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DECISION-MAKING UNDER UNCERTAINTY:
LINKING BRAIN, BEHAVIOR AND FAMILY FACTORS IN PATIENTS WITH TYPE 1 DIABETES

VOLUME 1

Tese no âmbito do Programa Interuniversitário de Doutoramento em Psicologia área de especialização em Psicologia Clínica, área temática Psicologia da Família e Intervenção Familiar, orientada pelo Professor Doutor Miguel de Sá e Sousa de Castelo-Branco e pela Professora Doutora Ana Paula Pais Rodrigues da Fonseca Relvas e apresentada à Faculdade de Psicologia e Ciências da Educação.

Dezembro de 2020

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IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Declaração

De acordo com o artigo 17º do regulamento do Programa Interuniversitário de Doutoramento em Psicologia, especialidade em Psicologia Clínica, vertente temática, Psicologia da Família e Intervenção Familiar da Universidade de Coimbra e da Universidade de Lisboa, esta dissertação engloba artigos científicos submetidos para publicação em revistas internacionais indexadas. A autora declara que foi responsável pela recolha de dados, análise e interpretação dos dados, assim como pela redação, submissão e revisão dos manuscritos enviados para publicação. A referenciação bibliográfica e outros aspetos de edição seguem as normas da APA, 7ª edição.

Helena Margarida Venâncio Miguel Jorge

Dezembro 2020

Difficult roads often lead to beautiful destinations.

Zig Ziglar

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Agradecer é um ato de reconhecimento
do esforço coletivo para atingir objetivos.
Agradecer é um elogio que enaltece o mérito
dos que partilharam conhecimento.
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lembrando que pedimos ajuda em cada momento.
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pelo tempo que roubámos ao Outro em vão.
Pelo tempo em que estivemos ausentes.
Agradecer não enfraquece, mas engrandece.
Agradecer valoriza o Outro e suscita empatia.
Agradecer faz repensar e a confiança restabelece.
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ABSTRACT

Type 1 Diabetes Mellitus (T1DM), a global health chronic disease with high-cost public health, requires iterated daily decision-making behaviors with interference on family routine as glycemic monitoring and special care with meals. Otherwise, they risk self-consequential short and long-term health complications.

The main question of the present thesis is to understand how people decide in face of self-consequent difficult choice, beyond the economic domain, namely health related decision-making, in a lifelong disabling disorder: Type 1 Diabetes Mellitus (T1DM). To understand social decision-making under uncertainty in the health domain and knowing that decision-making is context-dependent, we selected Neuroeconomics, Social Neurosciences and Family Systems Models of Chronic Diseases as the global frameworks to guide and design our literature review and methodology. We answered to this general question by two main roads.

First, we hypothesized that high rates of low adherence might be related to decision-making impairments and family variables. We defined self-perception and behavioral risk decision profiles that differentiate patients with impaired metabolic control (N=49, NoMC) and patients with successful metabolic control (N=42, MC) through a self-report survey and experimental tasks. A health control group (N=53) was also assessed but in this case metabolic status is stable and not disrupted.

The multidimensional battery of risk decision-making included three measures of risk perception [1)delay discounting, 2)past and present risk and 3)risk taking in economic and health domains], and risk-related behaviors as impulsivity and eating behavior. The three experimental interactive tasks were the Balloon Analogue Risk Task [BART] and two novel trust games, investigating neuroeconomic and health contexts. Psychosocial, personality, cognitive and sociodemographic factors were assessed

by a quantitative methodology with family and personality questionnaires, fluid and crystallized intelligence, executive functions (memory) and a sociodemographic survey, respectively.

We found out that groups of metabolic and no metabolic control could be independently discovered through data driven cluster analysis with risk and family variables. Metabolic control was defined through individual values of HbA1c over time revealing its dynamic, forming two groups within patients: impaired metabolic control (NoMC) and successful metabolic control (MC). Independent sample parametric and non-parametric tests allowed us to find out group differences. Groups were matched for age, gender and civil status and no cognitive differences were found. Different decision-making profiles emerged. Beyond high neuroticism and low extroversion, NOMC presented reduced self-control, misperception of risk in health context, higher past and present general risk and lower capacity to delay reward. They also performed worse in BART with a tendency to a risk averse profile and they maintained the same behavioral pattern throughout the game. During trust games, both groups showed be able to detect payoff contingencies of each player in each context, but their collaboration differ in health setting. NoMC groups is not indifferent to payoff contingencies whereas compliance patients opted to collaborate regardless of the doctor payoff. Family functioning and congruence, income, educational level, HbA1c values, and emotional eating behavior proved to be significant predictors of lower metabolic control.

Second, we hypothesized that suboptimal choices under uncertainty are related to altered neural risk processing and context dependent. Other group of patients with T1DM and controls (healthy participants) were scanned in fMRI while they performed the three experimental tasks.

Brain activity and behavioral results in BART showed that groups differ in face of uncertainty and ambiguity. Adaptive decision-making mechanisms and cognitive impulsivity are affected in T1DM and predict the biological status. Patients kept a same pattern of activation even after iterative decision-

making, showing activation of brain regions involved in anxiety and conflict monitoring. Interestingly, motivation, reward, and impulsive neural mechanisms in particular frontal and limbic areas as middle and inferior frontal cortex, striatum, midbrain dopaminergic nuclei and insula, seem to play a pivotal role to explain biological worsening in patients with impaired metabolic control.

Brain activity and behavior results in trust games revealed that T1DM that HbA1c is a biochemical index that predicts modified risk processing and neural activation patterns in Type 1 Diabetes. This pattern differs according to context and according to biological worsening. Health context was emotionally more relevant and required hard self-consequent decision for patients. The effect of biological worsening in investment was differently in economic and health context: neural activity in regions related to inhibitory control for economic context and for error monitoring/conflict (saliency network) in the health context.

To the best of our knowledge, experimental and neuroimaging studies of this thesis are innovative and pioneering in neuroeconomics and social neurosciences, providing a translation to health decision-making under uncertainty in lifelong disorders. Linking three interdependent dimensions – brain, behavior, and social context- with a biological variable of metabolic control variation (glycaeted hemoglobin) we got an integrated scientific evidence for impaired behavior and neural risk processing in T1DM which might be helpful for personalized interventions and to guide future basic and clinical research studies.

Keywords: Type 1 Diabetes Mellitus; Decision-making under uncertainty in economic and health domains; Decision Neuroscience; Family, Systems and Chronic Disease.

SUMÁRIO

A Diabetes Mellitus tipo 1 (DM1), uma doença crónica de saúde global com elevados custos para a saúde pública, requer comportamentos repetidos e diários de tomada de decisão que têm interferência nas rotinas familiares, como monitorização da glicémia e cuidados especiais com as refeições. Caso contrário, estes doentes correm o risco de desenvolver complicações de saúde a curto e longo prazo.

A questão central da presente tese é compreender como sáo tomadas decisões difíceis com consequências pessoais, para além do domínio económico, ou seja, a tomada de decisão em saúde, numa doença incapacitante ao longo da vida: a Diabetes Mellitus Tipo 1 (DM1). Tratando-se de uma decisão social sob incerteza no domínio da saúde e sabendo que a tomada de decisão depende do contexto, abordámos a Neuroeconomia, as Neurociências Sociais e os Modelos Sistémicos da Família e da Doença Crónica como enquadramento global para orientar a nossa revisão de literatura e metodologia. Respondemos a esta questão geral através de duas vias principais.

Em primeiro lugar, formulamos a hipótese de que elevadas taxas de baixa adesão terapêutica podiam estar relacionadas com alterações no processo de tomada de decisão e variáveis familiares. Definimos perfis de risco com base no auto-relato de decisão de risco comportamental que diferenciasse doentes com controle metabólico alterado (N=49, NoMC) e pacientes com controle metabólico bem-sucedido (N=42, MC), através de questionários e tarefas experimentais. Um grupo de participantes saudáveis (N=53) também foi avaliado, mas, neste caso, o estado metabólico é estável e não alterado. A bateria multidimensional de tomada de decisão de risco incluiu três medidas de perceção de risco (adiar a obtenção da recompensa, risco passado e presente e decisão de risco em diferentes domínios) e construtos relacionados com os riscos, impulsividade e o comportamento alimentar. As três tarefas experimentais interativas foram Balloon Analogue Risk Task [BART] e dois novos jogos experimentais, investigando os contextos neuroeconómicos e de saúde. Os fatores familiares, de personalidade,

cognitivos e sociodemográficos foram avaliados por questionários familiares e de personalidade, inteligência fluida e cristalizada, funções executivas (memória) e um questionário sociodemográfico.

Descobrimos que grupos com e sem controle metabólico podem ser identificados de forma independente por meio de uma análise de cluster baseada em dados com variáveis de risco e variáveis familiares. O controle metabólico foi definido através dos valores individuais de HbA1c ao longo do tempo revelando a sua dinâmica, formando assim dois grupos entre os doentes – sem controlo metabólico (NoMC) e com controlo metabólico (MC). Testes paramétricos e não paramétricos para amostras independentes permitiram-nos descobrir diferenças significativas de grupo. Os grupos foram emparelhados por idade, género e estado civil e não foi encontrada nenhuma diferença ao nível do desempenho cognitivo. Para além de elevado neuroticismo e reduzida extroversão, o grupo NoMC evidenciou reduzido autocontrolo, menor perceção de risco no contexto de saúde, maior risco geral no passado e no presente, menor capacidade de adiar a recompensa. Estes doentes também obtiveram pior desempenho no BART com tendência para um perfil avesso ao risco, mantendo o mesmo padrão de comportamento ao longo do tempo. Durante os jogos de confiança, os dois grupos identificaram as contingências associadas a cada jogador, mas a sua colaboração no contexto de saúde diferiu. Enquanto que os doentes sem controlo metabólico tiveram em conta as contingências da recompensa, os doentes com controlo metabólico colaboraram desse o início independentemente da recompensa. Tanto o funcionamento familiar, congruência, salário, nível educacional, HbA1c e comportamento alimentar emocional provaram ser preditores de menor controlo metabólico.

Em segundo lugar, colocamos como hipótese que as escolhas sob incerteza não adaptativas estão relacionadas com alterações no processamento de risco neural e são dependentes do contexto. Pacientes com diabetes tipo 1 e controles (participantes saudáveis) foram submetidos a um exame de ressonância magnética funcional enquanto realizavam a Tarefa BART e os jogos de Confiança. Os padrões de atividade cerebral e os resultados comportamentais no BART mostraram que os grupos diferem perante a incerteza e a ambiguidade. Os mecanismos da tomada de decisão adaptativa e a

impulsividade cognitiva estão afetados na Diabetes Mellitus Tipo 1 e predizem o estatuto biológico. Os doentes mantiveram o padrão de ativação mesmo após a sucessivas decisões, permanecendo numa situação de ansiedade e conflito, comprovada pela ativação das vias inibitórias e emocionais. Curiosamente, os mecanismos neuronais associados à motivação, recompensa e impulsividade, nomeadamente áreas límbicas e frontais como o mPFC e PFC inferior, estriado, núcleos dopaminérgicos do tronco cerebral e insula, desempenham um papel crucial para explicar padrões apresentados pelos doentes com controlo metabólico alterado.

A atividade cerebral e os resultados do desempenho nas tarefas de confiança revelaram que a HbA1c é um índice bioquímico preditor do processamento de risco e padrões de ativação neuronais alterados na diabetes tipo 1. Este padrão é diferente de acordo como o contexto e também de acordo com o comprometimento biológico. O contexto de saúde revelou ser mais emocionalmente relevante e exigiu aos doentes decisões mais difíceis e auto-consequentes. Doentes com controlo metabólico alterado revelaram ativações cerebrais relacionadas com controlo inibitório no contexto económico, e no contexto de saúde em áreas ligadas a conflito e monitorização do erro (rede neuronal da saliência).

De acordo com o nosso conhecimento até ao momento, os estudos experimentais e de neuroimagem desta tese são inovadores e pioneiros para a neuroeconomia e neurociências sociais, dando um salto na investigação para a tomada de decisões em contexto de saúde sob incerteza em doenças crónicas. Ligando três dimensões interdependentes - cérebro, comportamento e contexto familiar - com uma variável biológica de variação de controle metabólico (hemoglobina glicosilada), obtivemos uma evidência científica integrada para o comportamento não adaptativo e alterações no processamento de risco neural em adultos com Diabetes Mellitus Tipo 1. Este conhecimento é útil para a planificação de intervenções personalizados e para orientar trabalhos futuros de investigação básica e clínica.

Palavras-chaves: Diabetes Mellitus Tipo 1; Tomada de decisão sob incerteza na economia e na saúde; Neurociências da Decisão; Família, Sistemas e Doença Crónica.

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INTRODUÇÃO

Os custos relacionados com a Diabetes Mellitus em Portugal excederam os 740 milhões de euros em 2018. Estes resultados, apresentados no último Relatório Nacional da Diabetes, da Direção Geral de Saúde (2019), corroboram a notícia veiculada pelo Jornal Público, a 7 de novembro de 2019: por dia são diagnosticadas 200 pessoas com diabetes. Este trabalho académico traz evidências científicas para argumentar que este problema de saúde pública pode ser minimizado tendo em conta o processo de escolha individual.

Imaginemos duas pessoas com Diabetes a sair de uma consulta. Ambas receberam, dos seus médicos, indicações terapêuticas e concordaram em seguir as orientações clínicas. Isto significa que para atingir o controlo metabólico, têm de fazer sacrifícios diários, escolhas de modo a seguir os conselhos médicos, com a intenção de obter controlo metabólico (uma recompensa imediata e incerta) e evitar as complicações de saúde no futuro (uma recompensa a longo prazo e incerta). Nenhum tem complicações de saúde atuais significativas, nem história de doença psiquiátrica. Sem saber por quanto tempo e qual a gravidade de poderem vir a desenvolver uma complicação de saúde no futuro, um deles decide confiar e colaborar - risco nulo no domínio da saúde - e o outro não - risco no domínio da saúde! Porque fazem escolhas opostas? Porque é que isto é importante?

Compreender a variabilidade individual na tomada de decisão em saúde é altamente relevante para os cuidados de saúde personalizados. Essas decisões, que se enquadram num contexto social em situações do mundo real, incluindo a decisão de confiar ou cooperar com outras pessoas, são inerentemente incertas e dependentes do contexto. Denominam-se decisão social e foram estudadas no contexto económico por duas áreas disciplinares: a Neuroeconomia e as Neurociências Sociais. Embora sejam disciplinas separadas, ambas pretendem compreender a natureza da interação social humana e da tomada de decisão humana e pretendem identificar os seus mecanismos neuronais. No entanto, além do domínio económico, no contexto de saúde ainda não foi estudada. O que sabemos

sobre a tomada de decisão sob incerteza em contextos sociais e seus mecanismos neuronais? Porque é que a Diabetes Tipo 1 é um bom modelo de tomada de decisão de saúde sob incerteza? Como é que os modelos familiares de doenças crónicas podem ajudar a compreender a relação entre o contexto social e o controlo metabólico alterado? Será que a hemoglobina glicosilada (HbA1C), sendo uma variável biológica que está relacionada com a adesão à diabetes, esconde uma informação preponderante sobre o processo de tomada de decisão desajustada?

Esta tese de doutoramento visa compreender como é que as pessoas decidem perante uma escolha difícil que tem consequências individuais, no contexto de uma doença crónica, a Diabetes Tipo 1. Esta doença implica decisões diárias que interferem com as rotinas familiares e o seu descontrolo está associado a complicações médicas severas. Para responder a esta questão precisámos de dar um salto metodológico da neuroeconomia para a tomada de decisão em contexto de saúde. Inspirámo-nos teórica e empiricamente na Teoria dos Jogos, nas Neurociências Sociais e no Modelo Sistémico da Família-Doença de Rolland. Combinámos questionários de auto-relato, com tarefas experimentais e técnicas de neuroimagem para caracterizar doentes com e sem controlo metabólico.

Este trabalho é fruto de muitos encontros multidisciplinares inquietantes entre os investigadores, a Psicologia, a Economia, a Medicina e as Neurociências. No centro da mesa, encontraram um novelo que representa a nossa questão, um mistério intrigante por desvendar. Em conjunto, cada um trouxe a sua visão sobre o processo de tomada de decisão. Impregnados pela curiosidade, começaram a desfiar este novelo e encontraram desafios que suscitaram novas perguntas e obrigaram a tomar decisões estratégicas que exigiram criatividade, persistência, entreajuda e uma audácia individual e grupal controlada. Ao longo deste trabalho, vamos assistir à descrição destes diálogos co-construídos que permitirão edificar um novo conhecimento que será mais do que a soma das partes, que se rege pelo princípio da causalidade circular, num processo em que o investigador é igualmente participante, colocando hipóteses através das suas lentes, com o objetivo de delimitar a inatingível complexidade.

PART I

THEORETICAL AND EMPIRICAL FRAMEWORK

Overview

In PART I, I will first review fundamental work in Neuroeconomics to define the concept of decision--making under uncertainty as a prior step to decipher its neurocognitive and brain mechanisms. After, I will present a Chronic Disease - Diabetes Mellitus - as a Health model of social decision-making under uncertainty considering its clinical features, therapeutic demands, psychological, and social mutual implications, as family system. Consequently, I will focus on Family Health Systems Models to systematize the theoretical framework to clinical interventions on the interpersonal context of physical chronic diseases, as diabetes mellitus (Figure 1).

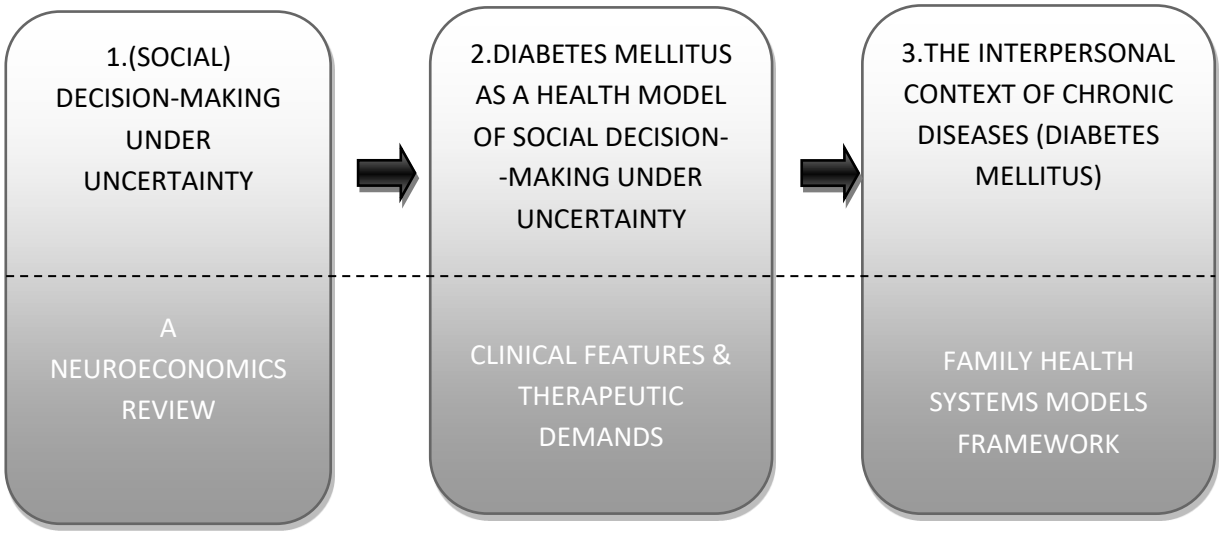


Figure 1. Map of contents for Theoretical and Practical Framework (Part I)

CHAPTER 1

(SOCIAL) DECISION-MAKING UNDER UNCERTAINTY: A NEUROECONOMIC REVIEW

From Descartes until nowadays, multiple theories have been developed to understand how people make decisions in face of uncertainty. Blaise Pascal, a seventeen-century brilliant mathematician, came up with an interesting argument for why one should believe in God. In face of the uncertainty of His existence that we cannot assign a number, if God does not exist, we do not lose anything, but if He exists so we gain in believe and we lost in being unbeliever. Translating to mathematical language, we maximize the gain being a believer. After that, some argue that we can lose, if we believe and God does not exist because being a believer involves deny same pleasures of life. So, Pascal reacted saying that the pleasures of life are finite and the gains if God exists are infinite, concluding that to believe in God in face of the uncertainty of His existence is the best choice. Currently, we are talking about choice preferences, deciding between immediate and low rewards or delay this reward in time to achieve a larger one. Pascal provided insights on how to follow the best option. However, even in presence of mathematical evidence and logic thinking, human behavior can be surprisingly different from expected. This is why two complementary frameworks came up from economic theories: normative and descriptive.

Normative theories predict what people should do in each decision situation if they were rational machines, forming axioms and theorems (how people should decide). Such theories, including

expected utility theory (von Neumann & Morgenstern 1944) associate each option with a numerical value, its utility. The option with the maximum utility is the optimal choice. If the outcome is not certain and has a probabilistic value, the optimal choice is the maximum expected utility. If the outcome is delayed, the optimal choice is the maximum utility. It`s easy to choose the highest value when the value of available option is known. But calculating the value of available options in complex choice is difficult. Normative theories deal with choices in an idealized context and often fail to account for actual choices made by humans and animals.

Nevertheless, in 1961, Daniel Ellsberg, empirically demonstrate that our actions, and those of other species, can be described in terms of attempts to obtain rewarding, or positive, outcomes and to avoid aversive, or negative, outcomes (Ellsberg Paradox). The notion of paradox comes from the fact that typically people are averse to both risk and ambiguity, avoiding much more outcomes that are associated with unknown probabilities, even if the known probability is low and the unknown probability corresponds to a certain win (Groot & Turik, 2018; Taya, 2012, for a review; Vives & FeldmanHall, 2018). Previously, in 1953, Allais had also come up with evidence that human behavior is different from axiomatic reasoning - Allais Paradox – (Mongin, 2019).

Thus, descriptive theories emerged. They consider empirical observation of factual behavior, a bottom-up approach to understand real human decision-making (what people really decide). They try to account for failures of normative theories by identifying a set of heuristic rules applied by decision makers. In 1979, Kahneman & Tversky, proposed the Prospect Theory which successfully accounts for the failures of expected utility theory in describing human decision-making under uncertainty.

WHAT MEANS DECISION-MAKING UNDER UNCERTAINTY? Takemura (2004) presented a taxonomy of uncertainties as the decision environment (Figure 1) to argue that a decision under uncertainty demands a constant estimation of possible risks associated with each option in consideration, based

on individual prior experience - from neurobehavioral to social interactions. There is an inability to apply known probabilities to a set of outcomes. Decision-making as the "ability to anticipate future outcomes of our choices" (Crone & van der Molen, 2008) is so considerably affected by the knowledge of decision-making conditions. Under uncertainty, a fundamental and intrinsic feature of human life, decision makers have missing information about outcomes and unknown information about its probability distribution. If we add ambiguity to uncertainty, it involves more complex situations with imprecise information about outcomes (Pushkarskaya et al., 2015). Thus, this sequential process of continuous representation of an option, its valuation, choosing an option, evaluate the outcome/reward and update its representation to guide future behavior is called the value-based decision-making. So, although people tend to avoid unknowns, if they choose unknowns, missing information will be available, allowing to improve performance in the long-term. This dilemma, called exploration-exploitation, belongs to a rule learning process that came from **Reinforcement Learning Theory (RL)** and it was the starting point to investigate the behavioral and neural mechanisms of decision-making.

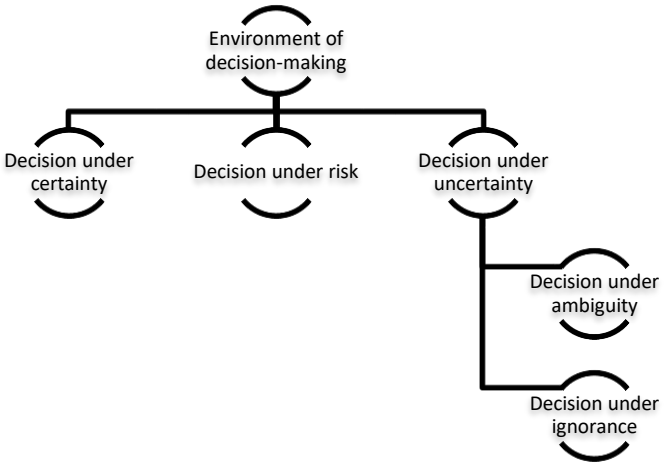


Figure1. Taxonomy of uncertainties as decision environment. In Takemura, 2014, p.7.

WHY DECISION-MAKING IS CONTEXT-DEPENDENT? Context in decision-making can assume two meanings. It can be related to decision-making conditions (under certainty, risk, or uncertainty; type of stimulus, as

food or money; computer or human beings). Considering social contexts and identical decisions, choices values may vary depending on distinct opponents, for example. Otherwise, context can be seen has a different setting. While one choice is highly valued in one contextual setting (economics), it may have a low or negative association elsewhere (health), assigning a subjective value. Understanding iterative decision-making, in the presence of two or more opponents (social decision-making) encouraged the arising of behavioral and neural experiments that integrate Game Theory (GT) and Theory of Mind (ToM), resulting Trust Games.

To sum up, behavioral decision-making was born from integration of psychological and mathematical descriptions of human choice behavior, linking economic, learning theories and social psychology. Next, I will focus on the most relevant framework of decision-making to this study: Reinforcement learning, Game Theory and Theory of Mind.

1.1 Reinforcement learning, Game Theory & Theory of Mind

Theories from psychology concluded that decision-making is tightly interlinked with learning and memory. The most consensual and well-known approach is Reinforcement Learning Theory. It posits that Decision-Making is a learning process that includes three repeated main sequential steps. First, the confrontation with two or more options and attribution of a subjective value through statistical computations (valuation system). Second, the selection for one of them (action selection). Third, the outcome monitoring (redefining valuation system) that will guide future actions, by stimulus-reinforcement contingencies. It means that decision-making involves a continuous learning action and stimulus values from experience with reward and punishment to anticipate future consequences/outcomes of choices. In this way, actions followed by a reward or punishment acquire a value through the computations of prediction errors - discrepancies between the expected and the

actual reward - updating the preceding value. Rangel et al. (2008) presented a schematic representation of this decision-making process from reinforcement learning perspective (Figure 2).

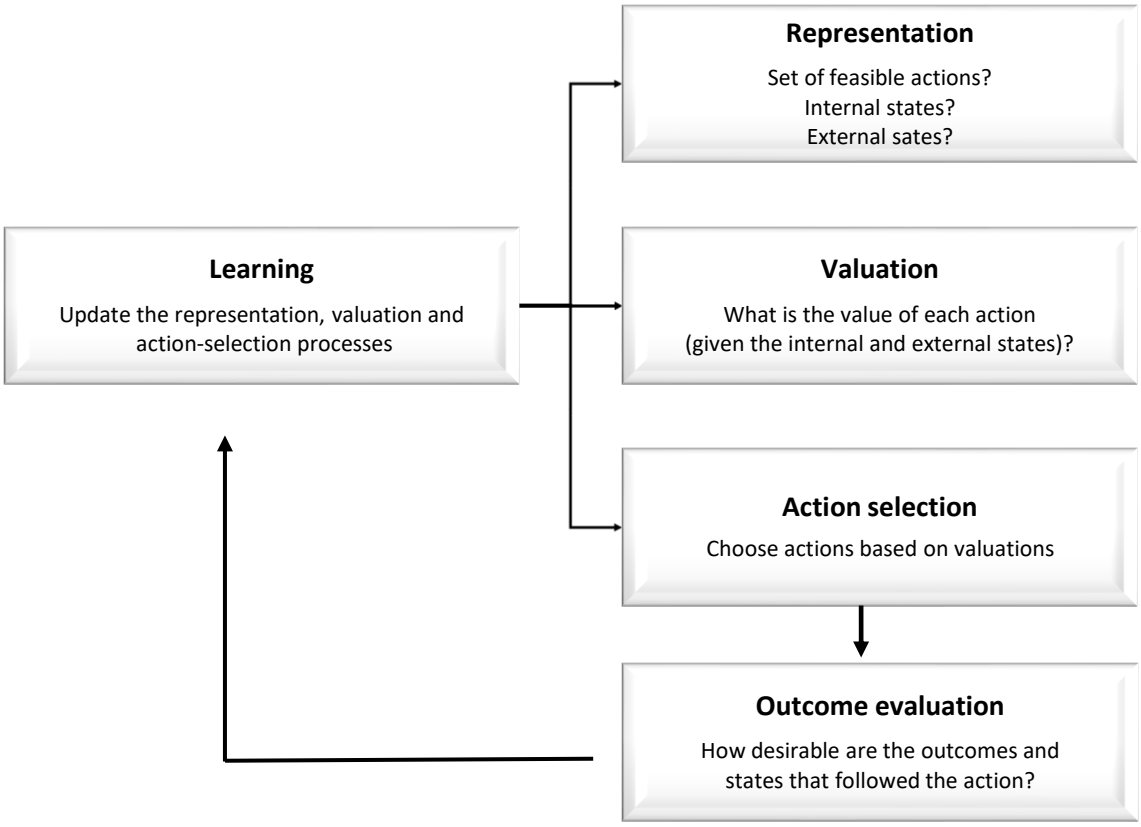


Figure 2. Schematic representation of decision-making process from reinforcement learning perspective in Rangel et al. (2008), p.555.

Linking economic and reinforcement learning theories in general, behaviors choice in economic theories are those that maximize the organism's utility (Lee et al., 2012). However, they do no mention how these utilities are constrained by evolution and individual differences. To enable preservation of the individual and species, adapted behaviors (e.g., danger avoidance, search for food, reproduction) are crucial. For this purpose, three specific psychological components are set in motion listed by Rolls

(2014): emotional, motivational, and cognitive-motor components. Positive or negative reinforcements could cause pleasure or pain, as aversive stimulus (emotional component). (2) The mental representation of this reinforcing could induce to get a reward or avoiding a punishment (motivational component). Finally, emotional, or behavioral response will be integrated with learning about this reinforcement (cognitive-motor component). These components belong to the brain reward system and cognitive control network that will be explored in next section (Brain networks of decision-making). While in the animal kingdom, rewards and avoiding punishments are motivated by survival and reproduction, in humans, threat also happens when they face a subjective constraining situation, such as complex decision-making.

From classic research on conditioning (Pavlov and Skinner) to new behavior psychology (as Prelec), expected utility from economics and reward expectation from conditioning observations, achieved a physiological and neural correspondence by studies recording neural activity before decision-making, the moment of assigning a subjective value to each option. Estimating the potential value has led researchers to essay models that can explain decision-making process, as Model-free and model-based learning. In model-free decision-making, the frequency of an outcome (reward or aversive) is the reference to update and make current estimates. For example, if the learning process is characterized by intermittent reward (uncertain), subjects tend to persist for some time in the activity that was previously rewarded, because prediction of reward is more difficult (more resistant to extinction). (Hogarth & Villeval, 2010). In model-based decision-making, outcomes are linked to states, forming a model of the world and current estimates are based on the evaluation of the overall value obtained by the integration of these states. In psychological sciences, making predictions are also explained by two other learning systems: 1) the habitual system that repeats previously successful action by a simple trial and error process; and 2) goal-directed system that updates values based on anticipated impacts. (Daw & O`Doherty, 2014).

The concept of mentalizing has been in use in psychoanalytic literature since the 1970s to refer to the process of mental elaboration, including symbolization, which leads to the transformation and elaboration of drive–affect experiences like mental phenomena and structures. Making part of social psychology, this theory was incorporated into the neurobiological, as well as the developmental literature. The "false belief test" was used to evaluate the ability of one person predict someone else actions, since children of four years old. Premack and Woodruff coined this term as **Theory of Mind** (ToM) to refer to the capacity to interpret other people's behavior within a mentalistic framework to understand how self and others think, feel, perceive, imagine, react, attribute, and infer (Sharp, 2011). Beyond false belief test, theory of mind task is also a performed experimental task to evaluate mentalizing. These studies lead to the emergence of theories and models to explain mentalizing such as theory of simulation and identification/attribution model. Later, studies in social neurosciences helped to understand this inference process integrating three different level systems, reporting to intentions, thoughts, and feelings. The mirror system- an automatic system that allow to first identification of mental states, motor intentions and actions; the intrinsic mentalizing system- providing simulation of "putting oneself in his shoes", what other people think; and empathy system, a kind of "resonance" of another`s emotions and feelings, what other people feel. The network related to theory of mind will be explored in next section (Brain networks of decision-making).

This human ability to anticipate other`s intentions is near the process of playing a trust game in **Game Theory**. Economic decision-making often takes place in the context of social interactions. As part of the neuroeconomic approach, researchers have begun to investigate the psychological and neural correlates of social decisions using experimental tasks derived from a branch of experimental economics known as Game Theory" (Sanfey, 2007). It`s modern form came from the book The Theory of Games and Economic Behavior written by von Neumann and Morgenstern in 1944 and followed shortly by John Nash in 1950 with the proof of the existence of Nash equilibrium (Glimcher & Fehr, 2014). Game Theory is necessary to develop a strategy (action likelihood) towards other`s move,

simulating other`s mode of reasoning. The most well-known experimental games on human subjects focused on two-person exchange involving social dilemmas are the prisoner's dilemma game (PDG), the dictator game (DG), the ultimatum game (UG) and trust games. By the purpose of this thesis, trust games will gain a prominent place. Berg et al. (1995) proposed the following trust game. One player is the investor, and the other player is the trustee. In one-shot, the first player sends some money, all or no money to the other player (a measure of trust). This amount of money is tripled. In turn, the trustee sees the money sent and decide to what amount of money he would like to send back to the investor (a measure of trustworthiness). So, trusting involves anticipating other`s behavior, mentalizing. As Singer and Tusche (2014) described Game Theory provides an effective quantitative framework for studying how information, incentives, and social knowledge influence optimal strategies for social interaction. Experimental tasks, like trust games, have been used to study psychological and neural mechanisms of social decision-making.

1.2 Brain networks of Decision-Making

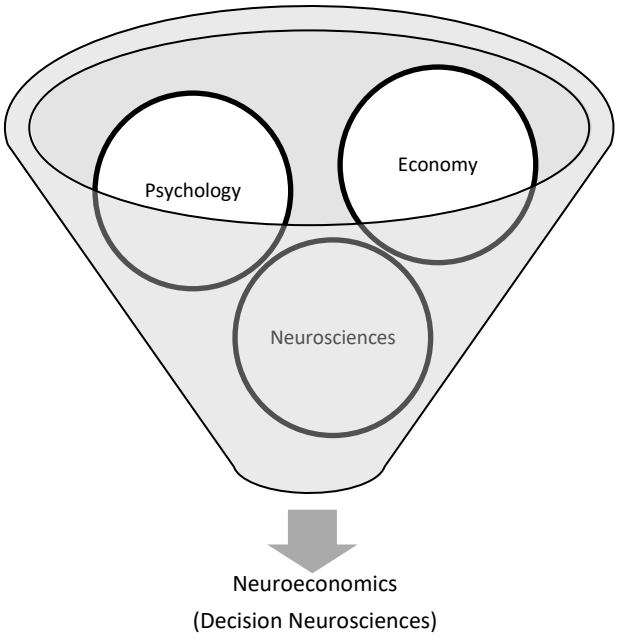


Figure 3. Theoretical framework of *Decision Neurosciences*.

Decision Neurosciences is a recent field (Smith & Huettel, 2010) and as part of the neuroeconomic approach, researchers have begun to investigate the psychological and neural correlates of social decisions using tasks derived from Game Theory, a branch of experimental economics known (Sanfey, 2007) as mentioned before. Just like behavior approaches, brain responses to uncertainty depend on the demands of the task (Figure 3).

Impaired decision-making was firstly driven through clinical observations of patients with frontal lobe damage, as Phineas Gage. In 1848, he survived after suffering damage to his frontal lobe with a tamping iron, but his personality was altered. Progress in localizing psychiatric neuropathology has come from advances in non-invasive neuroimaging techniques suitable for in vivo use in humans: Voxel Based Morphometry [VBM] Diffusion Tensor Imaging [DTI] Positron emission tomography [PET] and Functional Magnetic Resonance imaging [fMRI]. In healthy control subjects, application of these brain imaging techniques has been fruitful for delineating the overall functional architecture of the human brain. Neuroimaging techniques provide evidence that hypothesized psychological processes and individual and situational differences in such processes have physical manifestations in brain processes. A short introduction about structural and functional brain could be found in chapter 2 - Research Methodology – where the principles of the neuroimaging technique, fMRI, are discussed (Bandettini, 2020).

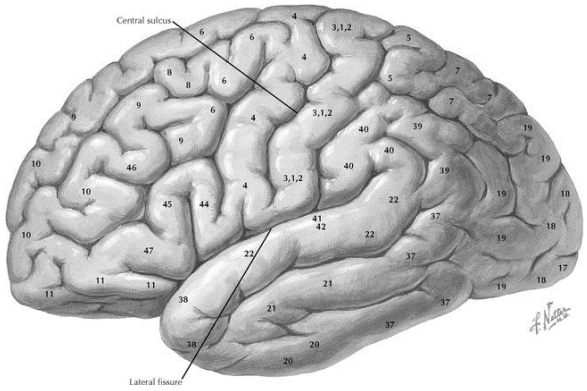


Figure 4. Lateral view of the forebrain: Brodmann`s areas. Numbering of cortical areas is based on histological observations originally made by Korbinian Broadman in 1909. Nowadays, they are still helpful to describe the functional regions of the cortex. Image from Felton et al. (2016, p.54).

From a macroscopic anatomic view, social decision-making under uncertainty involves a distributed subcortical-cortical network including multiple regions as prefrontal, parietal, temporal, limbic and subcortical ones (Rao, 2008). From a brain functional and neural connectivity point of view, social decision-making under uncertainty embodies three related systems or networks: reward and motivation; cognitive control, and social attribution.

The reward circuit is a complex neural network that underlies the ability to accurately evaluate reward value, predictability, and risk. It means assess the probability of outcomes from different choices to guide good decision-making and appropriate goal-directed behaviors. As Decision Neurosciences aims to investigate the neural processes underlying human choice being, the reward system is the neurobiological foundation of the economic models and learning theories addressed in last section. These neural processes are crucial to build a decision value: the neural representations of computational processes related to the valuation system or value representation and the choice. How brain encodes the representation of a value before and after individual choice behavior helps to understand the neural signal of prediction error responsible to update that representation and its choice impact. The inability to alter behavior when reinforcement contingencies change is the center of some psychiatric diseases. If the action-outcome contingencies are rapidly changing –contingency volatility- a high learning rate is required to avoid a pattern of behavior that is no longer optimal. Both anterior cingulate cortex (ACC) and the amygdala are implicated in the use of contingency volatility to modulate rate of learning (Behrens et al., 2007; Li et al., 2011; Roesch et al., 2012). Valuation, reward learning, and decision-making functions have been mainly associated with ventral and medial sectors of the PFC (vmPFC).

The role of dopamine, a neurotransmitter, in reward learning is the heart of reward system. Dopaminergic neurons (DA) increase their activity with the receipt of a reward. Activity in the dopamine system and brain regions innervated by this system, including the striatum and regions within the frontal cortex, encodes the prediction error- how much received and expected outcomes are different (negative and positive feedback). Dopaminergic neurons are also involved in movement control, as Parkinson`s disease is characterized by an impairment of DA transmission. Only 1% of the total neuronal population of the brain are dopaminergic neurons but they are critical for brain functioning, namely motivated learning, memory and action planning. Mostly located in the ventral part of the mesencephalon, they can project from: 1) substantia negra (SNc) to caudate-putamen

nucleus (the nigrostriatal system) 2) ventral tegmental area (VTA) to Nucleus Accumbens (NAc), the ventral striatum, that in turns innervate the septum, amygdala, and hippocampus (the mesolimbic pathway) or to prefrontal, cingulate and perirhinal cortex (the mesocortical system) (Arias-Carrión et al., 2010). DA increase activity by stimuli that predict reward (reward anticipation or conditioned stimuli) and decrease towards aversive stimulus. The "reward neurons" seem to activate mesolimbic pathway (ventral striatum), whereas aversive neurons are related to projections in the dorsal striatum (the nigrostriatal system), associated with motor behavior orientation. Otherwise, unexpected rewards cause also great activation of DA, so they respond to unpredictability. DA are key neuronal elements to understand reinforcement behavior (Schultz, 2002). They are relevant in the process of selective reinforcement because they respond to motivationally relevant stimuli- learning-, and in the process of retention of these informations – leading memory-, or habit formation. From a developmental point of view, there is a developmental imbalance between a faster maturating of reward-motivational processes (ventral striatum and amygdala) and a slowly maturating of regulatory processes for response inhibition (inferior frontal cortex and anterior cingulate cortex) explaining a bias on risk taking in adolescents (Korucuoglu et al., 2020).

Cognitive control refers to the process by which goals or plans influence behavior. Also called executive control, this process can inhibit automatic responses and influence working memory. Cognitive control supports flexible, adaptive responses and complex goal-directed thought. The capacity for cognitive control is strictly related to the salience network, that integrates sensory input, organizes behavioral responses to motivationally relevant stimuli, recruiting appropriate brain networks. This ability to use rules, action-outcome contingencies, to modify the response to a given stimulus allows behavior flexibility and adaptation to changing contexts. Cognitive control includes task switching, response inhibition, error detection, response conflict, and working memory. It has been associated with the dorsolateral prefrontal cortex (dlPFC) and the anterior cingulate cortex (ACC), as well as other sectors of the PFC that together may constitute a rostro-caudally organized hierarchy for behavioral control

and plan. Disruption of brain circuits involved in motor response inhibition is related to personality traits as non-planning and lack of persistence (impulsivity) that characterized some disorders as ADHD, gambling, or OCD. Network for impulsivity trait studies suggest that a network of frontotemporal regions, particularly the OFC and middle frontal cortex, plays a fundamental role in the expression of reported trait impulsivity. Brevers & Noel (2013) detailed three key neural systems to explain regulatory behavior that were born from decision neuroscience: hyperactive, hypoactive and interoceptive system. The hyperactive or impulsive system encourages fast, automatic, and habitual actions whereas hypoactive or reflective system is deliberative, projects future consequences and control basic impulses. This last one system works based on the integration of a "Cool" (cognitive) and a "hot" (affective) executive functions system. The cool executive system is mediated by lateral inferior and dorsolateral prefrontal involved in working memory and update while the hot executive system is mediated by the orbitofrontal (OFC) and ventromedial prefrontal (vmPFC) related to trigger somatic states from memories, knowledge, and cognition that are in conflict in each other, according to the Somatic Marker Hypothesis, proposed by Antonio Damasio (1996). Finally, the interoceptive system transforms somatic sates in subjective states and send this information to activate impulsive or reflective system. The reward processing under uncertainty seems to be driven by neural mechanisms that differ from reward processing with known probabilities (Figure 5).

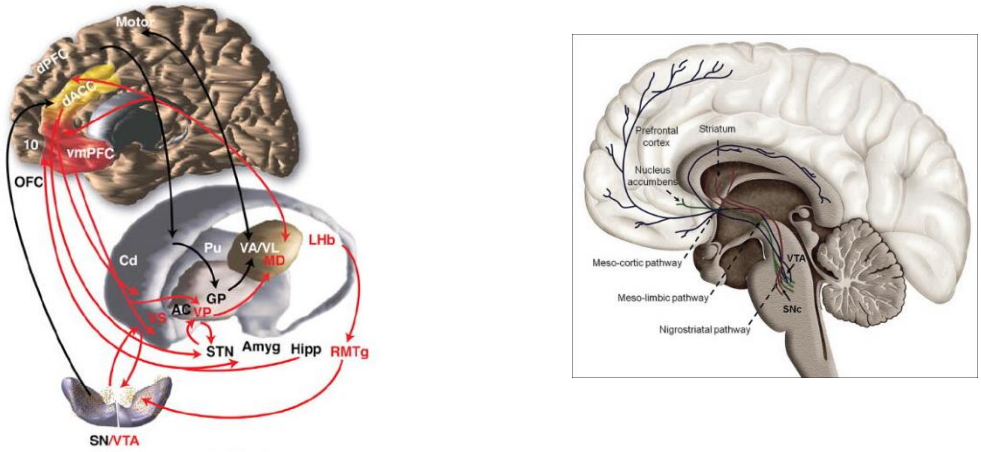


Figure 5 (A) Left, Reward circuitry. Haber & Behrens (2014). **Right, Reward structures in the human brain**. In Arias-Carrión et al. (2010).

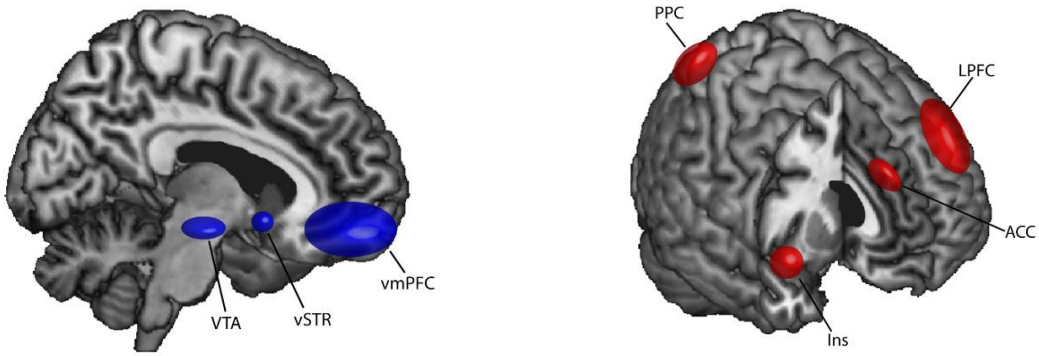


Figure 5 (B) Left, Reward processing and uncertainty. Brain regions involved in reward processing and valuation computation –VTA, vSTR, vmPFC. **Right, Brain regions involved in uncertainty situations** - Ins, ACC, lPFC and PPC. In Smith & Huettel (2010).

Beyond reward system and cognitive control, evaluation of the uncertainty of choice options are related to a cortical system as insular cortex (Ins), lateral prefrontal cortex (lPFC), dlPFC, and posterior parietal cortex (PPC) (Blankenstein et al., 2017; Levy, 2017; Mohr et al., 2010; Platt & Huettel, 2008). Particularly situations when the degree of the risk gradually increases and high rewards and loss are simultaneously at stake, inhibitory control may react to the trade-off between a magnitude of a potential reward and the probability of a negative outcome resulting in avoidance or behavior stop. In opposite, failure on representation of increasing degree of risk or increasing sensitivity for high payoffs may determinate a persistent risky choice (Lejuez & Korucuoglu, 2019). Some studies associate brain regions with risky or safe choices (Tisdall, 2020). Risky choices are often associated with ACC activation while avoidance has been related to ACC and insula or amygdala in monetary loss aversion (De Martino et al., 2010; Fukunaga et al., 2012).

Functions of “cognitive control” and “valuation” are subserved by distinct but interacting networks: valuation allows to compare rewards, starting the motivated goals that cognitive control functions will subsequently translate into response monitoring, action planning and flexible switching (Gläscher et al., 2012).

Nevertheless, brains do not exist in isolation, and their basic functioning reflects their participation in the social culture into which they were born. Social decision-making relies on representation of oneself and others. Social neuroscience and developmental psychology both prominently feature research on ToM yet emphasize different facets of this core social cognitive ability. Social neuroscientists tend to focus on where in the brain mentalizing resides, while developmental psychologists are centrally concerned with how mentalizing is acquired (and when it emerges). The mentalizing structure is built around frontotemporal pathways connecting frontal regions in PFC to temporal lobes (Molenberghs et al., 2016; Billeck et al., 2003, for a review) (Figure 6).

