Human longevity : crosstalk between the brain and periphery

Akintola, A.A.

Citation

Akintola, A. A. (2016, November 16). *Human longevity : crosstalk between the brain and periphery*. Retrieved from https://hdl.handle.net/1887/44266

Cover Page

Universiteit Leiden

CHAPTER 1

GENERAL INTRODUCTION

1
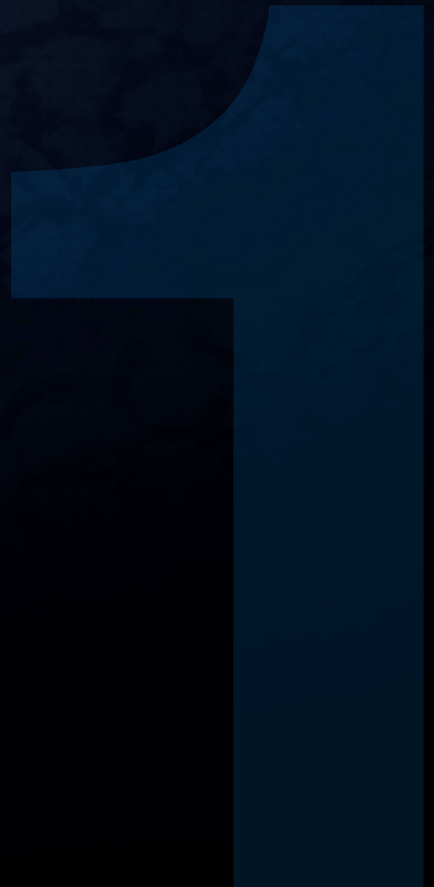
GENERAL INTRODUCTION

Even though mortality in old age has significantly decreased over the last fifty years in the developed world [1], there still remains a large inter- individual variability in ageing trajectories, morbidity and mortality [2]. The ageing process is associated with numerous physiological alterations across multiple organ systems, including the brain. Thus, the need to better understand the physiological mechanisms and processes that underlie the ageing process is vital.

Longevity potential is determined by genetic and environmental factors [2, 3]. Various attempts have been made to delineate the regulatory pathways that underlie human longevity. Studies in model organisms suggest that longevity is promoted by conserved genetic mechanisms that orchestrate the organism's responses to its changing environment, such as insulin/insulin-like growth factor-1 (IGF-1) signaling [4, 5]. Also in humans, the ability to maintain the stability of the body's internal environment while dynamically adapting to changes in external conditions, known as homeostasis, has been identified as being a key to healthy longevity [6]. This maintenance is brought about by an intact communication between the brain and the peripheral bodily functions. Loss of homeostatic control is hypothesized to contribute to both bodily and cognitive decline.

Crosstalk between brain and periphery

Homeostasis is essential for health throughout lifetime, since age- related changes to physiology accumulate from early life [7, 8]. Homeostatic control is a complex mechanism requiring reciprocal projections from the brain to the periphery, and have at least three interdependent components: receptor/sensor, control center and effector [9]. Homeostasis requires the integration of numerous peripheral cues (sensor) by the hypothalamus and nearby brain structures (control center), to mount a coordinated response to adapt and maintain the internal environment within narrow limits. Tight regulation of these systems is key to healthy ageing.

Among the key modifiers of the ageing process identified are insulin/ IGF-1 signaling (IIS), the hypothalamic/ pituitary/thyroid (HPT) axis, the hypothalamic/ pituitary/ adrenal (HPA) axis and the autonomic nervous system. While a healthy interaction between these systems is crucial for maintenance of homeostasis of vital parameters (figure 1), a lack of communication or their dysregulation is implicated in accelerated and unhealthy ageing.
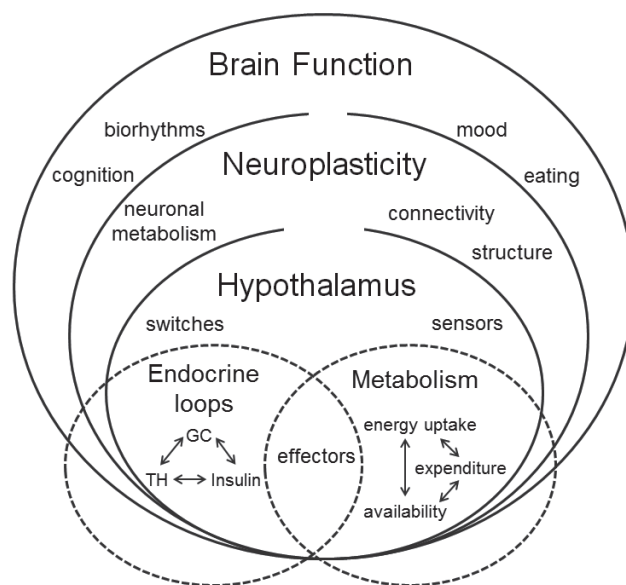
FIGURE 1.1 | Schematic figure depicting the brain-periphery dialogue. Taken with permission from the Switchbox project proposal.

