways which eventually influence our health. Yet, such real-time mind-body influences are rarely studied outside clinical settings.

The objective of this proposal is to explore the biological mechanisms of mind-body influences in every-day situations and how they contribute to physical health. The long-term goal of this project is to elucidate the scope and limits of mind’s influence over the body, redefining our understanding of the human brain.

Building on placebo research and mind-body intervention studies, we target attention as a key mediator of mind-body interactions. We hypothesize that being mindful (vs mindless) of one’s bodily actions (viz. eating and exercising) changes biological processes (e.g., energy expenditure, food metabolism) and the brain regions that govern them (e.g., hypothalamus). To test this hypothesis, we will conduct cross-over and intervention studies, assessing behavioral, physiological, hormonal and metabolic outcomes.

Results of this project have the potential to transform our understanding of the human brain and mind, and bear major implications on public health recommendations.

Our minds can exert a powerful influence over our bodies’ physiology. Research into the placebo effect has demonstrated that mere expectations of pain relief following a drug’s administration, even when the drug is inert, can lead to a genuine physiological reduction in pain. One underlying mechanism is the release of endogenous opioids in the brain, which then block spinal pain-transmitting neurons, thus mimicking the effect of real painkillers1,2. This potent effect has been observed in various chronic conditions, such as acute postoperative pain3, low back pain4 and irritable bowel syndrome5. It has also been observed in other disorders and clinical conditions, for example in Parkinson’s disease, wherein the placebo-induced expectation of motor improvement was found to activate endogenous dopamine in the striatum of parkinsonian patients6. Together, expectations and beliefs regarding treatment can induce rapid and different neurobiological responses, leading to improvement in symptoms.

The placebo effect is also present when an active drug is administered. For example, post-operative patients receiving opiates for their pain needed up to 50% less drugs and for a shorter duration when they were mindful of the drug being administered versus when it was administered without their attention (using an existing IV)3. The same effect was observed in healthy participants to whom acute pain has been induce3,7. Similarly, Parkinson’s patients undergoing deep-brain stimulation showed markedly reduced treatment efficacy when it was done covertly versus overtly8. These findings strongly suggest whether a person is attentive to receiving an actual drug can substantially influence the drug’s efficacy, naming attention as a key mediator of mind-body influences.

Could attention be mediating mind-body influences outside clinical settings as well? Longitudinal studies indeed show that performing daily physiological activities while mindful of them versus mindless leads to advantageous results over the course of several weeks. For instance, performing the same (demanding) physical activity as part of one’s daily routine, when mindful of its potential positive influences on physical health and body weight versus when not mindful of them, was found to have significant effects over the course of several weeks on objective physiological measures such as BMI, fat percentage and blood pressure9. Relatedly, “mindful eating” is a growingly popular intervention that encourages people to eat while being more attentive to the food they eat and to their bodily sensations. These interventions are repeatedly found to, over a period of several weeks to months, effectively reduce binge eating and cravings, and reduce body weight or prevent weight gain in both normal weight population10,11 as well as obese individuals12,13. Some evidence (and our preliminary results) report decreased food intake immediately following eating mindfully versus mindlessly14, indicating that the underlying mechanisms act rapidly.

Despite growing evidence supporting a role for attention in regulating mind-body influences, **the real-time effect of mind-over-body in everyday life, outside clinical settings, has rarely been studied**. In this proposal, we will test whether performing basic physiological actions, such as eating and exercising, under different attentive states (*mindsets?*) induces different real-time physiological and biological responses to the undertaken action. We propose that directing one’s attention away versus towards these actions has a detrimental effect on the ability of the body to optimally prepare for, and efficiently perform, that action. We aim to measure the effect of different attentional states (attentive/mindful vs distracted/mindless) on brain-body crosstalk, by measuring physiological engagement, hormonal secretion, and neurobiological changes. We hypothesize that following these real-time changes in brain-body crosstalk, the metabolic efficiency of the action is reduced, such that eating mindlessly will induce less satiety than eating mindfully, and exercising mindlessly will induce less muscle effort than exercising mindfully.

If our hypothesis is confirmed, we will demonstrate that aligning the mind, as operationalized by attention, with the body’s actions is necessary to achieve optimal biological bodily function. The success of this project, the first to assess how attention informs biological processes, will have basic-science, theoretical and translational impact. In terms of basic-science, these results are expected to transform our understanding of brain-body crosstalk, and suggest a novel mechanism whereby this crosstalk is routinely regulated by our minds. This is especially timely since the prevalence of performing basic actions mindlessly rises steeply. 65-88% of young adults eat most of their meals while watching TV or on their smartphones15, as do 20% of children ages 2-516, and most gyms have treadmills positioned across personal TV screens. If inattention impedes metabolism, it could lead to detrimental health consequences, and potentially explain part of the rising obesity incidence17. In fact, a common comorbidities of attention deficit hyperactivity disorder (ADHD), is obesity18, with increased prevalence of 70% among adults and 40% among children.