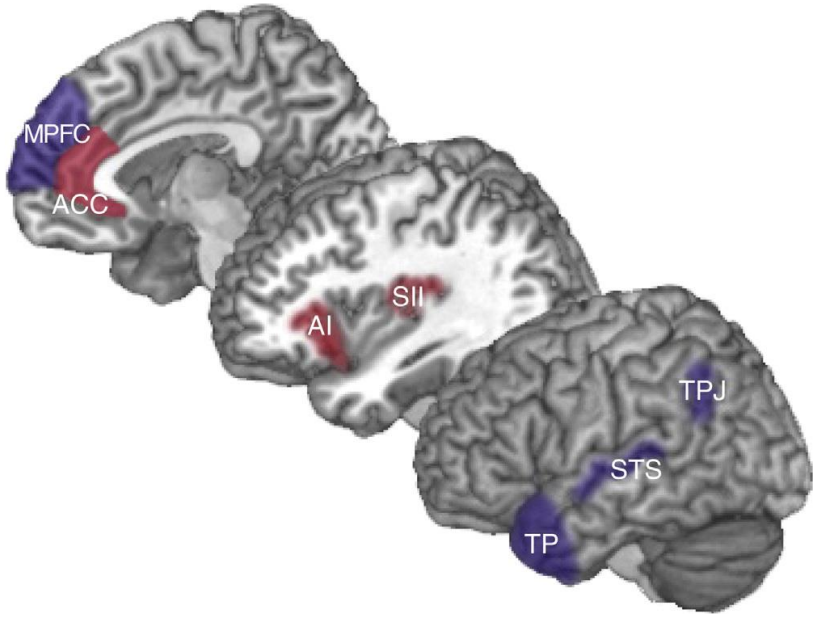


Figure 6 Brain networks involved in understanding others (Theory of Mind, ToM). Schematic representation of the brain areas typically involved in theory of mind (blue) and empathy (red) tasks. MPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; AI, anterior insula; SSC, secondary somatosensory cortex; TP, temporal pole; STS, superior temporal sulcus; TPJ, temporoparietal junction. In Singer & Tushe, 2014, p.517.

ToM network also includes medial and dorsolateral PFC (dlPFC), temporo-parietal junction, superior temporal sulcus, temporal, and the involvement of sensorimotor regions [i.e., premotor cortex and inferior parietal lobule] (Figure 7). Studies of cooperating with a computer and a human (Delgado et

al., 2005; Gallagher, 2002; King-Casas, 2005) provided evidence about different brain activation comparing social and no social interaction.

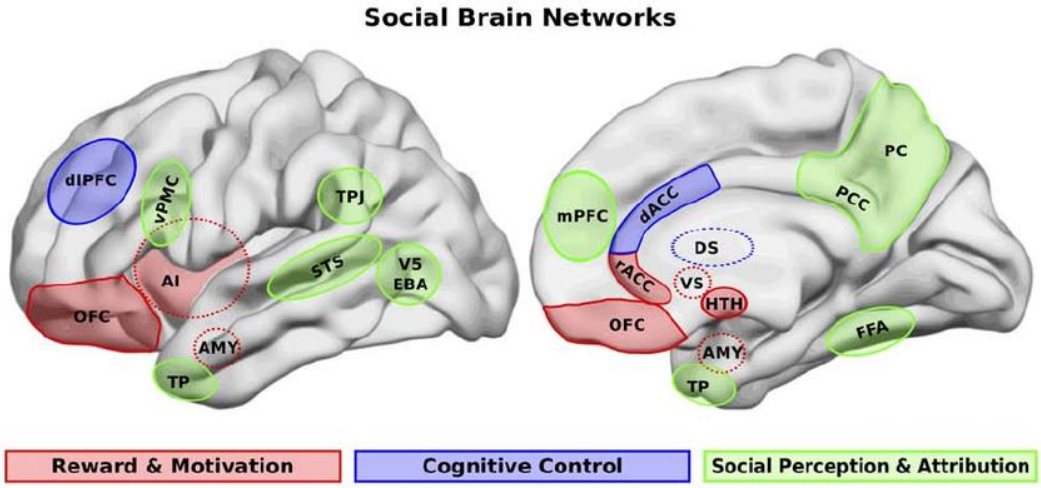


Figure 7. Brain areas involved in social processing that differentiate regions from three related systems "**The motivational and reward system (red)** that includes cortical areas, such as the amygdala (AMY), the anterior insula (AI), the rostral anterior cingulate cortex (rACC), and the orbitofrontal cortex (OFC). These cortical structures interact with subcortical structures, such as the ventral striatum (VS) and the hypothalamus (HTH). **The cognitive control system (blue)** participates in goal-directed and adaptive behaviors. This system includes areas such as the dorso-lateral prefrontal cortex (dlPFC), the dorsal anterior cingulated cortex (dACC), and the dorsal striatum (DS). Finally, **the social attribution system** includes areas that participate in the perception of social stimuli, such as the extra-striate body area (EBA) and the fusiform face area (FFA). There are other areas, such as the ventral premotor cortex (vPMC) and the cortex around the superior temporal sulcus (STS), that participate in the perception of intentions of the motor actions ("mirror system"). The attribution system also includes areas that participate in mentalizing processes, such as the posterior cingulate cortex (PCC), the precuneus (PC), the temporal pole (TP), the medial prefrontal cortex (mPFC), and the temporo-parietal junction (TPJ)." (Billeke et al., 2013, p.437).

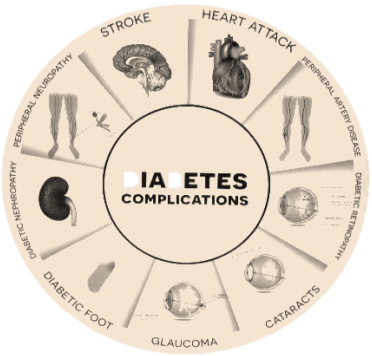
CHAPTER 2

DIABETES MELLITUS AS AN HEALTH MODEL OF SOCIAL DECISION-MAKING UNDER UNCERTAINTY

1.1 Clinical features

Type 1 Diabetes Mellitus, also known as insulin-dependent diabetes, is a metabolic disease that results from a cellular–mediated autoimmune destruction of the B-cells of the pancreas, requiring insulin therapies to ensure survival and reduce the complications of hyperglycemia (high levels of glucose in the blood). This is a disease of immunological cause and not of metabolic cause. Despite called juvenile-onset diabetes because it occurs commonly in childhood and adolescence, it can emerge at any age, even in 8th or 9th decades of life. Type 1 form of diabetes, which account for 5-10% of those with diabetes, continues to increase worldwide and is predicted that 76000 will develop the condition annually (International Diabetes Federation [IDF], 2009).

Type 1 is more severe than Type 2 diabetes, a non-insulin dependent diabetes. Since the onset of Type 1 diabetes is usually in early life, long-term nonadherence with diet and insulin control can result in serious consequences such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. Diabetes is the leading cause of blindness, nontraumatic lower limb amputation, physiological erectile dysfunction, and end-stage renal disease. It`s an epidemic disease with higher costs to public health (American Diabetes Association [ADA], 2004).



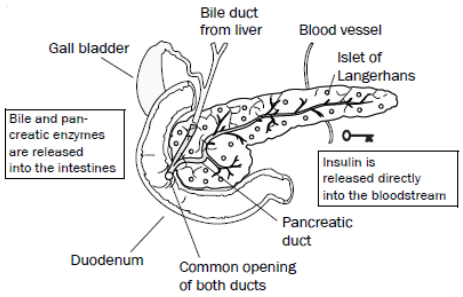


Figure 1. Diabetes Complications (right) and Pancreas functioning (left) in Hanas (2006, p.22).

First manifestation of disease corresponds to hyperglycemic symptoms such as glucose in urine (going more frequently to toilet and pass a lot of urine at a time), very thirsty, lack of energy, weight loss, blurred eyesight, difficulty in concentrating. It`s why, Mellitus mean “Sweet as Honey” and, historically, diabetes was diagnosed by tasting the urine. Before insulin was discovered in 1922, type 1 diabetes resulted in death, quite quickly. Understanding our body functioning will help to understand diabetes demands, its treatment and management (Hanas, 2006).

Concerning glucose metabolism and body functioning (Figure 1), cells are the smallest building blocks on our body, and they need glucose to produce energy or other metabolic processes. Even though we can obtain glucose (sugar) through food, without insulin, glucose cannot penetrate the wall of the cell. Inside the cell, oxygen will break down glucose into carbon dioxide, water, and energy. Carbon dioxide goes to the lungs being transformed into oxygen. The excess of glucose from a meal will be stored as a “reservoir” in the liver and muscle cells in the form of glycogen. In T1DM as glucose is unable to enter the cells, they act exactly as they would in a starvation situation (hypoglycemia), but they are in a time of plenty (a lot of glucose). The cells will try to increase glucose to get energy in a different but effortful way, a defensive reaction called contra-regulation. Pancreas through alfa cells produce glucagon to release glucose through glycogen reserves in liver and, simultaneously, the hormone adrenaline breaks

down fat in fatty acids (transformed into Ketones in the liver leading to ketoacidosis) and glycerol (transformed in glucose leading to hyperglycemia). Both are eliminated in the urine. ketones could also be excreted in the form of acetone, which is breathed out through the lungs, giving a fruity smell to the breath, and breathing become faster (Kussmaul Breathing).

When insulin is supplied, the cells can function appropriately again. However, in T1DM, pancreas is not working anymore. Besides alpha cells, pancreas produces enzymes to digest food but will be not able to produce insulin, to help control blood sugar, through beta cells. Both alpha and beta cells are present in islets of Langerhans (a million of them and together contains 200 units of insulin). The insulin levels will be extremely low and by no means sufficient to take care of the glucose coming from a snack or meal.

Glucose metabolism could be divided into two phases. During a meal and for the following 2-3 hours, complex carbohydrates (glucose from the meal) must first be broken down to simple sugars in the intestine before they can be absorbed into the bloodstream. Insulin is needed to transport glucose into cells. Glucose will be used by cells and storage as glycogen in muscles and liver. After 3-5 hours the carbohydrate content of the meal is consumed, and the blood glucose level starts to decrease. The glycogen stores in the liver will then be broken down to maintain a constant blood glucose level. The glucose produced in this way provides fuel for the brain during fasting as, unlike the rest of the body, the brain cannot make use of the free fatty acids produced by fat tissue for its fuel. The nervous system and some other cells (for example, those in the eyes and kidneys) can take up glucose without the help of insulin. There are advantages to this in the short term as the nervous system will not experience a lack of glucose, even if no insulin is present. However, in the long term, there are disadvantages for a person with diabetes, as the nervous system will be exposed to high levels of glucose inside the cells when the blood glucose level is high.

BRAIN FUNCTION AND CONSEQUENCES OF HYPOGLYCEMIA Brain cannot function without glucose (Figure 2). In these circumstances, some symptoms occur: weakness, dizziness, difficulty concentrating, double or blurred vision, disturbed color vision (especially red-green colors), difficulties with hearing, feeling warm or hot, headache, drowsiness, odd behavior, poor judgement, confusion, problems with short-term memory, slurred speech, unsteady walking, lack of coordination, lapses in consciousness, Seizures. Thus, ability to plan, make decisions and pay attention to detail, speed of reactions will be affected. Hypoglycaemia is often an unpleasant experience, involving loss of control over the body.

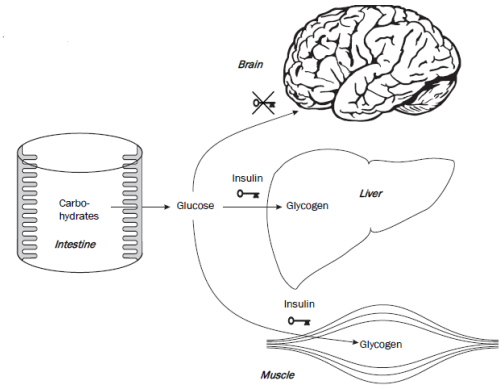


Figure 2. Brain function and glucose in Hanas (2006, p. 20)

1.2 Treatment demands, as continuous process of decision-making

Treatment and diabetes management require continuous decision-making several times in a daily routine. Each time people with diabetes want to eat, they must count carbohydrates, check blood glucose, and deliver insulin. Each time stressful situations, illness, exercise, or other different daily routines happen, people with diabetes must be attentive to body signals to prevent hypoglycemia. Therefore, while new developments and technologies have a great deal of potential to improve diabetes outcomes, glycemic control remains suboptimal and above the recommended targets for most patients and even in first world countries, only about 1 out of 4 youth with T1DM succeeds in reaching the A1c target level of <7.5%. This is likely due to the ongoing requirement for self-care behavior, there`s no holidays (Markowitz et al., 2016). Diabetes management requires planning, strategy, knowledge about disease and learn their own body signals over the time, paying attention to daily experiences. Patients must be their own pancreas. It means that they are constantly passing a

decision process based on sequential feedback learning from on experience to another, without knowing the outcome probabilities. They decide constantly under uncertainty in a health self-consequent context. It`s not surprisingly that Diabetes Management increases individual challenges every day. Therefore, psychosocial factors and psychiatric comorbidities are commonly associated with diabetes. Anxiety and depression are the most common comorbidities among adults with diabetes, while depression and eating disorders are common among adolescent diabetics (Snoek & Skinner, 2002). While people with type 2 diabetes report being blame/shamed because they are associate to being lazy or eating too much (habits), those with type 1 reported being associated with Type 2, once public often does not understand differences in etiology (Jabbour & Stephens, 2008).

Despite these effortful challenges to all patients with diabetes, some of them decide to persist in unhealthier behavior. Literature on diabetes and decision-making report some possible explanations to this group variability based on individual traits: tolerance to ambiguous stimulus, capacity to delay reward (delay discounting) and personality characteristics or perception of health risk (Hadj-Abo et al., 2020; Lawson et al., 2010). Neuroticism has been reported as the main personality traits related to unhealthy behaviors (Kitayama et al., 2018) as well as the influence of the interpersonal context of illness where social decision-making is played (Sperry, 2014).

CHAPTER 3

THE INTERPERSONAL CONTEXT OF CHRONIC DISEASE:

FAMILY HEALTH SYSTEMS MODEL FRAMEWORK (FHSM)

Nancy Rudd and Susan McDaniel (2016, p.472) defined chronic disease as an "uninvited guest who will not leave –it disrupts normal routines, creates uncertainty and increases tension" in patients and their families. Therefore, is not surprisingly that dealing with a health issue needs considering social contexts in which disease is inserted, namely family (Gilliss, 2019).

1.1 From Epistemology to Family as a System

To solve this gap in biomedical model, George Engel proposed in 1977 a Biopsychosocial Model emphasizing a hierarchical and interdependent relationship between biological, psychological, individual, familiar and community system. His work was based on General Systems Theory of the biologist and psychologist Ludwig Von Bertallanfy, in the mid-Forties. He argued that "sets of related events collectively are systems manifesting functions and properties on the specific level of the whole" (Engel, 1977, p.134). So, systems, such as the human body, interact with environment, acquiring qualitatively new properties. By this way, the whole is more than the sum of his parts. It introduced the study of disease and medical care as interrelated processes.

At this time, in United States, a paradigm shift process started, from analytic to systemic thinking view. In this regard, the epistemologist Edgar Morin described later (1990) this phenomenon as the Complexus Thinking (what is woven together), a multiple play of interactions and retroactions. Contrary to the simplicity paradigm of Disjunction from Descartes, this new paradigm privileges interdisciplinarity, incorporating physics, chemistry, biology, psychology, or anthropology.

Simultaneously, after the Second World War, emerged the Cibernetics by the work of Norbert Wiener (1961), in 1948, who studied the capacity of systems to use feedback about past performance to influence future performance (the process of change). While firstly systems were viewed as observable and manipulated (e.g., computer machines), the Second Cibernetics, in 1970`, studied the social systems including the observer in the observed system, with mutual influences, explaining how a system change, maintaining their organization, and transforming their structure. So, the social system is autonomous and continuous dynamic: as open system, it received the information from the environment (informed open) but it`s responsible for the selection of the information that internally fits with itself (called organizationally closed or internally coherent). Consequently, a quick disorder (entropy) origin a sequential reorganization (negentropy) different from the previous, irreversible, and unpredictable. Heins von Foester, Humberto Maturana, Francisco Varela and Ilyia Prigogine were the most contributors for this scientific framework.

Between 1950`and 1970`, also the British anthropologist, ethologist, epistemologist, and biologist Gregory Bateson helped to complete the cybernetic approach with the notion of co-evolution and implemented the Ecosystemic Theory of Communication (Heims, 1977). He worked at the research group of Palo Alto, California, with Jay Haley, Don Jackson, John Weakland and John Fry. He stated that human communication could be defined as “relations establish themselves within a life context (an ecosystem), (…) a relational scheme inserted in time; a co-evolution of individuals and their relationships” (Bénoit, 2004). He made a parallel between digital and analogue communication

proposed by computational sciences and verbal and non-verbal behavior, that lead to the notion of metacommunication (message about the relationship between speakers) and later the Double Bind Theory (as a communication paradox or inconsistencies in speech).

Joining the General Theory of Systems, the Cybernetics and the Human Communication Theory, the nuclear concepts of family as a system are collected. Even though family notion could differ, Relvas (1999) defined it as a "set of individuals who develop among themselves, in a systematic and organized way, particular interactions that give them group individuality and autonomy" (…) the family evolves, turns itself, the members that make it up change, but it is still a family, that family".

This definition holds system properties notions (System General Theory), its way of change, as functioning and development (Cybernetics) and the relation or ability to interact, translated particularly in pragmatic communication, the ingredient of relationship (Gameiro, 1992).

As system properties, individuals are simultaneously a part and the representation of the whole family (Hologrammatic principle). This is possible due to a continuous recursion (interaction and mutual influence) within the system and it gives the possibility to work the system with only one of its elements. Second, despite interactions define behavior, family behavior is not the pure sum of the behavior of its members or subsystems (Totality Principle). For understand individual behavior, it`s necessary to considering a circular view. In other words, each behavior should be perceived within the complex interaction between all family members (Retroaction Principle) (Alarcão, 2000).

Linked by a set of relationships, family members interact also with outside environment (Systemic Hierarchy, a system between systems) by an open semi-permeable boundary that led the information to enter and leave of the family. Through a dynamic and continuous exchange, considering developmental contextual process that crosses space and time, the family has a self-organization

ability that explain why it doesn`t change in function of environment but within a process of co-evolution between the system and the environment in interaction. Additionally, it also justifies individual and family resilience once different families could challenge differently to the same problem. As change is unpredictable, the same goal could be obtaining through different roads or starting by different initial conditions (Equifinality Principle).

As a spatial dimension, the family changes their structure keeping their organization in face of natural or accidental crisis. As a temporal dimension, the family goes through a predictable sequence of transformations [family life cycle] (…), according to well defined tasks [stages of the family life cycle] (Relvas, 2000) to comply two functions: an internal function related to the development and protection of its members, creating a feeling of belonging; and an external function associated with members socialization, it means the process of autonomy.

The balance between internal and external functions is observed through family relationship, as communication patterns, boundaries, family structure, coalitions/triangulations and power distribution or hierarchical organization. It defines a relational reorganization, called the Synchronous Axis. In the other side, family history, as myths, loyalties, legacies, serious diseases, accidents, or other relevant life events define a temporal axis, called Diachronic Axis (Relvas, 1999).

Therefore, each Stage of the Life Cycle pushes the family to a functional restructuration to allow its continuity. The family is well-succeeded if it`s able to move to a level of structural differentiation, exceeding a normative crisis (as marriage, birth of children, children entering school, teenage children, children leaving home), a moment of risk for disfunction and opportunity to amplify a change move.

Facing internal and external pressures, family stress arrives, spreading to all members. As Bateson describes, there`s a pattern that connects the members of the family, which means that change in one

person's behavior inevitably leads to a change in all family members, it`s interdependent. Beyond normative crisis that are expected, problems can unexpectedly occur, as the diagnosis of a chronic disease. A range of family therapy approaches have been developed to help families with internal challenges including disability and illness (Keitner et al., 2010; Sexton & Lebow, 2016), as multifamily discussion groups [MFDG] (Gonzalez et al., 1989). In the next step, we will explore deeply the development of family health system models that support family intervention with a chronic illness family member.

1.2 From Family Health System Model of Chronic Diseases to Diabetes Mellitus Demands

A Chronic Illness requires multiple individual and family adaptations once long-term therapies continually demand a collective and hard effort to accomplish treatment. Beyond disease impact, psychological symptoms as Depression and Anxiety were found in patients and their caregivers in an increased rate than healthier population. Family Health System Models approaches to help coping with Chronic Disease arrived extensively in the 1980`, even if the interest for this matter had begun in Twenties.

The first group of models looks at the interaction patterns in family system and are in danger of being considered models that label families as responsible for the problems. The model of Psychosomatic Families from psychiatrist Salvador Minuchin, psychologist Bernice Rosman and pediatrician Lester Baker emerged in 1978, after ten years of research on families with children with anorexia and diabetes. They proved that "when significant family interactions patterns are changed, significant changes in symptoms of psychosomatic illness also occurs" (Minuchin et al., 1978, p.21). In some children they found a relationship between family interactions and levels of HbA1c. In 1987, Peter Steinglass and cols. presented a model to families with an alcoholic patient. They stated that illness could became in an organizing principle of family system once patients changed brutally their routines

(Steinglass et al., 1987). Doherty, Colangelo and Hovander, in 1991, family change is focused in three main dimensions of family interaction: inclusion, control and intimacy.

The second group of models analyzes individual and family adaptation process to chronic illness, picking up the mutual influences of family and illness characteristics to have a good adjustment. They are related to family functioning and positive social support as family resources. In 1983, McCubbin and Patterson presented a model of adaptation to physical and chronic illness: Family Adjust and Adaptation Response (FAAR Model), articulating a theory of family stress with a systemic family theory. The family therapist William Doherty and the family clinician Macaran Baird stated in 1983 that the basic unit of health was a triangle composed by the clinician, the patient, and the family, and defined the level of clinician involvement with the families. However, John Rolland, in 1986, went forward adding the disease by itself as a four component of this equation.

Since nowadays (Rolland, 2019), the Psychosocial Model of Disease Type and Family Life Cycle of Rolland, described in his book Families, Illness and Disability (1994) became a complete, systemic, and notable framework for the understanding of the complex cycle of individual and family coping with physical chronic disease (Figure 1). For this reason, we will give more attention to its description. John Rolland postulated that developmental phases of illness (crisis, chronic terminal) and characteristics of the illness itself also affect the ways the family is challenged, and their options for coping

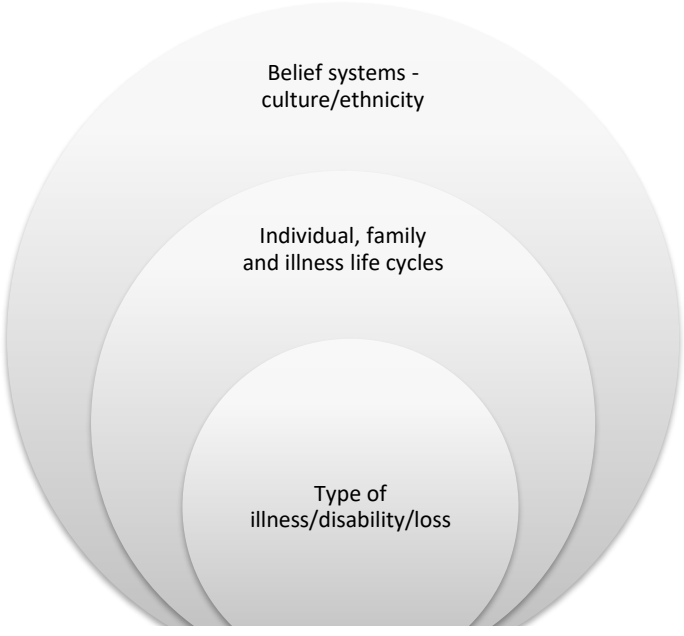


Figure 1. Family System Illness Model (Rolland, 1994)

(The affective issue). The illness type that could stress the family are the illness onset, course, outcome, predictability of the course and genetic component. In turn, also the family characteristics affect adaptation to the disease: preexisting patterns of communication, scripts or beliefs related to history of diseases and the family life cycle (The components of family functioning).

Based on this model, Diabetes Mellitus type 1 is characterized by a gradual onset, progressive course, probably fatal outcome, and is non disabling if well controlled. As Rolland exemplifies about a family with a patient with T1DM, "the progressive nature of illness meant that each new crisis resulted in a greater disability and a slightly altered quality of the family" (McDaniel et al., 1994) (Figure 2).

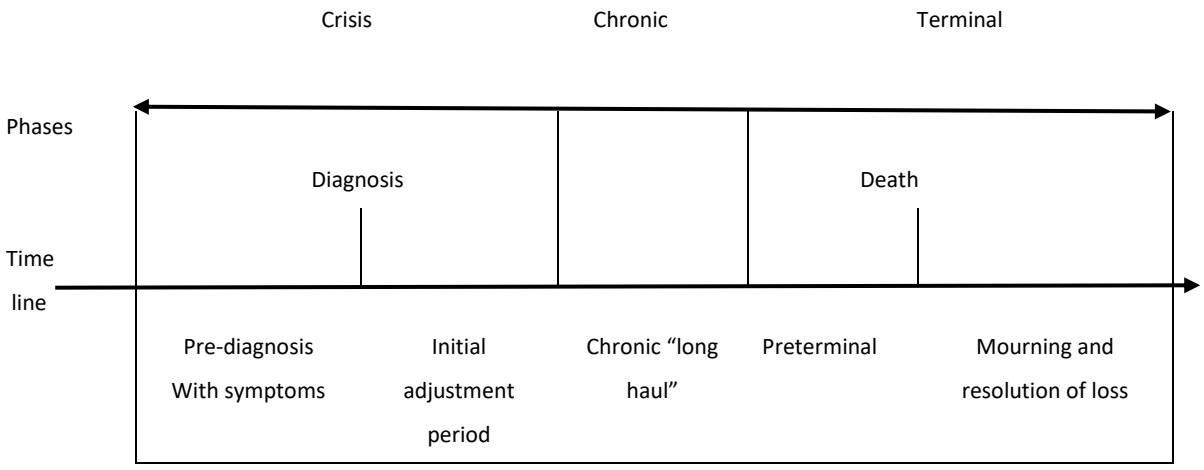


Figure 2. Timeline and Illness Phases (Rolland, 1987, p.4) Characteristics of illness: Onset (acute or gradual); Course (progressive, constant or relapse); Outcome (fatal or non-fatal); Disability (disability or non-disability). Developmental Phases: Crisis, Chronic, Terminal

Rolland notes that the course of the illness, for example, may affect considerably the family in terms of expected uncertainty, time need to make changes and cope with illness and necessary hope level. Additionally, Rolland (1999, p.250) posited that "in clinical assessment, basic questions are: What is the fit between the psychosocial demands of a condition and family and individual life structures and developmental tasks at a particular point in the life cycle? How will this fit change as the course of the

illness unfolds in relation to the family?" life cycle and the development of each member? This is a systemic model of human development because relationships change with time, transitions occur as childbirth and successive adaptations are needed over the life course (The developmental issue). By this way, McDaniel, Hepworth & Doherty (1994) warn that when we think about solutions to families with chronic illness, we cannot assume that all diseases have the same effects on all families or, in contrast, that each disease and family, needs to be viewed as unique.

The Rolland`s Model also considers the context (as economic sources or quality of health services), the multigerational influences (behavior cannot be understood out of its history- the historial data issue) and family belief systems as having impact on chronic disease. Beliefs systems refers to the meaning people give to the problem- the paradigm/meaning issue. The shared meaning is related to family sense attribution to the illness and loss. One of the determinants for successful adaptation to chronic condition is the matching between the family functioning/resources and the psychosocial demands of the illness over time (the practical issue).

Finally, this model intended to promote family resilience by supporting family system strengths and addressing its vulnerabilities. Faced with a health issue, patient and family members are concerned and it is also a challenge for them. It considers the impact of disease in the relationship of all members affected by illness related challenges, that in turn can affect the course of the illness. This holistic and integrative model expand their possibilities for adaptation and increase the sense of control, acceptance to deal with the condition and quality of life. By this way, it is considered family-focused, resilience-based and prevention-oriented model (Rolland, 2018).

In line with this framework, several studies have been conducted to provide evidence that family involvement in adult care with chronic disease improve health outcomes (Campbell, 2003; Chelsa, 2010; Lyons & Lee, 2019). Gilliss at al. (2019) went forward and investigated the difference between

psychoeducational interventions and relationship focused interventions through a systematic review. The first are related to learn skills and knowledge about disease management. The last are associated with skills to improve family relationships for living with a chronic disease at home, as communication, problem solving and conflict, addressing family functioning. They argued that previous studies showed benefits to the identify patient but not for the family if the focus of the intervention is not the family change.

Family interventions have been gradually received attention in diabetes disease even though is hard to identify health intervention targeting adults with diabetes and each one is based in different frameworks such as The Innovative Care for Chronic Conditions, the Self-Regulatory Model, or the Family System Theory (Torenholt et al., 2014) In current year, 2020, a group of researchers from the Netherlands, New York, United Kingdom and Denmark (Wit et al., 2020), conducted an extensive review about studies and interventions related to social contexts made with People with Diabetes Mellitus in the past 25 years. They identified several advances and gaps in child and adult research, namely:

- Social context (family, work, and society in general) is crucial to clinical, behavior and psychological outcomes in Diabetes across life span
- Family System Theory, Social Cognitive Theory and the Social Ecological Model are the main frameworks to study Diabetes Population and their context.
- The main topics to address relationships between family and HbA1c Values was parental involvement, parenting style and family functioning in children, and peers' relationships for young adolescents in T1DM.
- The main topics to address social context and diabetes management in adult literature was social support, family dynamics (and specifically, marital satisfaction). This studies only concerns adults with T2DM or included a small mix sample of adults with T1DM.

- Workplace is a real handicap on research despite well documented evidence about diabetes impact on employees, employers, and society, leading to work loss, reduced employment, or work limitations. Like other chronic disease, diabetes has impact on work life and vice-versa. People with diabetes experience stigma and discrimination at work, avoiding insulin injections or dietary restrictions, increasing probability of work absence once depression, anxiety and eating disorders are more prevalent. Detaille et al. (2006) summarize the five areas that help PWD cope with diabetes at work: "Ability to accept and cope, supportive health professionals, supportive work environments, work adaptation and knowledge among colleagues and employers about diabetes management".
- Little evidence-based interventions with families with children with diabetes, adults, and their partners and in the workplace.

To sum up, T1DM has traditionally been studied as a chronic disease of childhood, period of current diagnosis. However, as we have already described, T1DM adulthood-onset is also common. Therefore, children with T1DM grow up and become adults with other relationship`s configuration. Interpersonal context of adults with T1DM are under-researcher and, in general, research–based interventions should be developed and implemented to support this clinical population at interpersonal and societal levels to improve health outcomes.

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PART II

METHODOLOGICAL FRAMEWORK

Overview

In this PART II, we first present the aims of the thesis to introduce the research methodology. The study comprised two phases (Figure 1). In the first phase (1), patients and controls performed handwritten protocol assessing self-reported risk profile, family, and social context as well as they made experimental tasks on a computer, assessing behavior decision-making. In the second phase (2), other group of patients and controls fulfill the same handwritten questionnaires, and they were scanned through fMRI while performing experimental tasks.

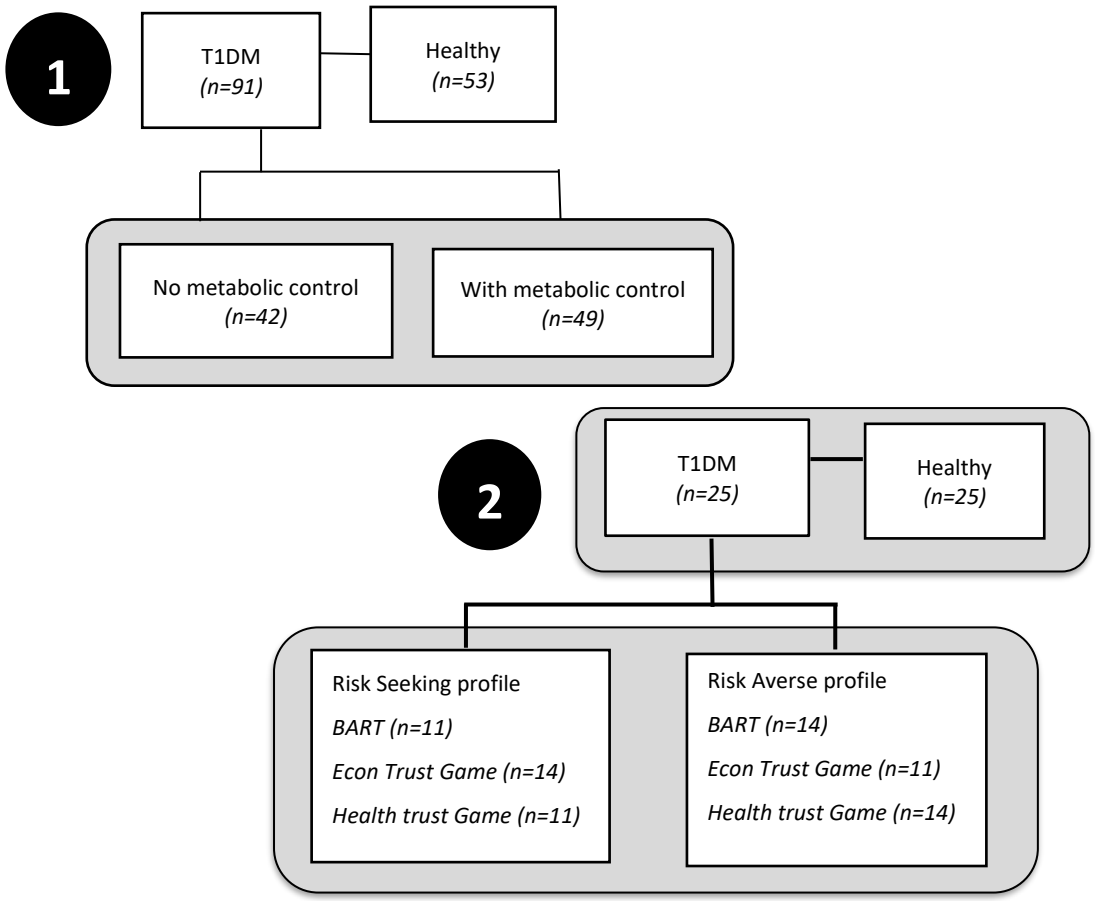

Figure 1. Flowchart of study sample. Number 1 represents the first part of the study (behavioral and self-report risk profile as well as family variables). The total sample of 91 people with T1DM was divided into two groups: patients with (N=49) and without (N=42) metabolic control. Because metabolic status is considered stable on patients with glycemic control (clinical control group), performance results from a healthy control group (N=53) are normative and presented as supplementary material. **Number 2** represents the second part of the study (neuroimaging). Participants were divided in two groups: T1DM and healthy. Additionally, T1DM patients were divided according their risk performance profile, forming two groups: risk averse and risk seeking. As decision-making is context-dependent, we obtained different groups profile for each experimental task (Balloon Analogue Risk Task, Economic Trust Game and Health Trust Game).

Aims of the thesis

This thesis aims to achieve four main goals.

ONE

WHAT We aim to understand why people engage in risky behavior not avoiding future complication with high probability within health domain, such as diabetes mellitus

HOW Defining decision-making endophenotypes based on HbA1c values and multidimensional behavioral risk profile related to success of metabolic control and impaired metabolic control, forming two distinct groups of patients. Focus on cognitive control. Understanding the social factors, namely family variables, that area related to each designed risk profile.

TWO

WHAT As decision-making is context dependent, we aim to generate a decision-making profile in dyadic interaction in different contexts: from neuroeconomic to health domain

HOW Testing a new experimental trust game. Focus on reinforcement learning and social decision-making, as trust (investment/collaboration) in economic and health domains.

THREE

WHAT We aim to identify the neural correlates of decision-making in cognitive impulsive decision-making that could explain suboptimal decisions. Focus on social brain networks, that integrate cognitive control, motivational-reward, and social neural pathways.

HOW Combining experimental games with fMRI, comparing clinical and control groups, risk averse and risk seeking performances and correlating brain activity with HbA1c.

FOUR

WHAT Finally, we aim to link brain, behavior and social factors that explain decision-making under uncertainty in health domain, namely impaired metabolic control, to define personalized interventions.

HOW Integrating all results in a well justified discussion with impact to define future works.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Commission of the Faculty of Medicine of the University of Coimbra (Comissão de Ética da Faculdade de Medicina de Coimbra). Written informed consent was obtained from participants. Additionally, written authorization from exclusive image assignment to this study was also obtained to do the stimulus of experimental tasks. Security fMRI Questionnaire was made by the specialized technician of ICNAS, Sónia Afonso, as well as all fMRI procedures for acquisition. A nurse was present to quickly solve any type of health complication related to disease or fMRI acquisition.

CHAPTER 1

PARTICIPANTS AND METHODOLOGICAL PROCEDURES

1.1 Participants

1.1.1 Inclusion and Exclusion criteria

Inclusion criteria

- Age between 18 and 55 years
- T1DM diagnosis, referee to the clinical assessment of Department of Endocrinology, Diabetes and Metabolism (EDM, Coimbra Public Hospital)
- Employed at least one year or to have a work experience in a recent past (if unemployed)
- No other person in the nuclear family diagnosed with diabetes for at least one year
- No other current major chronic disease
- No other current major chronic disease in nuclear family

Exclusion Criteria

- Past or current history of neurological and psychiatric disorders
- Recent diseases, major medical illness (cancer, anemia, and thyroid dysfunction)
- Severe visual or hearing loss
- Presence of a contraindication listed in the fMRI safety questionnaire (for participants of scanning session)

1.1.2 Clinical characterization of T1DM patients

Current symptoms and complications were evaluated by the clinicians involved in the consultation at the University Hospital. Body Mass Index (BMI) and biochemical data were also collected. Patients were divided into two groups according to values of HbA1c for the patient consultation history over multiple time points.

- For the first group (MC, metabolic control), we included patients with the following dynamic profiles: 1) continuously descending and improving values of HbA1c over time, 2) patients with low (normal) stable/invariant values that did not change beyond 0.5 and 3) patients whose values varied more than 0.5, but the maximum value of this oscillation was lower than 8.0 (64 mmol/mol). It defines successful metabolic control group.
- For the second group (NoMC, no metabolic control), we included patients with the following dynamic profiles: 1) continuously ascending values of HbA1c over the time, 2) patients with high (abnormal) stable values that did not change beyond 0.5 over the time and 3) patients whose values varied more than 0.5, but the minimum value of this oscillation was more than 8.0. It defines impaired metabolic control group.

1.2 Methods

1.2.1 Research Timeline

The study was divided into two phases (Figure 1, overview of Part II). Each volunteer only participated in one of the two phases: computerized version or fMRI scanning version.

In the first phase a group of participants (patients and controls) were evaluated cognitively, fulfilled self-report instruments, and played experimental games through a computerized form. The time required to accomplish this protocol was between one hour and half and two hours. The results of this phase will be presented in study one, two and three.

In the second phase, another group of participants (patients and controls) were scanned while they were performing experimental tasks, that were counterbalanced to prevent order effects. They had a pre-scanning session, and they fulfilled the same protocol that participants from phase I made. This visit could require two hours and half. The results of this phase will be presented in study four and five. Experiments were conducted between August 2014 and September 2015.

The only difference between phase One and Phase Two is the way participants did experimental tasks: in phase I, they made it in a computer, and in the phase II, they performed inside the fMRI scan. Experiments were conducted between October 2015 and August 2017. Clinical Analyses to controls were made in CHUC to assure that no one had diagnosis of Diabetes Mellitus. Exclusion criteria for controls were verified by phone call before exam schedule.

1.2.2 Assessment protocol with self-report instruments

A general survey was administered to collect sociodemographic data, cognitive assessment, family assessment, eating behavior and self-reported risk-taking profile, including risk -related constructs as personality and impulsivity.

1.2.2.1 Sociodemographic and Cognitive assessment

Participants filled out a demographic questionnaire providing information on age, gender, educational level, civil status, years of marriage (if existing co-habitation), household members and household income. Educational level was assessed as the highest level of education achieved (high school or university education). Household income was measured both as level of income (500-1000; 1000-1500; 1500-2000; >2000) and type of income (stable and unstable). Stable means have an employment contract for an uncertain time.

Cognitive and neuropsychological protocol included Fluid intelligence assessment (Raven Progressive Matrices) (Raven et al., 2009; Simões, 2008), Crystalized intelligence (Vocabulary Test of WAIS-III) and executive functions such as attentional processes and working memory (Digits Forward and Backward subtests of WAIS-III) (Wechsler, 2008). Participants with more than 50 years filled out MoCA (Montreal Cognitive Assessment) (Freitas et al., 2011) allowing a cognitive screening to ensure that inclusion criteria were fulfilled.

1.2.2.2 Risk-taking assessment

Multidimensional risk–related constructs (personality and impulsivity) and self-reported real-world risk behaviors were first measured by a comprehensive battery. The Eysenck Personality Questionnaire (EPQ) (Portuguese version, Castro-Fonseca et al., 1991) was administered to evaluate Personality traits in four dimensions: psychoticism [P], extraversion [E], neuroticism [N] and a lie (L) scale. It also helped to exclude patients with psychiatry disorders even though they were verified by doctors. Behavior Impulsivity Scale-11 (BIS-11; Translated; validation for the Portuguese population, Cruz & Barbosa, 2012; Fernandes, 2014) evaluated Impulsivity in general, lack of planning and inhibitory control, as personality trait and risk-related construct. Additionally, to achieve individual self-reported real-world risk profile, participants were confronted with three types of questionnaires:

I. Risk-taking according to context – economic and health domains
II. Risk-taking according to time – past and present risk-taking
III. Risk-taking according to being able to differ reward in time_ delay-discounting

Individual Perception of risk taking in health (6 itens) and economic contexts (6 itens) (Domain-specific risk-attitude scale [DOSPERT], Blais & Weber, 2006; Portuguese translation, Silva, 2012)

within a Lickert scale that range from 1 (no risk perception) to 7 (viewed as a high-risk behavior) (Table 1).

Table 1.

Self-report Individual risk perception in health and economic context scale based on DOSPERT scale in Portuguese language

Beber em excesso com frequência num evento social.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Expôr-se deliberadamente ao sol na praia sem usar creme protector.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Auto-medicar-se de forma regular.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Não usar cinto de segurança regularmente.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Andar de mota sem capacete.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Regressar a casa sozinho(a) a pé à noite por uma zona insegura da cidade.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Investir 5% do seu rendimento anual numa acção muito especulativa.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Investir 10% do seu rendimento anual numa nova oportunidade de negócio.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Investir o dinheiro de um dia de trabalho em máquinas de jogo.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Apostar 5% do seu rendimento anual no resultado de um evento desportivo.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Apostar o rendimento de um dia de trabalho em corridas de cavalos.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Investir 10% do seu rendimento anual num fundo de crescimento moderado	**1**	**2**	**3**	**4**	**5**	**6**	**7**

Variations of Risk profile (past and present risk taking in six distinct areas – leisure, health, career, finance, safety, and social life) within a Likert Scale that range between 0 (I never did it/ Nowadays, I never do it or if I could I`d not do it)) to 5 (I did it a lot of times/ Nowadays, I do it a lot of times or if I could I`d do it). (Table 2).

Table 2.

Self-reported past and present risk-taking in Portuguese language based on Risk Taking Index -[RTI] (Nicholson et al., 2005)

	Agora					**Passado**				
Riscos recreativos (fazer bungee jumping de uma ponte alta, acampar meio selvagem)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Riscos de saúde (fumar, alimentação deficiente, consumir muito álcool)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Riscos de carreira (mudar de emprego sem ter outro em vista; emigrar sem trabalho)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Riscos financeiros (jogar frequentemente, fazer investimentos de risco)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Riscos de segurança (conduzir com velocidade em excesso ou sem cinto de segurança)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Riscos sociais (emitir a sua opinião sobre um tema controverso)	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**

Delay discounting in three domains: economic, general health and diabetes context. It means a preference for smaller rewards versus larger delayed rewards because the subject value of an outcome decrease as the time to its receipt increases.

Economic context:

Image you receive an inherence of 1000 euros. You have three options. What do you prefer?

1.You can decide to receive it in 2 years twice (2000 euros).

2 You can decide to receive it in 5 years, 5x 1000 (5000 euros).

3.You can decide to receive it in 9 years, 9x1000 (9000 euros)

General Health:

Image you had a severe chest pain. At hospital, clinicians told you that you are at risk of stroke. You have three options of therapeutic drugs. What do you prefer?

1.You can decide to take drug A, it causes nausea and vomiting but prevents angina pectoris in 9 years.

2 You can decide to take drug B, it causes vomiting but prevents angina pectoris in 5 years.

3.You can decide to take drug C, it causes nausea but only prevents angina pectoris in 2 years.

Diabetes:

Image that after an eye exam, clinicians told you that you are in danger of blinding. You have three options. What do you prefer?

1.You can decide to take 5 daily pricks and prevent visual impairments in 15 years.

2 You can decide to take 2 daily pricks and prevent visual impairments in 10 years.

3.You can decide to take 0 daily pricks and prevent visual impairments in 5 years.

Furthermore, eating behavior was assessed by Portuguese validation of Dutch Eating Behavior Questionnaire (DEBQ, Van Strien et al., 1986; Viana & Sinde, 2003), a 33-item instrument, with a 5-item Likert Scale that evaluated three types of eating styles: restrained (avoid eating more than was initially defined), external (to eat motivated by external factors such as good food smell and how it looks) and emotional (to eat in response to emotions). Perception of family functioning and eating behavior was also considered since diabetes care requires a diet and weight management made mainly at home.

1.2.2.3 Family Assessment

From family to diabetes management

Implications of Family variables in diabetes management were evaluated by performing four questionnaires covering three family levels: individual, intrafamily and extra family level. Only

participants in a cohabitation close relationship for more than one year complete the marital functioning subscale. All the questionnaires used had adequate psychometric (validity and reliability) properties.

- Individual level. Congruence is defined by Lee (2002) as "a state of awareness, openness, and connection in the principal dimensions that constitute Satir's systemic understanding of the person. The three principal dimensions of the person are the interpersonal as connection between persons, the intrapsychic as connection within the person, and the universal-spiritual as connection with a universal and transcendent dimension" (Wretman, 2015). In this way, Congruence Scale (EC) (Lee, 2002; Portuguese version from Cunha, Silva e Relvas, 2014) is an instrument for global evaluation of individual functioning and its adaptability in holistic and systemic manner because it catches the relationship of the individual with other systems. It is organized into two subscales (Universal and Interpersonal/Intrapsychic) leading together to a Total Score of 16 items, answering on a 7-point Likert scale, ranging from 1 (Strong Disagreement) to 7 (Total Agreement).