In this thesis, emphasis will be placed on three key modifiers of the ageing process, namely the communication between the brain and glucose and insulin metabolism, HPT axis and the autonomic nervous system, using data from the Leiden Longevity Study and the Switchbox study.

Data Sources- the Leiden Longevity Study

The Leiden Longevity study (LLS) was designed to identify determinants of human longevity by studying offspring of long- lived siblings and their partners. Between 2002 and 2006, some 421 Dutch Caucasian families were recruited of which at least two long-lived siblings were alive and aged 89 years or older for men and 91 years or older for women, without selection on health or demographic characteristics. Furthermore, the offspring of these long- lived nonagenarians and their partners, were also enrolled (figure 2). These offspring carry 50% of the genetic advantage of their long- lived parent and were shown to have a 35% lower mortality rate compared to their birth cohort [10]. Their partners with whom most have had a relationship and shared environment for decades, were included as population-based, environment- matched controls.
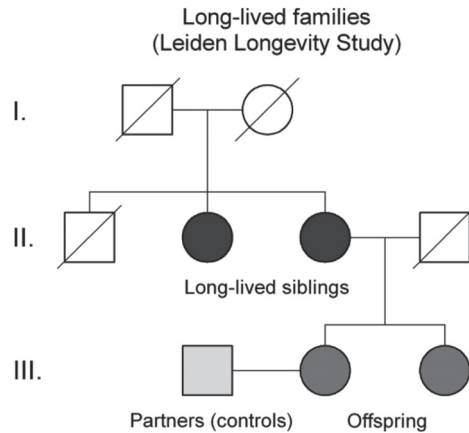
FIGURE 1.2 | Study design of the Leiden Longevity Study.

Brain MRI data from offspring and partners in the LLS were used to study the relation between parameters of glucose metabolism and brain function.

Data Sources- the Switchbox Study

The Switchbox study is a satellite study from the LLS. The study is entitled 'Maintaining health in old age through homeostasis', and has the acronym 'Switchbox'. It is an European project comprising partners from Paris, Munich, Budapest, Braga and Leiden, with the collective aim of improving healthy longevity by studying the brain- periphery dialogue with a view to re-setting the critical hypothalamic set-points. In Leiden, Switchbox was conducted in two phases- Phases I & II, over a period of 4.5 years (figure 3). The first phase (phase I) was an observational study of offspring of long- lived siblings and their partners, while phase II was a randomised controlled clinical trial involving healthy volunteers from the general population.
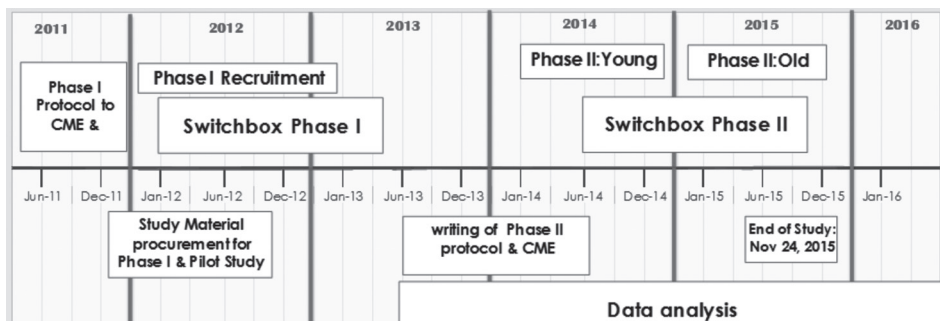

FIGURE 1.3 | Switchbox timeline covering the period of 4.5 years during which the Switchbox study was conducted.