Establishing a role of attention in food and exercise metabolism can also have critical translational implications, suggesting that healthy lifestyle recommendations should include, beyond how much we eat or exercise, also how to do so most effectively – while mindful of what we do. With rising incidence of obesity17, especially among children19, in parallel to the unprecedented amount of screen exposure children have20, results of this project could bear important public health impact.

This project offers a paradigm shift by: (i) studying influences of mind over body in daily situations, without the administration of sham or active drugs, and (ii) elucidating the real-time physiological and biological mechanisms that underlie these influences.

**Project description:**

We hypothesize that being mindful (vs mindless) of one’s bodily actions (viz. eating and exercising) changes biological processes (e.g., energy expenditure, food metabolism) and the brain regions that govern them (e.g., hypothalamus). To test this hypothesis, we will conduct cross-over and intervention studies, assessing behavioral, physiological, hormonal and metabolic outcomes. We will determine whether different mindsets (*mindless, mindful, neutral*) have distinct effects on real-time metabolic processes following food consumption (**Aim 1**) and during exercise (**Aim 2**). We will further conduct an intervention to probe longitudinal changes in structure and function of the hypothalamus, a brain region regulating metabolism, in gut microbiome, and in body composition (**Aim 3**).

Aims 1 and 2 will apply a similar within-subject crossover study design. In both experiments, participants’ performance will be tested under three different conditions: when instructed to be fully *mindful*, when distracted by TV-viewing (*mindless*) and neutrally (Figure 1). To do this, participants will come to the lab on three separate occasions. The conditions will be counter-balanced across sessions, therefore any individual differences in body mass, baseline physical activity or other related differences will be accounted for by the within-subjects study design. For these experiments, we will mainly use a respiratory mask (Figure 5) to oxygen consumption, carbon dioxide production, together with other ventilatory parameters, and metabolism substrate utilization (fat versus carbohydrates), on a breath-by-breath basis. Using this respiratory mask both at rest, during exercise and following a meal, we can measure metabolic efficiency of these actions (see below). In addition, we will draw blood to measure hormonal regulation of appetite and hunger, and the efficiency of food digestion through metabolites.

Aim 1 – comparing real-time metabolic and appetite regulation following food consumption:

After overnight fasting, participants will receive a standard shake (350 Kcal, 50% carbohydrate, 15% fat and 35% protein), and will be instructed to consume it within 15 minutes to control for eating duration. Outcome measures include: (1) Energy devoted to digestion: the amount of energy generated to digest and metabolize the food will be assessed by measuring oxygen uptake and carbon dioxide production, over the basic metabolic rate, using a respiratory mask (Figure 7). (2) Food utilization: Oral and gut bacteria play a crucial role in food digestion. We will quantify metabolites (including byproducts of digestion) secreted by the microbiome and the host, indicating food utilization. (3) Appetite regulation: we will draw blood before, 30 and 60 minutes after eating to measure changes in hunger and satiety-regulating hormones, Ghrelin and Leptin. (4) Subjective satiety: Participants will be asked to self-report their hunger levels.

Aim 2 – comparing real-time energy expenditure during exercise:

Participants will complete a structured 20-minute exercise run of moderate intensity (75% of their individual maximal aerobic endurance) on a treadmill. Outcome measures include: (1) Muscle metabolic efficiency will be assessed by oxygen uptake, carbon dioxide production, and the respiratory exchange ratio (RER), using a respiratory mask. (2) Macronutrient utilization will be assessed by comparing the proportion of energy utilized from fat oxidation versus carbohydrate oxidation. (3) Physiological engagement will be assessed by cardiopulmonary performance, namely heart rate and respiratory rate. (4) Subjective effort: Participants will be asked to rate their subjective effort.