- Intrafamily level. Family Functioning was assessed by Systemic Clinical Outcome and Routine Evaluation (SCORE-15) (Stratton at al., 2010; Portuguese version from Vilaça et al., 2014). Marital functioning and satisfaction were measured by the and Scale for Assessment in Areas of Life Satisfaction in Marriage (EASAVIC) (Narciso & Costa, 1996). SCORE-15 is a self-report family assessment instrument (for family members 12 years and older) developed to assess outcomes of family functioning in clinical settings. SCORE-15 items are given on a 6-point Likert scale ranging from 1= "describes us: extremely well", to 6= "describe us: not at all". Higher values correspond to poor family functioning in all three subscales: family strengths (and family`s adaptability), family difficulties (overcoming on family system), and family communication. EASAVIC is a 44-item self-report measure

that evaluates marital satisfaction in two subscales: Marital Functioning (Family Functions-FF; Free Time_TL; Autonomy_AUT; Extrafamily Relations_RS; Communication and Conflict_CC) and Love (Sexuality and Emotional Intimacy), answering on a 6-point Likert scale, ranging from 1 (Totally unsatisfied) to 6 (Totally satisfied). For our research purposes, Love subscale was not administered. Higher scores indicate higher levels of marital satisfaction.

- Extrafamily level. The Inventory of Family Quality of Life (QOL), de Olson & Barnes, 1982 (Portuguese version from Simões, 2008) is a 40-item scale, quoted 1 (No satisfied) to 5 (Completely Satisfied) in a Lickert-scale, covering 11 general areas of individual life satisfaction: Financial, Time, Neighborhood, Home Conditions, Mass media, Social/Health, Relationship, Job, Religion, Family/Marital, Children and Education. Global and subscales results highlight individual subjective evaluation about life`s family quality.

<u>From Diabetes Management to Family conflict.</u>

To access diabetes management's implications as a source of family conflict as well as on complementary diabetes management's characterization, the patients fullfilled a survey, specifically developed for this study. This questionnaire was created based on two instruments: The Diabetes Family Support and Conflict (Paddison, 2010) and The Diabetes Family Behaviour Checklist, de Schaffer et al., 1986 (Lewin et al., 2005). Briefly, it was composed by three parts.

1) First, a question about the contribution of disease to family conflict "How does diabetes management contribute to family conflict?", positioning itself on a scale of 0 to 7.
2) Second, the report of sources of conflict between the patient and the family due to diabetes in five distinct diabetes management matters: physical exercise; food restrictions; mealtime; glycemic results and medical advices. They also reported family support ("they encourage me, they understand, they congratulate me, they suggest; we plan together") and no supportive

behaviors (as “they have shame, they annoy me, they complain about food, they argue; they criticize; they do distinct activities”). Some no supportive behaviors from patient point of view (as “They annoy me to follow clinician advices” could be considered a supportive behavior from caregivers’ point of view because they are concerned with patient`health).

3) Third, patients report their perception about a) disease self-management at four domains in a 7-item scale (food, physical exercise, glycemic control, smoking habits), b) concern`s areas (food, future complications, no social support, hypoglycemic episodes, constant effort to deal with disease). This questionnaire helps to characterize the diabetes self-management.

1.2.3 Computerized Experimental Tasks

1.2.3.1 Balloon Analogue Risk Task (BART)

The BART is a computerized and laboratory-based paradigm developed originally by Lejuez et al. (2002) for direct measure of risk-taking behavior. In this task, ambiguous and unpredictable reward defines the risky profile. The average adjusted pump (inflation pumps in the win trials) defines the propensy to risk-taking. Participants were told that they would be presented with 30 balloons. By pumping up a balloon (through a button click), participants have the chance to earn money until a point where the balloon explodes. If this happens, they lose the accumulated money for this balloon. If participants decide to cash-out before the breakpoint, they collect the money earned in that trial. Riskier option (reward seeking) might confer greater potential reward and safer option gives fewer but more certain reward (avoiding loss). Participants are not informed about the balloons’ breakpoints. The absence of this information allows for testing participants' behaviors such as: 1) decision-making under uncertainty, getting initial responses to the task - initial risk taking), 2) adjusted decision-making over the game, studying changes in risking as they learn the task contingencies (learning with experience; choice impact- switching between risk averse to risk seeking behavior) and task efficiency (final amount of money earned) (Figure 5).

1.2.3.2 Trust Games

As in game theory, outcomes "depend on the actions of two or more decision makers, called players, and where each player has two or more ways of acting, called strategies" (Tarrant et al., 2012, p.462). Furthermore, Gray et al. (2003) sates that consulting is not just an intellectual process but is also an emotional one; and that in chronic diseases, particularly in diabetes, the knowledge accumulated about the patient was found helpful and mutual empathy generate compassion. Acceptance of advice (cooperation) depends greatly on trust, related to continuity of care. However, there is not empirically testable models of the doctor-patient interaction, a social interaction. To mimic this situation, we present two experimental repeated trust games with incomplete or imperfect information (Glimcher, 2014), named:

I. Computer & Human Mediator Neuroeconomics Experiment (Economic Trust Game)

II. Neuroeconomics inspired Health Context Interaction Experiment (Health Trust Game)

They were adapted from Berg, Dickaut and McCabe (1995) trust game experiment which means that some procedures were modified. Unlike Berg`s experiment, we use more than one interaction and we do not triple the amount of investment made by the participant (the trustor) before receive feedback from the mediator (the trustee).

Risky behavior in health context is an option among others with uncertain probabilistic negative consequence while in economic domain is understood as a statistical uncertainty studied as variance in both losses and gains (Schultz et al., 2011). The first experiment refers to situations without a medical context and the second is a tailored task with a medical risk and reward value. It will be played in iterated form, where the game is made up of several rounds (runs), repeated 7 times between the players. At each trial, participants know with who they are playing through face recognition of the mediator in that run. It requires that participants press one of three buttons to indicate their selection. Experimental events and data collection were handled by a remote ©Microsoft Windows-based PC. In

total, in economic contexts, each participant played with three human mediators and a computer (21 trials) and, in the health context, they play with other three human mediators (24 trials). Participants and mediators had the same gender (if they were man, they played with man mediators, if they were woman, they played with woman mediators) to minimize confounding effects related with choices influenced by appearance related to gender. In total, we needed 6 woman faces and 6 man faces. So, 12 volunteers that did not participate in this study got permission to be photograph to this study: at the same time and at the same place, 3 woman and 3 man wore a white coat and a stethoscope representing a clinician (mediators for health context). At the same time and at the same place, 3 woman and 3 men were instructed to wore formal clothes, representing a bank employee (mediators for economic context).

Computer & Human Mediator Neuroeconomics Experiment (Figure 1A)

Replicating previous studies in healthy participants, the first game is a classic neuroeconomic experiment and it helps define risk profiles. Participants` challenge during this trust game was to learn the optimal investment choice based on three mediator's outcomes. Within three distinct risk alternatives (0 €, 30€ or 50€), they had to choose one (decision or option selection) and after they receive the respective feedback (outcome). Before investment, towards the mediator face, participants indicate how much money they expect to receive from that mediator in next run (estimate expected uncertainty- the monitoring phase). Participants were exposed sequentially and alternately in 7 runs for each mediator, whose outcome pattern differed in terms of reward distribution (low, moderate, or extreme) for optimal choice (30 euros). More specifically, each trial was divided into three phases: monitoring phase, decision phase and outcome phase.

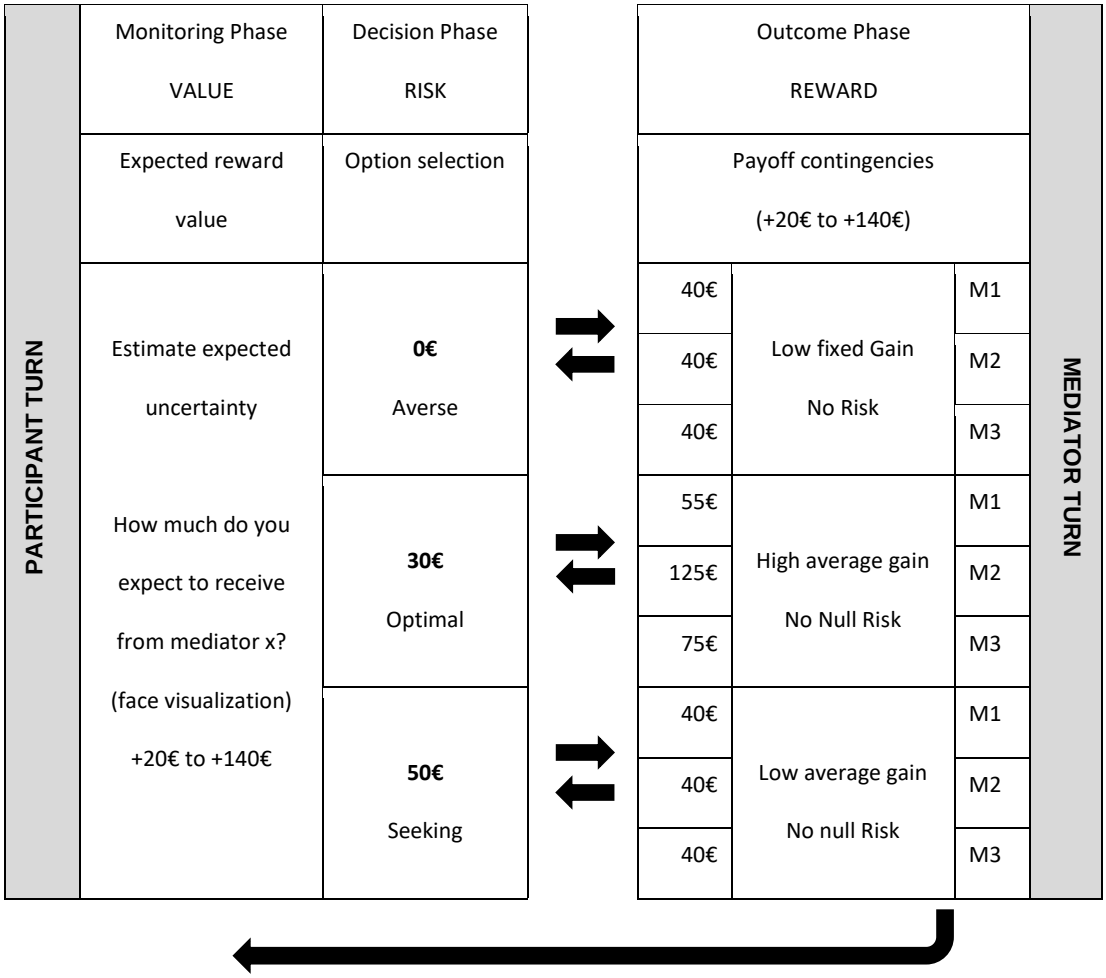

Figure 1. (A) Example of economic experimental design considering a run sequence in trust-trustee interaction. Mediator 1 has a low range for reward (trust investment is little reciprocated, seeming a social norm violation). Mediator 2 has an extreme range, reinforcing optimal decision. Mediator 3 has a moderate range, in the middle of M1 and M2 profile (trust investment is reciprocated in a moderate way, even so seeming a social norm violation). Outcome reward also differed according to participant option (0, 30 or 50 euros) for all mediators.1. For "0" option (no risk investment) was received a known low fixed gain (40 euros;) 2. For "50 euros" option (risk investment) was offered a low average gain (same mean reward, (40 euros) that could vary from 20 to 60 euros; 3. For the "30 euros" option (adjusted risk) a high average gain was earned - low, extreme and moderate reward-: Mediator 1 [35-75]; Mediator 2 [100-140]; Mediator 3 [55-95]. All of them have the same interval (40).

At the first trial, as the participant did not know each mediator payoff contingencies, we could obtain the initial risk profile (without learning) and how the subject performed with each mediator (presence

or absence of game strategy/planning). In sequential game, this value will allow us to calculate the prediction error (PE). Participants had to remember past feedbacks (outcomes) to update the expected value and decide the next investment for each mediator (estimate expected uncertainty). In that way, we will gather empirical evidence to support different profiles of rational decision-making.

Extending Utility based neuroeconomics to the Health Context (Figure 1B)

Neuroeconomics experiment inspired health context interaction experiment, using clinical human mediators. In the second game, we will extend previous experiments to the health context, but we added a rule/norm: More patient`s cooperation allowed less waiting time to consultation. So, we presented one of three different clinicians one at a time which represent three different human mediator feedback as in Game 1 (Low, Moderate and Extreme Rule Following).

In the first phase we present different health impact levels of developing negative symptoms (as diabetic foot) due to impaired glycaemic control. Subjects choose to cooperate or not (health investment) by accepting several therapeutic needle pricks (1 prick: No cooperation; 4 pricks: Medium cooperation; 6 pricks: Highest cooperation) without prior knowledge of the priority reward (amount of time needed to wait for consultation)- the outcome. The final priority outcome rank is a parallel with the outcome of Neuroeconomic Game 1. Note that in this case, less time for being consulted is better. Priority is defined by the number of minutes needed to wait before a consultation (0 to 260 minutes). In this game, a computer mediator was not used.

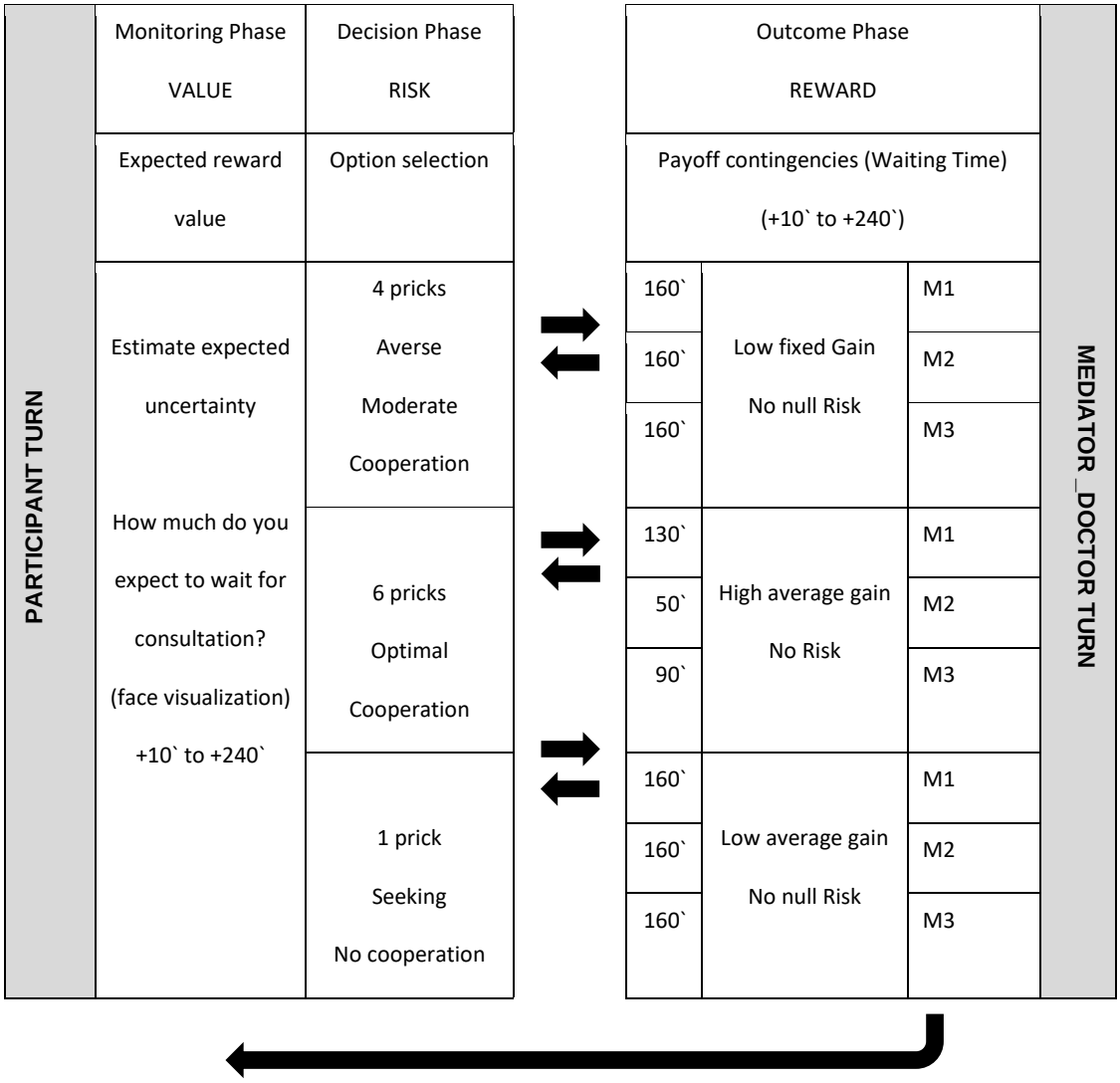

Figure 1 (B) Example of health experimental design considering a run sequence in doctor-patient interaction. Mediator 1 has a low range for reward (patient collaboration is little reciprocated, seeming a social norm violation). Mediator 2 has an extreme range, reinforcing optimal decision fulfilling the pre-established rule. Mediator 3 has a moderate range, in the middle of M1 and M2 profile (patient collaboration is reciprocated in a moderate way, even so seeming a social norm violation). Outcome reward also differed according to participant option (1,4 or 6 pricks) for all mediators.1. For "4" option (moderate cooperation) a known low fixed gain was received (160`) 2. For "1" option (no cooperation) a low average gain was offered (same mean reward, 160`) it can vary from 120 to 160 minutes. 3. For "6" option (highest cooperation) was earned a high average gain - low, extreme, and moderate – Mediator 1 [90-170]; Mediator 2 [10-90]; Mediator 3 [50-130]. All of them have the same interval [80]. The next illustration clarifies the payoff contingencies for each mediator (Figure 1C and Figure 1D).

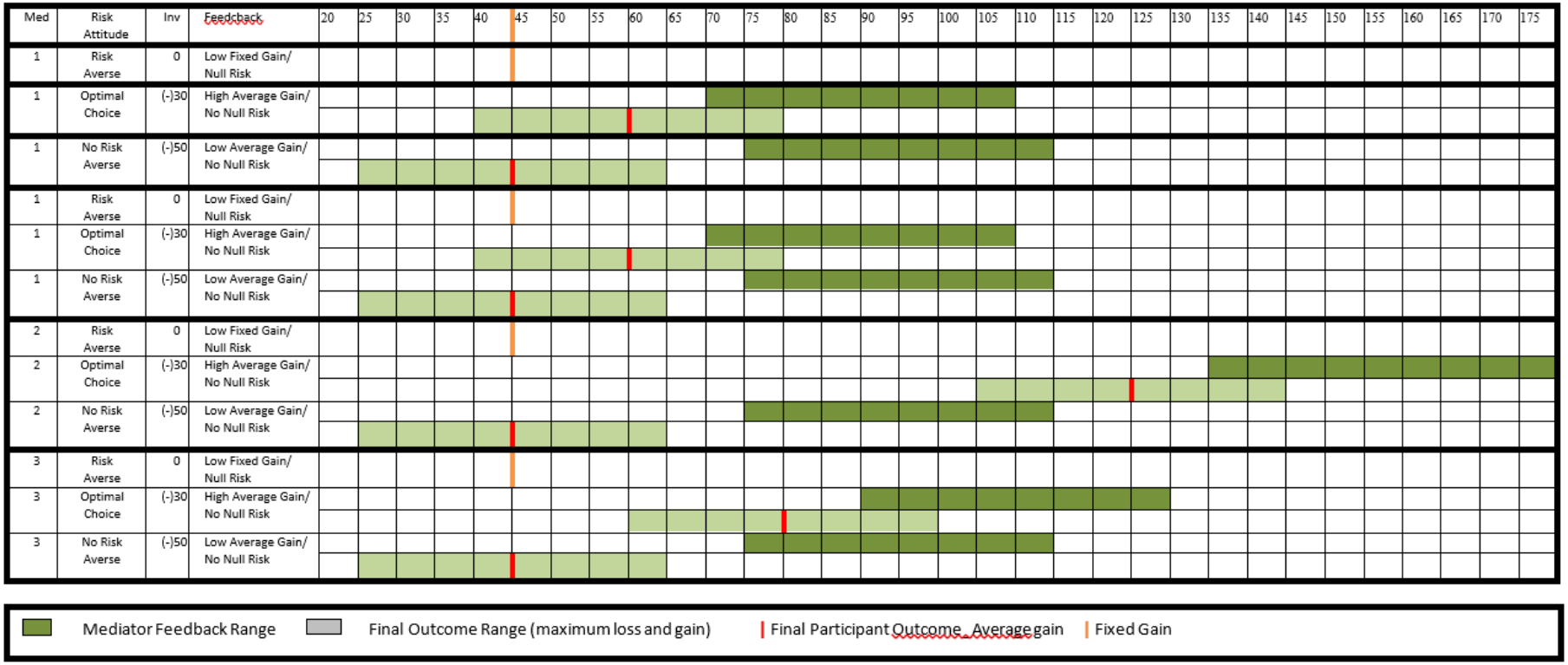

Figure 1C. Lottery computer and unknown human mediator interaction in economic trust game experiment

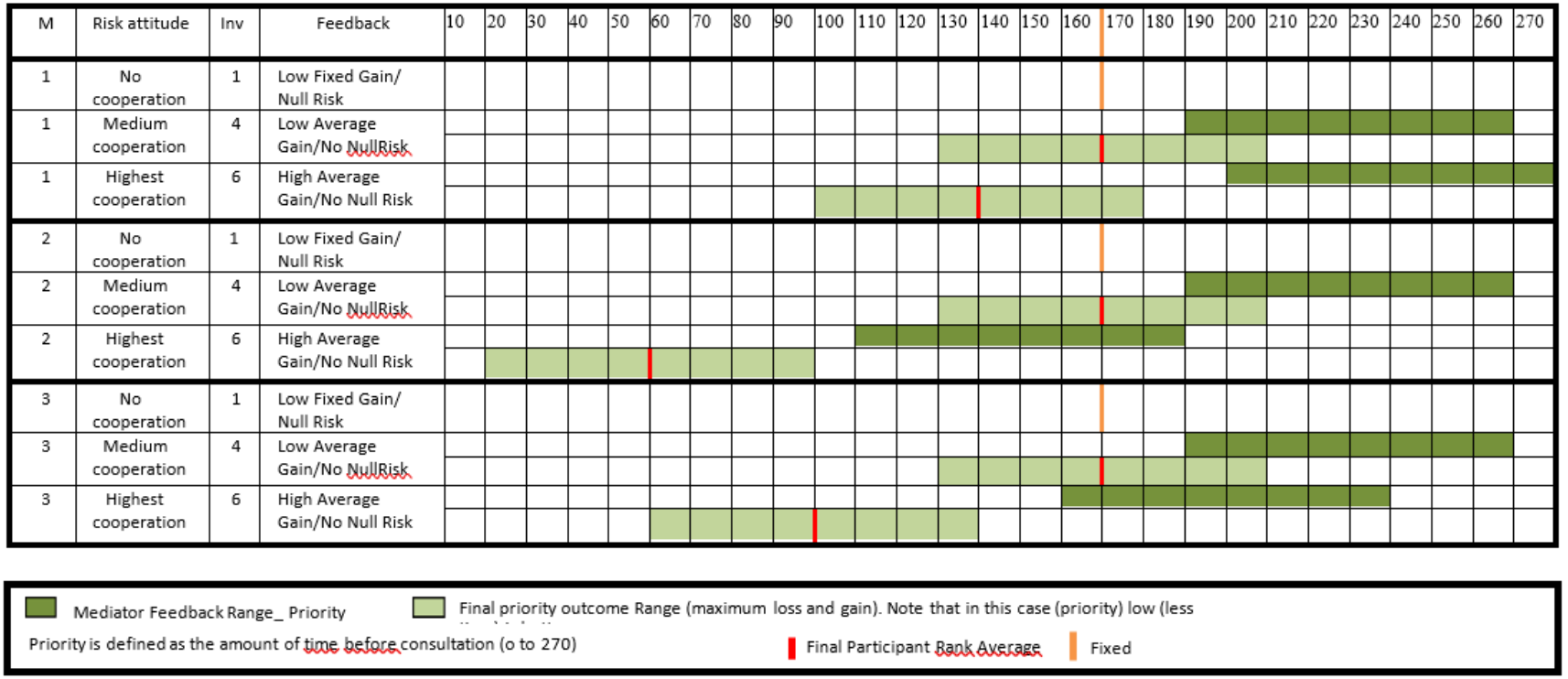

Figure 1D. Extending utility basted neuroeconomics to health context: Clinical human mediator experiment

Experimental Instructions

You will play a game with 4 mediators for 7 rounds. In each round they will appear at random way. You will recognize them through the face image or the image of a computer (once one of them is a computer) as you can see in this example [in the instruction, we showed only a silhouette of a human face to the participant]. What will happen then? On every move with a trustee, you must answer to two questions. First question: How much money do you expect to receive? It can range from 40 to 240 euros, pressing the buttons to the left or to the right to find your final option (pressing ok, the middle button). Second question: How much do you want to invest? Here, you will be confronted with three options: O, 30 or 50 euros. The order of the buttons corresponds to the order of the option presentation (blue, red and green). After your selection, you will be presented with the trustee return, that can be more or can be less than what you initially expected. So, the next time you play with this specific player you can decide if you want to keep your investment or change it. It`s especially important to pay attention to each player return. What remains to be said? Each player has a different way of return so throughout the game you will discover the best option of investment with each one. The main goal of the game is to earn money. I can say that 0 option gives you a small and fixed return and only the 50 option can lead to a jackpot return. Do you have any doubt? […]

Ok, I will ask you to play another game that has exactly the same structure but instead of economists you will play with doctors from a fictitious endocrinology service which has the following rule: if you decide to collaborate for a successful treatment you spend less time waiting for consultation. On every move with one of three doctors or a computer, you must answer to the first question: How much time do you expect to wait for consultation? After that, they will ask you to choose between 1, 4 or 6 picks that means how much do you want to collaborate for a successful treatment: a little bit (1), a little (4) or a lot(6). In exchange, they will offer more waiting time for consultation or less time, according to two reasons: your commitment option and the doctor profile. The fact that there are rules does not mean that they are followed. The main goal of this game is to wait as little time as possible for the consultation. So, play attention to your options and the doctors return to decide if you would like to change or not your commitment next time you play with this trustee. Do you have any doubt? [to participants that belonged to the healthy group, was made a short introduction to diabetes disease so that they could understand the relation between pricks and successful treatment].

Debriefing

After participation, we asked if they noticed differences between mediators in terms of reward (detection of payoff contingencies) so that we could previously identify participants` difficulties to play the game or to anticipate whether the subject did the task attentively.

1.2.4 Functional Magnetic Resonance Imaging (fMRI)

Preview Physical Principles

What does it measure? Functional Magnetic Resonance Imaging (fMRI) is a neuroimaging technique that allows to measure indirectly brain activity in health and disease. While subjects perform an experimental task, researchers can measure increases or decreases of blood oxygenation. So, they can link brain activation to mental function even though we need to consider that many regions belong to different networks. fMRI studies have some advantages in relation to other neuroimaging tools (Sejnowski et al., 2014). It`s a non-invasive technique, it can be repeated several times in the same individual and it allows to localize brain activity quickly, on a second-by-second basis (Logothetis, 2008). fMRI is a measurement technique and not a manipulation one because there´s not a change in the brain function or structure to further examine the effects of that change. It provides indirect information about brain metabolism, quantifying the energy used by a particular part of the brain (changes in oxygen) towards a particular behavior (perception or thought). (Sarty, 2007).

How does it work? Functional MRI is possible due to the biochemical properties of the brain and the blood. Brain neuronal activity consumes energy. To keep neural cells functioning there is a constant source of glucose and oxygen to the brain. When a group of neurons activate to perform a particular task, local biochemical changes causes the regional arterials to dilate and supply the necessary energy and oxygen. If there is an increase activity in some neuronal region, it`ll be also an increased oxygen delivery leading to a greater blood flow in that region- a process called hemodynamic response. When a stimulus is presented there is a fast intensification of oxygen consumption, but there`s not an immediate change in blood flow which causes a greater concentration of deoxygenated hemoglobin (Hb) in relation to oxygenated hemoglobin (HbO_2) (different states of hemoglobin). This is important to measure brain activity with fMRI because the magnetic resonance signal reacts differently depending on the state of hemoglobin. Only deoxygenated hemoglobin has paramagnetic properties

which means that leads to magnetic field distortions which changes the signal intensity in fMRI (Figure 3). So, changes in the ratio of oxygenated/de-oxygenated blood can be inferred with fMRI measuring blood-oxygen-level dependent response (BOLD signal) or BOLD contrast. In that way, we can classify that a brain region is active or inactive. The BOLD Signal change is the dependent variable which reflect the data measured by the researcher (Glover, 2011; Arthurs & Boniface, 2002).

Atoms contain three types of particles: protons, neutrons, and electrons. Different atoms have different nuclear composition. Hydrogen atoms are abundant in our body. Hydrogen nuclei consist of single protons. It possesses a nuclear magnetic resonance property (NMRP) and can be referred as a spin (they have a magnetic moment and an angular moment). In the magnetic field, protons behave as a spinning top in a gravitational field (Huettel et al., 2009) and tend to align with the magnetic field. When a radio frequency magnetic pulse (RF) is applied at the right frequency, the hydrogen nuclei`s absorb energy and create a weak signal (MR signal) that is detected by the RF coils in the system. Changes in brain anatomy are detected manipulating the timing of RF pulses and the delays before detecting the MR signal.

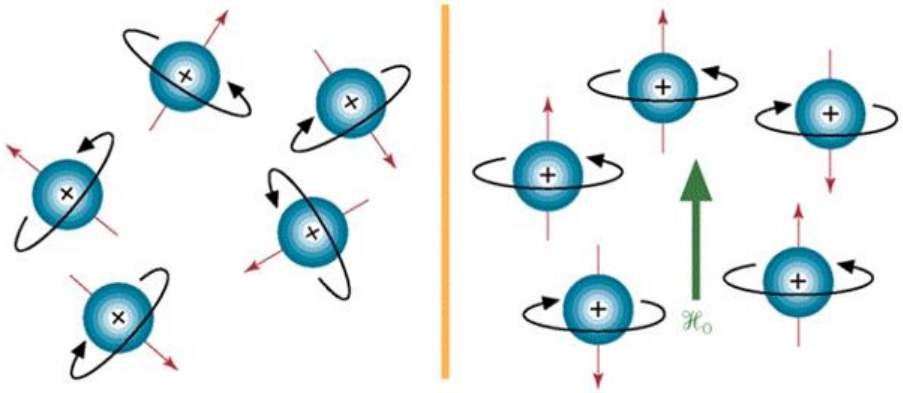

Figure 2. Nuclear spins (atoms nuclei). Left - In the absence of an external magnetic field, the spin axels of the protons are arranged randomly. Right- In the presence of an external strong magnetic field, the spin axes are aligned with the external field. (Image from Ridderinkhof et al., 2004).

How does brain images are acquired and cleaned up? Every few seconds, the MR image acquisition technique, echo planar imaging [EPI] is used to sequentially acquire brain images (several slices for x seconds that fulfill a functional MRI sequence). fMRI provides high resolution images with good contrast between tissues – grey and white matter. Several slices (2D images forming by pixels) produce a fMRI volume (3D image), as a lot of little cubes together, the voxels. Anatomical magnetic resonance imaging (MRI) provides brain anatomy and functional MRI (fMRI) provides the neural activation based on hemodynamic changes, as previous explained. Integrating analyses of anatomic and functional measurements it is possible to identify the brain region with neural activation in a specific period of time associated with the stimulus. But this activity does not necessarily indicate the brain activity specifically associated with the stimulus. Some blood flow is result from other activities that brain is engaged in. Through a process called subtraction, this problem can be solved – the patter of blood flow is subtracted from the pattern of blood flow in another condition, the resulting pattern can be related to the blood flow associated with the first condition (the contrast between conditions).

However, before such statistical analyses, fMRI data need to be screened for problems that could produce misleading results, ensuring data quality. An fMRI volume contains not only the signal that we are interested but also fluctuations (noise) that we are not interested: head motion, slice time smoothing and registration and normalization. Image fMRI images as photos that you take. Motion must be corrected (in this case, head motion) to get a much clear and sharply defined image. Each fMRI volume image is edited to look as if all slices were acquired simultaneously. In reality, each slice took different time to acquire. Also, to smooth the functional data it is necessary to replace the signal at each voxel by averaging over nearby voxels, reducing the noise and enhance the signal. Finally, to perform multigroup analyses, each voxel for each subject must correspond to the same part of the brain – it`s called registering and normalizing. Each brain needs to be transformed to have the same size, shape, and dimension. Anatomical and functional images had to be aligned (overlapped) through gyri, sulci and ventricles and after normalized, as putting them in the same box.

Human Brain anatomy at a glance

Towards data analyses, knowledge about brain regions is required to interpret the results. A brief description of brain anatomy will be carried out. Brain is composed by the telencephalon and diencephalon (Figure 4). The relative positions of the anatomical divisions can be described as medial versus lateral, rostral versus caudal, anterior versus posterior, and ventral versus dorsal. The horizontal section allows the division between dorsal and ventral. The Sagittal section drives to left and right sides (hemispheres). And finally, the coronal section enables to access brain from frontal to posterior regions. Anatomic division is also made based on sulcus landmarks leading to 4 lobes: frontal (prefrontal cortex), parietal, temporal, and occipital. The cytoarchitectonic areas of Broadmanns` areas (BA) reveal more brain partitions (52) that helps to related localized brain regions with its function. Anatomical structures could be categorized into cortical or subcortical regions depending on exterior part or real interior part (the diencephalon).

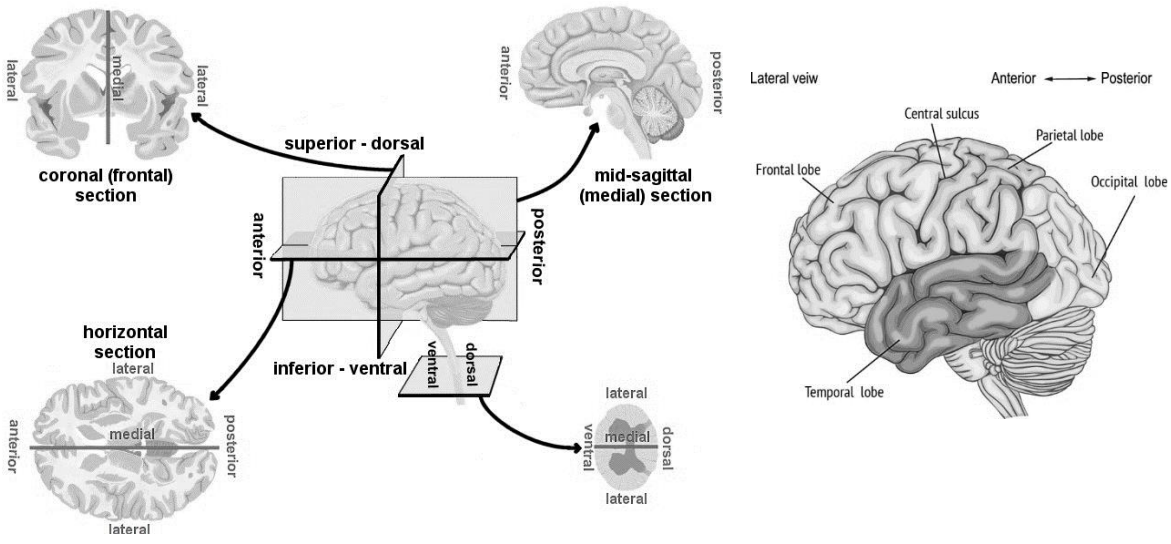

Figure 4. Human Brain from the left side: Directions, Cross-sections and divisions Taken from http://homepage.smc.edu/russell_richard/Psych2/Graphics/human_brain_directions.htm

The prefrontal cortex is normally subdivided in lateral (lPFC), medial (mPFC) and orbitofrontal cortex (OFC). Within lPFC, the literature describes two subdivisions: 1) dorsolateral prefrontal cortex (dlPFC) –BA 9, BA46, BA8 / ventrolateral prefrontal cortex (vmPFC)- BA44, BA45 and 2) inferior frontal junction (IFJ) (Felton, 2016; Huettel et al., 2009).

Experimental design

The three experimental tasks were adapted to fMRI scanning (Balloon Analogue Risk Task and the two Trust Games in economic and health domain). The BART was originally conducted in fMRI by Rao et al. (2008). Participants had unlimited time to respond (choice to inflate the balloon or to take the accumulated amount of money for a given trial). After, they received a feedback: the sound for balloon explosion (loss) or sound of money machine (gain). As fMRI study of Rao et al, (2008), there`s no jittering between the buttom press and the subsequent feedback.

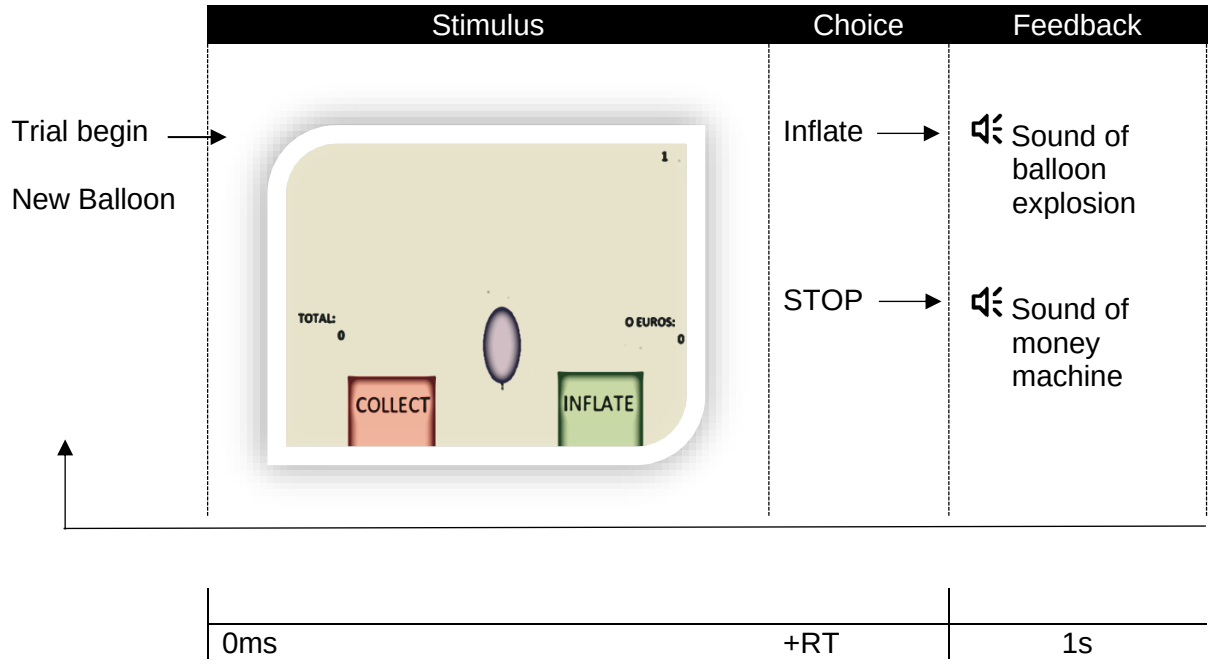

Figure 5. Schematic diagram for a trial sequence in the BART at fMRI. For each balloon (stimulus), participants had to decide (choice) inflate the balloon or collet the money earned. The consequence of that choice (feedback) was revealed by a sound of balloon explosion (if the balloon exploded) or a sound of a money machine (if they collected the money).

We used a Blocked design for trust games experiments as a fMRI paradigm (Figure 5 and Figure 6). It means the separation of experimental conditions into distinct blocks, each one presented during a period of time (Huettel et al., 2009). To ensure that possible confounding factors influence all conditions similarly, as practice or fatigue, and prevent order effects trust games were counterbalancing. Some participants started the scanning session with economic trust games and others with the health trust game.

The experimental blocked design for trust games included the following periods:

- fixation cross period (8 s)
- First Block. To Select the Expected Value, after presenting a face photo of the trustee on the screen and a horizontal slide bar to define the expected amount of money in return; block (maximum duration of 8 s, interrupted as soon as the participant selected the value to report)
- inter-stimulus interval (ISI) with a fixation cross (8 s)
- Second Block. To Select the Investment. Participants were asked the amount of money to send the trustee, 0€, 30€ or 50€; ISI (8 s) (Economic Game) or 1,4 or 6 picks (Health Game) (maximum duration of 8 s, interrupted as soon as the participant selected the value) -
- Third Block. Participants were informed (Feedback) how much money they received from the trustee in that interaction, in a period of 6 seconds
- Between interactions a fixation cross was presented for 6 seconds

  For both experiments, default values were defined if the participants did not select any value during “Expected value” and/or “Investment” blocks. In this case, the maximum value it was attributed. As punishment, the returned value would also be the maximum (in this case the most ‘penalizing’). Total experimental time was approximately 1h and 30 minutes in duration.

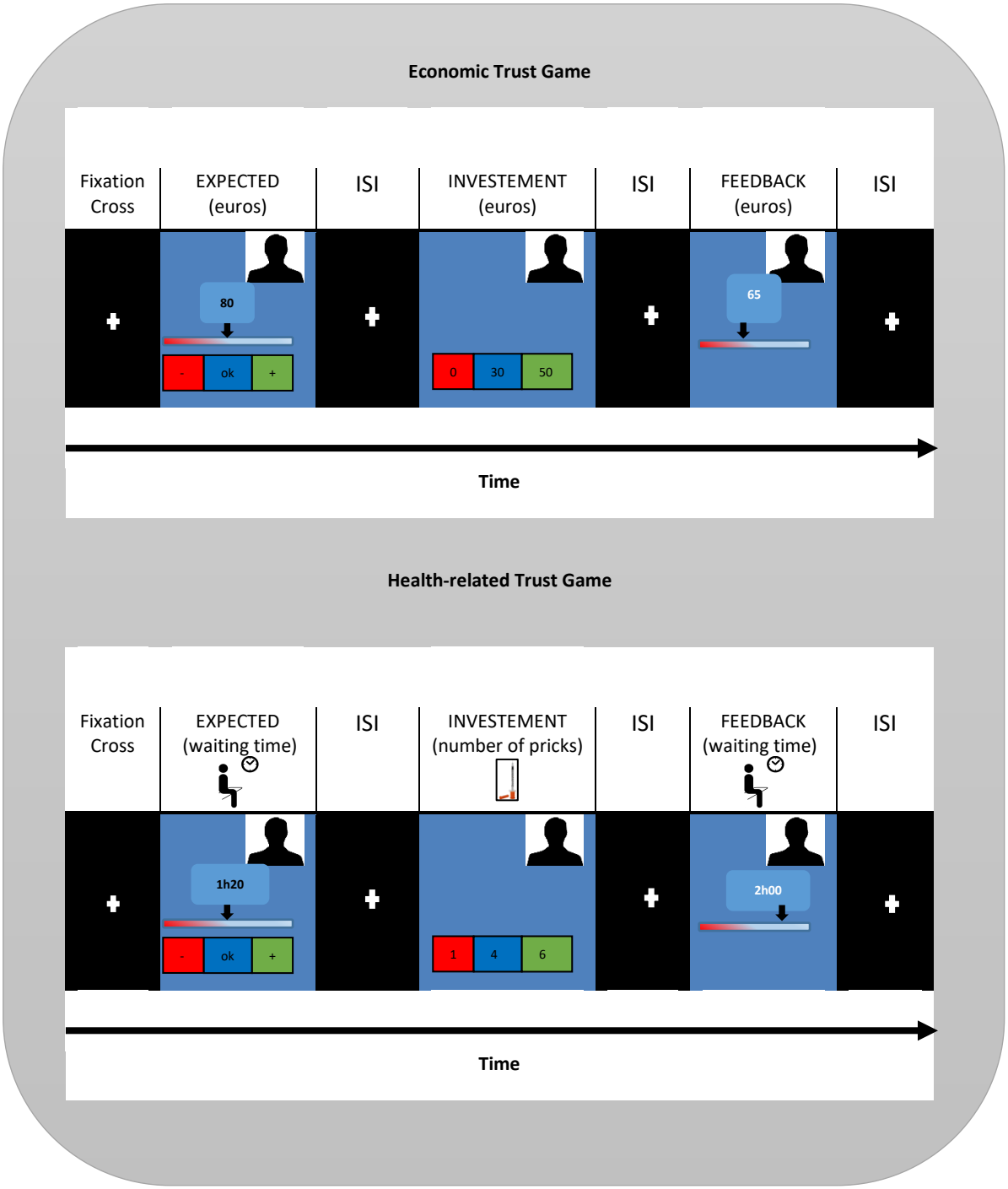

Figure 6. **Schematic representation of trust game tasks**. fMRI sequence for economic and health-related trust games. Each panel represents successive computer screens in time such as Fixation, Expected value, Fixation, Investment and Feedback Block. In economic trust game, participants invest money (0, 30, 50 euros) whereas in health trust game, number of pricks (1, 4 or 6). 30 euros means optimal choice and 6 pricks high collaboration. Positive and Negative Feedback predictors were obtained by calculation of the difference between Expected and Feedback values for each iteration.

fMRI acquisition

Pre-scanning practice session. Before entering the scanner, participants fulfilled the fMRI safety questionnaire and completed an initial practice session in a computer that was design to mimic the scanner experience. They also got familiar with the MR-compatible joystick (Hybridmojo, San Mateo CA, USA), containing three different response buttons. Sequence parameters. Once inside the scanner, after the anatomical run, the three different experimental tasks were presented in a randomized way, except BART that was present at the end of the experiment. Magnetic Resonance Imaging (MRI) scans were adcquired in a 3T Siemens TrioTim MRI scanner (Siemens, Erlangen, Germany) using a 12-channel head coil. The scanning session included a high resolution T1-weighted MPRAGE sequence that was measured with TR (repetition time) = 2530 msec, TE = 3.42 msec, TI = 1100 msec, flip angle 7º, single shot slices with voxel size 1 x 1 x 1 mm, FOV (Field of View) of 256 mm and a slice thickness of 1 mm. Functional images were acquired in the same 3T Siemens TrioTim MRI scanner using BOLD contrast echo planar imaging (EPI, TR = 2 sec, TE = 30 msec, 35 slices, voxel size 3 x 3 x 3, in-plane matrix 86 x 86 voxels) covering the entire brain. These values were identical for both functional acquisitions. The task was presented in an LCD monitor (NordicNeuroLab, Bergen, Norway) mounted 156 cm away from the participants' head. The monitor could be seen through a mirror mounted above the coil. The monitor has a frequency rate of 60 Hz and dimensions of 698.40 x 392.85 mm. The maximum number of volumes per run for each functional run was 621 volumes (Figure 7).

Debriefing

After participation, volunteers were asked if they noticed differences between mediators in terms of reward (detection of payoff contingencies) so that we could previously identify participants` difficulties to play the game or to anticipate whether the subject did the task attentively. Participants were than paid for performance based on points earned during the task (1 cent/pump in balloons that did not explode).