Switchbox Phase I

The hypothesis of the Switchbox phase I study is that control of homeostasis would be better preserved in the offspring of long-lived sibling, who grow older in better health compared to their partners who show 'regular' ageing. This was hypothesized to be reflected in differences in brain function, neuro-endocrine output and peripheral metabolism. Thus, we examined the links between the three main signaling axes- Hypothalamo-adrenal axis (HPA), Hypothalamo- thyroid axis (HPT) & Insulin- IGF-1 signaling axis (IIS) and critical measures that deteriorate during the ageing process, such as metabolism, brain structure and function, and heart rate and heart rate variability.

Between March 2012 and July 2013, 135 offspring and partners from the LLS were included for Switchbox phase I. Inclusion criteria were being middle-aged (55-77 years) and having a stable body mass index (BMI) between 19 kg/m2 < BMI < 33 kg/m2. All women in the study were postmenopausal. Participants were excluded if their fasting plasma glucose was above 7 mmol/L, if they had any significant chronic, renal, hepatic or endocrine disease, or if they used any medication known to influence lipolysis, thyroid function, glucose metabolism, GH/IGF-1 secretion or any other hormonal axis. Other exclusion criteria were difficulties to insert and maintain an intravenous catheter, anaemia (Hemoglobin < 7.1 mmol/L), blood donation within the last two months, smoking and alcohol addiction, severe claustrophobia and extreme diet therapies. Data for comparison of measures of brain function (structural and functional brain MRI, cognitive tests), neuro-endocrine output (24-hour hormone rhythms), and peripheral metabolism (continuous glucose monitoring, indirect calorimetry, diaries), cardiac parameters (continuous ambulatory ECG monitoring) to estimate sympathetic/ parasympathetic tone and motion (continuous tri-axial accelerometry) were collected over five days (figure 4) from offspring and their partners, to identify parameters most relevant for a slower pace of ageing.
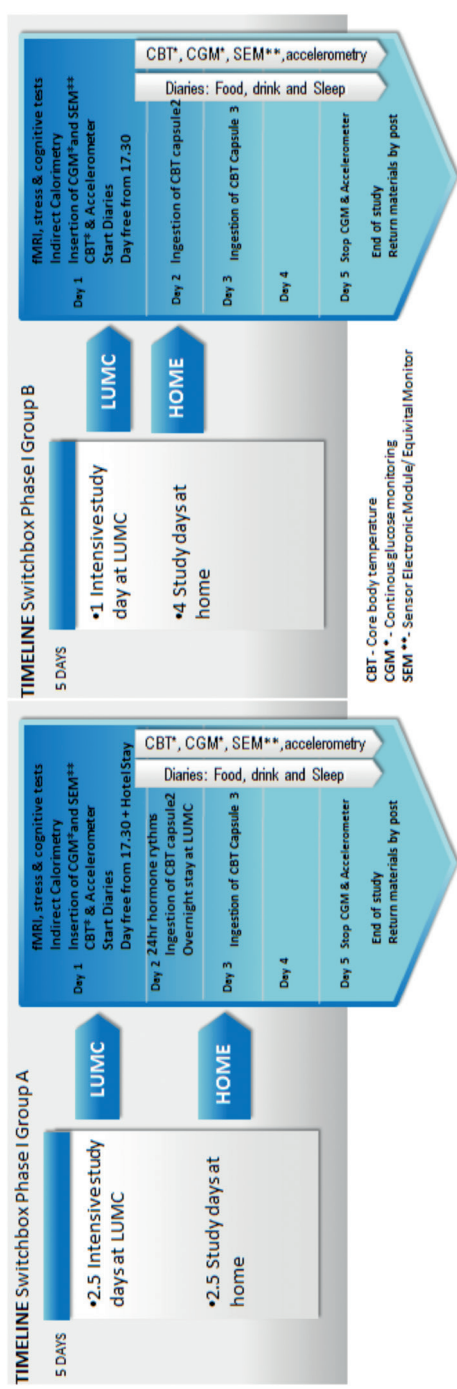
FIGURE 1.4 | Study protocol followed by both groups of Switchbox phase I participants.

Switchbox Phase II

Insulin is an important modulator of brain functions, including central regulation of energy homeostasis, cognitive functions, neuronal activity and other behavioral, cellular, biochemical, and molecular functions [11, 12]. Due to the presence of direct pathways from the nasal cavity to the CNS, insulin can be delivered, non- invasively and rapidly to the CNS through the intranasal route without being absorbed into the blood stream or having direct systemic effects [13].