We hypothesize that attention to bodily actions will yield a gradual benefit in metabolic efficiency (mindful>neutral>mindless), and provide encouraging preliminary results (Figures 3-5). To understand the mechanisms governing mind-body crosstalk, and measure its longitudinal impact, **Aim 3** includes two interventional randomized-controlled studies probing longitudinal changes in the hypothalamus, and in gut microbiome composition and body composition following eating or exercising mindlessly versus mindfully, respectively (Figure 2). A pre-intervention baseline period of two weeks will establish eating/exercising habits via self-report online diaries. We will assess baseline body composition, baseline brain structure and function using magnetic resonance imaging (MRI) and baseline microbiome composition using fecal sample analyses. Participants will then be randomized to groups and instructed to practice either mindful or mindless eating/exercising in the following four weeks. They will continue to record their eating/exercising habits, and post-intervention, their brain, body and microbiome measures will be re-assessed. By analyzing within- and between-individual differences, we aim to elucidate the brain-gut and brain-muscle mechanisms driving the influence of attention on metabolic processes.

**References**

1. Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S. & Zubieta, J.-K. Neurobiological Mechanisms of the Placebo Effect. *J. Neurosci.* **25**, 10390–10402 (2005).

2. Amanzio, M. & Benedetti, F. Neuropharmacological Dissection of Placebo Analgesia: Expectation-Activated Opioid Systems versus Conditioning-Activated Specific Subsystems. *J. Neurosci.* **19**, 484–494 (1999).

3. Benedetti, F. *et al.* Open versus hidden medical treatments: The patient’s knowledge about a therapy affects the therapy outcome. *Prev. Treat.* **6**, No Pagination Specified-No Pagination Specified (2003).

4. Chaparro, L. E. *et al.* Opioids compared to placebo or other treatments for chronic low‐back pain. *Cochrane Database Syst. Rev.* (2013) doi:10.1002/14651858.CD004959.pub4.

5. Kaptchuk, T. J. *et al.* Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* **336**, 999–1003 (2008).

6. de la Fuente-Fernández, R. *et al.* Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson’s Disease. *Science* **293**, 1164–1166 (2001).

7. Amanzio, M., Pollo, A., Maggi, G. & Benedetti, F. Response variability to analgesics: a role for non-specific activation of endogenous opioids. *Pain* **90**, 205–215 (2001).

8. Colloca, L., Lopiano, L., Lanotte, M. & Benedetti, F. Overt versus covert treatment for pain, anxiety, and Parkinson’s disease. *Lancet Neurol.* **3**, 679–684 (2004).

9. Crum, A. J. & Langer, E. J. Mind-set matters: Exercise and the placebo effect. *Psychol. Sci.* **18**, 165–171 (2007).

10. Kristeller, J. L. & Epel, E. Mindful eating and mindless eating: The science and the practice. in *The Wiley Blackwell handbook of mindfulness, Vols. I and II* 913–933 (Wiley Blackwell, 2014). doi:10.1002/9781118294895.ch47.

11. Warren, J. M., Smith, N. & Ashwell, M. A structured literature review on the role of mindfulness, mindful eating and intuitive eating in changing eating behaviours: effectiveness and associated potential mechanisms. *Nutr. Res. Rev.* **30**, 272–283 (2017).

12. Mason, A. E., Jhaveri, K., Cohn, M. & Brewer, J. A. Testing a mobile mindful eating intervention targeting craving-related eating: feasibility and proof of concept. *J. Behav. Med.* **41**, 160–173 (2018).

13. Dalen, J. *et al.* Pilot study: Mindful Eating and Living (MEAL): Weight, eating behavior, and psychological outcomes associated with a mindfulness-based intervention for people with obesity. *Complement. Ther. Med.* **18**, 260–264 (2010).

14. Robinson, E. *et al.* Eating attentively: a systematic review and meta-analysis of the effect of food intake memory and awareness on eating. *Am. J. Clin. Nutr.* **97**, 728–742 (2013).

15. Anderer, J. ‘Zombie Eating’: 88% Of Adults Dine While Staring At A Screen, Survey Finds. *Study Finds* https://www.studyfinds.org/zombie-eating-88-percent-adults-dine-while-staring-at-screen-survey-finds/ (2019).

16. Jusienė, R. *et al.* Screen Use During Meals Among Young Children: Exploration of Associated Variables. *Medicina (Mex.)* **55**, 688 (2019).

17. Adult Obesity Rates. *The State of Childhood Obesity* https://stateofchildhoodobesity.org/adult-obesity/.

18. Cortese, S. *et al.* Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. *Am. J. Psychiatry* **173**, 34–43 (2016).

19. Childhood Obesity Facts | Overweight & Obesity | CDC. https://www.cdc.gov/obesity/data/childhood.html (2022).

20. McArthur, B. A., Volkova, V., Tomopoulos, S. & Madigan, S. Global Prevalence of Meeting Screen Time Guidelines Among Children 5 Years and Younger: A Systematic Review and Meta-analysis. *JAMA Pediatr.* **176**, 373–383 (2022).