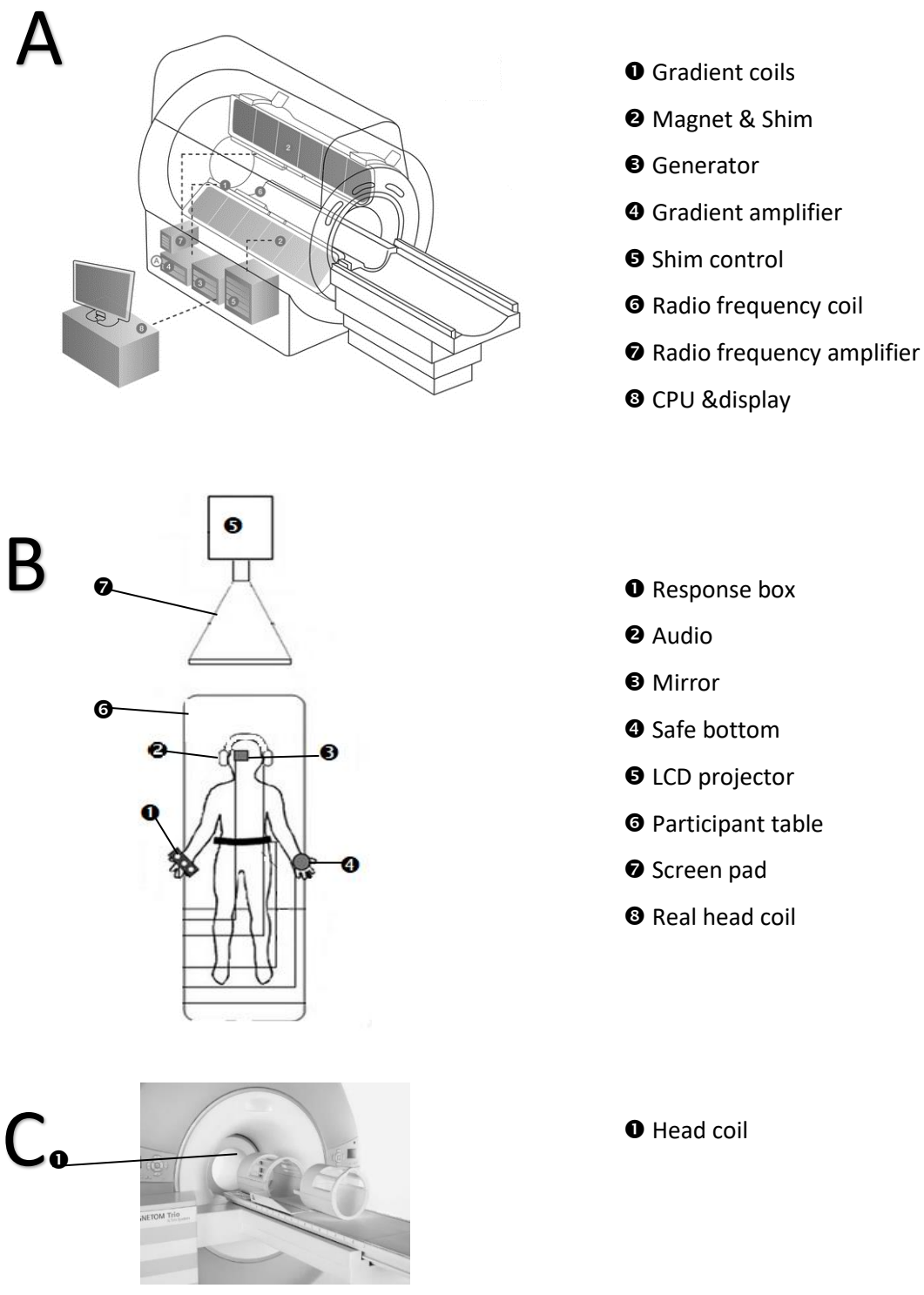

Figure 7. **fMRI setting.** Image from LEM (Life Energy Motion) public site https://www.lem.com/en/high-precision. **B**. **Magnetic room** Image adapted from (Voyvodic et al., 2011). **C. Real magnetic resonance**, a Magneton Trio, A Tim System, 3T eco. Image from Siemmens public site.

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PART III

RESEARCH RESULTS

CHAPTER 1

INDIVIDUAL RISK PROFILE & FAMILY CONTEXT OF PEOPLE WITH T1DM

Study 1

Successful metabolic control in Type 1 Diabetes Mellitus depends on individual neuroeconomic and health risk-taking decision endophenotypes: a new target in personalized care

Short title: Treatment adherence endophenotypes in Diabetes Type 1

> Life is complex, with multiple forces simultaneously exerting their influences on us, and this complexity makes it difficult to figure out exactly how each of these forces shapes our behavior. In Ariely, D. (2008). Predictably irrational. The hidden forces that shape our decisions, p.xxi). Harper Collins Publishers

Jorge, H., Duarte, I.C., Correia, B.R., Barros, L., Relvas, A.P., & Castelo-Branco, M. Successful metabolic control in type 1 diabetes mellitus depends on individual neuroeconomic and health risk-taking decision endophenotypes: a new target in personalized care. Manuscript submitted for publication. Under second round of review.

Abstract

BACKGROUND Neurobehavioral decision profiles have often been neglected in chronic diseases despite their direct impact on major public health issues such as treatment adherence. This remains a major concern in diabetes, despite intensive efforts and public awareness initiatives regarding its complications.

METHODS In this study of 91 participants with Type 1 Diabetes we hypothesized that high rates of low adherence are related to risk-taking profiles associated with decision-making phenotypes. If this hypothesis is correct, it should be possible to define these endophenotypes independently based both on dynamic measures of metabolic control (HbA1C) and multidimensional behavioral profile based on self-reported real world risk behaviors as well as experimental approaches such as the Balloon Analogue Risk Task (BART).

RESULTS K-means and Two-Step cluster analysis suggest a two-cluster solution providing information of distinct decision profiles (concerning multiple domains of risk-taking behavior) which almost perfectly match the biological partition, based on the division between stable or improving metabolic control (MC, N=49) versus unstably high or deteriorating states (NoMC, N= 42). This surprising dichotomy of behavioral phenotypes predicted by the dynamics of HbA1C was further corroborated by standard statistical testing. Finally, the BART game enabled to identify groups differences on feedback learning and consequent behavioral choices under ambiguity, showing distinct group choice behavioral patterns.

CONCLUSIONS These findings suggest that distinct biobehavioral endophenotypes can be related to the success of metabolic control. These findings also have strong implications for programs to improve patient adherence, directly addressing risk-taking profiles.

Keywords: HbA1c, multidimensional risk-taking assessment, ambiguous uncertainty, neuroeconomics, decision-making, treatment adherence

1. Introduction

Human decision-making is now recognized to involve factors well beyond rational computation of maximizing utility as theorized by some economists in the 20Th century. The field of behavioral economy emphasizes the deceptive incoherence that often emerges in everyday acts and decision areas of life (Glimcher, 2014). In the financial context, one of such "irrationalities" is asymmetric weighing of loss on gain leading to dampened loss aversion (Peng at al.2013) whereby accumulation of losses is associated with less sensitivity to risk, so people become more risk seeking, as it happens on pathological gambling (Genauck et al., 2017). In the health context, investigation about why people engage in risky health behavior not avoiding future complications with high probability has a high neuroscientific and public health value. Risk-taking health behaviors are critical in chronic diseases such as diabetes (Ginter & Sinko, 2013), which management requires patient continuous daily decisions (self-monitoring of blood glucose, food, and exercise). In general, research highlights individual differences in proneness to maladaptive behavior or suboptimal decisions (van der Gaat et al., 2020). Therefore, the early identification of risky profiles that predict treatment responses is therefore of paramount importance (St. John at al. 2010).

The challenge to collect information that comes close to real world individual behavior leads to the need to apply alternative methods of measuring risk-taking in addition to limited self-reported instruments (risk perceived and individual traits). Experimental tasks are one of them and are based on "a decision variable approach" (Smith & Huettel, 2010) focusing on potential outcomes and their values and the level of certainty of future rewards, translated into learning probabilities (uncertainty). This methodology has also been used to estimate individual risk-taking attitudes in normal and clinical populations as Alzheimer' Disease, OCD, binge eating, pathological gambling and other addictive disorders (Kim, 2015; Moallen & Ray, 2012;). For example, the BART (Canário, 2019; Lejuez, 2002;) is a widely used experimental task developed to assess actual risky behavior, choosing to risk for a higher

reward or opt for a safe lower reward, without prior probability information (leading to high ambiguity).

This study aimed to investigate if HbA1C (A1C glycated hemoglobin) dynamic variations are associated with distinct risk-taking profiles. If correct, these behavioral phenotypes would serve as indicators for tailoring investment in terms of management policies. HbA1C is the standard dynamic biomarker for the adequacy of glycemic self-management (Mamykina at al.2015). We designed a cross-sectional observational study with 91 patients aged between 22-55 years with Type 1 Diabetes Mellitus (T1DM). We compared risk-taking performance profiles between 42 adults with type1 diabetes NoMC (no metabolic control) and 49 MC aged and gender matched patients (control group with metabolic control) while they completed a robust set of risk-taking measurements to allow for multidimensional clustering: self-reported risk-taking questionnaires and a risky decision-making experimental task under uncertainty with large ambiguity (BART). Concerning the latter, participants did not know outcome probabilities in advance, so their initial decisions were made under complete ambiguity with the possibility for learning across sequential feedback. Sociodemographic, cognitive, personality, psychophysical and clinical data were also collected.

This is the first study to demonstrate a significant multidimensional risk decision-making profile that distinguishes between individuals with better and worse dynamic HbA1c values, linking behavioral and biochemical variables in diabetes. We tested whether groups could be independently discovered through data driven cluster analysis. We predicted that a distinct decision-making risky profile would be identified. We expected that this would be associated with impairments in risk perceptions, more general present and past risk attitudes and larger impulsivity. We hypothesized that the control group (with glycemic control) would yield more efficient game strategies, consistent with adaptive behavior (avoiding too aversive or too risky options). We hypothesized that individuals from the control group consider update values with choice impact, while no significant switching is expected in the group

without metabolic control. Concerning relationships among variables, we expected to find positive associations between self-reported real-world risk behavior and BART performance, given the notion that both address the dimension of risk-taking.

2. Materials and methods

All subjects signed the informed consent of this study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra, in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants, after an explanation of the nature and duration of the study.

We designed a cross-sectional observational study with 91 patients aged between 22-55 years with T1DM. We compared risk-taking performance profiles between 42 adults with type1 diabetes NoMC (no metabolic control) and 49 MC aged and gender matched patients (control group with metabolic control) while they completed a robust set of risk-taking measurements to allow for multidimensional clustering: self-reported risk-taking questionnaires and a risky decision-making experimental task under uncertainty with large ambiguity (BART). Concerning the latter, participants did not know outcome probabilities in advance, so their initial decisions were made under complete ambiguity with the possibility for learning across sequential feedback. Sociodemographic, cognitive, personality, psychophysical and clinical data were also collected. Participants fulfilled the protocol in one visit of one hour and half.

Eligible subjects are all evaluated with the same procedures, regardless of their clinical status: 1) referred to the clinical assessment of Department of Endocrinology, Diabetes and Metabolism – University Hospital of Coimbra, Portugal (SEDM) ii) only one person in the nuclear family diagnosed with diabetes for at least one year and no other current major chronic disease iii) having an IQ>90. Participants are excluded if there is evidence for past or current history of neurological and psychiatric

disorders, recent diseases, major medical illness (cancer, anaemia, and thyroid dysfunction) and severe visual or hearing loss. In total 2 patients were excluded by presenting a history of psychiatric disorder.

2.2 Sociodemographic and cognitive/neuropsychological measures

Participants filled out a demographic questionnaire providing information on gender, age, educational level, civil status, home distance to hospital (residence), household members and household income. This last one was measured both as level of income (500-1000; 1000-1500; 1500-2000; >2000 Euros) and type of income (stable and unstable; stable if there is a permanent employment contract).

Cognitive and neuropsychological protocol, carried out by a psychologist, included Fluid intelligence assessment (Raven Progressive Matrices) (Raven et al., 2009; Simões, 2008), Crystalized intelligence (Vocabulary Test of WAIS-III) and executive functions such as attentional processes and working memory (Digits Forward and Backward subtests of WAIS-III) (Wechsler, 2008). Participants with more than 50 filled out MOCA (Montreal Cognitive Assessment) (Freitas et al. 2011) allowing a cognitive screening to ensure that inclusion criteria were fulfilled (Ryan et al.1993; Sommerfield et al., 2003).

2.3 Measures from clinical history

Current symptoms and complications were evaluated by the clinicians involved in the consultation at the University Hospital. Body Mass Index (BMI) and biochemical data were also collected.

Values of HbA1c for the patient consultation history over multiple time points were first used to divide groups with or without successful metabolic control. Patient`s medical history could have 3 to 5 samples of HbA1c since they began hospital treatment. For the first group (MC), we included patients with the following dynamic profiles: continuously descending and improving values of HbA1c over time, patients with low (normal) stable/Invariant values that did not change beyond 0.5 and patients whose values varied more than 0.5, but the maximum value of this oscillation was lower than 8.0 (64

mmol/mol). For the second group (NoMC), we included patients with the following dynamic profiles: continuously ascending values of HbA1c over the time, patients with high (abnormal) stable values that did not change beyond 0.5 over the time and patients whose values varied more than 0.5, with the minimum value of this oscillation being more than 8.0.

2.4 Multidimensional Risk–related constructs and self-reported real-world risk behaviors

Risk-taking profile was first measured by a comprehensive battery. To fully characterize personality traits and also exclude patients with psychiatry disorders the Eysenck Personality Questionnaire (EPQ) (Portuguese version, Castro-Fonseca et al.,1991) was administered, in four dimensions: psychoticism [P], extraversion [E], neuroticism [N] and a lie (L) scale. Behavior Impulsivity Scale-11 (BIS-11); Translated, (Cruz & Barbosa, 2012); validation for the Portuguese population, (Fernandes, 2014) evaluated Impulsivity in general, lack of planning and inhibitory control, as risk-related constructs. Additionally, to achieve individual self-reported real-world risk profile, participants were confronted with two types of questionnaires:

1. Individual Perception of risk-taking in health and financial contexts (DOSPERT) (Blais & Weber, 2006); Portuguese translation (Silva, 2012).
2. Variations of Risk profile in the life span (past and present risk-taking in six distinct areas – leisure, health, career, finance, safety, and social life).

Additionally, perception of family functioning and eating behavior was also considered since diabetes care requires a diet and weight management made mainly at home. Family functioning was assessed by the Systemic Clinical Outcome and routine Evaluation (SCORE-15) (Stratton et al.,2010; portuguese version from Vilaça at al., 2014). SCORE-15 is a self-report family assessment instrument with a 6-point Likert scales, which also gives specific information about family strengths (and family`s adaptability), family difficulties (overcoming on family system) and family communication. Total lower values are related to good family functioning. The Portuguese validation of Dutch Eating Behavior Questionnaire (DEBQ) (Van Strien et al.,1986; Viana & Sinde, 2003) is a 33-item instrument, with a 5-item Likert Scale

evaluated three types of eating styles: restrained (avoid eating more than was initially defined), external (to eat motivated by external factors such as good food smell and how it looks) and emotional (to eat in response to emotions) (Figure 1).

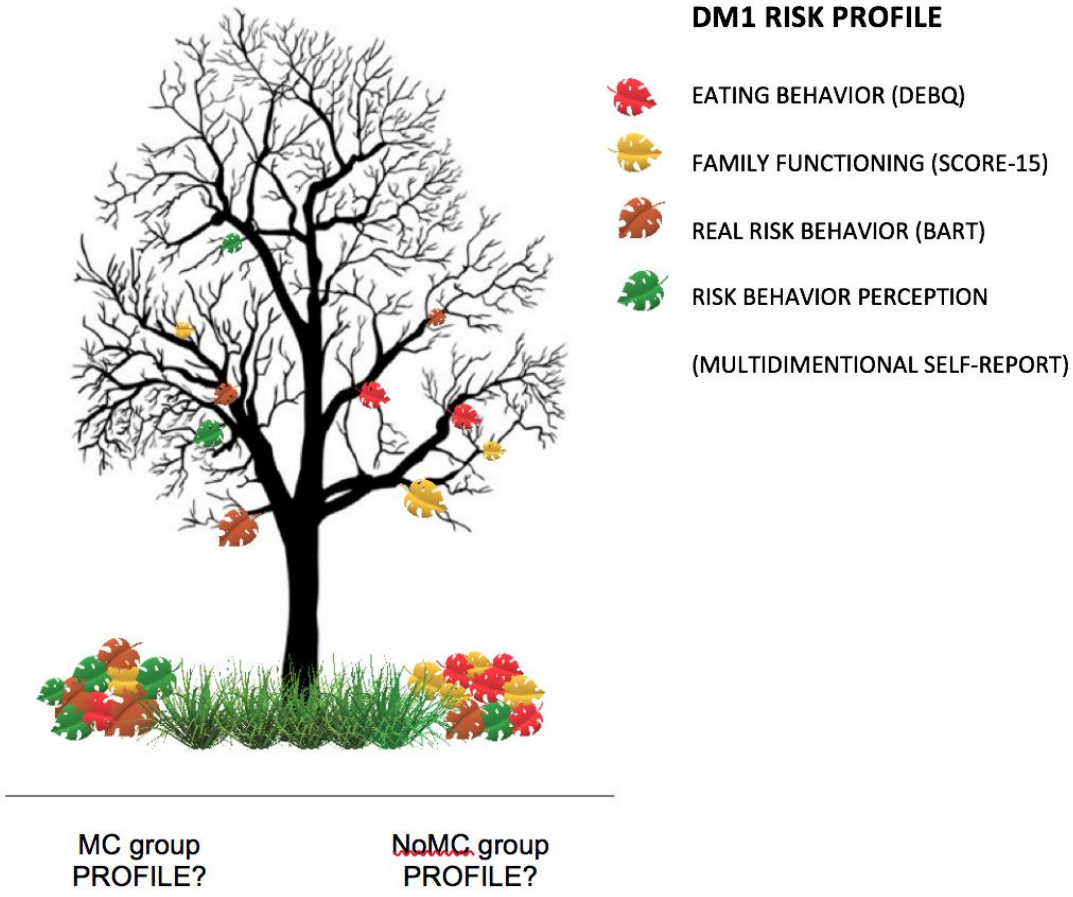

Figure 1. Representation of conceptual framework underlying our hypothesis as a two-cluster risk profile. T1DM risk profile including individual and family variables, named Multidimensional

Self-report Risk Behavior Perception (assessed by two questionnaires), Eating Behavior (evaluated by Dutch Eating Behavior Questionnaire), Real Risk Behavior (acquired by Balloon Analogue Risk Task, a computerized measure of risk taking) and Family Functioning (represented by Systemic Clinical Outcome Routine Evaluation-15).

2.5 Balloon Analogue Risk Task (BART)

BART is a computerized direct measure of risk-taking behavior with ambiguous and unpredictable reward. Participants were told that they would be presented with 30 balloons. By pumping up a balloon

(through a button click), participants have the chance to earn (if they decide to stop inflate), or to lose money (if they let the balloon explode). Riskier option (reward seeking) might confer greater potential reward and safer option (avoiding loss) gives fewer but more certain reward. Participants are not informed about the balloons' breakpoints. The absence of this information allows for testing participants' behaviors such as: 1) the first play move, initial decision-making under uncertainty, 2) the sequential play move, it means the adjusted decision-making over the game, studying changes in responding as they gain experience with the task contingencies (learning with experience; choice impact as switching from risk averse to risk seeking behavior and vice-versa) and task efficiency (final amount of money earned) (Figure 2).

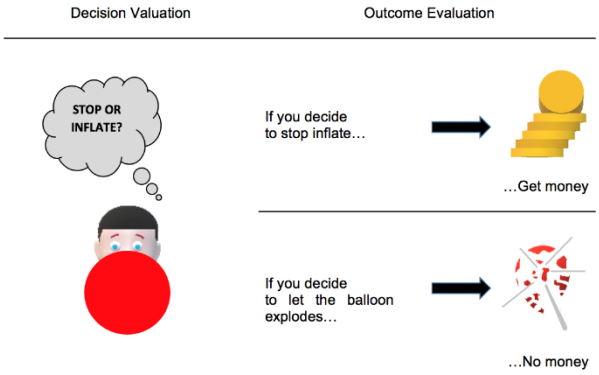

Figure 2. Representation of Balloon Analogue Risk Task (BART) from Decision Valuation (Stop or inflate) to Outcome Evaluation (earn money or not depending on balloon explosion).

2.6 Data Analysis

Data were analyzed using IBM SPSS Statistics (v24). Descriptive statistics are reported as mean ± SEM. Prior to analysis, raw data were examined for normality by the Shapiro-Wilks goodness-of-fit test (Ghasemi & Zahediasl, 2012).

Firstly, two methods of non-hierarchical clustering analysis (Two Steps and K-means), multivariate techniques were used to explore a partition driven by individual risk profile variables and to investigate whether they correspond to HbA1c values (Clatworthy et al.,2005). General actual and past risk-taking, general impulsivity, general perception of risk, global earned money at BART and eating behavior expressed by DEBQ`s three subscales (to preserve each type of eating behavior as itself) were chosen

given their correspondence with individual risk profile assessment. By using this methodology, we also aimed to determine the stability of clusters found, searching if different methods can replicate the same grouping (Kos & Psenicka, 2000). Using an iterative partitioning method instead of hierarchical agglomerative cluster analysis allows us to minimize the probability of wrong case inclusion at same cluster because it can reallocate entities continually. Following our methodological strategy, we also need to ensure that all introduced variables for both cluster analysis methods are the same. No continuous variables were excluded from this procedure. Before initiating the cluster analysis, variables were standardized so that all of them contribute equally to the same computations (Maroco, 2007). Data were examined for multivariate outliers and multicollinearity, resulting no significant correlation between variables selected (2 outliers were found but all analysis were performed with and without outliers with no significant effect on the results). Therefore, all subjects are included in the analysis. Both K-means and Two steps methods used centroid distance with Squared Euclidean distance as the similarity measure. Concerning K-means measures we calculated qui-square statistics to determine the percentage of correspondence between clusters found and dynamic HbA1c categories. Finally, we performed a series of independent-samples t-tests so that we better understand the differences between the two groups formed by cluster analysis including also the remaining variables described in Material and Methods section. By performing these inferential statistical tests, we also got evidence about criterion-related validity to cluster analysis, by introducing no clustering variables as suggested by Ketchen and Hult (2000). We examined all data for intercorrelations (Pearson's). Null-hypothesis statistical tests were evaluated according to an alpha value of $p = 0.05$. The chi-square test was used to compare categorical variables and nonparametric tests (Kruskal-Wallis) were used to compared ordinal variables.

3. Results

2.1 Subjects and clinical features

91 adults type 1 diabetes patients (56 males and 35 females, ages 22-55), who presented to the university clinic, were first divided in 2 groups according to the dynamics of HbA1c values over time: 42 patients with no metabolic control (mean age:36.19 ± 8.67, [20,55], mean educational level (below and above 12 years): 1.36± 0.075) and 49 patients (clinical control group) with metabolic control (mean age: 37.20 ± 9.47, [21,55]), mean educational level 1.65± 0.07. A healthy control group (n=53) was also assessed but since in this case metabolic status is by definition stable and not disrupted (unlike the clinical control group), the value of these data is normative and presented as supplemental material (Supplemental Table 2).

Table 1 summarizes the groups' demographic and clinical characteristics. Groups are matched for age, gender, and civil status. By using the chi-square test, we identified a significant association between HbA1c variations and the number of years of education (greater in MC group, $X^2(1) = 7.47$, $p=0.006$) as well as the household income (stable, for MC). Results from cognitive assessment reveal no group differences. However, comparing groups in terms of disease onset suggests statistically significant differences on Digits Forward and Backward subtests of WAIS-III results (<18 years, M=13.58, SD=1,68; >18 years, M=15.26, SD=2,21; U=1508, $p<0.001$, $d=0.87$). Additionally, memory impairments are also related to complications [Yes, M=13.82, SD=1.77; M=15.33, SD=2.13, $t(89) = -3.67$, $p<0.001$, $d=-0.77$]. Furthermore, NoMC and MC subjects showed no differences in all evaluated clinical characteristics, except for HbA1c values and Complications related to DM1 disease (greater in NoMC, as expected from worse metabolic control). Table 1 summarizes the groups' demographic and clinical characteristics.

Table 1 Demographic Characteristics, relevant Clinical Features for NoMc and MC groups (N=91) and Cognitive & Personality Traits results.

Table 1 Demographic characteristics, cognitive results, and relevant clinical features for NoMC and MC groups (N=91)

Variables	MC (N=49)	NoMC (N=42)	X^2	t	U	gl	p	d
Demographic data								
Gender (M/F)	31/18	25/17	0.134	-----	-----	-----	0.824	0.07
Age (y)	37.20 (9.47)	36.19 (8.67)	-----	0.529	-----	89	0.59	-0.11
Civil State (Single/Couple)	22/27	24/18	1.367	-----	-----	1	0.244	0.07
Household members (1/2/3)	17/28/3	16/21/5	1.695	-----	-----	1	0.428	0.08
Household income B (1/2)	33/15	16/26	8.94	-----	-----	1	0.003	0.66
Residence	20/12/16	16/17/9	2.97	-----	-----	2	0.226	0.36
Education level (1/2)	17/32	27/15	7.93	-----	-----	1	0.005	0.61
Cognitive data								
Vocabulary	32.33 (3.47)	33.60 (2.81)	-----	-----	807	-----	0.075	0.034
Digit Memory	14.82(2.15)	14.10 (1.92)	-----	-----	1273	-----	0.05	0.416
RPMT	8.04(0.90)	8.05 (1.01)	-----	-----	981	-----	0.688	0.08
Clinical features								
Disease onset (</>18)	24/25	24/18	0.605	-------	------	1	0.382	0.16
Disease Dealing Time	17.56 (10.38)	17.21 (9.58)	-------	-0.161	------	89	0.870	-0.034
HbA1c(%/mmol/mol)	7.19/55 (0.65)	8.52/70 (1.22)	-------	6.329	-----	89	<0.001	0.07
BMI	24.95 (3.31)	25.20 (3.81)	------	-------	989	----	0.750	0.067
Complications (Y/N)	21/28	30/12	7.94	------	-------	1	0.006	0.62
Smoking status (Y/N)	11/38	7/35	0.48	------	-------	1	0.49	0.14
Personality results								
Neuroticism	6.49(4,02)	9.95 (4.22)	------	4.005	-----	89	<0.001	0.84
Extroversion	13.12(3.49)	10.98(3.61)	------	-2.88	-----	89	0.005	-0.61

Household members (1= living alone 2=living as a couple 3=living with children); Household income (1=stable; 2=unstable); Residence as distance to health services in spending time (1=Coimbra; 2= <1h; 3= >1h); Educational level (1= below 12 years; 2= above 12 years); RPMT Raven's Progressive Matrices Tests; BMI body mass index.

3.1 Cluster characteristics

Both non-hierarchical cluster analyses revealed a two-cluster solution, even if we specified other number of clusters. Results showed a dichotomic partition that almost perfectly matched with a single dynamic biological parameter (HbA1c).

Through a K-means algorithm, we detected that, Health and Financial Risk, as well as Restrained Eating were the only ones that did not provide a significant contribution to the clustering, as shown by ANOVA (Table 2). Final output (right part of table 2) revealed that all remaining variables had a significant role. Finally, we found a significant match with metabolic state, as defined by dynamic HbA1C, as proven by the qui-square output ($X^2(1)=29.56$, $p<0.001$, $d=1.27$), concluding that 73.8% of participants from metabolic control group (MC) belong to cluster 1 and 86.7% of the other group belong to cluster 2.

We found similar results using a two-step cluster confirmatory analysis using the same final variables applied to calculate K-means algorithm. We examined the silhouette coefficient (=0.4) as well as size ratio (=2.03; 60/31). The Silhouette coefficient determines the distance between the mean distance of one cluster to the mean distance to the other cluster. It ranges between -1 and 1, being that close to 1 indicate that one point in the cluster is far away from its neighbor, so variables fit well within cluster agglomeration. Size ratio refers to proportion of subjects inserted in each cluster. Knowing that our data has a size ratio of 1.16 (49/42) and introducing dynamic HbA1c variable forward, we concluded that cluster 1 corresponds to participants +with diabetes with metabolic control (MC) and cluster 2 to the other group. Moreover, variables introduced are sorted by weight for cluster formation in descending order through a chart revealing their level of importance.

3.2 Self-reported real-world risk related constructs

Groups differed in terms of general impulsivity [$t(89)=2.138$, $p=0.035$, $d=0.45$] and lack of planning (measured by BIS-11) ($U=657.5$, $p=0.003$, $d=3.34$). Higher scores were found in the NoMC group. Additionally, patients with impaired metabolic control over the time presented less health risk perception than MC patients ($U=1273$, $p=0.029$, $d=0.41$). The groups did not differ in terms of risk perception in the financial context. The NoMC group also showed more perceived general past risk ($t(89)=3.83$, $p<0.001$, $d=0.81$) and present risk than the MC ($U=566$, $p<0.001$, $d=0.80$).

These results indicate that groups differ in all evaluated dimensions of self-reported real world risk-taking (self-control, contextual risk perception, general risk profile over time and delay reward discounting). Participants from NoMC group showed evidence for reduced self-control, misperception of risk in health context, higher past and present general risk (Table 2).

Table 2

Non-hierarquical k-means cluster analysis for continuous risk-taking variables forming a two-cluster solution

	First K-means computations						Rerun K-means computations without Health and Finantial Risk & Restrained Eating					
	Final Center clusters		ANOVA				Final Center clusters		ANOVA			
Variables	*Cluster1* N=60	*Cluster2* N=31	*df*	*F*	*p*	*d*	*Cluster1* N=61	*Cluster2* N=30	*df*	*F*	*p*	*d*
Health Risk	0.12	-0.23	89	2.45	0.121	0.35						
Financial Risk	0.00	-0.01	89	0.00	0.949	0,00						
Past RT	-0.36	0.69	89	29.79	0.000	1.23	-0.34	0.68	89	26.77	0.000	1.16
Present RT	-0.28	0.53	89	15.47	0.000	0.89	-0.24	0.49	89	12.07	0.001	0.78
Inibitory Control	-0.27	0.52	89	14.67	0.000	0.85	-0.26	0.53	89	14.75	0.000	0.86
Lack of planning	-0.19	0.37	89	6.69	0.011	0.56	-0.21	0.43	89	8.90	0.004	0.67
Total Wins*	0.14	-0.27	89	3.50	0.065	0.42	0.16	-0.32	89	4.73	0.032	0.49
Restrained *Eating*	-0.05	0.09	89	0.36	0.550	0.14						
Emotional *Eating*	-0.44	0.85	89	54.96	0.000	1.67	-0.44	0.89	89	58.62	0.000	1.71
External *Eating*	-0.33	0.65	89	25.03	0.000	1.13	-0.32	0.66	89	24.65	0.000	1.11
Strenghs and adaptability	-0.19	0.37	89	6.79	0.011	0.59	-0.20	0.40	89	7.63	0.007	0.62
Overwhelmed by difficulties	-0.49	0.94	89	76.16	0.000	1.97	-0.48	0.98	89	81.31	0.000	2.02
Disrupted Communication	.0.45	0.91	89	69.08	0.000	1.87	-0.45	0.92	89	65.26	0.000	1.81

RT- Risk Taking; *Money earned at BART

3.3 Behavioral Measure of the risk-taking task (BART)

Risk-taking Behavior was analyzed in three components: The First Play Move, The Sequential Play Move and Task Efficiency, as Final Gain.

For decision-making under uncertainty and ambiguity (the first play move), we examined initial strategy (“let the first balloon explode”) and initial risk profile (number of successful inflations in first balloon), finding no associations with groups ($p<0.05$).

Adjusted decision-making during probabilistic learning (sequential play move and probabilistic learning) was analyzed through several variables: distance to balloon explosion, magnitude of change behavior, minimum, maximum, mean successful inflations and performance after loss.

Firstly, we examined how groups performed in terms of estimating the distance towards to the balloon burst, a so-called gain maximization strategy (balancing risk while avoiding losing). For this purpose, we divided the task in three parts, each one with 10 balloons. Groups differed in gain maximization values for the first two parts of the game (MC with larger capacity to estimate unknown values). The NoMC group maintained the same behavioral pattern throughout the game, with no reaction to the changes of the context (no subsequent choice impact). In general, more efficient participants (who earned more money in BART) were more responsive to contextual clues. Afterwards, we examined the magnitude of this change comparing the initial number of pumps and the score mean of adjusted average pumps. MC presented a moderate change (-10 to 10 pumps) and NoMC showed an imperceptible magnitude (-5 to 5), so that change magnitude is significantly associated with group membership ($X^2(2)=8.11$, $p=0.017$, $d=0.63$). We also investigated the performance after a loss (subsequent choice after prediction error). We found no association, but both groups became more risk seeking in the next balloon after a loss.

Final gain value, as task efficiency measure and expressed in Total Wins, was higher in the MC group as well as adjusted average pumps so participants with metabolic control are more efficient in gathering rewards.

In general, NoMC participants performed worse in BART than the control group in all evaluated levels (see supplemental table 1).

4. Discussion

As we predicted, we identify a distinct decision-making profile. One first finding is that dynamic biological profiles of metabolic control seem to be associated to decision-making profiles which define a behavioral phenotype. These profiles were first detected by two methods of non-hierarchical cluster data-driven analysis cluster analysis, showing two clusters matching distinct dynamics of metabolic control and corroborating a model driven approach based on hypothesis testing. It is important to note that we included only patients with no or at least initial complications related to diabetes disease. This means that we consider that relationship between behavior and biology in this study is largely related to context and not to disease complications per se. These results suggest the existence of behavioral endophenotypes based on multidimensional risk-taking measures and underline the specificities of diabetes care as family functioning and individual eating behavior style assessment. It seems of paramount importance in personalized medicine programs namely the ones emphasizing improved treatment adherence.

Second, we expected to find a positive association between self-reports real world risk behavior and BART. Our results from self-report assessment are well related to experimental approaches being a good indicator that our protocol gathers a good approximation to the real-world behavior, maximizing the breadth of risk-taking assessment.

However, the initial riskiness in the experimental task (Peng et al., 2013) addressing risk-taking, impulsivity and decision (BART) was negatively correlated with scores on self-report measures of risk-related constructs (self-control) and with the self-report measures of real-world behavior (risk perception, general risk past and present profile). This is interesting because concerning uncertainty, ambiguity and first level of feedback (first 10 balloons) similar results were found in the prosocial behavioral context (Vives & Feldman Hall, 2018) explained as tolerance to ambiguity. Social

interactions are equally considered ambiguous due to difficulty to predict how people will act. So, maybe MC patients are more ambiguity-tolerant to engage in highly uncertain behavior as people in prosocial behavior are more likely to do when have to decide to trust a stranger since they are more optimistic about results in their own favor.

Fourth, we hypothesized that MC group would play more efficiently updating values with choice impact. We found that BART helps to discriminate groups so that MC participants (control group) seem to actively update their expected reward value, changing their initial risk seeking decision-making strategy to a more effective one. A set of studies could help to get additional insights to this result. Earning more money (successful balloons), this group revealed a higher capacity to estimate unknown values getting closer to them, showing more continuous gain maximization and strategy. Bechara et al. (1997) described a similar effect as making decisions advantageously and Dijksterhuits and Nordgren (2006) called “intuition” or “intuitive”, as presented in theory of unconscious though, including a feeling based on past experiences. On the contrary, the NoMC group showed a tendency to inflexible risk strategy over time, misperception of risk or less adaptation to uncertain environmental changes (update error or lack of update). In addition, this unchanging strategy is characterized by lower risky options than the MC group. This could be explained by impulsivity or inability to engage with stressful situations given that less inflations led to quicker outcomes, reducing the exposure time to stressor reinforced as the balloon size increases (Models of emotion-based choices and emotion sensory systems) (Damasio, 1997). According to the triadic neurocognitive model applied to additive and problematic eating behaviors (Chen et al., 2018), it could be also reported as an imbalance between a hyper functioning of impulsive system, a hypo-functioning reflective/inhibition and an altered interoceptive awareness system that suppresses cognitive processes to inhibit maladaptive behavior. Similarly, a systematic review about temporal discounting and reinforcement learning by Story et al. (2014) posit that unhealthy behavior is explained by a trade-off between incorporating new information (flexibility) and good use of past experience, dividing

decision makers in two strategies of learning action-value: a model-based, goal-directed, ruled-based with rapid sensitivity to change and, on the other hand, model-free, with a gradual integration of outcome values, becoming habits, as unhealthy behavior.

5.Limitations and future directions

Despite the reported findings, limitations should be considered. Firstly, we are not able to differentiate different stages of the decision process to better understand risk profile and learning results. The BART experiment focuses on successive action selection but does not allow to directly measure how participants are valuing an uncertain quantity before option selection and update outcomes after cash out or Balloon explosions. Future studies which design contemplates partitioning decision-making process could be helpful to disentangle participants action intentions and understand if there is a learning impairment or difficulty to estimate uncertainty. Second, patients undergo a nonsocial decision-making task. Despite several results suggesting impairments in decision-making in the BART task in neurological disorders, it was interesting to investigate how patients perform on self-relevant contexts with health outcomes. Third, emotional states driven from balloon explosion (reaction to loss) could be relevant to understand mediator effects to subsequential decision-making. Further studies should be done to accomplish more evidence of connection between HbA1c and risk behavior profiles. Future work could measure the effectiveness of this interventions targeted to risk-taking decisions in clinical and no clinical populations. It would be helpful to consider other constructs and measures of risk-taking to complete risk profiles, as well as considering contextual and relational factors currently linked by the literature to patient adherence (Gray et al., 2003). Future neuroimaging studies could be helpful to understand the neural correlates of the distinctly observed decision-making profiles, helping to understand variability in decision-making.

5.Conclusion

In the present study, we provide data supporting distinct multidimensional risk behavior decision-making endophenotypes in subjects suffering from diabetes Type 1, which were related with the success of metabolic control as defined by dynamic variations of the biological variable Hba1c. This early endophenotype of impaired decision-making under economic or health related uncertainty and ambiguity, impacts on health outcomes and should be the target of future healthcare approaches. This work provides scientific evidence for biological association with decision-making profiles not necessary causal, as validated by cluster analysis and provides important information for the future guidance of adherence improvement programs which is of great public health relevance.

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Supplementary data

Supplementary Table 1.

Descriptive statistics and results for performance on the BART experimental task

Variables	Participants with NoMC (N=42)					Participants with MC (N=49)								
	M	*SD*	*1*	*2*	*3*	*M*	*SD*	*1*	*2*	*3*	*U*	*t*	*p*	*d*
Inflations (1st balloon)	15.00	10.73	6.75	10.00	30.00	17.57	9.71	8.00	20.00	26.50	1197	------	0.178	0.28
Gain maximization*	46.51	33.5	21.10	31.25	93.75	56.51	30.61	26.57	62.50	85.94	1227.5	------	0.112	0.34
Sucessful Inflations	17.16	8.02	9.55	15.86	23.59	21.23	6.97	16.23	22.61	26.69	1354	------	0.100	0.56
Explosions (N)	6.67	2.33	4	7	9	8.00	1.56	7	8	9	1375	------	0.005**	0.60
Maximum	29.62	12.61	19.50	30.00	37.00	35.00	10.81	28.50	33.00	42.50	1304	------	0.028**	0.47
+Risk after loss (%)	62.31	26.94	50.00	66.67	83.93	68.69	21.55	58.57	75.00	80.00		-3.04	0.283	0.23
-Risk after loss (%)	37.69	26.94	20	25	41,43	31.31	21.55	16,08	33,33	50	894.5	------	0.283	0.23
Balloon 1-10**	59.28	20.76	42.58	57.09	76.35	70.69	13.66	63.25	74.34	80.04	1366.5	------	0.007**	0.58
Balloon 11-20**	59.22	17.21	47.26	60.89	71.87	68.66	14.87	57.85	73.03	80.23	1382	-------	0.005**	0.62
Baloon 21-30**	61.28	18.81	43.35	62.37	78.24	68.21	16.95	62.70	71.33	79.98	1246	------	0.084	0.37
Total wins	16.37	4.74	12.50	15.65	20.03	18.91	3.78	17.42	19.85	21.05	1376	------	0.006**	0.61

*Distance to first balloon explosion (%); **successful inflations in distance to balloon explosion (%)

Supplementary Table 2.

Demographic Characteristics, Cognitive and relevant results of Performance on the BART experimental task from health participants (N=53)

Variables	N	M	SD
Demographic data			
Gender (M/F)	27/26		
Age (y)		35.66	8.51
Civil State (Single/Couple)	22/31		
Household members (1/2/3)*	32/5		
Household income B (1/2)**	25/28		
Residence (1/2/3)***	53/0/0		
Education level**** (1/2)	4./49		
Cognitive data			
Vocabulary		32.19	3.15
Digit Memory		16.57	2.83
RPMT		8.21	0.82
Performance on BART			
Inflations (1st balloon)		16.72	9.96
Gain Maximization		52.24	31.14
Balloon 1-10*****		56.23	19.04
Balloon 11-20*****		57.46	17.07
Baloon 21-30*****		54.14	17.94
Total w ins		17.99	3.96
Personality dat (EPQ)			
Neuroticism		7.55	3.99
Psicoticism		0.28	0.49
Extreoversion		11.87	3.58
Lie/Social Desirability		9.13	3.72

*Household members (1= living alone 2=living as a couple 3=living with children); **Household income (1=stable; 2= unstable); ***Residence as distance to health services in spending time (1=Coimbra; 2= <1h; 3= >1h); ****Educational level (1= 12 years, secondary education; 2= university degree or more); RPMT Raven's Progressive Matrices Test; *****Distance to first balloon explosion (%).

Study 2

Healthconomics: trust-based decision-making in the health context discriminates biological risk profiles in Type 1 Diabetes

Jorge, H., Duarte, I.C., Batista, C., Relvas A.P., & Castelo-Branco, M. Healthconomics: trust-based decision-making in health context discriminates biological risk profiles in type 1 diabetes. Manuscript submitted for publication.

Abstract

Background Theoretical accounts on social decision-making under uncertainty have postulated that individual risk preferences are context dependent. Generalization of theoretical models of decision-making in dyadic interaction in domains such as the personal health context, remain to be experimentally addressed.

Methods Methodologically, in economic utility-based models, interactive behavioral games provide a framework to study different stages of social decision-making as monitoring (value), decision (risk) and outcome (reward) phases, allowing to access probabilistic learning of sequential reinforcement. Here, we model an economic trust game in the health status context of a chronic disease (Diabetes Type 1) which involves iterated daily decisions in complex social contexts. Ninety adult patients performed two behavior trust games in both economic and health setting and were characterized by a multiple self-report set of questionnaires.

Results Our results indicated that decision-making under uncertainty varied according to context and groups. Although both groups can correctly infer pay-off contingencies, they behave differently because patients with a biological profile of preserved glycemic control show adaptive behavior both in the economic domain (considering update of values for individual choice) and in the health domain (being collaborative even towards social norm violation). On the other hand, patients with a biological profile of loss of glycemic control presented an opposite behavior, showing non-adaptive choices on both contexts.

Conclusions These results provide a direct translation from neuroeconomics to decision in the health domain and biological risk profiles, in a behavioral setting that required difficult and self-consequential decision with health impact. Our findings also provide a contextual generalization of mechanisms underlying individual decision under uncertainty.

Keywords: Human decision-making; Context-dependent trust game; Probabilistic learning; Norm violation; Treatment adherence; HbA1c

1.Introduction

A large array of behavioral studies investigating decision-making under uncertainty have been used to explain individual preference differences through experimental neuroeconomic games involving a difficult choice under ambiguity with money as reward (Charness et al., 2012; Glimcher & Porris, 2004; Lane & Chereck, 2000; Mohr et al., 2010; Ruff & Huettel, 2014). These studies involve the following cognitive processes: option representation, valuation, action selection, outcome evaluation and learning, using update rules.

Some of these studies focus on the valuation system, pointing out how people assign a value to potential rewards and punishments that could result from the choice (based on subjective value; sensitivity to reward; how delayed a reward will be in time). They also consider the factors that may contribute to this computation (payoff, probability, variance, cost/effort, context) (Christopoulos et al., 2009; Kim et al., 2015; Rangel et al., 2008). Others highlight individual perceptions about outcome probability that could be higher or lower than real outcome (estimation, anticipation risk, error monitoring, prediction error and its frequency) (Mohr et al., 2010). Even more studies are interested in sequential decision-making as risk behavior changes due to probabilistic learning, including the balance between previous choices and experienced outcomes (learning from experience, updating and capacity to decide advantageously with non-conscious bias) (Bechara et al., 1997; Dong et al., 2015; Mégias et al. 2018). Finally, other studies investigate prosocial contexts/situations by keeping some contingencies, relevant to social interactions (Vives & FeldmanHall, 2018).

Here we address decision-making in the context of self-consequential health issues. Individual decision-making is driven by context which is distinct concerning economic investment, or compliance (health investment) to treatment. In both cases, past experiences update by feedback and emotional

processes play an important role. As Tarrant et al. (2004, p.465) suggested “game theory models indicate that a history of past interactions between a doctor and patient and anticipation of future interactions make cooperation and good quality care more likely”. So, to study patient’s decisions to comply and collaborate in doctor-patient interactions can be envisaged within the framework of interactive decision-making and economic utility models.

Risk-taking and feedback processing in social interactions within the economic domain have been widely studied in distinct populations and is relevant as well when people engage in risky health behavior not avoiding future complications with high probability. In general, this type of research in traditional approaches highlights individual differences in proneness to maladaptive behavior (Lane et al., 2005) or suboptimal economic decisions during a repeated interaction trust game in which participants learn to expect different monetary returns through trial-to-trial feedback to choose the most advantageous one to invest. In other words, participant investment (option selection) is based on positive or negative feedback, because the participant is expected to be reciprocated. Similarly, social collaboration or prosocial behavior is less likely to occur continuously if other’s behaviors are perceived as unfair or result from norm violation (Delgado et al., 2005; Zinchenko & Arsalidou, 2018).

Importantly, successful decision-making under uncertainty requires adaptative learning as the “ability to estimate expected uncertainty” (related to the variability of outcomes) (Soltani & Izquierda, 2019) or correctly infer probabilistic models. So, learning rate is based on the computation of difference between the expected value and the outcome called reward prediction error (RPE). Methodologically, using different reward magnitudes associated with different probability distributions (same mean reward) and with a fixed relative uncertainty over trial to trial allows to estimate the expected uncertainty (standard deviation of a reward distribution) (Li & Dudman, 2013). Furthermore, as participants do not know outcome probabilities in advance, their initial decisions are made under complete ambiguity so that they can learn through feedback (Platt & Huettel, 2008).

These economic utility-based models are limited to contexts of economic decision-making. Here we aimed to generalize this framework to the health domain. Participants (91 adults with type 1 Diabetes) completed two experimental interactive neuroeconomic game tasks, trust games with uncertain decision in economic and health contexts. As decision-making is suggested to be strongly context dependent (Blais & Weber, 2006) we expected that different decision-making profiles emerge from both economic and health tasks.

We expected that decision-making profiles are associated with the quality of metabolic control in diabetes. We hypothesized that compliant (trustworthy in dyadic interactions) patients having better metabolic control than non-compliant patients. Furthermore, we hypothesized that both groups (with adequate and non-adequate metabolic control) can learn context contingencies in all tasks, but the control group (with good metabolic control) will consider update values when they are selecting an option, while no significant switching is expected in the group without metabolic control. Third, we aimed to investigate how patient collaboration (health choice) changes faced with different patterns of doctor-patient interaction (feedback) in a trial-and-error feedback processing paradigm.

2. Materials and methods

Written Informed consent was signed by all subjects after an explanation of the nature and duration of the study. It was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra, in accordance with the Declaration of Helsinki.

2.1 Sample characterization

A total of 91 volunteers from University Hospital, referred to the clinical assessment of Department of Endocrinology, Diabetes and Metabolism – University Hospital of Coimbra, Portugal (EDM), were divided in 2 groups according to the dynamics of HbA1c values over time: 42 patients with no glycemic

control (mean age:36.19±8.67, mean educational level: 1.36±0.075) and 49 patients (clinical control group) with glycemic control (mean age: 37.20 ±9.47; mean educational level:1.65±0.07). Because metabolic status is considered stable on patients with glycemic control (clinical control group), performance results from a healthy control group (N=53) are normative and presented as supplementary material.