Phase II involved testing whether and to what extent parameters identified in Phase I could be modulated by intranasal insulin application. To this end intranasal insulin and placebo were administered to 19 adults (8 young and 11 elderly) volunteers from the general population in a blinded, cross- over designed randomized clinical trial in which each participant served as his own control. Participants were randomized into two groups for the order of intranasal application of insulin and placebo (insulin first or placebo first groups), In addition, the younger participants additionally received either 75 gr glucose solution or water during the MRI protocol. Thus, the younger participants were randomized to four study days (insulin and glucose, insulin and water, placebo and glucose, placebo and water) (figure 5) whereas the older had two visits (insulin and water and placebo and water).

In this thesis, we report on the neuro-endocrine, metabolic and autonomic characteristics that appear to be pertinent for slower pace of ageing.
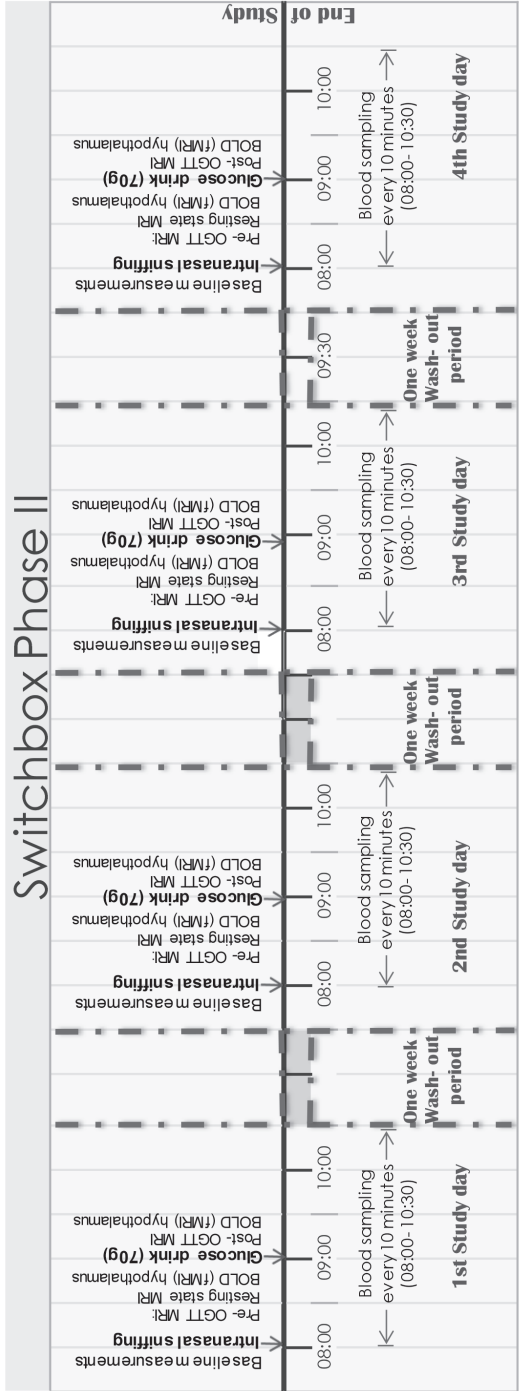
Switchbox Phase II

FIGURE 1.5 | Study protocol followed by Switchbox phase II participants.

REFERENCES:

1. Oeppen J, Vaupel JW. Demography. Broken limits to life expectancy. Science. 2002;237:1029

2. Westendorp RG. What is healthy ageing in the 21st century? Am J Clin Nutr. 2006;83:404S-9S

3. Zwaan BJ. The evolutionary genetics of ageing and longevity. Heredity (Edinb). 1999;82 (Pt6):589-97

4. Holzenberger M,Dupont J,Ducos B, Leneuve P, Geloen A, Even PC, et al. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature. (2003) 421(6919):182–7. doi:10.1038/nature01298

5. Bartke A, Chandrashekar V, Dominici F, Turyn D, Kinney B, Steger R, et al. Insulin-like growth factor 1 (IGF-1) and E: controversies and new insights. Biogerontology. (2003) 4(1):1–8. doi:10.1023/A:1022448532248

6. Marieb, Elaine N., Hoehn, Katja N. (2009). Essentials of Human Anatomy & Physiology (9th ed.). San Francisco, CA: Pearson/Benjamin Cummings. ISBN 0321513428.