Table 1 Demographic characteristics, cognitive results, and relevant clinical features and self-report risk measures for NoMC and MC groups (N=91)

Variables	MC (N=49)	NoMC (N=42)	X^2	t	U	gl	p	d
Demographic data								
Gender (M/F)	31/18	25/17	0.134	-----	-----	-----	0.824	0.07
Age (y)	37.20 (9.47)	36.19 (8.67)	-----	0.529	-----	89	0.59	-0.11
Civil State (Single/Couple)	22/27	24/18	1.367	-----	-----	1	0.244	0.07
Household members (1/2/3)	17/28/3	16/21/5	1.695	-----	-----	1	0.428	0.08
Household income B (1/2)	33/15	16/26	8.94	-----	-----	1	0.003	0.66
Residence	20/12/16	16/17/9	2.97	-----	-----	2	0.226	0.36
Education level (1/2)	17/32	27/15	7.93	-----	-----	1	0.005	0.61
Cognitive data								
Vocabulary	32.33 (3.47)	33.60 (2.81)	-----	-----	807	-----	0.075	0.034
Digit Memory	14.82(2.15)	14.10 (1.92)	-----	-----	1273	-----	0.05	0.416
RPMT	8.04(0.90)	8.05 (1.01)	-----	-----	981	-----	0.688	0.08
Clinical features								
Disease onset (</>18)	24/25	24/18	0.605	-------	------	1	0.382	0.16
Disease Dealing Time	17.56 (10.38)	17.21 (9.58)	-------	-0.161	------	89	0.870	-0.034
HbA1c(%/mmol/mol)	7.19/55 (0.65)	8.52/70 (1.22)	-------	6.329	-----	89	<0.001	0.07
BMI	24.95 (3.31)	25.20 (3.81)	------	-------	989	----	0.750	0.067
Complications (Y/N)	21/28	30/12	7.94	------	-------	1	0.006	0.62
Smoking status (Y/N)	11/38	7/35	0.48	------	-------	1	0.49	0.14
Self-report measures								
Neuroticism	6.49(4,02)	9.95 (4.22)	------	4.005	-----	89	<0.001	0.84
Extroversion	13.12(3.49)	10.98(3.61)	------	-2.88	-----	89	0.005	-0.61
Impulsivity	54.11 (7.06)	58.05(8.03)	------	2.138	-----	89	0.035	0.45
Lack of planning	14.32(3.76)	17.03(4.41)	------	------	657.5	----	0.003	3.34
Health risk perception	37.65(5.25)	35.98(8.8)	------	-----	1273	----	0.029	0.41
Past Risk	14.60(3.73)	12.00(3.29)	------	3.52	------	89	0.001	0.74
Present Risk	10.67(2.80)	13.64(4.31)	------	3.83	------	89	<0.001	0.81
Health Intertemporal Choice	25/15/9	13/24/5	6.51	-----	-----	2	0.039	0.55
Emotional Eating Behavior	2.34 (0.54)	2.29(0.78)	------	2.84	-----	89	0.006	0.59
External Eating Behavior	2.34(0.54)	2.58(0.51)	------	2.10	-----	89	0.039	0.44

Educational level (1= 12 years, secondary education) 2= university degree or higher; Household income (1=stable; 2= unstable); Members of the Household (1= living alone 2=living as a couple 3=living with children); Residence as distance to health services, in travel time (1=Coimbra; 2= <1h; 3= >1h) RPMT Raven's Progressive Matrices Tests; BMI body mass index. Health Intemporal choice (longer and larger reward; intermediate reward; small sooner reward)

Table 1 summarizes the groups demographic, cognitive/neuropsychological, clinical characteristics, and risk measures. Groups are matched for age, gender, and civil status. Clinicians involved in the consultation at the University Hospital evaluated current and past symptoms and complications. Body Mass Index (BMI) and biochemical data were also collected. To divide groups with or without successful metabolic control, values of HbA1c for the patient consultation history over multiple time points were collected. For the first group (Metabolic Control - MC), we included 1)patients with continuously descending and improving values of HbA1c over time, 2)patients with low (normal) stable/invariant values that did not change beyond 0.5 and 3) patients whose values varied more than 0.5, but the maximum value of this Oscillation was lower than 8.0 (64 mmol/mol). For the second group (No Metabolic Control - NoMC), we included patients with the following dynamic profiles: 1)continuously ascending values of HbA1c over the time, 2) patients with high (abnormal) stable values that did not change beyond 0.5 over the time and 3)patients whose values varied more than 0.5, but the minimum value of this oscillation was more than 8.0.

Participants were asked to completed a number of self-reported questionnaires, validated to Portuguese population, to characterize the sample: the Eysenck Personality Questionnaire (EPQ) (Portuguese version from Castro-Fonseca et al., 1991) to evaluate personality traits; Behavior Impulsivity Scale-11 (BIS-11; Translated by Cruz & Barbosa, 2012; validation for the Portuguese population by Fernandes, 2014) for evaluate impulsivity in general; DOSPERT (Weber et al., 2002; Blais & Weber, 2006; Portuguese translation by Silva, 2012) for individual perception of risk taking assessment in economic and health domains; past and present risk taking to evaluate variations of risk profile across the life span; an intertemporal choice questionnaire, where participants were asked to choose one of three options that differ in time to delay reward for three different contexts, economic, general health and diabetes specifically (Fernie et al., 2010); and, finally, Dutch Eating Behavior Questionnaire (DEBQ) (Van Strien et al., 1986; Viana & Sinde, 2003) which evaluate three types of eating styles: restrained, external and emotional. Participants also performed cognitive tests with

portuguese population norms, to verify if they could be included in this study: Fluid intelligence (Raven Progressive Matrices) (Simões, 2004), Crystalized intelligence (Vocabulary of WAIS-III) and executive functions such as attentional processes and working memory (Digits Forward and Backward subtests of WAIS-III) (Weschler, 2008). Participants aged more than 50 filled out MOCA (Montreal Cognitive Assessment) (Freitas et al, 2011).

Other people in the nuclear family diagnosed with diabetes for at least one year and other current major chronic disease, evidence for past or current history of neurological and psychiatric disorders, recent diseases, major medical illness (cancer, anaemia, and thyroid dysfunction) and severe visual or hearing loss were exclusion criteria. In total, 2 patients were excluded by presenting a history of psychiatric disorder.

2.2 Experimental Interactive Game Decision-making Tasks

As in game theory, each player has a way of acting, the strategy, and actions of two or more decision-makers lead to option selection (Moallen & Ray, 2012). To mimic this situation, we present two experimental interactive games, named: 1. Computer & Human Mediator Neuroeconomics Experiment and 2. Health Context Interaction Experiment (inspired on the Neuroeconomics framework) (see Figure 1).

Risky behavior in the health context is an option among others with uncertain probabilistic consequence (leading to heath preservation or loss) while in the economic domain is understood as a statistical uncertainty expressed as variance in monetary gain or losses (Schultz et al., 2011). The first experiment refers to situations without a medical context and the second is a tailored task with a medical risk and reward value. It was played in iterated form, where the game is made up of several rounds (runs), repeated 7 times between each type of players. At each trial, participants know with

who they are playing through face recognition of the mediator in that run. All trials, 21 in total, require that participants press one of three buttons to indicate their action selection.

Experiment 1_Computer & Human Mediator Neuroeconomics Experiment _Economic Trust Game

The first game is a classic neuroeconomic experiment and it helps define risk profiles. Participants` challenge during this trust game was to learn the optimal investment choice based on three mediator's outcomes. Within three distinct risk alternatives (0 €, 30€ or 50€), they had to choose one (option selection), to wait for respective outcome (feedback) and to indicate how much money they expect to receive from that mediator in the next run (estimate expected uncertainty). Participants were exposed sequentially and alternately in 7 runs for each mediator, which outcome pattern differed in terms of reward distribution (low, moderate, or extreme) for optimal choice. More specifically, each trial was divided into three phases: monitoring phase, decision phase and outcome phase.

The experiment begins with the monitoring phase: the subjects had to indicate an expected value (EU - gain or loss) for the next trial which varies between +20 to +140 answering to the template question. At the first trial, as the participant did not know each mediator payoff contingencies, we can obtain the initial risk profile and learn how the subject initially performed with each mediator (presence or absence of game strategy/planning). In a sequential game, this value (which is then continuously updated) will allow us to calculate the prediction error (PE). Participants had to remember past feedbacks (outcomes) to update the expected value and decide the next investment for each mediator (estimate expected uncertainty). In that way, we will gather empirical evidence to support different psychological profiles of rational decision-making (Figure 1. A).

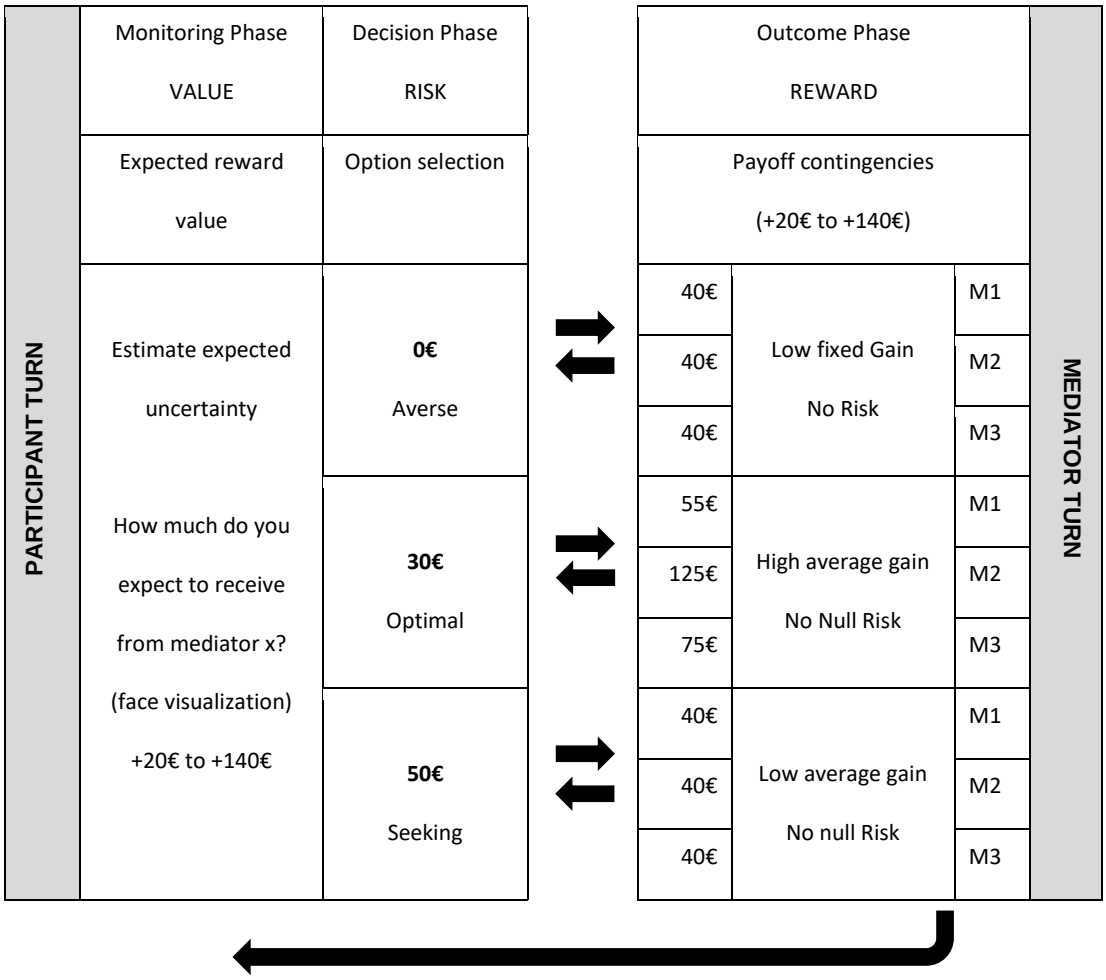

Figure 1. (A) Example of economic experimental design considering a run sequence in trustor-trustee interaction. Mediator 1 has a low range for reward (trust investment is quite reciprocated, seeming a social norm violation). Mediator 2 has an extreme range, reinforcing optimal decision. Mediator 3 has a moderate range, in the middle of M1 and M2 profile (trust investment is reciprocated in a moderate way, even so seeming a social norm violation). Outcome reward also different according to participant option (0, 30 or 50 euros) for all mediators.1. For "0" option (no risk investment) was received a known low fixed gain (40 euros;) 2. For "50 euros" option (risk investment) was offered a low average gain (same mean reward, (40 euros) that can vary from 20 to 60 euros; 3. For "30 euros" option (adjusted risk) was earned a high average gain - low, extreme and moderate reward-: Mediator 1 [35-75]; Mediator 2 [100-140]; Mediator 3 [55-95]. All of them have the same interval (40).

Experiment 2_Extending Utility based neuroeconomics to the Health Context_Health Trust Game

The health context interaction experiment, inspired on the classical neuroeconomics experiment, used clinical human mediators. In this second game, we adapted previous experiments to the health context and added a rule/norm: More patient cooperation allowed less waiting time to consultation (less waiting time meaning larger reward). So, we presented one of three different clinicians one at a time which represent three different human mediator feedback as in Game 1 (Low, Moderate and Extreme Rule Following) for optimal choice. In the first phase we presented different health impact levels of developing negative symptoms (for example, diabetic foot) due to impaired glycaemic control. Subjects choose to cooperate (health investment) or not by accepting several therapeutic needle pricks (1 prick meaning No cooperation; 4 pricks meaning Medium cooperation; 6 pricks meaning Highest cooperation) without prior knowledge of the priority reward (amount of time needed to wait for consultation). The final priority outcome rank is a parallel with the final monetary outcome Neuroeconomic Game 1. Note that in this case (priority for being received) low amounts (less time) correspond to a better outcome. Priority is defined by the number of minutes needed to wait before a consultation (0 to 260). In this game, a computer mediator (available from experiment 1) was not used (Figure 1, B).

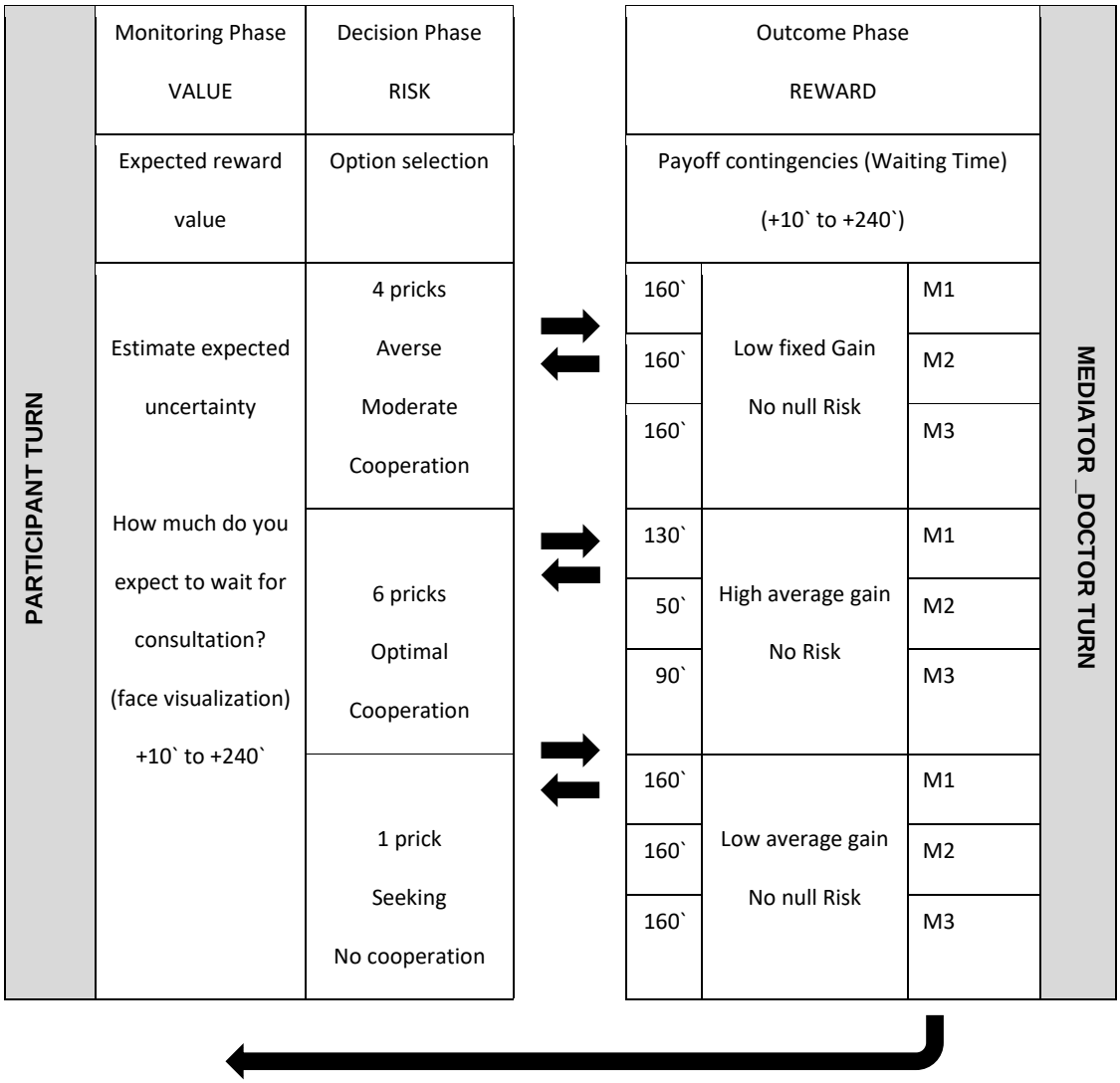

Figure 1 (B) Example of health experimental design considering a run sequence in doctor-patient interaction. Mediator 1 has a low range for reward (patient collaboration is quite reciprocated, seeming a social norm violation). Mediator 2 has an extreme range, reinforcing optimal decision fulfilling the pre-established rule. Mediator 3 has a moderate range, in the middle of M1 and M2 profile (patient collaboration is reciprocated in a moderate way, even so seeming a social norm violation). Outcome reward also differed according to participant option (1,4 or 6 pricks) for all mediators.1. For "4" option (moderate cooperation) was received a known low fixed gain (160`) 2. For "1" option (no cooperation) was offered a low average gain (same mean reward, 160`) it can vary from 120 to 160 minutes. 3. For "6" option (highest cooperation) was earned a high average gain - low, extreme, and moderate – Mediator 1 [90-170]; Mediator 2 [10-90]; Mediator 3 [50-130]. All of them have the same interval [80].

2.3 Data Analysis

Data were analyzed using IBM SPSS Statistics (v24) (Maroco, 2007). Descriptive statistics are reported as mean ± SD. Prior to analysis, raw data were examined for normality by the Shapiro-Wilks goodness-of-fit test (Ghasemi & Zahediasl, 2012). Null-hypothesis statistical tests were evaluated according to an alpha value of $p = 0.05$. The chi-square test was used to compare categorical variables and nonparametric tests (Kruskal-Wallis) were used to compare ordinal variables. To assess possible between group-differences from expected value, investment and feedback, data were submitted to independent sample t-tests. Non-parametric tests, as Friedman tests were applied to analyze differences between expected value, investment, and feedback within each group for economic and health context, searching for post-hoc differences between mediators. We also performed Friedman test to investigate main effects of the experimental 7 runs for each mediator (M0, M1, M2 and M3) and subsequent post-hoc comparisons

3. Results

We investigated the role of context (economic and health) and risk behavior in diabetic patients as a function of group profile (with and without metabolic control) considering initial decision options and their subsequent update through sequential learning.

Interestingly, self-report measures showed important behavioral differences of the groups defined by the biological partition of metabolic control (for details see Table 1). The group lacking disease control showed higher levels of impulsivity, lack of planning, low perception of health risk, high past and present risk, and intermediate reward for health intertemporal choice. Scales of emotional and external eating behavior were also significantly different between groups with more externa, eating behavior for the NoMC group.

Concerning the experimental tasks assessing choice behavior under uncertainty and initial game strategy, we examined the initial risk profile as assessed by initial Decision Phase results. Thereafter, we investigated how participants adjusted decision-making (choice impact) if probabilistic learning feedback is accomplished. For learning achievement, we measured differences on the Expected Value for each mediator, according to mediator feedback payoff contingencies. In this way, we were able to verify if there were different risk profiles according to context and groups and make inferences about learning probabilities and their impact on investment, particularly in the health context, which featured different patterns of doctor-patient interactions in patient compliance. Compliance in this context is seen as a personal investment in health. Table 2 presents results from descriptive statistics of expected value, investment and feedback depending on each mediator (M0, M1, M2 and M3) for both groups in economic and health context.

Table 2. Descriptive statistics on economic and health context experimental task for both groups

	Economic Context			
	NoMC		MC	
Variable	M	SD	M	SD
Expected Value				
M0	66.96	21.55	64.13	19.47
M1	63.64	20.91	67.88	18.41
M2	72.91	24.42	74.90	22.64
M3	67.08	25.58	61.96	27.19
Investment				
M0	37.41	23.59	36.56	18.73
M1	36.83	19.42	39.64	17.71
M2	40.82	21.16	40.07	16.44
M3	55.97	31.26	54.88	33.28
Feedback				
M0	75.55	18.53	73.95	16.52
M1	73.28	18.36	79.56	18.36
M2	106.86	38.14	106.80	33.94
M3	106.80	33.94	71.83	29.43

	Health Context			
	NoMC		MC	
Variable	M	SD	M	SD
Expected Value				
M1	125.53	23.55	116.81	28.22
M2	106.70	26.26	96.70	36.67
M3	106.99	27.16	105.62	29.32
Investment				
M1	4.68	0.76	4.82	0.86
M2	5.17	0.72	5.10	0.86
M3	4.87	0.85	4.87	1.04
Feedback				
M1	149.14	17.52	144.95	14.22
M2	98.13	37.69	97.42	36.21
M3	125.91	22.51	119.08	26.59

3.1 Decision-making under uncertainty (the first play move)

Considering the first play move, we observed distinct profiles. The group with preserved metabolic control (MC) showed a consistent behavior across both contextual tasks and initial strategy (similar investment for all mediators at the first play move- with planning investment). There`s an association between initial strategy for both contexts and MC group [x^2 (1) = 5.38, p=0.02]: subjects tended to be strategically consistent (if they invested the same with all mediators in the economic task, they use the same procedure in the clinical task). We did not find an association between initial strategy for both tasks and NoMC group (no planning investment).

3.2 Adjusted decision-making during probabilistic learning (sequential play move)

Friedman tests showed a significant main effect of mediator concerning Expected Values, Investment and Feedback, for both groups in both tasks. With the exception that in MC there was no mediator effect for investment in health task. Posthoc tests showed that sensitivity to mediators stemmed mainly from mediators M2 and M3 (the ones that show clear feedback differences in the trust games). (For details see Supplementary material, Table 4).

Concerning changes along the tasks, subjects were able to learn each mediator profile (Monitoring Phase) presenting differences in expected values according to feedback mediator contingencies, expecting to receive more money (economic task) and less waiting time (health related task) from Mediators 2 and 3 (Table 1).

Despite being able to learn mediator feedback contingencies, groups differ in their option for investment in economic and health domains. According to Table 3, patients without metabolic control chose to invest in mediator 3 (M3) whereas in the health context they opted finally for collaborate with Mediator 2 (the clinician than did not violate the norm). In turn, patients with adequate metabolic control (M2), revealed no significant preference (or only very marginal) of investment in both contexts. Interestingly, in the health context they opted to collaborate regardless of the doctor payoff contingencies.

Table 3. A Repeated measures comparison of investment between 7th runs for each mediator (Friedman Non-parametric test) on economic and health related context experimental tasks for patients without metabolic control

NoMC group								
Variable	Economic Context (N=42)				Health Related Context (N=42)			
	Friedman	gl	p	W	Friedman	gl	p	W
Investment								
M0 (1-7)	7.23	6	0.300	0.03	....	....	....	....
M1 (1-7)	4.86	6	0.560	0.02	7.29	6	0.294	0.03
M2 (1-7)	7.14	6	0.308	0.03	17.85	6	**0.007****	0.07
M3 (1-7)	14.13	6	**0.028****	0.60	7.79	6	0.254	0.03

Table 3.B. Repeated Measures comparison of investment between 7th runs for each mediator (Friedman Non-parametric test) on economic and health related context experimental tasks for patients with metabolic control

MC group								
Variable	Economic Context (N=49)				Health Related Context (N=49)			
	Friedman	df	p	W	Friedman	df	p	W
Investment								
M0 (1-7)	12.76	6	0.050	0.05	....	....	....	....
M1 (1-7)	10.54	6	0.104	0.10	2.53	6	0.865	0.03
M2 (1-7)	6.86	6	0.334	0.02	5.57	6	0.473	0.02
M3 (1-7)	12.47	6	0.052	0.04	2.53	6	0.860	0.01

4.Discussion

Our main aim of this study was to investigate the role of health context (defining patterns of risky behavior) in decision-making under uncertainty in clinical groups where such decisions are extremely relevant, such as in diabetes. This was achieved using trust games, going beyond traditional economic utility-based tasks in economic to health context. By separating different stages of the decision-making process, we gained evidence about feedback processing (update) and how groups differ in considering these update values on subsequent investment. Finally, our findings provide insight in a special form of social decision-making based on patient-doctor interactions and how different payoff contingencies influence differently patient collaboration with and without glycemic control. This enabled to directly relate decision-making profiles with biological status.

Our results extend prior evidence that human decision-making is context dependent (Blais & Weber, 2006) in the health domain, while providing clues for its relation with biological outcome. Different decision-making profiles emerged from both economic and health tasks. In the same way, different decision-making profiles emerged from categorical differences in the quality of metabolic control.

Either in initial strategy for investment, each group behaved differently, showing that strategy and planning were related to the adequacy level of metabolic control. Considering iterative decision making, groups behave also differently according to context even though both deal with the same disease (allowing for group matching while differentiating biological outcome). In general, both groups showed to be able to detect payoff contingencies (incorporate feedback processing, updating the experience, O`Doherty et al., 2017). However, regarding the health domain, patients without metabolic control seems to be more dependent on external reinforcement than the glycemic control group. Our results suggest that they tend to be more sensitive to social norm violations in the clinical setting because patient collaboration change when faced to different doctors' payoff contingencies.

These results reveal that patients without metabolic control are not indifferent to the patient-clinician relationship, which is a reassuring finding from this study, despite the non-compliant profile. In contrast, MC patients seem to keep taking good health decision, right from the start, independently of payoff contingencies. Therefore, compliant patients had good metabolic control as we expected. Our pattern of studies could be linked to the statement of Gray et al. (2003) said: "A patient may become 'stuck' with a doctor in whom he or she lacks confidence, and adherence to medical advice suffers as a result". For clinical practice, this requires counteracting health providers desire to withdraw when patient persist in maladaptive behavior, preventing a non-cooperative or reciprocal circle (Rilling et al., 2002).

It seems that risk taking behavior profiles can lead to distinct levels of outcome of a biological variable (in our case glycemic control), suggesting distinct mechanisms of behavioral control. It is important to note that, which implies that early detection of these behavioral profiles can enable swift intervention approaches to improve compliance and prevent complications.

5.Limitations and future directions

Our results suggest that group differences in learning time (how many runs they need to distinguish payoff contingencies for optimal choice -low, moderate, and extreme) could be further investigated in the future, in particular considering the role of the mediator, which here were only considered as supplementary material because they could only be investigated in an exploratory manner (due to sample size issues when dealing with stratification). With our experiment, differences in decision phase (investment) were due to context and a biological variable, but it remains unclear if there are other mediator variables or if contextual cues are ignored or salient depending on other variables.

Despite these shortcomings, the current study could guide future studies on dyadic interactions (as family members current linked by the literature to patient adherence) and neuroimaging studies. They

will be helpful to understand the neural correlates of prediction error (High/Low Expected Value versus Low/High Feeback); the neural correlates of considering update values explaining shifting (High/Low Feedback versus High/Low Investment) and to investigate brain areas involved in risk perception and risk taking (High/Low Expected Value versus Low/High Investment). On the other hand, as a motivation for future neuroimaging studies, the Outcome phase is expected to recruit more emotional processing brain areas than the monitoring phase related to computational processes and episodic memory. In the health domain, fMRI studies could be advantageous to examine key areas on perceived social norm violation getting insight why health social norm violation (clinician feedback) is more relevant to NoMC group then for the MC group. Finally, further studies could validate intervention programs that promote treatment adherence with training of socioaffective and interaction skills (Singer & Tusche, 2014).

5.Conclusion

Through modelling interactive trust games and translating them into the health domain, our findings suggest a strong role of context and biological status in decision-making under uncertainty since different decision-making profiles emerged patients with and without metabolic control. Furthermore, by partitioning different stages of the decision-making process (monitoring, decision, and outcome) we were able to disentangle feedback processing from choice itself getting evidence that probabilistic learning is not enough to explain decision-making in both contexts and groups. These findings also contributed to better understand patient collaboration in reaction to social norm violation in health domain highlighting a biologically determined decision-making profile and, consequently, proving information that could guide adherence to treatment programs with clinical implications.

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Supplementary Data

Table 1.

Demographic Characteristics, Cognitive results, personality, self-report risk measures and eating behavior for health participants

Variables	Health Control Group (N=53)
Demographic data	
Gender (M/F)	27/26
Age (y)	35.66(8.51)
Civil State (Single/Couple)	22/31
Household members (1/2/3)	16/32/5
Household income B (1/2)	25/28
Residence	53/0/0
Education level (1/2)	4/49
Cognitive data	
Vocabulary	32.19 (3.15)
Digit Memory	16.57(2.83)
RPMT	8.21(0.82)
Self-report measures	
Neuroticism	7.55(3.99)
Extroversion	11.87(3.58)
Impulsivity	57.64(7.64)
Lack of planning	15.62(4.01)
Health risk perception	35.91(7.59)
Past Risk	14.33(3.80)
Present Risk	12.38(3.71)
Health Intertemporal Choice	23/13/25
Emotional Eating Behavior	1.96(0.91)
External Eating Behavior	2.74(0.65)

Table 2.

Descriptive statistics on economic and health context experimental task for healthy participants

	Economic context		Health Context	
Variables	M	SD	M	SD
Expected value				
M0	62.40	13.54	..	..
M1	61.68	13.64	113.67	28.32
M2	81.13	21.28	80.67	34.43
M3	60.98	11.71	102.16	27.33
Investment				
M0	27.76	7.24	..	..
M1	27.54	10.86	4.84	1.14
M2	31.17	10.42	5.33	1.01
M3	29.81	10.20	5.04	1.04
Feedback				
M0	91.29	17.57	..	..
M1	78.01	17.68	141.11	11.90
M2	119.26	26.55	73.80	29.44
M3	91.29	17.57	113.34	23.97

Table 3.

Repeated measure comparison (Friedman Non-parametric test) on economic and health related context experimental tasks for healthy participants

Variable	Ecponomic Context (N=53)				Health Context (N=53)			
	Friedman	gl	p	W	Friedman	gl	p	W
Expected Value	54.62	3	0.34	0.34	41.00	2	<0.001	0.39
Investment	10.05	3	0.09	0.06	11.90	2	0.003	0.11
Feedback	85.93	3	<0.001	0.54	91.31	2	<0.001	0.86

Variables	Economic context (N=53)	Healtth context (N=53)
	Sig.Aj	Sig.Aj
Expected Value		
M0-M1	1.000	--
M0-M2	<0.001***	--
M0_M3	1.000	--
M1-M2	<0.001***	<0.001***
M1-M3	1.000	0.098
M2-M3	<0.001***	<0.001***
Investment		
M0-M1	1.000	--
M0-M2	0.635	--
M0_M3	0.063	--
M1-M2	0.917	0.008**
M1-M3	0.107	0.522
M2-M3	1.000	0.296
Feedback		
M0-M1	1.000	--
M0-M2	<0.001***	--
M0_M3	<0.001***	--
M1-M2	<0.001***	<0.001***
M1-M3	<0.001***	<0.001***
M2-M3	0.002**	<0.001***

Table 4. (A)

Repeated measures comparison between each mediator for Expected Value, Investment and Feedback (Friedman Non-parametric test for main effects of mediator and posthoc tests) on economic and health related context experimental tasks for NoMC and MC groups

NoMC								
Variable	Economic Context (N=42)				Health Related Context (N=42)			
	Friedman	df	p	W	Friedman	df	p	W
Expected Value	12.86	3	**0.005**	0.11	17.71	2	**<0.001**	0.21
Investment	15.16	3	**0.001**	0.13	16.39	2	**<0.001**	0.19
Feedback	27.83	3	**<0.001**	0.24	47.81	2	**<0.001**	0.57
MC								
Variable	Economic Context (N=49)				Health Related Context (N=49)			
	Friedman	df	p	W	Friedman	df	p	W
Expected Value	16.91	3	**0.001**	0.12	16.10	2	**<0.001**	0.17
Investment	14.29	3	**0.003**	0.10	4.9	2	0.086	0.05
Feedback	48.82	3	**<0.001**	0.35	52.34	2	**<0.001**	0.56

Table 4. (B) Posthoc tests for each variable (expected, investment and feedback) on economic and health related context experimental tasks for NoMC and MC groups

	NoMC			**MC**	
	Economic context (N=42)	Health context (N=42)		Economic context (N=49)	Health context (N=49)
Variables	Sig.Aj	Sig.Aj	**Variables**	Sig.Aj	Sig.Aj
Expected Value			**Expected Value**		
M0-M1	1.000	--	M0-M1	1.000	--
M0-M2	0.136	--	M0-M2	**0.020**	--
M0-M3	1.000	--	M0-M3	1.000	--
M1-M2	**0.006**	**<0.001**	M1-M2	**0.040**	**<0.001**
M1-M3	0.107	**0.004**	M1-M3	1.000	0.061
M2-M3	1.000	1.000	M2-M3	0.093	0.365
Investment			**Investment**		
M0-M1	1.000	--	M0-M1	0.168	--
M0-M2	0.066	--	M0-M2	**0.021**	--
M0_M3	**0.010**	--	M0_M3	**0.005**	--
M1-M2	0.212	**0.001**	M1-M2	1.000	ND
M1-M3	0.039	1.000	M1-M3	1.000	ND
M2-M3	1.000	**0.023**	M2-M3	1.000	ND
Feedback			**Feedback**		
M0-M1	1.000	--	M0-M1	0.099	--
M0-M2	**<0.001**	--	M0-M2	**<0.001**	--
M0_M3	1.000	--	M0_M3	1.000	--
M1-M2	**<0.001**	**0.002**	M1-M2	**<0.001**	**<0.001**
M1-M3	1.000	**0.002**	M1-M3	1.000	**<0.001**
M2-M3	**<0.001**	**0.002**	M2-M3	**<0.001**	0.070

Study 3

Recursive interplay of family and biological dynamics: Adults with type 1 diabetes mellitus under the spotlight

"Like families in high complex situations, our practice and research efforts are more likely to succeed with a multidisciplinary team approach, integrating multiple perspectives, sustaining ongoing networking, and striving to gain a sense of coherence. This involves "mastering the art of the possible": focusing on what can be learned, accepting what is beyond control or comprehension, and tolerating considerable uncertainty. Doing research, indeed, is akin to living our complicated lives."

Walsh, 2016

"…el impacto resultante es producto del interjuego entre las variables familiares y las proprias de la enfermedad"

Góngora, 1998

Jorge, H., Correia, B.R., Paiva, I., Castelo-Branco, M. & Relvas, A.P. Recursive interplay of family and biological dynamics: Adults with type 1 diabetes mellitus under the spotlight. Manuscript submitted for publication.

Abstract

Background: Diabetes Mellitus involves demanding challenges that interfere with family functioning and routines and expose family members to additional and continuous distress, that requires problem solving. The study of family systems with adults with type 1 diabetes (T1DM) is mostly neglected whereas literature on childhood diabetes shows many parent-child relationship studies.

Methods: To identify mutual influences of family systems and diabetes management, 144 participants, aged 22-55, filled out a set of self-report measures of family systems assessment. Patients (91) were also invited to describe their perception about disease management interference regarding family functioning.

Results: Cluster analysis results identify a two-cluster solution validating initial classification of two groups of patients: 49 with metabolic control (MC) and 42 without metabolic control (NoMC). Independent sample tests suggested statistically significant differences between groups in some family subscales. Binary logistic regression shed light on specific predictors of explained variance to no metabolic control. Furthermore, patient groups differ on family support and sources of family conflict caused by diabetes management issues. Considering only patients who co-habit with a partner for more than one year (N=44), NoMC patients score lower on marital functioning.

Discussion: Recognizing that Family-Chronic illness interaction plays a significant role in patient's adherence to treatment, this study highlights the Standards of Medical Care for Diabetes, considering caregivers and family members on diabetes care.

Keywords: Family Assessment; Chronic Illness; Adults with Diabetes Type 1; Systems Theory

1.Introduction

Family system is multidimensional and self-organized (Maturana & Varela, 1995), so that people with diabetes and their families face complex challenges in daily life (Young-Hyman et al., 2016), forcing a continuous disorder on dynamic stability in a coherent whole. Diabetes management requires repeated daily behaviors that interfere with the family's routines, especially meals, glycemic monitoring, and symptomatic expression on biochemical changes, such as a hypoglycemia crisis (American Diabetes Association [ADA], 2019). This continuous and mutual interchange between illness management and psychosocial factors presents challenges to research, such as identifying adequate measures and methodologies that mirror this circular causality.

In terms of methodology, family assessment in research on adults with T1DM and their families (Latham, 2016) has been conducted via observational rating scales, clinical semi-structured interviews or self-report instruments related to diabetes social support (Hamilton & Car, 2016), through individual (McCarthy & Grey, 2018; Smith et al., 2018;) or dyadic studies with couples (Lister et al., 2013). Several authors (Melo & Alarcão, 2014; Relvas & Major, 2014; Steinglass & Horan, 1988; Walsh, F., 2016) suggest a combination of quantitative and qualitative analysis to considerate the relations between diverse family dimensions.

Extensive literature corroborates the impacts of diabetes on different systemic levels, such as marital interaction (Franks et al., 2012; Lister et al., 2016; Litchman et al., 2019; Ritholz et al., 2013), family, work and social network (Due-Christensen et al., 2018) and psychosocial well-being (Anderbro et al., 2018; De Groot et al, 2016; Dunisheva et al., 2018; Hessler et al., 2017; Metsch et al., 1995; Rancourt et al., 2019; Strandeberg et al., 2015; Sultan et al., 2008; Taylor et al., 2003; Watts et al., 2010). For their part, several studies have focused on how the individual and the family can predict effective diabetes management, as family and social support (Helgeson et al., 2019; Hill et al., 2018; Robinson,

2017; Trief et al., 2003), coping styles (Karlsen & Bru, 2002), individual attributes of a partner's illness (Weard et al., 2006), diabetes knowledge (Taylor et al., 2003), health-related social control strategies such as overprotection (Schokker et al., 2011), or individual traits/perceptions (Peyrot et al., 2005; Ridge et al., 2011; Spek et al., 2018).

However, little attention has been directed to the relationship-based approach for T1DM exclusively in adulthood (Rintala et al., 2013; White et al., 2005). And this is important for two reasons. First, T1DM onset can start in childhood or adolescence, revealing a shared history of interrelated meanings about diabetes management (Helgeson et al., 2015; Jacobson et al., 1997; Palladino et al., 2013; Pinhas-Hamiel et al., 2010; Schabert et al., 2013). Second, the onset of T1DM may also appear later, in adulthood, after one's relationship or employment status has become consolidated, which involves family actors in a different way (Due-Christensen et al., 2018). Unfortunately, the broader research that includes T1DM (Dickinson & Maryniuk, 2017) focus in other stages of development (childhood or young adult) and examines parent-child interactions. Studies with couples, families and multi group interventions have been mostly carried out only with T2DM (Baig et al., 2015; Lópes-Larrosa, 2013). Finally, family studies with adults with T1DM embody this pathology in global studies about multiple chronic illness (Martire & Helgeson, 2017; Robinson, 2017).

Systems Theory provides a theoretical framework to look at chronic illness as a developmental process over time through Biopsychosocial (Engel, 1978; Institute of Medicine, 2001) and Complexity (Morin, 2003) lenses. The Family Systems-Illness Model (FSIM) (Rolland, 1987; Rolland, 1994; Rolland, 2012) addresses the illness, the individual and family developments by claiming that an individual's adjustment to illness depends on the good fit between the demands of the illness over time and family functioning, considering its life cycle and an individual member's development. Highlighting interaction and context, the FSIM depicts the family as an interactive system within itself and integrating other systems. This comprehensive model emphasizes the relevance of narratives about

disease experience provided by families and their members on dealing with individual maladaptive behavior (Rolland, 2018; White & Epston, 1990). Family dynamics is deeply attached to Human Communication and Cybernetics Theories, like Anderson & Goolishian (1988) described in their theorizing thinking about clinical practice: “through dialogue, human systems mutually evolve their own language and confirm its meaning” (p.2).

This article supports the research findings on how the family and diabetes management exert mutual influence on each other (Figure 1). It also highlights the features of family conflict that arise due to the patient’s viewpoint of the illness. We hypothesized that differences between MC and NoMC groups are explained by how the demands of diabetes may have a negative effect on the family dynamic, which recursively presents challenges to effective diabetes management.

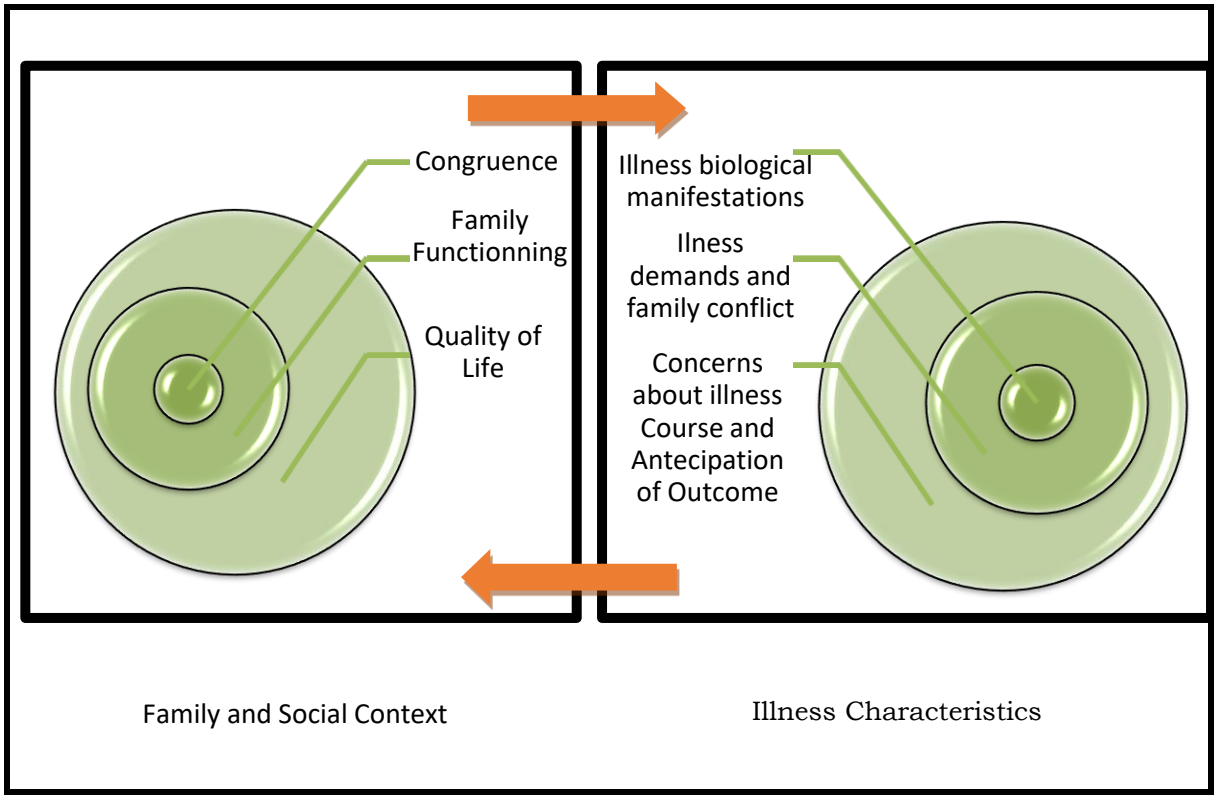

Figure.1 Study Conceptual Map. The illness characteristics, family and social reciprocal influences in diabetes management, based on Family System Illness Model (FSIM).

2. Methods

2.1 Overview

After receiving an explanation of the nature and duration of the study, all subjects signed an informed consent document as approved by the Ethics Committee of (…) in accordance with the Declaration of Helsinki.

2.2 Participants

The study involved 91 adults with T1DM, aged 22-55 (mean age: 36.74±9.08). They were divided into two groups according to Glycated Hemoglobin (Hba1c) values over time: 49 (MC group) mean age: 37.20 ± 9.47, [21,55] and 42 (NoMC group) mean age: 36.19 ± 8.67 [20,55]. Fifty-three volunteers without diabetes (27 males and 26 females, mean age: 35.66± 8.51) were also recruited, but given that

metabolic status in healthy population is by definition stable and not disrupted (unlike the clinical control group), the value of these data are normative and presented as supplemental material.

The same procedures were applied to all eligible participants: i) referral to clinical assessment for at least one year at the Department of Endocrinology, Diabetes and Metabolism (EDM, Public Hospital), grouped by HbA1c values over time ii) no other current major chronic disease in the nuclear family, including Diabetes iii) no cognitive impairments. Participants were excluded if they reported past or current history of neurological and psychiatric disorders, recent diseases, major medical illness (cancer, anemia and thyroid dysfunction) or severe visual or hearing loss. In total, two patients were excluded by presenting a history of psychiatric disorder.

2.3 Sociodemographic, cognitive and clinical features characteristics

Participants filled out a demographic survey and a cognitive protocol (Table 1). Participants with more than 50 filled out MoCA (Mont Real Cognitive Assessment, Freitas et al, 2011). Body Mass Index (BMI), values of Hba1c and current symptoms or complications were evaluated by clinicians directly or indirectly consulting the patient's process. Patients fit in the Metabolic Control Group if they present Continuous Descendent values of HbA1c, low invariable values that did not change beyond 0.5mm/mmol or values that varied more than 0.5mm/mmol, but the maximum value of this Oscillation was lower than 8.0mm/mmol. The inverse pattern characterized the No Metabolic Control Group (NoMC).

Table 1
Demographic characteristics, cognitive results, and relevant clinical features for NoMC and MC groups (N=91)

Variables	MC (N=49)	NoMC (N=42)	X^2	t	U	gl	p	d
Demographic data								
Gender (M/F)	31/18	25/17	0.134	-----	-----	-----	0.824	0.07
Age (y)	37.20 (9.47)	36.19 (8.67)	-----	0.529	-----	89	0.59	-0.11
Civil State (Single/Couple)	22/27	24/18	1.367	-----	-----	1	0.244	0.07
Household members (1/2/3)	17/28/3	16/21/5	1.695	-----	-----	1	0.428	0.08
Household income B (1/2)	33/15	16/26	8.94	-----	-----	1	0.003	0.66
Residence	20/12/16	16/17/9	2.97	-----	-----	2	0.226	0.36
Education level (1/2)	17/32	27/15	7.93	-----	-----	1	0.005	0.61
Cognitive data								
Vocabulary	32.33 (3.47)	33.60 (2.81)	-----	-----	807	-----	0.075	0.034
Digit Memory	14.82(2.15)	14.10 (1.92)	-----	-----	1273	-----	0.05	0.416
RPMT	8.04(0.90)	8.05 (1.01)	-----	-----	981	-----	0.688	0.08
Clinical features								
Disease onset (</>18)	24/25	24/18	0.605	-------	------	1	0.382	0.16
Disease Dealing Time	17.56 (10.38)	17.21 (9.58)	-------	-0.161	------	89	0.870	-0.034
HbA1c(%/mmol/mol)	7.19/55 (0.65)	8.52/70 (1.22)	-------	6.329	-----	89	<0.001	0.07
BMI	24.95 (3.31)	25.20 (3.81)	------	-------	989	----	0.750	0.067
Complications (Y/N)	21/28	30/12	7.94	------	-------	1	0.006	0.62
Smoking status (Y/N)	11/38	7/35	0.48	------	-------	1	0.49	0.14

Educational level (1= 12 years, secondary education) 2= university degree or higher; Household income (1=stable; 2= unstable); Members of the Household (1= living alone 2=living as a couple 3=living with children);Residence as distance to health services, in travel time (1=Coimbra; 2= <1h; 3= >1h) RPMT Raven's Progressive Matrices Tests; BMI body mass index

2.4 From Family to Diabetes Management

Implications of Family in diabetes management were evaluated by applying four questionnaires with adequate psychometric (validity and reliability) properties for the Portuguese population. They covered three levels of systemic evaluation. If any participants had been living in a situation of a couple cohabitation for more than one year, they also completed the marital functioning subscale (EASAVIC, Narciso & Costa, 1996), a 44-item self-report subdivided into two subscales, Marital Functioning and Love. For our research purposes, the Love subscale was not administered.

2.4.1 Individual level as a whole

The Congruence Scale (CS) (Lee, 2002; Portuguese version from Cunha et al., 2014) evaluates individual functioning and its adaptability in holistic dimensions such a individual connection with the universe/transcendence (Universal), between people (Interpersonal) and within oneself (Intrapsychic) (Walsh, 2010; Wretman, 2015). It is organized into two subscales (Universal and Interpersonal/Intrapsychic) for a total of 16 items answered on a 7-point Likert scale, ranging from 1 (Strong Disagreement) to 7 (Total Disagreement).

2.4.2Intrafamily level

Family Functioning was assessed by the Systemic Clinical Outcome and Routine Evaluation (SCORE-15) (Stratton et al., 2010; Portuguese version from Vilaça et al., 2014), a self-report measure (for family members up to 12 years of age) developed to assess outcomes of family functioning in clinical settings. SCORE-15 items are given on a 6-point Likert scale ranging from 1= “describes us: extremely well”, to 6= “describe us: not at all” in three subscales: family strengths, family difficulties and family communication.

2.4.3 Extrafamily level

The Inventory of Family Quality of Life (QOL), from Barnes & Olson, 1982 (Portuguese version from Simões, 2008) is a 40-item instrument, marked 1 (Not Satisfied) to 5 (Completely Satisfied) on a 5-point Likert-scale, covering 11 general areas of individual life satisfaction.

2.5 From Diabetes Demands to Family Conflict

To access how the demands of diabetes affect their family, patients completed a survey, based on two instruments: The Diabetes Family Support and Conflict Scale (Paddison, 2010) and The Diabetes Family Behavior Checklist, Schaffer et al., 1986 (Lewin et al., 2005). Briefly, it comprises three parts:

1. The question, "How does diabetes management contribute to family conflict?"
2. A list of Sources of conflict/support between the patient and the family due to diabetes, such as physical exercise, food restrictions, mealtime, glycemic results and medical advice.
3. Patients' perception about their disease self-management (physical exercise, food, glycemic control, smoking habits), critical problems (food choice, future complications, lack of social support, hypoglycemic episodes, constant efforts to deal with disease) and Eating Behavior, assessed through Portuguese validation of Dutch Eating Behavior Questionnaire, DEBQ (Van Strien et al., 1986; Viana & Sinde, 2003). It is a 33-item instrument which evaluates three types of eating styles such as restrained (avoid eating more than initially defined), external (eating motivated by external factors such as the food's good smell and appearance) and emotional (eating in response to emotions).

2.6 Data Analysis

We used IBM SPSS Statistics (version 24) to conduct data analysis. Descriptive statistics are reported as mean ± SEM. Prior to analysis, raw data were examined for normality by the Shapiro-Wilk goodness-of-fit test (Ghasemi & Zahediasl, 2012). Firstly, we examined the extent to which family variables grouped dataset in order to determine if there were similarities and dissimilarities that fit with our initial diabetic groups' classification. Instead of one multivariate method, we calculated K-means and two-steps algorithms so that consistent results could be achieved, as proposed by Kos and Psenicka (2000). No hierarchical cluster analysis was used given that we would like to test the two-cluster hypothesis. We introduced only continuous variables because K-means cluster analysis does not support categorical ones. Before the cluster analysis, variables were standardized to minimize

dimensional statistical errors (Maroco, 2007). Both K-means and Two steps methods used centroid distance with Squared Euclidean distance as the similarity measure. For K-means measure we calculate Chi-squared statistics to determine the percentage of correspondence between clusters found and dynamic HbA1c categories. Continuous variables were analyzed using a series of independent-samples t-tests, if normality and variances homogeneity was assumed. To examine the main predictors of barriers to diabetes management, we carried out a binary logistic regression, choosing dynamic variable of Hba1c as the dichotomous dependent variable (MC and NoMC). We examined intercorrelations (Pearson's) in order to accomplish the assumption of no multicollinearity to regression analysis, with 0.8 meaning a huge correlation (Cohen, 1992). We conducted four regressions, each one related to a group of distinct variables such as sociodemographic data (1), clinical features (2), family (3) and eating behavior (4), resulting in four final models. Statistics are reported with 95% confidence intervals [95% CIs]). Null-hypothesis statistical tests were evaluated according to an alpha value of 0.05. The chi-squared test was used to compare categorical variables, and nonparametric tests (Kruskal-Wallis) were used to compare ordinal variables.

3.Results

3.1 Two cluster solution and metabolic control bipartition

The two-cluster solution was verified at both cluster analysis methods, matching each cluster with diabetic group's bipartition in similar proportions (MC and NoMC). We introduced only continuous variables: general results of 1) family functioning, 2) quality of life and 3) congruence since data reduction could be achieved. These three general results are significantly ($p<0.01$) and moderately correlated: SCORE-15 with QoL ($r=-0.57$) and CE ($r=-0.471$) and QoL with CE ($r=0.34$). K-means cluster analysis indicate that all variables have a significant weight to the formation of a two solution clusters agglomeration, $p<.001$, by ANOVA output: SCORE-15 [$F(89)=102.54$]; CE [$F(89)=52.83$] and QoL

General [F(89)=73.19]. $X^2(1)$ =26.05, p<.001 informs that 76.9% (40/52) of MC group belongs to cluster 1 and 76.9% (30/39) of NoMC group belongs to cluster 2, supporting our group classification. Two-steps cluster analysis showed a high silhouette coefficient (=0.5) and a size ratio of 1.39 (53/38), near the size ratio of the dataset (1.22; 49/42). Posterior inclusion of dynamic variable of HbA1c related cluster 1 with the MC group and cluster 2 with the other group. The positive or negative direction of each variable was obtained in cluster comparison, which confirms the correlations results. The MC group is characterized by lower results on SCORE-15 (indicating high family functioning) and higher on General Quality of Life and General Congruence. For the NoMC group, the other cluster, we observed the opposite direction (Figure 2).

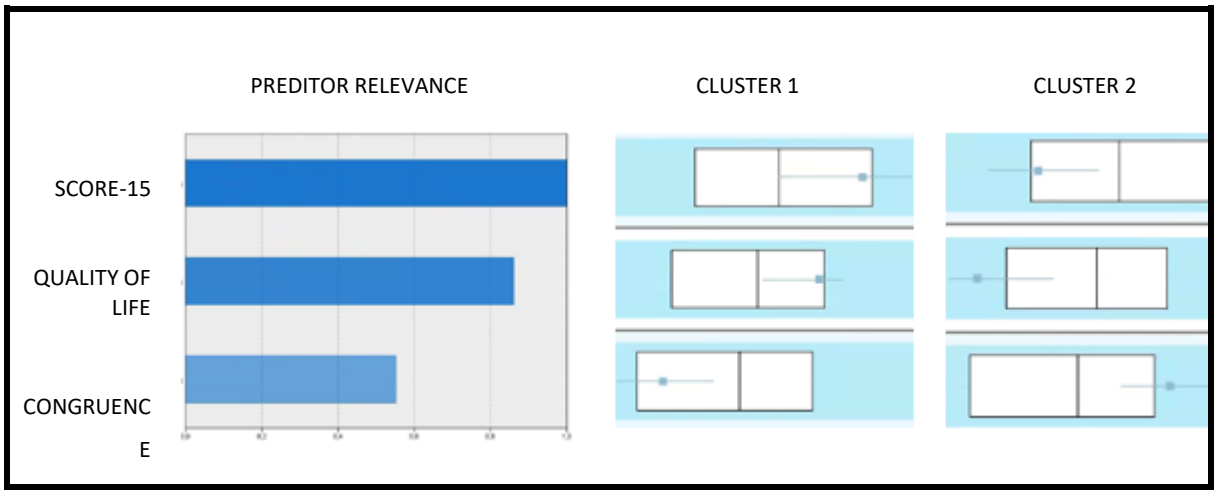

Figure.2 On the right. Weight of each introduced variable for cluster formation: SCORE-15, Quality of Life and Congruence. On the left, direction of each variable for Cluster 1 (MC group) and Cluster 2 (NoMC group) through cluster comparison.

3.2 From Family to Diabetes Management

Forward analysis with independent sample parametric and non-parametric tests allowed us to deep dive on group differences. Table 2 summarizes the results. The group with NoMC scored higher on Family Difficulties and Family Communication, presented low Quality of Life (QoL) and less connection with themselves, others and the context.

Table 2 Descriptive statistics and results of mean comparison between groups for subscales of SCORE-15, Quality of Life and Congruence Scale (N=91)

Variables	Participants with MC (n=49)					Participants with NoMC (n=42)									
	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3rdQ	U	t	gl	p	d
SCORE-15															
Family Strengths	1.65	0.64	1.40	1.80	2.13	1.86	0.65	1.20	1.40	2.00	1141.5	---	--	0.002	0.33
Family Difficulties	1.63	0.60	1.80	2.60	2.85	2.43	0.71	1.20	1.60	2.00	411	---	--	<0.001	1.22
Family Communication	1.87	0.65	2.20	2.80	3.20	2.68	0.74	1.40	1.80	2.15	423	---	--	<0.001	1.16
CONGRUENCE SCALE															
Intra/Interpersonal	48.57	7.37	45.50	50.00	53.50	42.81	8.33	37.75	42.00	48.00	1495.5	---	--	<0.001	-0.73
Universal Congruence	33.76	10.78	28.50	35.00	42.00	25.45	9.25	17.00	25.00	32.00	1504	---	--	<0.001	-0.83
QUALITY OF LIFE															
Financial	22.37	4.81	19.00	22.00	27.00	19.07	4.34	16.00	19.00	22.00	1430.5	---	--	<0.001	-0.72
Time	12.43	2.98	11.00	13.00	15.00	11.57	2.08	10.00	11.50	13.00	---	-1.56	89	0.120	-0.33
Neighborhood	20.35	3.74	18.00	20.00	23.00	18.33	3.33	16.00	18.00	21.00	---	-2.69	89	0.009	-0.57
Home Conditions	18.22	3.32	16.00	18.00	20.00	18.33	3.06	16.00	18.50	20.25	---	0.16	89	0.870	0.03
Mass Media	9.22	2.18	8.00	9.00	10.00	9.24	2.58	7.00	9.00	11.00	---	0.027	89	0.978	0.01
Social/Health Relationships	14.90	2.48	14.00	15.00	16.00	12.81	2.38	11.00	13.00	14.00	1553	---	--	<0.001	-0.86
Job	9.90	2.73	8.50	10.00	11.50	8.62	2.19	7.00	8.00	10.00	---	2.44	89	0.017	-0.51
Religion	6.39	1.90	6.00	6.00	8.00	5.05	2.28	3.00	5.00	7.00	1365	---	--	0.006	-0.64
Family/Marital	8.24	1.70	8.00	8.00	10.00	6.95	1.89	6.00	7.00	8.00	1447.5	---	--	0.001	-0.72
Children	6.94	2.18	5.00	7.00	9.00	7.00	2.07	5.00	7.50	8.25	1026	---	--	0.981	0.03
Education	7.49	1.48	7.00	8.00	8.00	6.40	1.49	5.00	6.00	8.00	1411.5	---	--	0.002	-0.73

Knowing the group differences, we studied which variables explained the variance of no metabolic control. The results are summarized in Table 3. Income, Educational level (first model), HbA1c values (second model), SCORE-15 & CE (third model) and Emotional Eating Behavior (fourth model) proved to be significant predictors of lower metabolic control. Participants with diabetes that cohabit for longer than one year also filled out the subscale Marital Functioning of EASAVIC, N=44 (18, NoMC; 27, MC). The group with MC scored higher than the other group for all variables studied (see Table 5).

Table 3 Summary of binary logistic regression analyses of four categories of variables (Sociodemographic, Relevant Clinical Features, Family Systems and Eating Behavior) predicting participants' NoMC

Variables	Binary Logistic Regression for NoMC			
	B	Exp(B)	95%IC	p
Sociodemographic data				
Income	-1.22	0.29	0.12-0.74	0.009
Level of education	-1.29	0.27	0.11-0.68	0.005
Clinical Features				
HbA1c Values	1.73	5.62	2.59-12.24	<0.001
Family Systems				
SCORE-15	1.43	4.17	1.15-11.27	0.005
ECongruence	-0,05	0.96	0.92-0.99	0.01
Eating Behavior				
Emotional Ingestion	0..69	2.27	1.24-4.13	0.008

The model containing Income and Educational Level was statistically significant (X^2 (2)=16.28, p<0.001, R^2 Negelkerke=0.22). The model related to clinical features was significant (X^2 (2)=43.17, p<0.001, R2 Negelkerke=0.51) being reduced from Distance to Health Services, Length of disease, disease onset, IMC, Smoking Habits to HbA1c values as predictor variable and explained 81.3% of the variance of risk to NoMC. The third model explains 77.4% of variance of NoMC in PWD (X^2 (2)=28.87, p<0.001, r2=0,393. The fourth model explaining 70.3% of the variance to NoMC, remaining Emotional Ingestion (X^2 (1)= 8.07, p=0.005, R^2Negelkerke=0.11.

Table 4 Marital functioning (EASAVIC subscale) results for participants with diabetes (N=45)

Variables	Couples with MC (n=27)					Couples NoMC (n=18)							
	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3trQ	U	p	d
Total	3.86	0.78	3.40	3.80	4.35	2.88	0.63	2.25	2.77	3.45	406	<0.001	1.21
FF	4.76	1.09	3.75	4.75	6.00	3.61	1.03	2.50	3.35	4.50	376.5	0.002	1.29
FT	3.97	1.16	3.00	4.00	5.00	2.94	0.92	2.00	3.00	3.63	365.5	0.004	1.33
AUT	3.95	1.03	4.00	4.75	5.50	4.76	0.86	3.00	3.75	4.75	353	0.010	1.36
EFR	3.75	0.88	4.30	4.75	6.00	4.95	0.84	3.00	3.63	4.17	408	<0.001	1.21
CC	3.56	1.02	4.52	5.00	5.70	4.91	1.05	3.00	3.14	4.53	400	<0.001	1.23

3.3 From the Demands of Diabetes to Family Conflict

According to question 1 “How does diabetes management contribute to family conflict”, NoMC showed a moderate level of conflict (47.6%) while MC perceived low level of family conflict (71%). This difference was statistically significant [X^2 (2) =11.74, p=0.003], indicating an association between group and perception of family conflict. We found similar results related to family support [X^2 (2) =9.54, p=0.002], given that 87.8% of people with MC reported having support as compared with 59.5% of the NoMC group. The first major source of conflict for NoMC was “annoying me to follow the doctor’s advice” (23.8%) while MC group 36.7% pointed out “no sources of conflict” (36.7%). The second source of conflict was “when they tell me what I can’t eat” (18.4% for MC and 21.4% for NoMC). Mealtime is a major concern, so the person preparing the meal plays an important role. In our sample, there was no association between groups and who cooks at home [X^2 (2) = 0.84, p>0.05]. However, it is related to gender since 91.4% of females cook by themselves whereas males relegate this task to their mothers (44.6%) or their wives (26.8%), thus presenting a statistically significant difference [X^2 (2)=34.15, p<0,001]. Finally, the MC group worried more about future complications (69.4%) than the NoMC (33.3%), which is also focused on daily, present, and permanent efforts required by disease.

4. Discussion

Three main conclusions can be drawn. First, this study found a coherent meaning in family to binary characterization of diabetes management based on a related biological variable (dynamic values of HbA1c). Second, findings supporting group differences are consistent with many previous studies reinforcing the recursive interplay of family variables and diabetes management. Third, even though this study does not focus on intervention, it points to specific information that may help to design interventions in a "simple, easily operational and clinically relevant" manner (Fisher, 2006).

As for the first statement, a two-solutions cluster analysis based on self-report measures encourages family assessment of adults with T1DM in health and clinical settings. SCORE-15 is a promising candidate to take part in an interdisciplinary protocol assessment by the health team. As recommended by ADA, "providers should consider an assessment (…) in the initial visit, at periodic intervals, and when there is a change in disease, treatment, or life circumstance" (Young-Hyman et al, 2016) and must include caregivers in family assessment.

Concerning the second conclusion, previous literature (Fisher, 2006; Lister et al., 2013; Rintala et al., 2013) is consistent with the connection between communication patterns, overwhelming feelings or thoughts, congruence and poor diabetes management. Individual mental health well-being should be done carefully and monitored in a timely fashion to avoid symptomatic evolution to complex levels of interventions with cost effects. Psychosocial interventions should consider sociodemographic data (financial concerns and education level), once it is related to reports of unstable values of HbA1c (unemployment, particularly) perhaps because it limits individual choice. Besides repercussions on family dynamics (Fonseca et al., 2016) it exhibits biochemistry direct interference for patients. A pattern of hopelessness and exhaustion on results from sources of family conflict and low congruence seems to be consistent with emotional eating as a major predictor, instead of restrained or external

eating behavior. This can encourage a deeper review of nutritional interventions based on adherence to regimen changes, family meal routines or food habits related to feelings (Broadley et al., 2019).

Meal preparation is one of the most frequent sources of family conflict for both groups. It is a mark of gender regardless of marital status (mothers and sons). Family life cycle, individual development, or disease challenges are all present in several domains in the patient description. So, Rolland's Family Systems-Illness Model fits for theoretical and practical comprehension of relationship-based approaches to health and illness management and should be adopted for clinical interventions.

Additionally, patients' reports of others support could be a source of conflict, translating into annoying but well-intentioned expressions of concern. Controlling health behaviors such as overprotection may damage a patient's management in both parental and couple relationships in adulthood (Schafer et al., 1986). Thus, mutual perceptions of caregiver and patient should be considered. As Martire & Helgeson (2017) states both involvement and over-involvement are associated with poorer management.

The present study has some limitations. First, depression, anxiety or other emotional problems were not verified. The prevalence of depression among adults with diabetes is higher than in adults without diabetes (Anderson et al., 2001; Jacobson et al., 2002). Second, once population of the study has diabetes in a chronic phase (Rolland, 1994), conclusions should be not extended to diagnosis or the terminal phase. Future family research studies could focus on several issues. 1) narratives built around growing up with diabetes offered by patients, their caregivers and people without diabetes ("what is transformed or preserved through time", Melo & Alarcão, 2014), in order to understand the disease's impact on future choices, such as careers and close relationships; 2) family assessment, as SCORE-15, helping to improve family assessment screening to evaluate therapeutic process evolution; 3) mixed methodology is recommended, such as self-report measures and interviews with circular questioning

techniques, dyadic problem-solving interactions, or observations at different times and integrating different family members.

Our findings inform prevention and intervention programs based on four interlocking triangles made up of the four components of the Therapeutic Quadrangle: the illness, the family, the patient and the health-care system framed in the context (Rolland, 1994). Placed within multidisciplinary teams, design of theory-based interventions should outline social, family and marital support and their perceptions; caregivers and their role in diabetes management at home; communication patterns and problem-solving skills for family members and couples; individual and family developmental life cycle considering life transitions and its normative and unpredictable tasks; family history of coping with the illness; shared disease knowledge and illness management skills; beliefs systems related to health care, the health system, health providers and medicines (Pereira et al., 2014); eating behavior considering emotional assessment and workplace conditions. Training psychologists to specifically provide psychosocial care for patients with diabetes is inherent to intervention programs of which there are too few (Hunter, 2016; Johnson, 2013; Johnson, 2019).

5. Conclusion

In this study, we divided a sample of 91 adults with type 1 diabetes into two groups concerning metabolic control over time to explore the recursive interplay between biological, family and social dynamics within diabetes management. Despite a notable absence of studies that address adults with T1DM and their families, existing literature highlights enough evidence of this recursive play on different theoretical and practical approaches. This study revealed considerable transversal results from individual to family and large contextual systems that are interconnected and include all diabetes management stakeholders. However, family-based intervention approaches, their evaluation in terms of efficacy, and family and psychosocial assessment through the diagnosis phase in a collaborative multidisciplinary team face a slow process on the path to rooting themselves in the health system.

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Supplementary Data

Table 5 Demographic Characteristics and Cognitive results for health participants

Variables	**Health participants (N=53)**				
	N_level1	N_level2	N_level3	M	SD
Gender (males/females) (1/2)	27	26	--------	-------	-------
Age (in years)	-------	-------		35.66	8.51
Marital Status (Single/Couple)	22	31	--------	--------	-------
Household members (1/2/3)	32	5	--------	--------	-------
Household income B (1/2)	25	28	--------	-------	-------
Residence (1/2/3)	53	0	0	-------	-------
Educational level (1/2)	4	49	--------	-------	-------
Vocabulary	-------	--------	--------	32.19	3.15
Digit Memory	-------	-------	--------	16.57	2.83
RPMT	-------	--------	--------	8.21	0.82

Educational level (1= 12 years of education; 2= university degree or higher); Household income (1=stable; 2= unstable); Household members (1= living alone 2=living as a couple 3=living with children); Residence as distance to health services, in travel time (1=Coimbra; 2= <1h; 3= >1h); Area of Residence (1=Urban; 2=Semi-Urban; 3= Rural); RPMT Raven's Progressive Matrices Tests; BMI body mass index

Table 6 Descriptive statistics of family variables for health participants (mean, standard deviation, max and min)

Variables	Health participants (N=53)		
	Range	M	SD
SCORE-15			
Total	1-4.60	1.80	0.63
Family Strengths	1-3.40	1.69	0.56
Family Difficulties	1-3.00	1.70	0.52
Family Communication	1-3.40	1.85	0.63
CONGRUENCE SCALE			
Total	51-100	71.13	12.05
Universal	10-49	27.74	10.86
Intra/interpersonal	31-57	43.64	6.53
QUALITY OF LIFE			
General	113-170	137.81	14.49
Financial	11-29	22.08	4.63
Time	5-18	12.53	3.18
Neighborhood	14-29	21.70	3.30
Home Conditions	12-25	18.45	3.02
Mass Media	5-15	8.66	2.17
Social/Health Relationships	8-21	15,28	2.60
Job	5-14	9.77	2.03
Religion	3-10	6.57	1.92
Family/Marital	4-10	8.45	1.74
Children	2-10	7.66	2.25
Education	4-10	7.58	1.66

Table 7 Marital functioning (EASAVIC subscale) results for participants without diabetes (N=28)

Variables	Health Participants (n=28)	
	M	SD
Total	4.42	1.10
Family Functions (FF)	4.77	1.06
Free Time (FT)	4.25	1.33
Autonomy (AUT)	4.81	0.87
Extra-family relations (EFR)	4.97	1.14
Communication and Conflicts (CC)	4.88	0.71

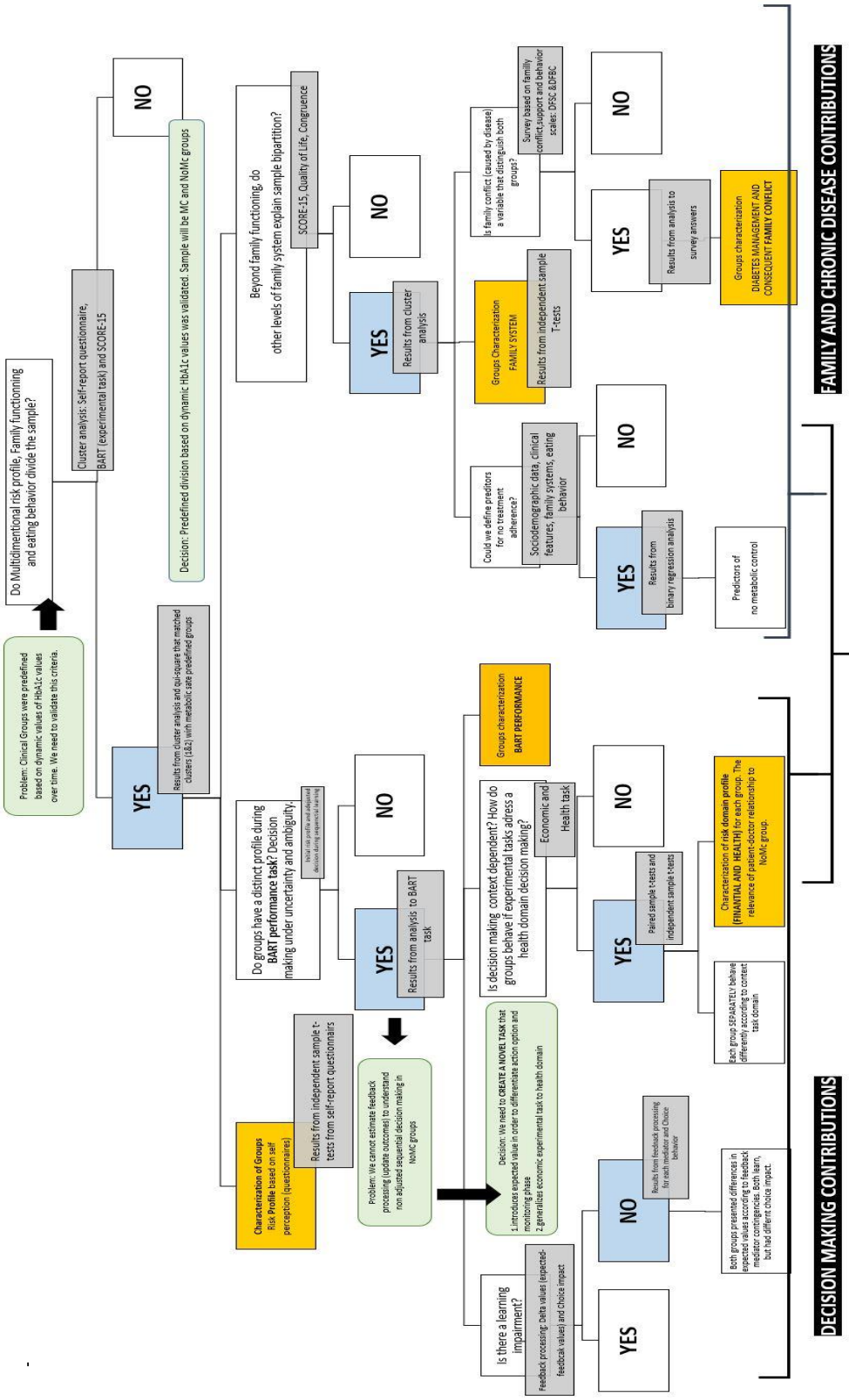


Figure 2. Schematic review of *Part III.Chapter1*. Decision tree over study 1 to 3, including findings and successive groups characterization for risk profile and social context of patients with T1DM.

CHAPTER 2

UNDERSTANDING RISK DECISION-MAKING PROFILE:

Neuroimaging studies

Study 4

Impaired neural responses in motivation and impulsive control circuits affect decision-making and metabolic control in type 1 diabetes mellitus

Jorge, H., Duarte, I.C., Paiva, S., Relvas, A.P. & Castelo-Branco, M. (2020). Impaired neural responses in motivation and impulse control circuits affect decision-making and metabolic control in type 1 diabetes mellitus. Manuscript submitted for publication.

Research in context

What is already known about this subject?

- Type 1 Diabetes (T1DM) requires daily decision-making to achieve metabolic control
- Decision theory has associated neural risk processing with suboptimal choices under uncertainty

What is the key question?

- To understand the neural mechanisms underlying impulsive decision-making, and biological worsening in T1DM

What are the new findings?

- In face of uncertainty, neural risk processing in T1DM in reward/motivation related regions is different from healthy participants, with an impact on neural choice processes in this life-long disease.
- Impaired metabolic control is correlated with activity changes in prefrontal and striatal regions, whereas successful metabolic control is correlated with modulations in posterior and parietal regions in iterated decision-making tasks, explaining patterns of biologic worsening

How might this impact on clinical practice in the foreseeable future?

- Understanding the neurobehavioral correlates of risky decision-making profiles will inform more effective clinical management given the importance of these features in a lifelong disorder such as T1DM

Abstract

Aim/Hypothesis

Decision-making and impulse control are quite relevant in clinical populations suffering from chronic diseases such as Type 1 diabetes (T1DM). Risky health decisions may have short and long-term related consequences. We hypothesize that general decision-making mechanisms and cognitive impulsivity are affected in the context of T1DM and can predict biological status.

Methods

Here we combined functional imaging using fMRI study with behavioral assessment using the cognitive impulsivity paradigm, the Balloon Analogue Risk Task (BART) in 50 participants (25 T1DM and 25 Controls).

Results

Behavioral results showed that T1DM participants followed a less risky strategy that remained unchanged along the iterative game. Neuroimaging results showed that the patient group revealed larger activation in nucleus accumbens, amygdala and prefrontal regions related to motivation and goal directed behavior in the prelearning phase. However, after iterative decision-making differential brain activations were related to error monitoring (anterior cingulate) and impulsive processing (inferior frontal gyrus). Negative correlations between impaired metabolic control and neural responses were found for frontal, limbic and inhibitory control regions. Patients with risk aversive profiles showed larger activation for striatal, posterior cingulate and middle frontal regions.

Conclusion/interpretation

Our findings reveal important new clues on the neural basis of motivational and impulsive control in chronic disorders such as T1DM when decisions occur under uncertainty. We found evidence

suggesting that impaired neural responses during risky decision-making process explain maladaptive behavior and impaired metabolic control. These results may ultimately inform more effective clinical management given the importance of these behavioral and neural features in lifelong disorders.

Keywords: Motivational and Impulsive decision-making; Balloon Analogue Risk Task (BART); fMRI; Type 1 Diabetes mellitus

1.Introduction

T1DM patients are faced with systematic habit-related daily decision-making related to clinical recommendations for numerous restrictions to achieve metabolic control and to avoid future uncertain health complications. It is expected that they monitor blood glucose, follow a diet, calculate carbohydrates for each mealtime while being vigilant to body signals of glycemic status, which they learn by routine. These disease-related tasks to achieve efficient self-management lead to substantial load on cognitive processes, such as strategic planning, episodic memory, inhibitory and self-control as defined by Barlows et al. (2002).

For people facing this lifelong chronic disorder, it demands an extraordinary ability to choose based on prior experience. They must evaluate cost/benefits, to anticipate risk/reward outcomes and to assess delay in time for rewards to avoid risky unhealthy actions or inhibiting appetitive behaviors. This includes updating, inhibiting, and shifting internal value-based decision-making (Hadja-Abo et al., 2020). In general, it requires a robust motivational and goal-directed behavioral system mediated by executive function and self-regulation skills which helps to learn and adaptively respond to dynamic contexts. Neuroscientific and computational research has shown that motivated goal-directed behavior with self-relevant consequences is related to brain systems such as prefrontal cortex, nucleus accumbens and amygdala (Costa et al. 2016).

Impulsive and risky decision-making has been related to maladaptive behaviors. Studies with people with diabetes reported impulsive behavior or related personality traits as mediators between self-management and glycemic control (Hadj-Abo et al.,2020). Similarly, insulin resistance has been associated to impulsivity towards food stimuli (Eckstrand et al., 2017; Eisenstein et al., 2015). The reduced cognitive capacity to avoid excessive risk taking is also the basis of numerous neuropsychiatric diseases, involving persistent risk seeking (Probst & van Eimeren, 2013).

Moreover, studies addressing decision-making under ambiguity (i.e., under unknown outcomes and respective probabilities) reports a tendency to avoid risk in the presence of uncertainty (Ellsberg, 1961; Muthukrishnan et al., 2009; Purshkarskaya et al., 2015). Under ambiguous decision, the recruitment of insular and lateral prefrontal cortex with increasing uncertainty has been found (Farrar et al., 2018; Huettel et al., 2005). Also, abnormal activations of frontocingulate (Congdon, 2013), orbitofrontal Cortex (OFC), amygdala and dorsolateral prefrontal Cortex (dlPFC) (Hsu, 2005) have been reported in this context (Taya, 2012 for a review).

Neuroimaging studies using the Balloon Analogue Risk Task (BART) reported cortical and subcortical regions associated with risky and risk averse decisions and uncertainty (Fukunaga et al., 2012), suggesting that this task is appropriate to study risky behavior in clinical populations. Studies in adults showed that anterior cingulate cortex (ACC) is specifically activated with risky choices or persistent risky choice, whereas safe choice yields co-activation of both ACC and insula (Apps et al. 2016). This activation pattern is also related with task difficulty, ambiguity and in response to environments crowded with uncertainty (Lamichhane et al., 2016a; 2016b). "Cash-out" events [also interpreted in previous BART studies as "win" (Rao, 2008) and "relief" (Scholberg, 2012)] recruited dopamine-innervated regions such as dorsal striatal regions, while "Explosions" (reflecting sudden loss of reward) recruited ACC as well as posterior cingulate cortex, right inferior frontal gyrus and bilateral insula (Heilbronner & Hayden, 2016; Korucuoglu et al., 2020).

Decision-making, and cognitive control are linked to several interrelated networks that respond to sensorimotor, cognitive, and emotional regulation relevant to disease monitoring and therapeutic management. First, a central pathway, the salience network that is primarily composed of the anterior insula and dorsal anterior cingulate cortex, connects cortico-striatal-thalamic loop circuits, is relevant to the integration of emotional, cognitive, and behavioral self-regulation (Peters et al.,2016) or to the representation of the motivational value and its link to the outcome (Mannela et al., 2013). Second,

the limbic system is pivotal in emotional regulation, being pivotal to memorize negative or positive salient outcomes and guide future behavior. The limbic system comprises subcortical (amygdala, hippocampus, septum, hypothalamus, mammillary bodies, thalamus, ventral tegmental area [VTA] and nucleus accumbens) and frontocingulate areas, such as the ACC (Knight et al., 2013; Rajmohan & Mohandas, 2007). Thus, the motivational system is associated with pathways that share limbic structures: the mesolimbic dopamine pathway, that projects from the VTA to NAcc and the mesocortical dopamine pathway, that projects from VTA to frontal regions. These dopaminergic systems are responsible for reward anticipation and forming habits, modelling subjective values (Arias-Carrión et al., 2010; Daw & Doya, 2006). Third, cognitive control is also related to top-down (dorsal) and bottom–up (ventral) networks for attention**.** The Right Middle Frontal gyrus (MFG), the node that links the ventral and dorsal networks, acts as a circuit-breaker interrupting ongoing processes in the dorsal network and reorienting a person's attention to a novel task-relevant external stimulus. The Inferior frontal gyrus (IFG) is also part of the ventral attention network, as well as the anterior insula, and it is related to attention but also to response inhibition (Japee et al., 2015). In sum, two interrelated main brain systems are implicated in decision-making: the valuation system (reflects the subjective value, process rewards/outcomes, updates subjective value, responds to reward contingencies, and produces learning signals) and the evaluation of uncertainty through executive, computational processes that regulates decision and action (Schultz, 2015).

The present study combines functional magnetic resonance imaging with concomitant behavioral assessment using the Balloon Analogue Risk Task (BART), an experimental task to testing risk taking under ambiguity, in a sample of T1DM and healthy participants. We used BART to examine the neural correlates of impulsivity, which in the case of diabetes, comprises the impulsivity features that patients need to take for successful metabolic control. Using this task during fMRI, we aimed to understand the neural mechanisms of risky decision-making for two main reasons: 1) it simulates a tension between reward seeking and loss aversion, involving cognitive control and cognitive-affective

processes 2) it correlates with several naturalistic risk-taking behaviors. This sequential decision-making task is defined by an escalating risk with an increased reward in a trial-by-trial basis. It allows for error monitoring through successive inflations and unexpected explosions, leading to potential shifts between averse and seeking choices, helping to define a dynamic risk-taking behavior profile after iterative decisions.

We compared both groups during four periods: 1) Before iterative decision-making. This is named as the initial period (first balloon series) or unlearned task performance occurring with the first task administration, called guessing (Vorhold, 2008); 2) After iterative decision-making. This period is also described as the final period (last balloon series) or learned risk-taking task performance after iterations. 3) Appetitive Outcome (Cash-Out decisions related to inhibitory behavior; or immediate rewards); 4) Aversive Outcome (The Explosion outcome related to choices that led to negative outcomes).

Along this line, this study aims to identify whether risk averse versus risk seeking patients, whose profile comes from task performance, present distinct neural phenotypes. Risk averse is defined here as preference for choose Cash out Decisions than to risk the balloon explosion. It means a preference for lower and immediate rewards than large and less probable amounts of money.

Finally, this study set out to find out the correlation between the neural correlates of motivation and impulse control with biological worsening, by relating brain responses with the progression of individual values of HbA1c over time.

Given patients' daily experience with intensive decision-making concerning health-related inhibitory behaviors, which are context and emotional dependent, we designed our BART-fMRI study to test the hypothesis that T1DM will present an overactivation of brain regions related to motivational and goal-directed behavior such as nucleus accumbens (ventral striatum) and amygdala and hippocampus

(limbic and memory regions) and present differential modulation of cortical processing in regions such as ACC, PCC, IFG and bilateral insula.

2.Methods

2.1 Participants

Written consent was obtained from all participants and the study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra, in accordance with the Declaration of Helsinki. All participants had normal or corrected-to-normal vision, were right-handed and had no history of neurological or psychiatric disorders. Each participant met standard safety requirements for entry into the magnetic resonance imaging scanner. They were paid depending on the money they earned during the experimental task to render it ecologically valid.

We recruited 50 adults aged 22-55 years. Twenty-five of them were diagnosed with Type 1 Diabetes (mean age=38.72, SD=10.38; age range:22-55, 11 males and 14 females) and the remaining 25 were matched healthy individuals (mean age=35.08; SD=8.77; age range:24-55, 10 males and 15 females). Groups were matched according to gender, age, civil state, and household members. (Table 1).

Table 1

Demographic Characteristics, Cognitive results, and self-reported measures in DM1 and Healthy participants (N=50)

Variables	T1DM (N=25)	Healthy (N=25)	X^2	U	gl	p	d
Demographic data							
Gender (M/F)	11/14	10/15	0.08		1	0.770	0.08
Age (y)	38.72(10.38)	35.08(8.77)		240.0		0.159	0.40
Civil State (Single/Couple)	11/14	11/14	0.00		1	1.00	0.00
Household members (1/2/3)	7/14/4	9/15/1	2.08		1	0.353	0.40
Household income B (1/2)	18/7	10/15	5.19		1	0.023	0.60
Residence	13/6/6	25/0/0	15.78		2	<0.001	
Education level(1/2)	11/14	2/23	8.42		1	0.005	0.90
Cognitive data							
Vocabulary	32.28(3.10)	31.52(2.41)		256.0	-----	0.261	0.31
Digit Memory	14.56(2.12)	15.88(3.14)		374.5	-----	0.221	0.34
RPMT	8.16(0.98)	8.12(0.88)		303.5	-----	0.853	0.05
Self-report measures							
Neuroticism	8.16(4.19)	6.80(3.50)		269.5		0.403	0.23
Extroversion	11.68(3.87)	12.12(4.01)		334.0		0.675	0.11
Impulsivity	54.92(8.55)	58.40(6.33)		400.5		0.087	0.49
Inhibitory control	40.68(7.18)	43.08(5.58)		382.0		0.176	0.38
Lack of planning	14.81(4.15)	15.32(2.76)		335.5		0.654	0.01
Health risk perception	38.56(9.58)	34.68(6.51)		250.0		0.224	0.34
Past Risk	13.72(3.82)	15.24(4.20)		373.5		0.235	0.34
Present Risk	12.76(2.84)	13.44(4.00)		329.0		0.747	0.09
Delay discounting - context variation	2/23	10/15		7.018		0.008	0.80
Emotional Eating Behavior	1.95(0.83)	2.17(1.10)		329.5		0.741	0.09
External Eating Behavior	2.32(0.53)	2.78(0.65)		440.0		0.013	0.75
Restrained Eating Behavior	1.94(0.74)	2.44(0.91)		420.5		0.036	0.62

Household members (1= living alone 2=living as a couple 3=living with children); Household income (1=stable; 2=unstable); Residence as distance to health services in spending time (1=Coimbra; 2= <1h; 3= >1h); Educational level (1= below 12 years; 2= above 12 years); RPMT Raven's Progressive Matrices Tests; BMI body mass index.

2.2 Procedures

2.2.1 Self-reported individual risk

Individual self-reported real-world risk profile was accessed by a comprehensive battery of questions made for this purpose covering three levels: 1) context - DOSPERT scale (Blais & Weber, 2006; Portuguese translation, Silva, 2012) allowed to achieve individual perception of risk taking in health and financial contexts; 2) time perspective of risk - General Past and Present risk-taking questions catch

out the influence of time in risk profile perception because participants were asked to compared the same type of risk in different time points (10 years ago and present time); and finally, 3) capacity to delay reward (Temporal Discounting) (Damme et al., 2019)- Intertemporal Choice questions were used to access the preference for delayed over immediate rewards. Here, participants chose between three options: a smaller earlier reward (SS), an intermediate (II) or larger longer reward (LL). They had three thematic decision challenges: financial, health and specific health context (diabetes). Risk related constructs as Impulsivity, Personality and Eating Behavior were evaluated by BIS-11 (Behavior Impulsivity Scale-11, translated by Cruz & Barbosa, 2012 and validated for the Portuguese population by Fernandes, 2014), EPQ (Eysenck Personality Questionnaire, Portuguese version, Castro-Fonseca, Eysenck & Simões, 1991) and Portuguese validation of Dutch Eating Behavior Questionnaire, DEBQ (Van Strien et al., 1986; Viana & Sinde, 2003). It evaluates three types of eating styles such as restrained (avoid eating), external (eating motivated by smell or visual attractiveness) and emotional (eating in response to emotions).

2.2.2 Balloon Analogue Risk Task

Participants performed a version of the Balloon Analogue Risk Task (BART) developed based on the original implementation of the BART for fMRI (Rao et al., 2008). Before starting the scanning session, the task was explained using a static template accompanied by specific instructions (supplemental material). The money accumulated throughout the experiment was paid in cash to assure participants' engagement during the task. BART behavioral measurements were compared to characterize the groups.

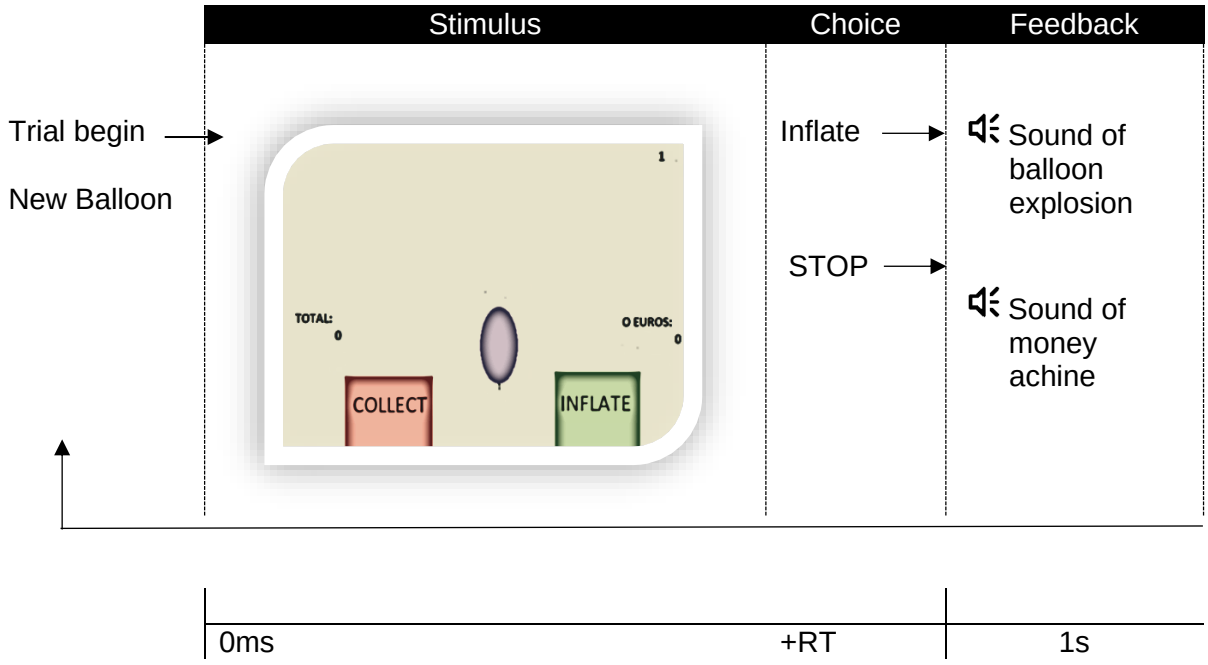


Figure 2. Schematic diagram for a trial sequence in the BART at fMRI. For each balloon (stimulus), participants had to decide (choice) inflate the balloon or collet the money earned. The consequence of that choice (feedback) was revealed by a sound of balloon explosion (if the balloon exploded) or a sound of a money machine (if they collected the money).

2.2.4 fMRI Data Analysis

For each subject, functional images were pre-processed using BrainVoyager QX software and consisted of slice scan time correction, High temporal filtering and 3D motion correction via realignment. The functional image was co-registered to the anatomical image. Before statistical analysis, images were normalized to the Talairach space and were then spatially smoothed using an 8 mm full-width-half-maximum Gaussian kernel. Because we would like to define predictors that are closely spaced, we applied a deconvolution analysis for each subject to separate the overlapping responses to four conditions or single data points: first balloon in series, last balloon in series, Cash Out Decision and Explode outcome. We performed a group analysis and run a deconvolution analysis on task events. The predictors were defined based on the selection of 10 data points (each condition with 10 “sticky” predictors of interest, from D0 up to D9). In GLM, we specified the overlay contrasts as D0-D3 (minus),

D4-D6 (plus) and D7-D9 (minus) and we balanced and we created separate maps for each subject, comparing the two groups (T1DM and healthy participants) for each condition. All contrast maps (beta maps) within a between subject analysis were calculated to identify the neural substrates associated with each condition to both groups. To correct for multiple comparisons a statistical threshold of $p<0.05$ was fixed and a minimum cluster size threshold was estimated using Monte Carlo simulations (1000 iterations). The number of contiguous voxels considered as the minimum cluster extension for each map is presented with the statistical maps. We conducted analysis of fMRI data separately for the first balloon (prior to learning) and the last balloon (after learning through iteration). We generated statistical maps contrasting T1DM and healthy groups during first balloon in series and during last balloon in series. We repetead the same procedure to generate statistical maps contrastring risk averse and risk seeking subgroups within patients. These subgroups were planned. Thereafter, we use the same between group analysis (T1DM versus Healthy participants; and risk averse versus risk seeking groups) with two different predictors: Cash Out Decision and Explode outcome. Finally, a linear function was adjusted to the progression individual values of HbA1c over time. The regressor calculated to each patient was used to define successful metabolic control (negative slope, i.e. decreasing HbA1c values over the time) and difficult metabolic control (positive slope, i.e. increasing HbA1c values over the time).