7. Gavrilov LA, Gavrilova NS. Early-life programming of aging and longevity: the idea of high initial damage load (the HIDL hypothesis). Annals of the New York Academy of Sciences. 2004;1019:496-501.

8. Gillman MW. Developmental origins of health and disease. The New England journal of medicine. 2005;353(17):1848-50.

9. Source: Boundless. "Homeostatic Control." Boundless Anatomy and Physiology. Boundless, 21 Jul. 2015. Retrieved 09 Oct. 2015 from https://www.boundless.com/physiology/textbooks/boundless-anatomy-and-physiology-textbook/introduction-to-human-anatomy-and-physiology-1/homeostasis-32/homeostatic-control-284-3141/

10. Schoenmaker M, de Craen AJ, de Meijer PH, Beekman M, Blauw GJ, Slagboom PE, Westendorp RG (2006) Evidence of genetic enrichment for exceptional survival using a family approach: the Leiden Longevity Study. Eur J Hum Genet. 14:79–84. doi:10.1038/sj.ejhg.5201508

11. Duarte AI, Moreira PI, Oliveira CR. Insulin in central nervous system: more than just a peripheral hormone. JAging Res. 2012;2012:384017.

12. Schwartz MW, Seeley RJ, Tschop MH, Woods SC, Morton GJ, Myers MG, et al. Cooperation between brain and islet in glucose homeostasis and diabetes. Nature. 2013;503(7474):59-66.

13. Hallschmid M, Benedict C, Schultes B, Perras B, Fehm HL, Kern W, et al. Towards the therapeutic use of intranasal neuropeptide administration in metabolic and cognitive disorders. Regulatory peptides. 2008;149(1-3):79-83.

OUTLINE OF THIS THESIS

The main objective of this thesis is to provide new insights into the crosstalk between the brain and the periphery, with a focus on glucose and insulin metabolism, the thyroid axis and the autonomic nervous system. Each section begins with the validation of a measurement device for use for a key parameter in this crosstalk.

Part I of this thesis discusses the role of the brain in glucose and insulin metabolism, in both offspring of families enriched for familial longevity and their partners. Since glucose metabolism was previously shown to associate with longevity potential, we explored ways to measure glucose levels non-invasively. Thus, we started in **chapter 2** with the validation of a continuous glucose monitor for non-invasive glucose measurement in older persons. Based on the hypothesis that maintenance of glucose metabolism is important not just for metabolic health but also for the brain, we assessed the relation between glucose and insulin metabolism on brain macro- and microstructure in **chapter 3**. Then, we further tested the effect of age and being a descendant of families enriched for familial longevity on the relation between parameters of glucose metabolism and the brain integrity in **chapter 4**. To gain mechanistic insights into the role of the brain in glucose metabolism, we examined the effect of intranasal administration of insulin on the brain, as it was found previously to improve cognition in humans. In **chapter 5**, we examined the effect of intranasally administered insulin on cerebral blood flow and perfusion in young and older adults. Part I concludes with **chapter 6**, where we reviewed the crosstalk between glucose and insulin metabolism, ageing and the brain.

In **Part II** of this thesis, we investigated another system that is implicated in human longevity; i.e. the thyroid axis. Thus, we set out to characterize the thyroid axis. First, we devised a versatile method for frequent blood collection in older participants. This is presented as **chapter 7**. Then, in **chapter 8**, from frequently sampled blood, we investigated the thyroid stimulating hormone (TSH) secretion pattern on the one hand, and whole body energy metabolism on the other hand in relation to longevity. In **chapter 9**, via a systematic review and meta-analysis of existing literature, we further looked at the effect of subclinically raised TSH levels on cognition.

Summarily, our study of the thyroid axis showed that human longevity is characterized by higher TSH levels, but without differences in basal metabolism. Since the thyroid gland is innervated by the autonomic nervous system, and its activity might be affected by the

sympathetic/ para-sympathetic tone, we tested the influence of the autonomic nervous system, using heart rate and heart rate variability as a proxy, on human longevity. This forms the basis for the **third part (Part III)** of this thesis. In this part, in **chapter 10**, we first validated a device- the Equivital (EQ02) lifemonitor- for non-invasive measurement of ambulatory ECG, heart rate and heart rate variability in older adults. Then, in **chapter 11**, we examined the role of heart rate rhythms and heart rate variability in familial longevity.

Finally, in **chapter 12**, the key findings of this thesis are summarized. These are then discussed in context of current knowledge of human longevity.