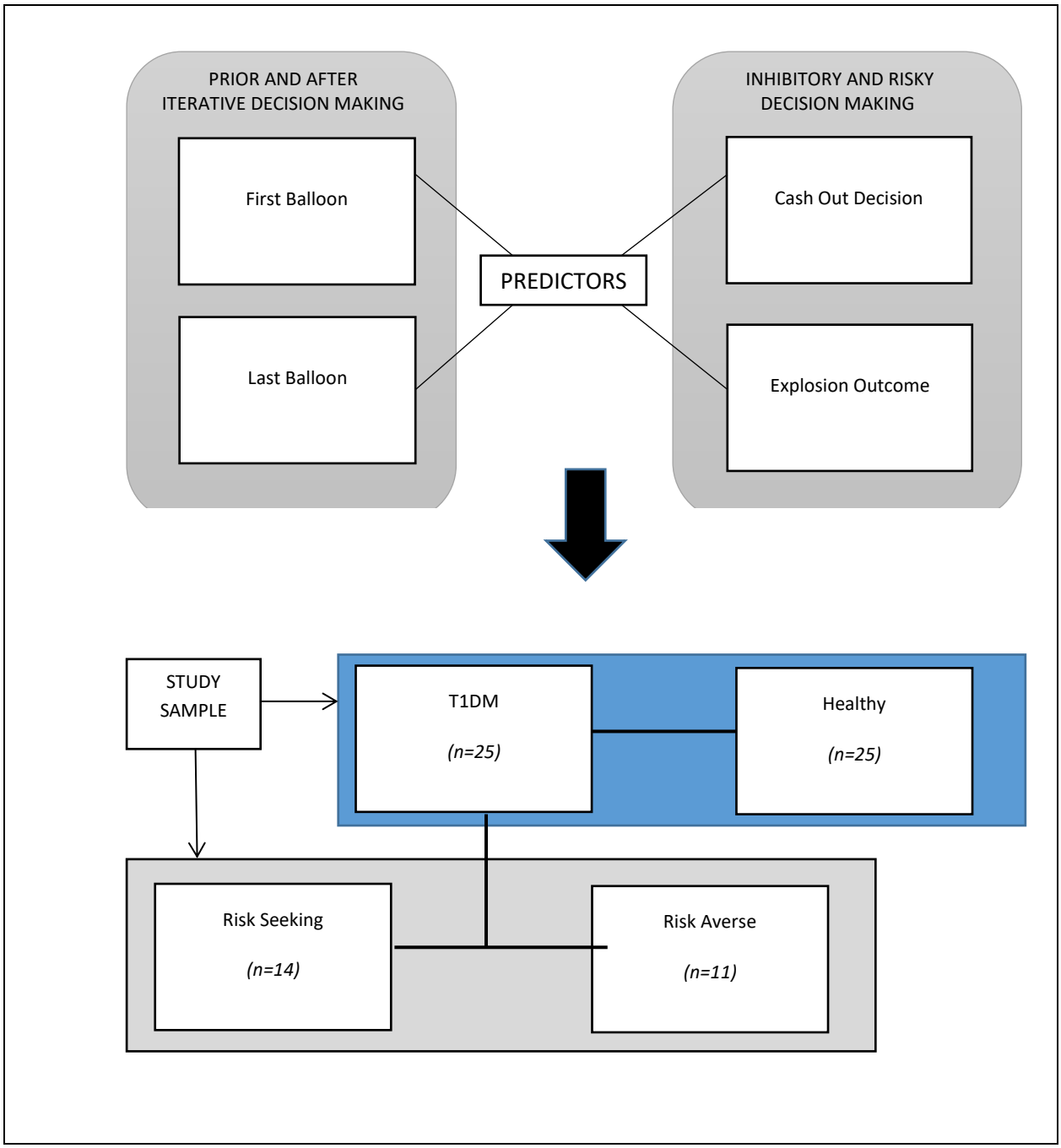


Figure 1. Flowchart of fMRI predictors and study sample

3.Results

3.1 Behavioral Risk Measures between T1DM and Healthy participants

Self-report individual risk. Mann-Whitney tests revealed that T1DM and healthy groups did not differ in self-reported measures of risk-taking, except for delay rewards. Whereas healthy subjects tend to opt for delayed over immediate rewards in all contexts, T1DM opted only for delay rewards in the diabetes` context. Regarding eating behavior, people with T1DM reported lower scores in external and restrained eating behavior as compared to the healthy group (Table 1).

Balloon Analogue Risk Task. Table 2 (A) shows behavioral results acquired during the fMRI experiment. Nonparametric independent sample tests revealed significant differences between groups. T1DM group chose more Cash Out than the control group and the number of inflations for the first balloon is like the last balloon: t (24) =-2.64, p=0.794. For healthy subjects, the opposite pattern is found: the number of inflations in the last balloon is highest than in the first balloon, converging to a change in risk profile: t (24) =-2.53, p=0.018 (Figure 3).

Table 2 Behavioral results on BART task (N=50), T1DM and healthy groups (A). Behavioral results on BART task (N=25), for risk averse and risk seeking performances within T1DM participants (B).

A.

	People with T1DM (N=25)					**Controls (N=25)**						
	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3rdQ	W	p
Total win	3.08	0.81	2.48	3.16	3.68	3.48	0.77	2.75	3.55	4.05	401.5	0.084
Cash Out	23.88	2.26	22.00	24.00	26.00	20.20	4.05	17.50	21.00	24.00	481.0	**0.001**
Explode	6.12	2.37	4.00	6.00	8.00	9.80	4.05	6.00	9.00	12.50	144	**0.001**
Inflations per balloon	14.84	6.42	9.53	15.22	18.13	17.39	7.47	11.21	16.29	23.80	383.0	0.171
Distance to 1st balloon Explosion (%)	18.48	10.39	12.0000	23.00	25.50	17.04	9.83	7.00	22.00	24.00	269.5	0.401
Inflations in 1st Balloon	13.52	10.39	6.50	9.00	20.00	14.96	9.83	8.00	10.00	25.00	355.5	0.401
Inflations Last Balloon	14.08	8.54	11.50	20.00	19.76	19.76	8.39	14.00	19.00	26.00	434	**0.018**
Maximum	26.04	10.25	16.50	25.00	30.50	31.36	11.47	20.50	32.00	42.00	400.0	0.089
Minimum	5.92	3.66	3.50	5.00	9.50	10.20	5.80	5.50	10.00	12.00	457.0	**0.005**
Risk After Explosion %	53,13	26,92	33,33	60,00	74,61	63,98	17,16	52,78	66,66	75,95	2410	0.995
Reaction Time	1.37	0.59	0.91	1.26	1.66	1.78	0.65	1.32	1.72	2.16	434	**0.018**

B.

BART	Risk Averse N=11					Risk Seeking N=14						
Variables	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3rdQ	**U**	**p**
Total win	2.84	0.62	2.50	2.64	3.50	3.26	0.91	2.41	3.50	4.07	222	0.217
Cash out	25.82	1.60	24.00	25.00	26.00	22.36	1.64	21.00	22.50	23.50	10	**<0.001**
Explode	4.18	1.61	3.00	4.00	6.00	7.64	1.64	6.75	7.50	9.00	144	**<0.001**
Inflations per balloon	9.80	2.89	8.04	9.26	12.17	18.80	5.60	15.72	17.50	23.14	145	**<0.001**
Distance to 1st balloon explosion %	23.01	6.89	15.63	25.00	28.13	57.36	36.76	23.44	56.25	100.00	119	**0.021**
Inflations in 1st Balloon	7.36	2.20	5.00	8.00	9.00	18.35	11.76	7.50	18.00	32.00	119	**0.021**
Inflations Last balloon	8.82	6.03	5.00	8.00	10.00	18.21	8.05	10.75	17.50	26.75	132.5	**0.001**
Maximum	18.27	5.19	15.00	17.00	25.00	32.14	9.06	26.75	30.00	37.00	146	**<0.001**
Minimum	4.45	2.33	3.00	5.00	5.00	7.07	4.16	3.75	7.50	10.00	109	**0.085**
Risk after explosion %	39.39	29.12	0.00	50.00	66.67	63.93	20.01	55.36	68.34	78.34	117.50	**0.025**
Reaction Time	1.02	0.31	0.72	0.94	1.35	1.63	0.63	1.12	1.58	2.05	128	**0.004**

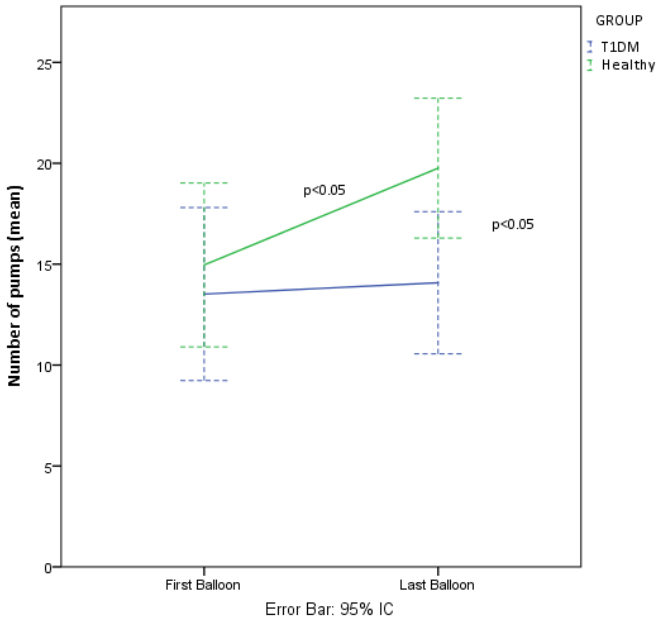


Figure 3. Performance at BART on first balloon and last balloon for T1DM and healthy participants, comparing two moments of experimental task: prior and after iterative decision making. T1DM group mean performance on First Balloon was not significantly different from Last Balloon (unchangeable performance). Healthy participants group mean performance on Last Balloon was significantly different from First balloon (learning after iterative decision making) ($p<0.05$). Both groups differ in group mean for Last balloon (different risky profile) ($p<0.05$).

3.2 Behavioral Risk Measures between Risk averse and Risk Seeking Groups within T1DM

To address the relevance of risk-taking profiles, we performed a posthoc within group analysis. Considering T1DM patients (n=25), we divided them in two groups according to the performance on the risk task. We used a cut-off point on 20 pumps for each balloon (average of pumps for the group). For each participant, we recorded the frequency of number of pumps for each participant (30 balloons) using a division criterion of ≥ 20 pumps. We divided the group into two parts. We obtained a group with 11 patients with risk averse profile (age=36.18, SD=10.34; age range:22-47, 6 males and 5 females) and a group with 14 patients with risk seeking profile (mean age=40.71; SD=10.57, age range:22-55, 5 males and 9 females). Groups were matched according to all sociodemographic variables.

Self-reported risk measure. Between group analysis showed that T1DM with risk averse performance scored higher on lack of planning (U=38.5, p=0.034) and scored lower on health risk perception (U=119.5, p=0.018) than T1DM with a risk seeking performance. Risk averse participants almost scored higher on Inhibitory Control (U=41.5, p=0.051).

Balloon Analogue Risk Task. As expected, both groups differ in almost all behavioral variables of BART experimental task (Table 2, B).

3.3 Neuroimaging Results

3.3.1 T1DM vs Controls (Figure 4)

First Balloon Series**.** During the first balloon series, participants were deciding to inflate under complete uncertainty and ambiguity. Results showed increased activations in regions involved in decision under ambiguity (Insula) or inhibitory control and probabilistic learning [bilateral IFG, basal ganglia (Putamen, Caudate) and ventral striatum (Nucleus Accumbens) for T1DM patients comparing

to health participants. The activated regions included a three-cluster group encompassing neighboring right amygdala and ventral striatum, both known to be associated with stimulus-reward contingencies.

Last Balloon Series. During the last balloon series, participants were deciding after iterative decision-making. Results for T1DM participants compared to control participants showed increased activations in areas related to error monitoring, bilateral ACC, and inhibitory control, left IFG and right middle frontal gyrus. Healthy participants activated more than T1DM participants in the left PCC and superior parietal lobe, brain regions related to episodic memory, and attentional deployment.

Cash Out Decision. Comparing T1DM versus control groups, Cash Out Decision led to higher activity in a core set of four core brain networks: frontal (medial frontal gyrus, BA9, BA10, BA46), temporal (middle and inferior gyrus, BA21, BA20, BA38), parietal (posterior dorsal e ventral, BA7, BA39, BA40) and insular cortex (bilateral insula). We also observed higher recruitment of subcortical areas (putamen, pallidus, and thalamus) related to implicit learning. T1DM group also showed higher activity than the control group in episodic memory regions such as posterior cingulate gyrus (BA23, BA31) and hippocampus. In turn, healthy participants showed higher activity in frontoparietal areas, (right inferior frontal gyrus BA45, left middle frontal gyrus BA10, inferior parietal lobe BA40, Insula and BA22 (posterior dorsal area of the insula).

Explode outcome. Comparing T1DM groups versus control group, Surprising events as being faced with the “explode” outcome, showed higher activity in brain areas related to uncertainty and error monitoring, namely the middle frontal gyrus (BA9, BA10), anterior cingulate cortex (BA24, BA32) and pre-motor and frontal regions BA6 and BA8.

Correlation with dynamic profile of metabolic control (Figure 5). We found positive correlation with impaired metabolic control with similar areas for first and last balloon: cingulate (BA32, BA25) and

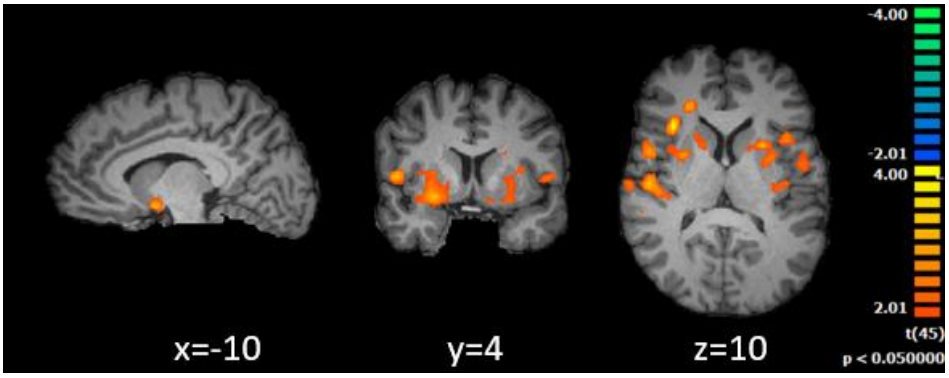
subcortical regions (caudate). Differently, in first balloon we observed correlated brain activation in frontal regions and thalamic activations. In turn, in last balloon subcortical regions are more extended (putamen, nucleus accumbens and insula). For negative rewards (explosion), negative correlations with successful metabolic control were found with posterior cingulate cortex (BA31, BA23), posterior parietal dorsal and ventral regions (BA7, BA39, BA40) and superior temporal lobe (BA22) for the last balloon. Patterns related to successful metabolic control and activation in healthy participants seems to be very much alike (parietal and posterior regions) in contrast with impaired metabolic control (distinct in frontal and anterior regions).

3.3.2 RisK Averse and Risk Seeking Contrasts within T1DM (Figure 6)

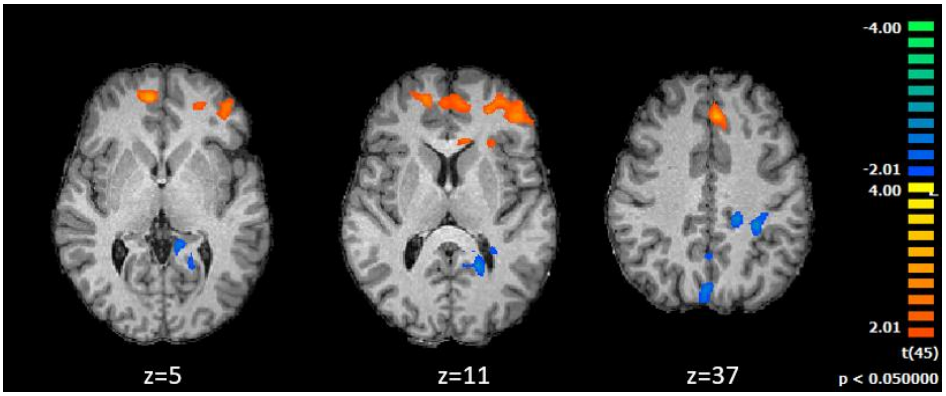
First Balloon Series and Last Balloon series. The contrast between Risk averse and Risk seeking during the first balloon and also for the last balloon series yielded larger activations for risk seeking patients in parietal regions.

Cash Outcome Decision Risk Averse patients showed larger activations in insula, whereas risk seeking revealed activations in limbic regions as anterior cingulate gyrus and caudate. Both groups shared activations in frontal inhibitory regions as middle (BA9, BA10) and inferior frontal gyrus (BA44).

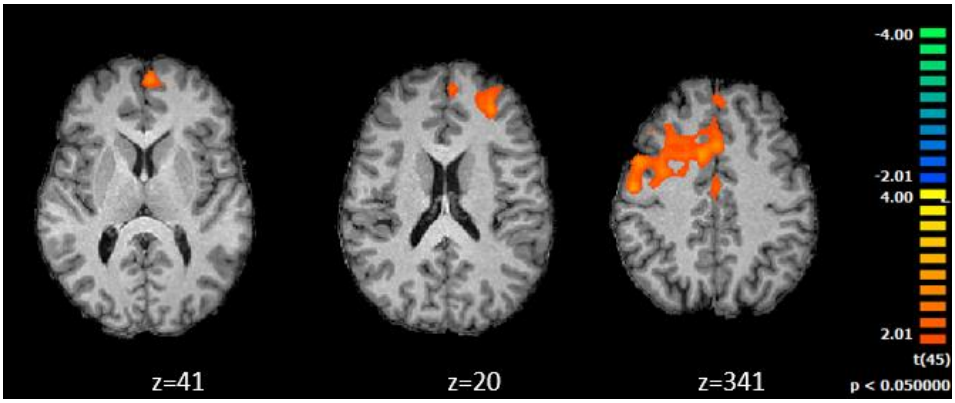
Explode outcome. ACC, middle and inferior frontal gyrus regions activated into a larger extent for risk averse patients in contrast with risk seeking profile, suggesting a distinct activation pattern in regions involved in cognitive and inhibitory control.



Statistical maps for the comparison between T1DM and Controls during the First Balloon condition. Activated regions included a three-cluster encompassing neighboring right amygdala and ventral striatum. Note higher bilateral (insula, inferior frontal gyrus and putamen), right (caudate and amygdala) and left (nucleus accumbens) BOLD activity (minimum cluster size 78 voxels).

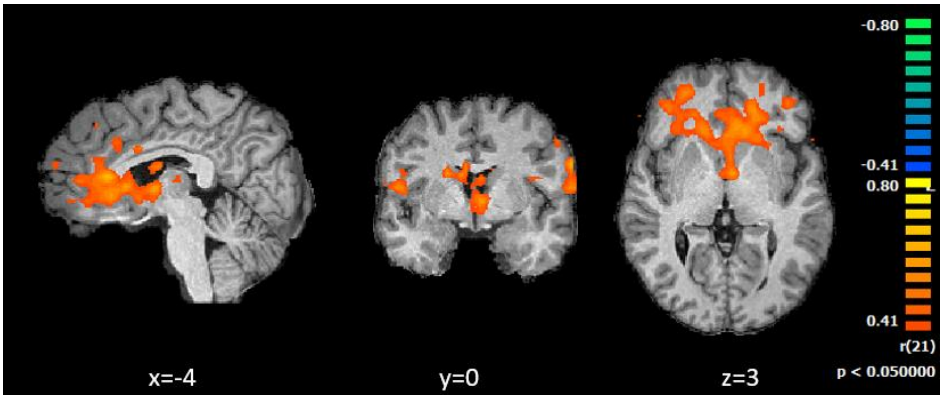


Statistical maps for the comparison between T1DM and Controls during the Last Balloon condition (after iterative decision-making). T1DM showed higher activity in regions related to error monitoring, such as bilateral ACC (BA32, BA24) and frontal regions (9,10, 8, 45). Controls (blue) revealed higher BOLD activity in regions related to episodic memory as posterior cingulate cortex (BA23, 30, 31) (minimum cluster size 95 voxels)

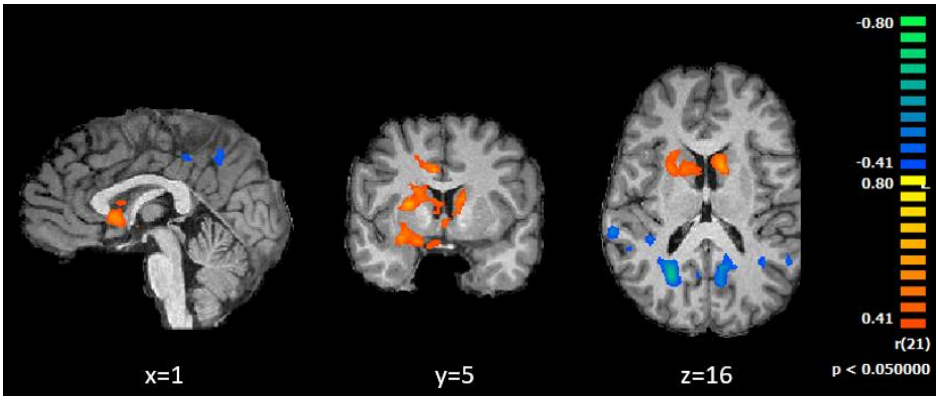


Statistical maps for the comparison between T1DM and Controls during Explode Outcome condition. T1DM showed higher BOLD activity in areas related to error monitoring and uncertainty, as prefrontal, ACC and premotor regions: BA10, BA9, MFG, BA24, BA32, BA8, BA6 (minimum cluster size 103 voxels).

Figure 4. A fMRI whole brain comparison between T1DM and Control Group during first balloon, last balloon and explode outcome conditions.

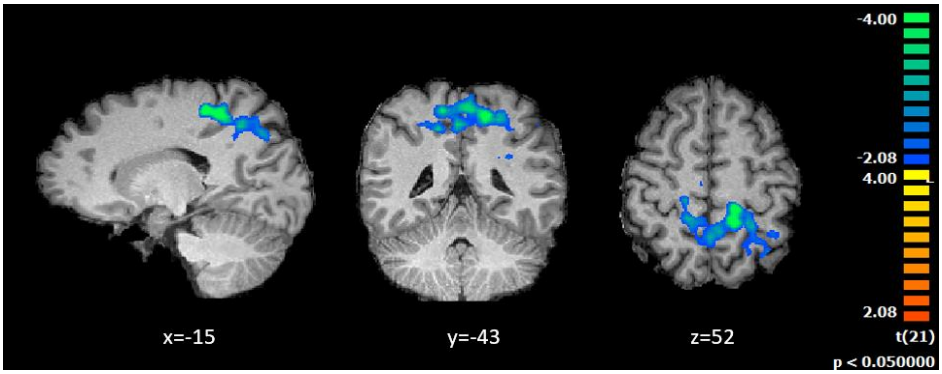


Whole brain correlation analysis between BOLD activity during First Balloon condition and HbA1c (higher HbA1c values traducing a poorer metabolic control). A positive value (red) for the correlation, means that poorer the metabolic control (higher the HbA1c), higher the BOLD activity during the First balloon condition. This was found in frontal and anterior regions such as (BA47, 11,10,46,45,9,44), ACC and subgenual ACC (32,25), Subcortical (Thalamus e caudate) (minimum cluster size 111).

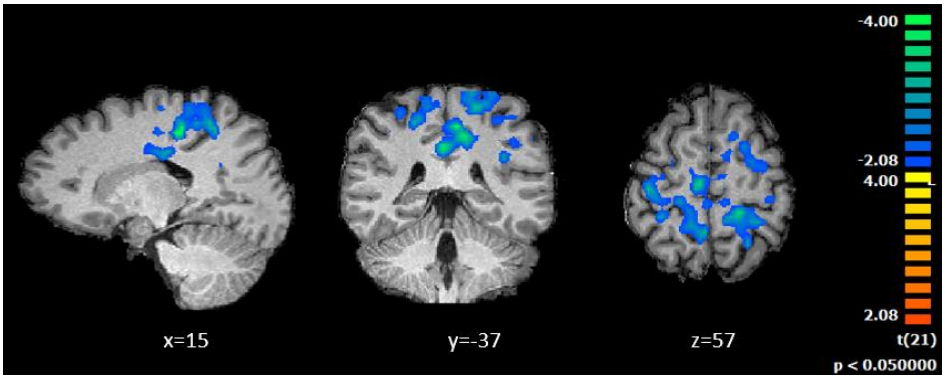


Whole brain correlation analysis between BOLD activity during condition and HbA1c (higher HbA1c values traducing a poorer metabolic control). A positive value (red) for the correlation, means that poorer the metabolic control (higher the HbA1c), higher the BOLD activity during the First balloon condition. This was found in frontal and anterior regions (ACC, 32,25; as well as subcortical regions (Caudate, Putamen, NAcc and Insula), whereas negative correlations were found mainly in posterior and parietal regions (BA31, BA23, BA7, BA39, BA40) and temporal (BA22). (minimum cluster size 119).

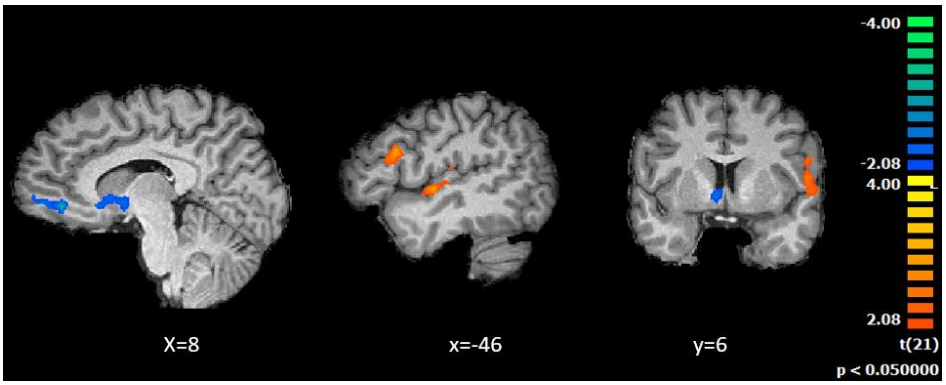
Figure 5. A fMRI Whole brain correlation analysis between HbA1c values and the BOLD activity during the first balloon and last balloon condition, performed by the T1DM patients.



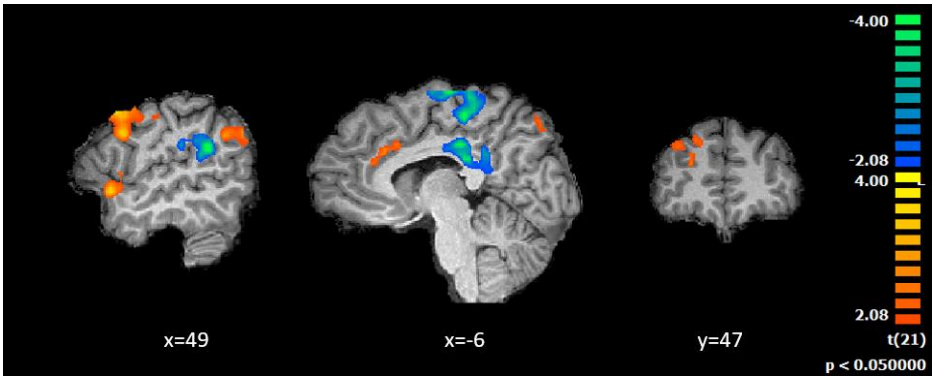
Statistical maps for the comparison between Risk Averse and Risk Seeking T1DM patients during the First Balloon condition. Differences were found in parietal regions. (minimum cluster size 85).



Statistical maps for the comparison between Risk Averse and Risk Seeking T1DM patients during the First Balloon condition. Differences were found in parietal regions. (minimum cluster size 113).



Statistical maps for the comparison between Risk Averse and Risk Seeking T1DM patients during Cash Out condition. Risk Averse T1DM patients showed higher BOLD activity than Risk Seeking T1DM patients in insula, left BA44 and B9. On the other side, Risk Seeking T1DM patients showed higher BOLD activity than Risk Averse T1DM patients in right caudate, left anterior cingulate cortex (BA24, BA32), prefrontal cortex (BA10) and inferior frontal gyrus (BA44). (minimum cluster size 85).



Statistical maps for the comparison between Risk Averse and Risk Seeking T1DM patients during Explode Outcome series. Risk Averse T1DM patients showed higher BOLD activity than Risk Seeking T1DM patients in anterior cingulate cortex (BA32), inferior frontal gyrus (BA44), prefrontal cortex (BA99) and motor regions (BA6, BA7). On the other side, Risk Seeking T1DM patients showed higher BOLD activity than Risk Averse T1DM patients in parietal regions. (minimum cluster size 97).

Figure 6. A fMRI Whole Brain activation within patients for risk averse and risk seeking profiles contrasts for first balloon, last balloon, cash out decision and explode outcome.

Discussion

Consistent with our prediction, the present fMRI study suggests for the first time, to the best of our knowledge, that Type 1 Diabetes, a chronic lifelong disease, leads to modified neural risk processing, hindering adaptive behavior and impaired decision-making and impulse control. We focus on four aspects of decision-making: 1) before and 2) after iterative decision-making and at 3) appraisal -cash out decisions and 4) aversive outcomes, as balloon "explosions". We focused on differences between group brain activations (T1DM vs healthy participants) while also comparing patients with Risk Averse vs Risk Seeking profiles. Lastly, HbA1c values over time were used for correlation analysis. Accordingly, progressive variations from worse to the best control metabolic control (positive versus negative slope, respectively) were related to brain activity patterns.

Before and After iterative decision-making

We found that, in first balloon, patients activated into a larger extent the motivational system related to assigning values to goals. NAcc-amygdala`s association have been present when novel stimulus, appetitive and aversive motivational values are involved (Kim et al., 2018; Mannela et al.,2013; Mavridis, 2019), forming action-outcome contingencies. Activity of the mesolimbic dopaminergic system that includes VTA which projects to NAcc and the olfactory bulb innervating the amygdala is related to reactivity to emotional information and anticipation of monetary reward (Hommer et al., 2003). Additionally, the IFG (Hampshire et al., 2016) and Insula area together are related to inhibition response, which joining the caudate and putamen play a role in the control of action selection. Patients preferred low rewards and losses. This may explain the risk averse profile. Opposite results are found in studies with pathological gamblers who tend to prefer high rewards at the cost of higher losses (Brevers & Noël, 2013).

Importantly, patients with worsening metabolic control showed increased activity in limbic and inhibitory control regions. They presented a distinct pattern of activations from successful metabolic

control that stay close from healthy participants' brain activations, with dominant parietal and posterior regions, contrasting with impaired metabolic control (distinctive activity frontal and anterior regions).

In general, our findings support an overactivation of brain regions related to motivation and impulse control and in T1DM patients. Under conditions of complete uncertainty and ambiguity and even after iterative decision-making, it seems that there`s no impact of choice. Looking at behavior data, they prefer cash out decisions related to avoidance or removal of aversive stimulus. Similar findings were found in OCD patients performing computerized BART task (Sohn et al., 2014). A theoretical account can be out forward based on these data: 1) patients miss the chance to get more information, showing perhaps that they value information of safe outcomes higher than the information about risk outcomes, anticipating negative outcomes (insula activation) promoting anxiety (amygdala). 2) They are exposed with strong invariances in the contingencies of action and outcome which may also explain that behavior become regular or habitual. 3)The trade-off between magnitude of a potential reward and probability of a negative outcome will eventually trigger the inhibitory control process and result in the avoidance or terminus of the behavior.4) It is possible that activation of Middle Frontal cortex may also explain maintenance of a rigid emotional state (Waugh,2014), and thus prevents behavioral changes.

Appraisal and Aversive Outcomes

Risk averse and risk seeking performance in BART offered useful measures to understand extreme behavioral profiles. Patients with risk seeking profile were exposed to more tension between reward seeking and loss aversion and this behavioral feature increases opportunities to find out task learning rules (Peters et al., 2016). This may explain the observation of dorsal striatum (caudate) and error monitoring circuit activations for cash out decisions (larger rewards) as well as inhibitory control regions (BA44, BA10). Risk averse patients in economic settings, even in appraisal rewards, showed

joint activations of the IFG and Insula, as well as middle frontal gyrsus (BA9), suggesting a neural correlate for hardful and potentially anxiogenic decisions.

As a limitation of this study, we are convinced that with a larger sample, subgroup stratification of risk could be better optimized. Second, we considered general cash out decision and “explode” outcomes even if a cash out decision with lower reward brings a different tension from larger rewards. In the same way, a balloon explosion with few pumps (loosing less money) has a different impact than lose a huge amount of money. However, such differentiation would require larger sample sizes. An additional limitation is that the absence of jitter between choice and outcome preventing us from fully separating option and outcome. Despite the focus of this study did not lack this separation future studies may take it into account.

Results of this research may offer insights to future directions concerning adaptive decision-making and impulse control in chronic life-long diseases such as diabetes. It will be helpful to discriminate if the biological status is a mediator or instead a consequence of the neural mechanisms that inhibits learning of appropriate behavioral responses. The similarity with findings within anxiety spectrum disorders, as obsessive-compulsive disorders (OBS) (Peterson et al.,2014; Tolin et al., 2003) is quite interesting. It is likely that the biological worsening over time has an impact on cognitive flexibility that may explain suboptimal decision-making, as continuous oscillations of HbA1c have been also related to cognitive impairments. Interestingly, the systematic attention to disease control, also brings these patients closer to the typical pattern observed in post-traumatic stress disorder (PTSD) in which neuroimaging studies report excessive saliency processing, hyperactivity of AI and dACC and decreased top-down cognitive control involving fear and negative affect (Rauch at al., 2006).

Conclusions

Under uncertainty and ambiguity, adaptive decision-making mechanisms and cognitive impulsivity are affected in T1DM and predict the biological status. Interestingly, motivation, reward, and impulsive neural mechanisms in particular frontal and limbic areas as middle and inferior frontal cortex, striatum, and insula, seem to play a pivotal role to explain biological worsening in patients with impaired metabolic control. These results have strong implications for improved disease and therapeutic monitoring, as well as in the design of prevention efforts.

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Supplementary material

Bart Experiment - Rational and description

Before scanning, we gave theses instructions:

> #You will be presented with 30 blue balloons, one at a time in the center of the screen. In order to earn money, you must inflate the balloon. For each time you inflate the balloon you win 1 cent. If the balloon explodes, you lose the money you earned for that balloon. To save the money, you must decide to stop pumping the balloon before balloon explosion. To make your decisions, you will use a button-press response box to click to inflate (press right button) or to stop inflate and save the money for that balloon (press left button). During the task, at the left inferior corner of the screen, the accumulated money is presented. At the end of fMRI task, the money accumulated throughout the entire experiment will be paid in cash".

A maximum of 32 inflations were possible per balloon and the number of inflations for each trial was randomized (Pumps were distributed with a Skewness=0.05). Participants did not know in advance the exact probability of explosion nor the maximum number of inflations. So, the larger the balloon (increasing balloon size), the greater the risk of explosion. The participants decided on inflation on a voluntary way. Risk attitude is obtained through the objective calculation of the average number of inflations made without explosion. A baseline period was defined between trials (balloons).

> Explode Outcome condition is given by the time the participant pumped and the balloon exploded. Cash Out Decision is given by the time the participant decided to save the money earned for a given balloon. Both pumping, cashing out and the balloon explosion had a different associated sound.

fMRI data acquisition

Structural and functional MRI scans were acquired in a 3T Magnetom Trio Tim MRI scanner (Siemens, Erlangen, Germany), using a 12-channel head coil). The scanning session included a high resolution T1-weighted magnetization-prepared rapid gradient-echo sequence that was measured with repetition time of 2530 msec, echo time of 3.42 msec, flip angle of 7 degrees, voxel size of 1×1×1 mm and field of view of 256 mm. Functional images were acquired using blood oxygen-level dependent (BOLD) contrast echo planar imaging (EPI), with repetition time of 2000ms, echo time of 30ms, flip angle of 90 degrees, field of view of 256 mm, matrix size of 256×256, voxel size 3×3×3 mm, and 35 slices with no gap, covering the entire brain. The number of volumes was participant dependent. The task was presented to the participant in an LCD monitor (NordicNeuroLab, Bergen, Norway) mounted ~156 cm away from the participants' head. The monitor could be seen through a mirror mounted above the coil. The monitor has a frequency rate of 60 Hz and dimensions of 698.40 x 392.85 mm. The subject could select his response using a MR-compatible response box (Hybridmojo, San Mateo CA, USA): right hand was used to press the right button to inflate and left hand was used to press the left button to stop inflate and save money.

Table 3

Differences in brain activation for T1DM and controls between group analysis (A) Differences in brain activation within T1DM according to variations of metabolic control - correlation (B) Differences in brain activation for risk averse and risk seeking patients between group analysis (C).

A

Anatomical Region	BA	H	Talairach (peak voxels) x	y	z	T-max	p
First Balloon T1DM>Controls							
Inferior frontal gyrus, insula, putamen, caudate, and right amygdala	44, 45, 48, 49, 13, 53	R	33	20	10	4.50	0.000047
Nuccleus Accumbens, putamen, insula, inferior frontal gyrus	52, 48, 13, 44	L	-12	2	-8	3.63	0.00071
Insula, lateral premotor area	13, 6	L	-39	-16	4	4.067	0.000018
Last Balloon T1DM>Controls							
Middle frontal gyrus, anterior cingulate gyrus, inferior frontal gyrus	9,10 24,32, 45	R L L	6	50	7	3.43	0.0012
Anterior cingulate gyrus, medial supplementary motor area	32 8	L R/L	-3	26	31	5.046	0.00008
Middle frontal gyrus	10	R	-30	50	13	3.59	0.00008
Explode outcome T1DM>Controls							
Lateral premotor area, and anterior cingulate gyrus	6, 8 23, 24,	R L	9	11	43	3.51	0.001
Middle frontal gyrus	9,10	L	0	50	37	3.02	0.004

B

Anatomical Region	BA	H	Talairach (peak voxels) x	y	z	r	p
First Balloon Slope Impaired metabolic control							
Gyrus rectus, Inferior frontal gyrus Middle frontal gyrus ACC, Subgenual Insula, Thalamus, Caudate	11,47,45, 10,9,46 32,25 13,50,49		36	53	13	0.76	0.000024
Last Balloon Slope Impaired metabolic control							
Anterior cingulate cortex, subgenual	32, 25		0	11	4	0.63	0.0011
Nuccleus accumbens, Caudate Putamen, Insula	52, 49 48, 13		-9	8	16	0.64	0.00081

C

Anatomical Region	BA	H	Talairach (peak voxels) x	y	z	T-max	p
Cashout RiskAverse>RiskSeeking Within patients							
Primary auditory	41	R	63	-16	10	4.69	0.000125
Middle Frontal gyrus	9	R	36	50	32	3.71	0.00128
Superior Temporal Gyrus	22	L	-51	11	-2	4.26	0.0003
Insula	13						
Cashout RiskSeeking>RiskAverse Within patients							
Anterior Cingulate Gyrus	32	L	-6	38	10	-4.38	0.000259
Caudate	48	R					
Explode RiskAverse>RiskSeeking Within patients							
Middle frontal gyrus	9	R	27	41	37	3.28	0.0035
Motor area (SMA)	8						
Anterior cingulate gyrus	32	R	3	-1	40	4.42	0.000232
Inferior Frontal gyrus,	44	R	67	-13	7	4.76	0.000106
Primary auditory	41						
Explode RiskSeeking>RiskAverse Within patients							
Superior Parietal Lobule	7	L	-15	-40	61	-5.6	0.00015
Posterior cingulate gyrus	31						

Study 5

Leaping from neuroeconomics to healthconomics in disabling chronic disease: Risk attitude and neural basis of trust-based health decision-making in type 1 diabetes

Jorge, H., Duarte, I.C., Afonso, S., Melo, M. Relvas, A.P. & Castelo-Branco, M. Leaping from neuroeconomics to healthconomics in disabling chronic disease: Risk attitude and neural basis of trust-based health decision-making in type 1 diabetes mellitus. Manuscript submitted for publication.

Abstract

Background Experimental approaches in neuroeconomics have in general focused on monetary utility. Other forms of utility, namely one's own health, have barely been explored. This is particularly relevant in chronic diseases such as diabetes. In this condition, constant daily life decisions are critical for self-consequential long-term outcomes.

Methods Here, we used fMRI to compare the neural correlates of self-consequent decision-making in the economic and health domains in a lifelong disabling disorder, Type 1 Diabetes Mellitus. We focused on two critical phases of decision-making: Investment, Positive Feedback and Negative Feedback. Fifty participants, T1DM and controls, performed two experimental trust games, on the health and economic domains.

Results We identified between group differences in patterns of activity which were context dependent. Limbic, motivational, and dopaminergic regions were more recruited by controls in the economic setting, whereas for patients that happened in the health trust game. We found that the worse the metabolic control, the higher the BOLD activity in regions of saliency network. This was manifested by positive correlations between brain activity during investment in anterior cingulate cortex and insula and HbA1c blood level progression over time.

Conclusion The neural correlates of self-consequent decision-making in the health domain differ from economic context in Type 1 Diabetes Mellitus. Furthermore, HbA1C blood levels showed to be correlated with saliency of neural risk processing. The knowledge of a differential risk processing in the health domain when compared with the neuroeconomic context, provides a translational research contribution from the field of decision neurosciences with potential impact on the development of personalized interventions.

Keywords: Trust games; Neuroeconomics; Decision Neurosciences; fMRI; Type 1 Diabetes Mellitus

1.Introduction

Both economic and health real-world decision-making involves assessing potential outcome values in presence of uncertainty, while processing trust, considering the information about other individuals in socially complex settings (Molenberghts et al., 2016). The theoretical framework behind this type of strategic thinking includes contributions from Game Theory (von Neumann & Morgensten, 1944), and Theory of Mind (Premack & Woodruff, 1978). Decision-making disfunctions were found in psychiatric disorders when performing neuroeconomic games in social setting (Paulus, 2007; Robson et al., 2020).

Social decision-making in economic exchanges was early on been studied with one shot Trust Games in a landmark study by Joyce Berg, John Dickhaut and Kevin McCabe (1995). Here, one player, the investor, decides to give an amount of money (all, some, or none – the investment, a measure of trust) to the other player (the trustee), knowing in that case that it will be tripled. Then, the trustee decides which received amount of the money he would like to reciprocate -- a measure of trustworthiness. Played as an iterated game, decision-makers can strategically improve their outcomes. Players can approximate to optimal strategies, adjusting strategies according to the predicted behaviors, beliefs, and intentions of the other players. Camerer & Hare (2003) highlighted four components of making predictions in social decision-making: 1) know what other players perceive; 2) know how they value observable payoffs; 3) predict other players behavior either in one-shot game or in the first iteration in a repeated game; and 4) learn how behavior changes with experience.

Making decisions in social situations requires integrating quickly complex information which from the neuroscientific point of view requires the involvement of a complex set of interconnected brain regions (Sanfey, 2007). A review and a meta-analysis about the neural mechanisms that underlie trust games in the economic context (Belluci et al., 2017; Tzieropoulos, 2013;) revealed that in a multiround game the trust stage was associated with activity in ventral striatum and the dorsal striatum was more largely

recruited in the feedback stage (Belluci et al., 2017). In her short review, Hélène Tzioeropoulos (2013) mentioned that as the repayment of trustee increased the head of caudate nucleus was proportionally more active. Moreover, consistent positive feedback yielded activation in ventral striatum and orbitofrontal cortex, both implicated in reward processing. She argued that these regions have a role in reputation formation (building an expectation based on experience), a learning and adaptation process, knowing that the outcome will activate reward circuitry and feedback evaluation mechanisms. When breaking a promise (negative feedbacks) anterior cingulate and insular cortex, regions of the saliency network, were more active possibly in relation to conflict monitoring and processing of unfair outcomes. Moreover, in successive moves (implying learning) the ventral striatum seems to signal reward prediction errors about outcomes and representations of partner's trustworthiness. In first moves, anterior insula is more often activated during decision, which is in line with its role in initial uncertainty of the decision outcome processing. At these stages, the intentions of the others in social exchange are unpredictable so that trust is always risky (Glimcher et al., 2009; Krueger et al., 2008).

Moreover, several fMRI experiments that involved ToM reported changes in BOLD activity within three networks: 1) superior temporal sulcus, temporal pole, and temporal parietal junction, 2) limbic-paralimbic regions and 3) prefrontal cortex. Both mentalizing and empathy affect the valuation–decision system to learn and predict the choices of other players and to guide future behavior, engaging or not in a cooperative/trust behavior (Chen et al., 2019; Olson et al., 2008; Rilling et al., 2002; Singer & Tusche, 2014; Stallen et al., 2018; Vives & FeldmanHall, 2017).

Surprisingly, trust-based decision-making in health settings and chronic disease have been barely explored from the neuroscientific point of view. In lifelong diseases, such as diabetes mellitus, daily risk attitudes can lead to self-consequential long-term outcomes. These social exchanges in the health domain are comparable to economic exchanges in trust games. The level of patient's engagement following a clinical treatment or management decision differs from one individual to another. We

speculate that this is intrinsically related to a particular and own valuation system for health-related actions. This will affect the way decision-making is achieved in the context of interaction with human health care providers. T1DM patients are insulin-dependent, accomplishing metabolic control by monitoring insulin levels several times each day, calculating carbohydrate levels and having dietary restrictions. Otherwise, they risk hypoglycemia, ketoacidosis and other potential complications as retinopathy, nephropathy, neuropathy, and cardiovascular disease that can lead to extreme and irreversible consequences, including death (American Diabetes Associations [ADA], 2004).

Here we first investigated the neural basis of health-related decision-making in diabetes, a paradigmatic chronic disorder with strong personal impact. The rationale is that living with a chronic disease which control depends on systematic daily decisions produce changes in adaptive decision-making processes. The neural correlates of such behavioral patterns remain to be unraveled. The health domain involves an inherently more personal conflict.

We addressed these questions using fMRI in T1DM patients to understand the neural mechanisms of trust-based decision-making in the economic to the health-related domains. We focused on two phases of decision-making: investment (dependent on trust) and outcome monitoring (positive and negative feedback), comparing T1DM patients with controls. Positive and negative feedback relates to being reciprocated or not and it is calculated by two different delta reward values based on Expected and Feedback values: Positive Reward events (to get more than expected) and Negative Reward events (to get less than expected) (Figure 1). We hypothesize that T1DM when compared to controls show higher BOLD activity in ToM regions and cingulate-limbic regions involved in emotional processing and autobiographic memories in the health decision setting.

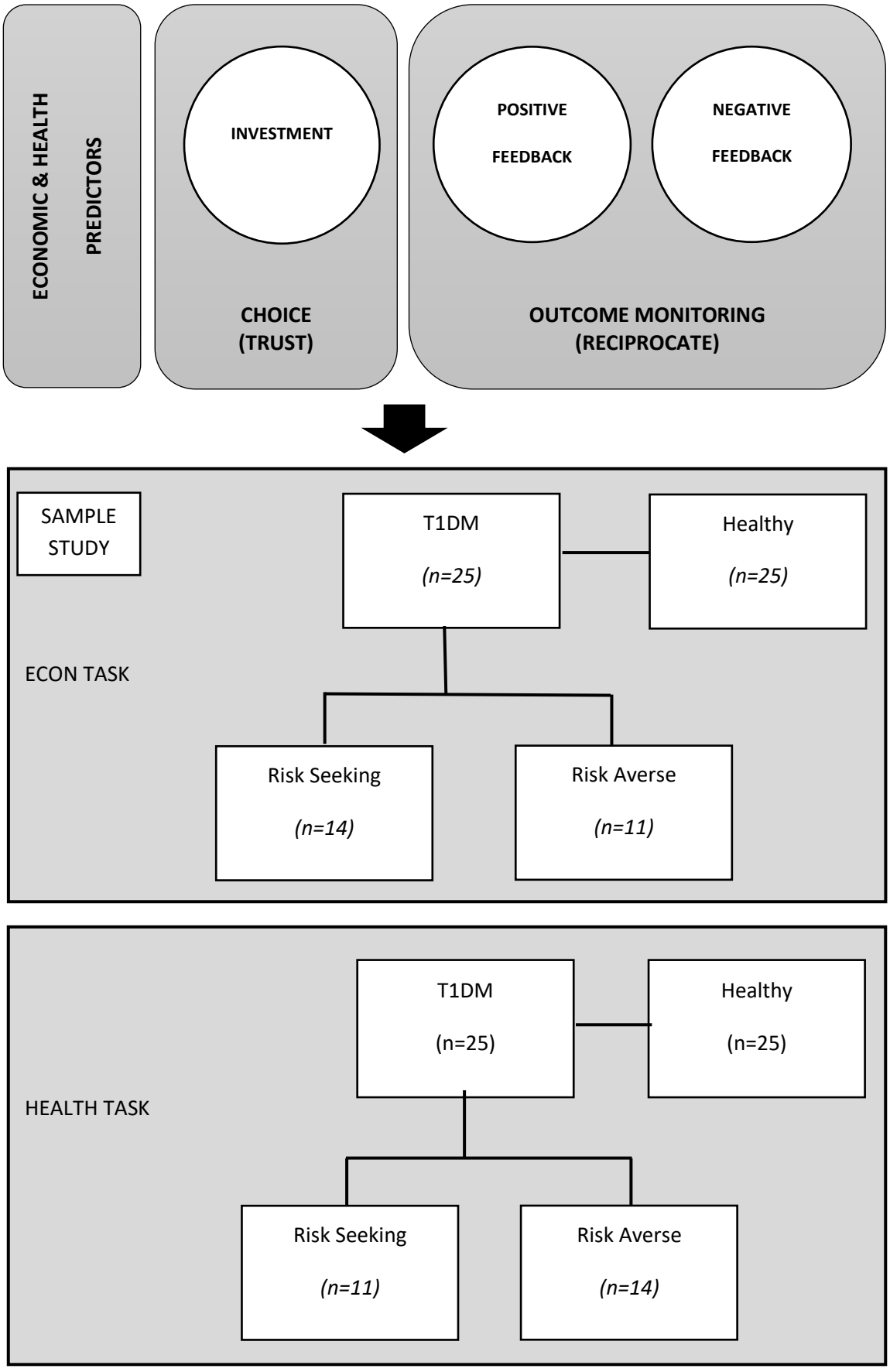


Figure 1. Flowchart of fMRI predictors and study sample

Finally, we investigated the neural mechanisms underlying risk averse and risk seeking profiles within T1DM participants and tested for correlations between metabolic control and the BOLD activity associated with the main three conditions: Investment, Positive Feedback and Negative Feedback. We hypothesize that risk averse patients (those choosing more often to cooperate with doctors) recruit differentially the brain network related to inhibitory control and goal-directed behavior, as a function of flexibility and larger self-control as compared to risk seeking patients with a less cooperative profile.

A goal with important clinical relevance was the aim to test the correlation between the BOLD activity during investment, positive feedback, and negative feedback with the individual capacity for metabolic control. This biological profile was defined by developing a linear function adjusted to the progression of the individual values of HbA1c over multiple time points.

2.Methods

2.1 Participants

We recruited 50 adults aged 22-55 years. Twenty-five of them were diagnosed with Type 1 Diabetes (mean age=38.72, SD=10.38; age range: 22-55 years, 11 males and 14 females) and the remaining 25 were matched healthy individuals (mean age=35.08; SD=8.77; age range: 24-55 years, 10 males and 15 females). Groups were matched according to gender, age, civil state, and household members. Comparing to controls, there were more patients with stable than instable household income, and patients had lower educational level. There were no differences in cognitive performance (Table 1).

Table 1

Demographic Characteristics, Cognitive results, and self-reported measures in DM1 and Healthy participants (N=50)

Variables	T1DM (N=25)	Healthy (N=25)	X^2	U	gl	p	d
Demographic data							
Gender (M/F)	11/14	10/15	0.08		1	0.770	0.08
Age (y)	38.72(10.38)	35.08(8.77)		240.0		0.159	0.40
Civil State (Single/Couple)	11/14	11/14	0.00		1	1.00	0.00
Household members (1/2/3)	7/14/4	9/15/1	2.08		1	0.353	0.40
Household income B (1/2)	18/7	10/15	5.19		1	0.023	0.60
Residence (1/2/3)	13/6/6	25/0/0	15.78		2	<0.001	0.99
Education level (1/2)	11/14	2/23	8.42		1	0.005	0.90
Cognitive data							
Vocabulary	32.28(3.10)	31.52(2.41)		256.0	-----	0.261	0.31
Digit Memory	14.56(2.12)	15.88(3.14)		374.5	-----	0.221	0.34
RPMT	8.16(0.98)	8.12(0.88)		303.5	-----	0.853	0.05
Self-report measures							
Neuroticism	8.16(4.19)	6.80(3.50)		269.5		0.403	0.23
Extroversion	11.68(3.87)	12.12(4.01)		334.0		0.675	0.11
Impulsivity	54.92(8.55)	58.40(6.33)		400.5		0.087	0.49
Inhibitory control	40.68(7.18)	43.08(5.58)		382.0		0.176	0.38
Lack of planning	14.81(4.15)	15.32(2.76)		335.5		0.654	0.01
Health risk perception	38.56(9.58)	34.68(6.51)		250.0		0.224	0.34
Past Risk	13.72(3.82)	15.24(4.20)		373.5		0.235	0.34
Present Risk	12.76(2.84)	13.44(4.00)		329.0		0.747	0.09
Delay discounting - context variation	2/23	10/15		7.018		0.008	0.80
Emotional Eating Behavior	1.95(0.83)	2.17(1.10)		329.5		0.741	0.09
External Eating Behavior	2.32(0.53)	2.78(0.65)		440.0		0.013	0.75
Restrained Eating Behavior	1.94(0.74)	2.44(0.91)		420.5		0.036	0.62

Household members (1= living alone 2=living as a couple 3=living with children); Household income (1=stable; 2=unstable); Residence as distance to health services in spending time (1=Coimbra; 2= <1h; 3= >1h); Educational level (1= below 12 years; 2= above 12 years); RPMT Raven's Progressive Matrices Tests; BMI body mass index.

Two patients did not complete all the required tasks in fMRI scan, which were nevertheless also performed out of the scanner. Participants used the response box in the right hand given their handedness. All the subjects had normal or corrected to normal vision. Written consent was obtained from all participants, according to the Ethics Committee of the Faculty of Medicine of the University of Coimbra, guided by Declaration of Helsinki.

Sub-group analysis within DM1 participants: risk averse and risk seeking profiles

T1DM were also divided according their risk attitude, forming two groups: risk averse and risk seeking (RS) for each context. The cut-off point was defined according to the frequency of risky decisions for all participants in all trials. For economic context, risky decision was defined as the ”50 euros” selection). For the health context, risky decision was defined as “1 prick” (in the economic task participants invest money and in the health task, number of “pricks”, for details see Figure 2 and description below). In the economic domain, risk averse was defined (in terms of amount invested) as FREQ (50 euros) ≤4 ;(N= 11, mean age=35.45, SD=9.02: age range:22-46, 5 males and 6 females) and RS as FREQ (50 euros)>4 (N=14; mean age=41.29, SD=10.85, age range:22-55, 6 males and 8 females). Between risk averse and risk seeking groups within patients, there were no differences in sociodemographic, cognitive, and clinical features. They differed in disease onset time which is lower for the risk averse group ($U=118.0$ $p<0.05$). In the health domain, risk averse was defined as the frequency of deciding to cooperate more than 1 prick (4 or 6)>1: [N= 14, mean age=35.07, SD=10.78: age range:22-53, 7 males and 7 females] and RS as the opposite - ≤1: [N=11; mean age=43.36, SD=8.07, age range:27-55, 4 males and 7 females].

2.2 Risk measures

Risk taking profile was measured by a comprehensive battery of questions with Portuguese norms. Personality traits were evaluated by EPQ (Eysenck Personality Questionnaire). Impulsivity was measured using Behavior Impulsivity Scale-11 (BIS-11) as risk-related constructs. Additionally, we designed a brief questionnaire where participants were confronted with three types of risk attitude measures (Risk context-dependent, Temporal risk and Delay discounting) to achieve individual self-reported real world risk profile. Furthermore, eating behavior was also assessed considering its intrinsic relation to T1DM and self-control- The Portuguese validation of Dutch Eating Behavior

Questionnaire (DEBQ) (Van Strien et al., 1986; Viana & Sinde, 2003) evaluating three types of eating styles: restrained (avoid eating more than was initially defined), external (to eat motivated by external factors such as good food smell and how it looks) and emotional (to eat in response to emotions).

2.3 Trust Games

Before the scanning session, the participants were familiarized with the tasks and with the response box. Participants performed two modified versions of the Trust Game (Berg et al., 1995). We did not triplicate the amount of money as originally set (unrealistic for the health game) and the games involved iterative decision-making. Reward outcomes differed according to the context: money in economic setting and amount of waiting time for consultation as a health-related reward (Figure 6 A and B, supplementary material). The scanning sessions consisted of an anatomical run and two functional runs that were counterbalanced to prevent order effects. Both tasks involved iterated interactions with four mediators (trustees) to guide the participant for the best option. Participants received specific instructions as detailed in supplementary material.

2.3.1 Analysis of behavioral data

Statistical analyses were conducted in SPSS 24.0. The Non-parametric Wilcoxon signed-rank test was used to compare expected value, investment, outcome value and response time between groups (T1DM versus controls) for each context (economic and health). Because Expected, Investment and Feedback values have different metrics for both contexts, we transformed data into z-scores. Significance level was considered at $p<0.05$. The same procedure was repeated to compare other two groups based on risk task performance, forming risk averse and risk seeking groups for each context (economic and health).

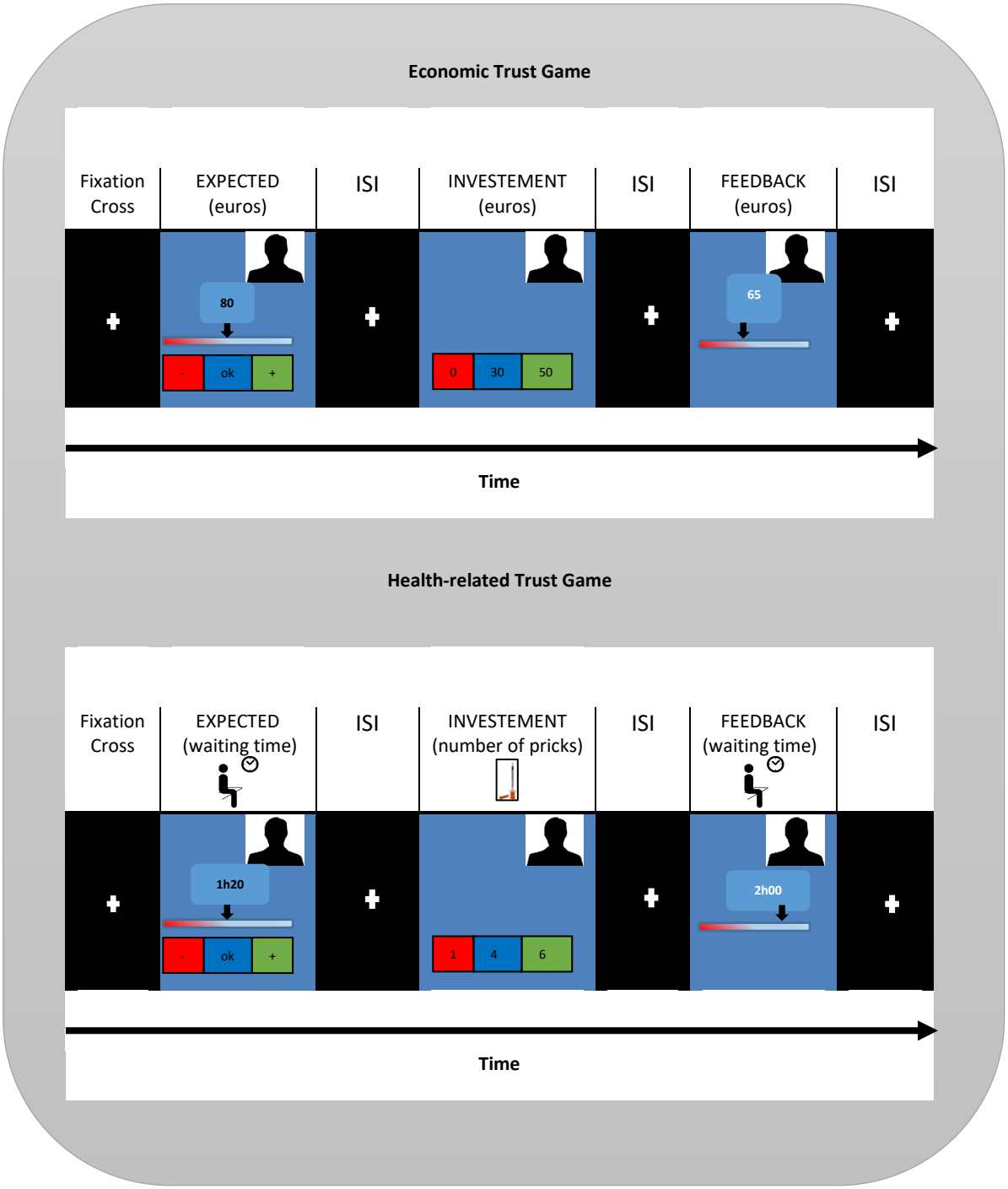


Figure 2. fMRI sequence for economic and health-related trust games. In economic trust game, participants invest money (0, 30, 50 euros) whereas in health trust game, number of pricks (1, 4 or 6). 30 euros means optimal choice and 6 pricks high collaboration. Positive and Negative Feedback predictors were obtained by calculation of the difference between Expected and Feedback values for each iteration.

2.3.2 fMRI data acquisition

Structural and functional MRI scans were acquired in a 3T Magnetom Trio Tim MRI scanner (Siemens, Erlangen, Germany) using a 12-channel head coil). The scanning session included a high resolution T1-weighted MPRAGE sequence that was measured with TR (repetition time) = 2530 msec, TE (echo time)= 3.42 msec, TI = 1100 msec, flip angle of 7, single shot slices with voxel size 1 x 1 x 1 mm, FOV (Field of View) of 256 mm and a slice thickness of 1 mm. Functional images were acquired using blood oxygen-level dependent (BOLD) contrast echo planar imaging (EPI), with TR = 2000ms, TE = 30ms, voxel size 3 x 3 x 3 mm, and 35 slices covering the entire brain. The task was presented in an LCD monitor (NordicNeuroLab, Bergen, Norway) mounted ~156 cm away from the participants' head. The monitor could be seen through a mirror mounted above the coil. The monitor has a frequency rate of 60 Hz and dimensions of 698.40 x 392.85 mm. The subject could select the response using an MR-compatible response box (Hybridmojo, San Mateo CA, USA) according to three options.

2.3.4 fMRI Data Analysis

Functional images were preprocessed using Brain Voyager software and consisted of slice scan time correction, high temporal filtering, 3D motion correction via realignment, and co-registration to the structural image. Images were transformed into Talairach space for normalization and were then spatially smoothed using a Gaussian kernel of 8 mm of full width at half maximum.

We defined three predictors: Investment, Positive Feedback and Negative Feedback. Investment was defined as the moment participants had to choose one of the three risk options (0, 30, 50 euros or 6, 4, 1 prick, depending on experimental contextual task). Positive and Negative Feedback predictors were obtained by calculation of the difference between expected and feedback values for each iteration. Groups analysis were performed to compare T1DM versus Controls or to compare Risk

Averse versus Risk Seeking subgroups. To correct for multiple comparisons a statistical threshold of $p<0.05$ was fixed and a minimum cluster size threshold was estimated using Monte Carlo simulations (1000 iterations). The number of contiguous voxels considered as the minimum cluster extension for each map is presented in the results section. Finally, a linear function was adjusted to the progression individual values of HbA1c over time. The regressor calculated to each patient was used to define successful metabolic control (negative slope, i.e. decreasing HbA1c values over the time) and impaired metabolic control (positive slope, i.e. increasing HbA1c values over the time).

3.Results

3.1 Behavioral Risk Measures

3.1.1. T1DM and healthy Groups

Self-reported measures - Mann-Whitney tests revealed that T1DM and controls did not differ in self-reported measures of risk-taking, except for choice of delay discounting. Importantly, whereas controls tend to opt for delay rewards in all contexts (stable choice), the T1DM participants showed delay rewards only in the diabetic health domain. Regarding eating behavior, people with T1DM reported lower scores in external and restrained eating behavior (neither eating longer based on food attractiveness nor avoiding eating less than expected) as compared to the healthy groups.

Trust Games - Behavioral results acquired during the fMRI experiment were analyzed and non-parametric independent sample tests revealed significant differences between groups for clinical expected value, because T1DM expected more general waiting timing than they received comparing to healthy population.

3.1.2 Risk averse and Risk Seeking Groups within T1DM

Self-reported measures - Mann-Whitney tests revealed non statistical significance ($p>0.05$) between risk averse profile and risk seeking within T1DM patients in neuroeconomic and health contexts.

Trust Games - Non-parametric independent sample tests revealed significant differences between groups for investment in both contexts, as expected. Additionally, in the health setting, risk seeking patients (less collaborative) receive more waiting time than risk averse patients (feedback in the health trust game).

Table 2

Behavioral results on economic and health trust games. Between groups analysis for T1DM and healthy groups (N=50) considering Investment, Expected Value and Feedback (A). Risk Averse and Risk Seeking between groups analysis within patients with T1DM (N=25) considering Investment, Expected Value and Feedback (B).

A.

	Economic Trust Game											
	T1DM (N=25)					**Controls (N=25)**						
Variables	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3rdQ	**U**	**p**
Investment	27.52	8.85	17.14	28.57	32.85	26.35	8.49	25.00	30.72	32.14	286.5	0.614
Expected	72.86	10.68	66.34	73.57	81.25	72.08	9.2	69.05	74.71	77.45	322.0	0.854
Feedback	85.81	14.36	74.11	89.64	96.25	88.80	15.82	84.11	94.46	97.50	244.0	0.184
	Health Trust Game											
Variables	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3rdQ	**U**	p
Investment	4.62	1.11	3.93	4.78	5.57	4.85	1.11	4.55	5.22	5.57	258.5	0.294
Expected	113.79	22.44	98.39	112.50	136.07	100.11	24.33	89.46	98.93	117.50	415.5	0.046
Feedback	128.29	20.22	113.57	128.93	141.43	119.35	16.81	107.14	113.93	130.36	395.0	0.107

B.

	Economic Trust Game											
	Risk Averse N=11					**Risk Seeking N=14**						
Variables	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3rdQ	**U**	p
Investment	22.46	8.09	15.00	23.58	30.00	31.36	7.31	25.00	32.86	36.43	127.5	0.004
Expected	73.45	11.05	65.94	74.02	81.79	72.15	10.66	65.18	73.22	80.00	69	0.687
Feedback	83.71	15.96	70.72	83.13	95.54	88.48	12.22	81.78	92.86	96.25	91.0	0.467
	Health Trust Game											
	Risk Averse N=10					**Risk Seeking N=15**						
Variables	M	SD	1stQ	2ndQ	3rdQ	M	SD	1stQ	2ndQ	3rdQ	**U**	p
Investment	5.56	0.41	5.15	5.71	5.95	3.98	0.98	3.86	3.96	4.72	200.0	<0.001
Expected	113.57	21.90	101.78	112.32	134.29	113.94	23.55	93.22	112.50	136.79	75.0	1.000
Feedback	116.07	23.23	99.64	110.71	124.38	136.45	13.28	128.93	133.93	144.29	130.0	<0.001

3.2 Neuroimaging Results

3.2.1 T1DM and Controls

Investment in economic trust game

We carried out a whole-brain group comparison between T1DM and controls while they performed the investment condition (Figure 3,A). Controls revealed higher activity in parietal-temporal-occipital association area, involved in visual processing and attentional control (BA39, BA40, BA19, BA37) as well as limbic and frontal areas, left insula (BA13), the right (BA31; BA30) and left (BA23) posterior cingulate cortex. Patients showed larger activation most importantly in the left Middle Frontal Gyrus (BA9, BA10).

Investment in health-related trust game

Similar analysis was carried out comparing T1DM and healthy participants during health related investments (measured by the number of accepted insulin pricks). Note that pricks may be associated to anticipated pain or at least an aversive stimulus. Patients differ from controls in limbic subgenual ACC (BA25), as well as other limbic regions (amygdala, hippocampus and parahippocampus) and prefrontal regions [medial PFC, dorsolateral PFC (BA10, BA46) and regions involved in inhibitory control such as the inferior frontal gyrus (BA45, BA47)] (Figure 3,B). Conversely, controls recruited cingulate (ACC, BA24; and PCC, BA31), parietal regions (BA39/BA40) and PFC (BA10, BA46, BA46, A47) more than T1DM participants. Concerning subcortical structures, controls showed higher activity in the caudate while patients showed higher activity in the putamen (as well as midbrain regions), suggesting that the controls are more goal oriented as compared to patients.

Positive and Negative Feedback

For Positive Reward predictor, no differences were found when comparing T1DM with the control group, in both contexts. In contrast, for the Negative Reward predictor, in the health setting (receiving more waiting time than expected) T1DM versus control group contrast showed increased activation in bilateral hippocampus and right parahippocampus.

3.2.2 Risk Averse and Risk seeking Groups within T1DM

Investment in economic trust game

Comparing risk averse versus risk seeking patients during the economic investment, we found higher activity from the risk seeking individuals in subcortical structures as thalamus, the ventral tegmental area (VTA), substantia nigra, hippocampus, parahippocampus and amygdala suggesting an important role for reward and limbic structures in emotional and memory processing (Figure 4, A).

Investment in the health trust game task

Also comparing risk averse versus risk seeking patients, but now during health -related investment, we found out increased brain activations from risk seeking patients, whose options for no collaboration were more frequent, showing increased activity in parietal (BA40, BA39) temporal regions (BA21), putamen and insula cortex. (Figure 4, B).

No significant differences were found between risk averse and risk seeking participants during positive and negative rewards.

3.2.3 Correlation with metabolic control profiles

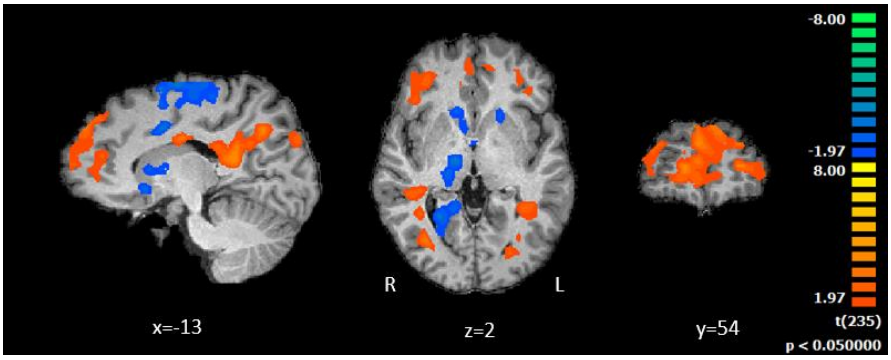
Investment in both contexts

Whole brain correlations maps were calculated between the BOLD activity during choice condition and the metabolic control profile as given by the dynamics of HbA1c value (see methods) (higher values of HbA1 meaning poor metabolic control). In the economic task, correlation between neural activity and variation of HbA1c revealed a positive correlation in the middle frontal gyrus (BA9, BA10), the inferior frontal gyrus (related to impulsivity) and the insula (Figure 5, A). Which means that poorer the metabolic control, higher the BOLD activity in these areas, related to executive function and decision. In the health task, there was a positive correlation between BOLD activation in the Anterior Cingulate Cortex (BA24 and BA32)- related to saliency and conflict monitoring- and the variation of HbA1c (poorer metabolic control) (Figure 5, B).

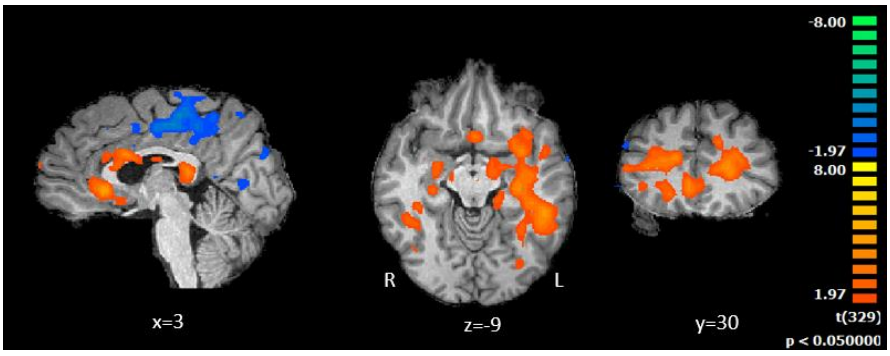
Positive and Negative Feedback

In the economic setting, lateral motor area responded to negative rewards (receiving less money than expected) as a function of impaired metabolic control (correlation between neural activity and variation of HbA1c). In opposite, better metabolic control had an association with left insula, posterior (BA21), inferior frontal gyrus (BA44), superior parietal lobe (BA7) and posterior cingulate cortex (BA23) activation.

In the health context, for positive reward (receiving less waiting time) and no successful metabolic control patients, AAC (bilateral BA32) showed a positive correlation as well as prefrontal regions – MFG and SMA , superior motor area(BA9 and BA8). (Figure 5 C). The group with successful control only had correlated activations in visual pathway regions. (Figure 5, D).

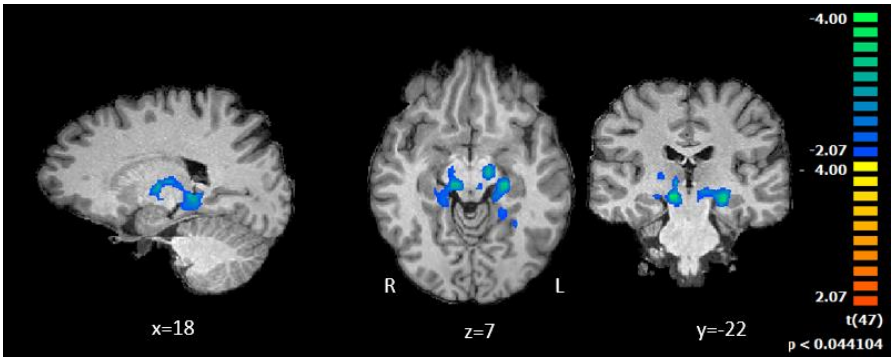


(A) Statistical maps for the comparison between T1DM and Controls during economic investment condition. Brain activity for Economic Investment in between group analysis (T1DM>Controls) included the right (BA31; BA30) and left (BA23) posterior cingulate cortex and middle frontal gyrus (BA9, BA10). Controls activated in a parietal-temporal-occipital association area, middle and superior (BA39, BA40, BA19, BA37), and a set of regions related to cortico-basal ganglia-thalamus pathway (as ACC, bilateral anterior caudate, putamen, globus pallidus and right thalamus) and left insula. (minimum cluster size 107).

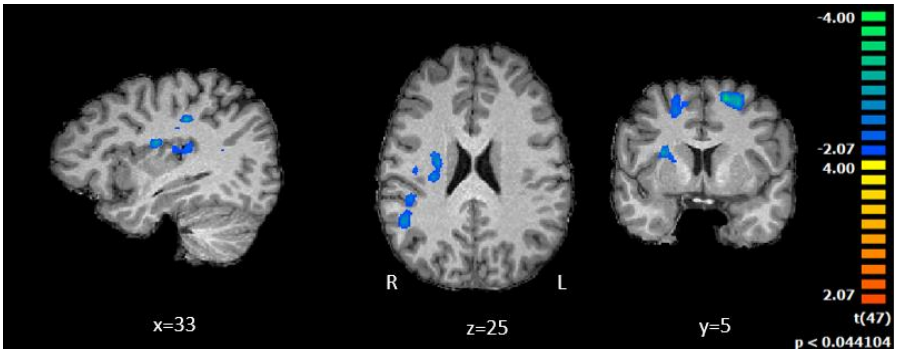


(B) Statistical maps for the comparison between T1DM and Controls during health investment condition. For T1DM patients subgenual (BA25) activation, as well as other limbic regions (amygdala, hippocampus and parahippocampus) and prefrontal regions [medial (BA10, BA46) and inferior (BA45, BA47)]. Controls recruited cingulate (ACC, BA24; and PCC, BA31), parietal (BA39/BA40) and PFC. Concerning subcortical structures, controls dominantly the caudate while patients activated more the the putamen and mid brain regions. (minimum cluster size 108).

Figure 3. A fMRI whole brain comparison between T1DM and Control Group during economic and health investment conditions.

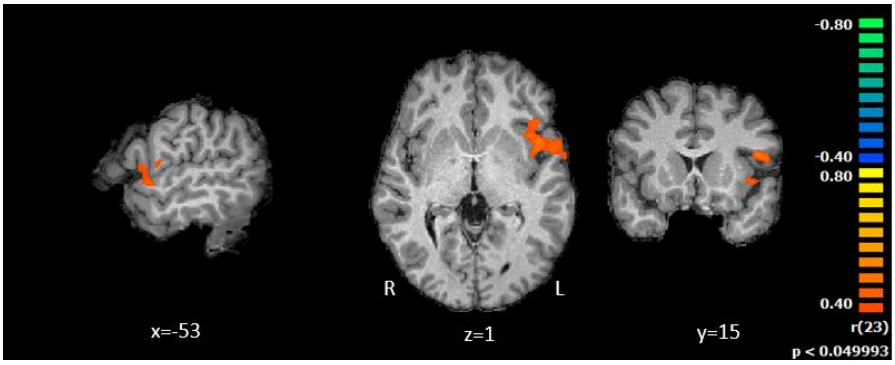


(A) Statistical maps for the comparison between Risk Averse and Risk Seeking T1DM patients during the Economic Investment condition. Brain activation in thalamus, substancia negra, ventral tegmental area, hippocampus, parahippocampus and amygdala for risk seeking group (invest more money) (minimum cluster size 38).

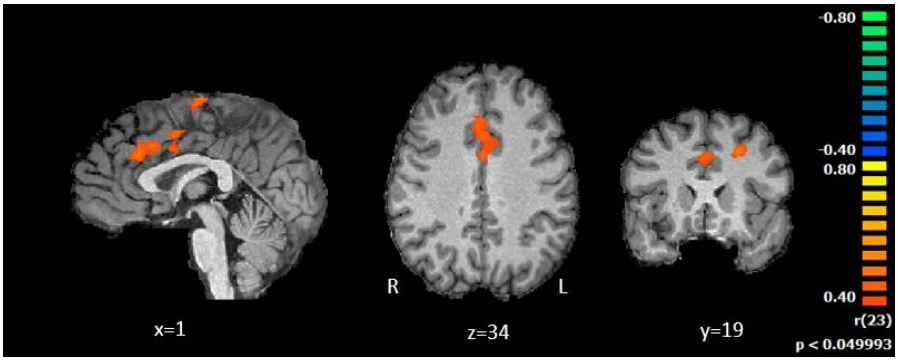


(B) Statistical maps for the comparison between Risk Averse and Risk Seeking T1DM patients during the Health Investment condition. Brain activation within patients with health collaboration, to risk seeking patients, whose options for no collaboration with doctors were more frequent, showed more activations in parietal (BA39, BA40 and BA6), temporal regions (BA21) and subcortical, right putamen and insular cortex. (minimum cluster size 33).

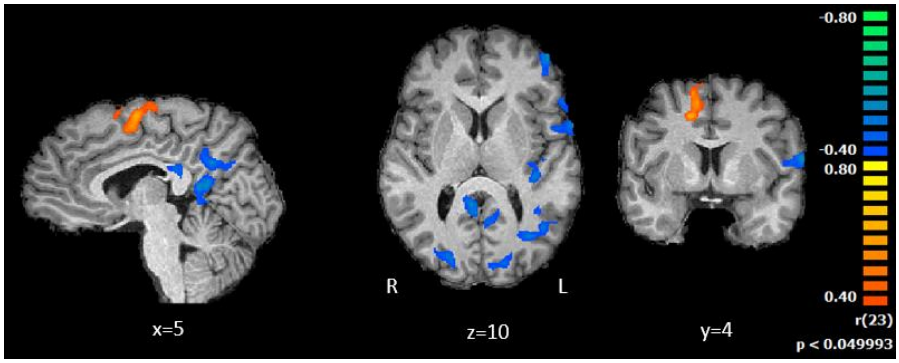
Figure 4. A fMRI Whole Brain activation within patients for risk averse and risk seeking profiles contrasts for economic (A) and health investement (B).



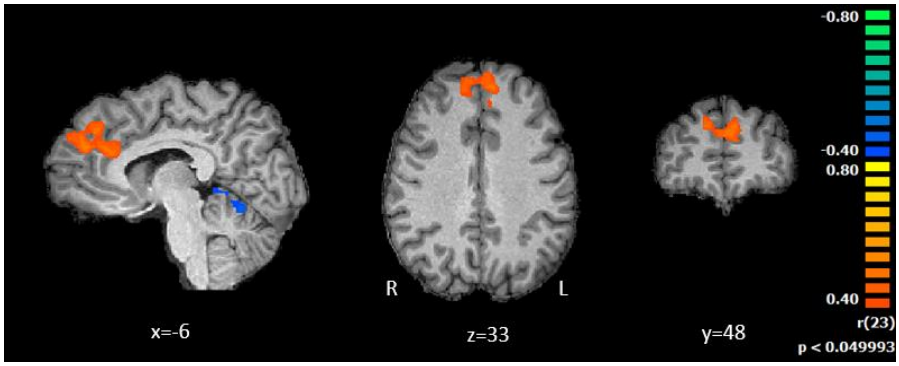
(A) Whole brain correlation analysis between BOLD activity during Economic Investment condition and HbA1c (higher HbA1c values traducing a poorer metabolic control). A positive value (red) for the correlation, means that poorer the metabolic control (higher the HbA1c), higher the BOLD activity during the Economic Investment condition. Brain activity for impaired metabolic control with MFC, Inferior frontal Gyrus and left insular activation (insulo-opercular complex). (minimum cluster size 76).



(B) Whole brain correlation analysis between BOLD activity during Health Investment condition and HbA1c (higher HbA1c values traducing a poorer metabolic control). A positive value (red) for the correlation, means that poorer the metabolic control (higher the HbA1c), higher the BOLD activity during the Health Investment condition. Brain activity for impaired metabolic control with dorsal ACC activation. (minimum cluster size 100).



(C) Whole brain correlation analysis between BOLD activity during Negative Reward condition (Receive less money than expected) and HbA1c (higher HbA1c values traducing a poorer metabolic control). A positive value (red) for the correlation, means that poorer the metabolic control (higher the HbA1c), higher the BOLD activity during the Health Investment condition. Correlation patterns with impaired metabolic control within lateral premotor area (red). Successful metabolic control (blue) leads to correlated activations in posterior cingulate, inferior frontal gyrus, middle temporal gyrus and posterior insula. (minimum cluster size 76).



(D) Whole brain correlation analysis between BOLD activity during Positive Reward in health trust game (receiving less waiting time than expected) condition and HbA1c (higher HbA1c values traducing a poorer metabolic control). A positive value (red) for the correlation, means that poorer the metabolic control (higher the HbA1c), higher the BOLD activity during the Health Investment condition. Brain activity correlated with impaired metabolic control in bilateral ACC and middle frontal gyrus (BA9) activation (positive correlations-red). Successful metabolic control (negative correlations-blue) is related to ventral activation. (minimum cluster size 99).

Figure 5. A fMRI Whole brain correlation analysis between HbA1c values and the BOLD activity during the economic investment (A), health investment (B), negative reward in economic trust game (C) and positive reward in health trust game (D) performed by the T1DM patients.

4. Discussion

To the best of our knowledge, this is the first fMRI study that examined the neural correlates for trust-based decision-making in the economic and health context, within a lifelong disabling disorder, diabetes mellitus. Our hypothesis was based on the current knowledge on decision-making under uncertainty which assumes that context has a determinant impact on individual choice. Our findings can be summarized as follows: 1) overall, T1DM differ from controls particularly in investment, and less so in Positive and negative feedback, although responses to the latter were tightly linked to metabolic control. Our results suggest that both groups learn during iterative interactions, but in general they underwent different investment strategies. 2) Our findings also indicated that there were a significant association between neural activity and impaired metabolic control, highlighting the role of HbA1c in risk processing. 3) we also gathered evidence for activation of the main brain networks related to reward and emotion, in both experiments, showing ecological validity. 4) Concerning contexts, our findings suggest that the health context is deeply self-consequential with high emotional impact in patients with poor metabolic control.

4.1 T1DM and Controls

Economic Investment

Our results suggest that groups differ in neural activity for investement in economic trust based game. Controls evoked brain activity typically involved in money tasks, namely the basal ganglia, the insula and PCC. In turn, brain activation in patients are allocated to speficic frontal-posterior cingulate regions, namely mPFC and posterior cinculate cortex.

Health Investment

For the health trust based game, we found out a remarkable pattern of differential limbic activation in patients: larger emotional network and memory processing for patients than for controls. Activations in Hippocampus and left Parahippocampus is possibly related to autobiographic memories that are

relevant in iterated patient-doctor relationships. Subgenual (BA25), a part of the limbic system has been related to emotional-motivational executive functions (Nawa et al., 2020).

In controls, in the health related task, caudate activation can been related to more efficient goal-directed behavior, more sensitive to encoding the association action-outcome and outcome evaluation, optimizing flexible and adaptive behavior. In contrast, in patients, putamen activation seems to be related to repetitive habitual actions, thereby rendering them less sensitive to error-correction learning rules. Patients might be less sensitive to positive feedback (less waiting time) given their previous experiences in hospital, which fill-in their autobiographic memories. In this case, patients maybe processing aversive stimuli (pricks and waiting time) in a way that activates putamen activations and habitual actions triggered by increased anxious states (Banca et al., 2015). Bilateral activations in hippocampus and parahippocampus for negative feedback (waiting more time than expected for consultation) suggested an enhanced role for memory mechanisms for patients as corroborated by behavioral results in terms of expected value (Nawa et al., 2020).

4.2 Risk Averse and Risk Seeking Groups within T1DM

Patients that were Risk seeking participants in economic trust game reveal activation in brain areas related to the limbic system and dopaminergic midbrain regions related to arousal of motivation and reward (Ilango et al., 2014), such the ventral tegmental area. For health context, participants with absent collaboration profile (Risk Seeking) revealed activations in parietal (BA40, BA39) and temporal (BA21) regions, putamen, and insula related to emotional and social attribution. This might be attributed to the fact that they were receiving negative rewards and might therefore try to pay attention to infer the intentions of others. No contrast activation was found in patients that collaborate (risk averse) probably because they are indifferent to payoff contingencies once they care about their health independently of other intentions.

4.3 Correlation between neural activity and variations of HbA1c

The effect of biological worsening in investment was related differently in economic and health context: neural activity in regions related to inhibitory control for economic context and for error monitoring/conflict (saliency network) in the health context.

In relation to positive and negative feedback, it seems that in health setting, impaired metabolic control patients generate responses mainly in regions of saliency network (in particular ACC as well as MFG. These regions showed larger activation for waiting less time to be consulted (health context). These regions are also related to emotional processing (Etkin et al., 2011; Krueger et al., 2009; Lockwood & Wittman, 2018). In the economic setting, successful metabolic control patients activated brain regions related to signaling the aversive outcomes (Clarck et al., 2008) such as left Posterior insula and Inferior Frontal gyrus activation (related to impulsive control) (when receiving less money) (Tops & Broksem, 2013). The same activations were found in studies about the degree of resentment of an "unfair offer", providing future information about the future action (Krueger et al. 2020).

In sum, for investment, positive or negative feedback, biological worsening in health context was related to impulse control and emotional processing brain areas. Comparing patients to controls, emotional processing seems to be more present in health setting for patients.

The main focus of this study was to understand the neural basis of trust-based decision-making in the health domain. Some limitations have to be acknowleged. We focused our analysis in investment as a general predictor in different contexts. However, brain activity in response to different degrees of payoffs could vary in a non linear manner. The pool of participants available to identify this effect was relatively limited. Further studies should investigate the role of different types of mediator: the effect of different payoffs contingencies to build trust or in contrast mistrust, as a consequence of norm

violation. It will be also interesting to investigate neurobehavioral relationships in initial and late rounds to understand better the learning process in both contexts.

Conclusion

In conclusion our findings suggested that HbA1c is a biochemical index that predicts modified risk processing and neural activation patterns in Type 1 Diabetes. This pattern differs according to context and according to biological worsening. Health contexts were emotionally more relevant and required hard self-consequent decision for patients and impaired metabolic control seems to be related to greater saliency network and limbic responses in the health setting. This study represents a novel approach to neuroeconomics and social neurosciences, translating to the health context the neural correlates of human trust-based decision-making, based on biological and neuropsychological feature within and between clinical and health populations.

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Supplementary material

Table 3. Differences in brain activation. Differences in activation T1DM and Controls between group analysis for economic (A)and health investment(B). Correlation between neural activation and variations of metabolic control within T1DM patients (C) Between group analysis for Risk averse and risk seeking groups within patients in economic and health investment (D)

Anatomical Region	BA	H	Talairach (peak voxels)			T-max	P<
A. T1DM and control contrasts for economic investment							
Economic investment T1DM>Controls							
Posterior cingulate gyrus	30,31	L	-15	43	16	4.98	0.000001
	23	L					
Middle frontal gyrus	9,10	L	27	11	31	4.99	0.000001
Economic Investment Controls>T1DM							
Anterior cingulate gyrus,	24	R	27	-10	55	-5.82	0.00000
Posterior cingulate gyrus,	31	R					
Inferior parietal lobe	39	R					
	40	R					
Caudate, putamen, globus pallidus,thalamus	48,49,51,50	R	6	-13	-8	-4.43	0.000014
Fusiform, visual associatiom and	37,19	R	21	-64	7	-4.36	0.000019
posterior cingulate gyrus	23						
Caudate, putamen, insula	48,49,13	L	-18	14	10	-4.37	0.000018
Lateral premotor area, and	6, 8	R	9	11	43	3.51	0.001
anterior cingulate gyrus	24	R					
posterior cingulate gyrus	23	R					
Middle frontal gyrus	9,10	R	1	50	37	3.02	0.004

Anatomical Region	BA	H	Talairach (peak voxels)			T-max	P<
B. T1DM and Controls contrasts for health investment							
Health Investment T1DM>Controls							
Superior Sensoriomotor Cortex	7	L	-24	-52	31	7.45	0.000000
PMA	6	L	-6	14	64	3.63	0.00031
Middle frontal Gyrus	10	B	-42	54	13	4.23	0.00030
aMFG	46	R					
Inferior Frontal Gyris-pars Triangularis	45	B					
Inferior Frontal Gyrus –Pars orbitalis	47						
Parahippocampus	36	L	-3	-37	1	3.36	0.00086
Hippocampus	54	B					
Amygdala	53	B					
Insula	13	R					
Putamen	49	B					
Thalamus	50	B					
Superior Temporal Gyrus	22	R					
Middle Temporal Gyrus	21	R					
Temporal Lobe	38	L					
Sugenual Gyrus	25	L					
Anterior cingulate cortex	32	L					
Posterior cingulate cortex	23	L					
Health Investment Controls>T1DM							
Middle Temporal Gyrus	21	R	61	-19	-11	-3.03	0.002
Superior Sensoriomotor Cortex	7	L	-24	-52	31	7.45	<0.001
IPLobe_Supramarginal Gyrus	40	R	57	-19	13	-4.59	<0.001
IPLobe_Angular Gyrus	39	R	63	-43	23	-4.75	<0.001
Superior Temporal Gyrus	22	R	60	-4	4	-3.82	0.0001
PMA	6	R	57	-7	43	-4.27	0.001
IPLobe_Angular Gyrus	39	R	45	-67	28	-4.75	<0.001
Middle Frontal Gyrus	10	R	39	59	7	-4.43	0.000013
Insula	13	R	30	-25	13	-3.88	0.0009
Visual	19	R	12	-76	34	-3.95	0.000096
PMA	6	R	9	-7	67	-4.26	0.000026
Fusiform	37	R	24	-52	-8	-3.56	<0.0001
PFC-PMA	8	R	3	38	46	-3.22	0.001
Anterior Cingulate Cortex	32,24	L	-9	14	37	-5.13	<0.001
Posterior Cingulate Cortex	23,31						
Caudate ,Thalamus	48	L	-9	-4	13	-3.63	0.0004
Superior Sensoriomotor Cortex	7	L	-18	-67	49	-3.24	0.001
PFC-PMA	8	L	-27	32	43	-2.62	0.0009
IPLobe_Angular Gyrus	39	L	-33	-70	47	-2.92	0.003
PMA	6	L	-39	-7	46	-3.73	0.000231
Fusiform	37	L	-63	-53	1	-3.47	0.0005
IPLobe_Angular Gyrus	39	L	-60	-40	38	-3.34	0.00093
IPLobe_Supramarginal Gyrus	40						
Thalamus, Putamen,Globus Pallidus, Insula	50,49,51,13	L	4	65	7	4.32	0.0003

Anatomical Region	BA	H	Talairach (peak voxels)			T-max	P<
C. Correlation with variation of HbA1c within patients							
Economic Investment Impaired metabolic control (red)							
Middle Frontal Gyrus, Inferior Frontal Gyrus	10,9,44	L	-42	20	22	0.63	0.000605
Insula	13	L					
Health Investment Impaired metabolic control (red)							
Anterior Cingulate Cortex	32,24	L	-21	17	40	0.60	0.0013
Positive Reward Impaired metabolic control Health Context							
Anterior Cingulate Cortex	32	L	-12	14	37	0.55	0.003
SMA	8	L					
Middle frontal gyrus	9	L					
Anterior Cingulate Cortex	32	R	12	32	16	0.57	0.002
Negative Reward Correlation with variation of HbA1c Impaired metabolic control Economic Context							
Lateral premotor area	6	R	6	-4	58	0.73	0.000031
Negative Reward Correlation with variation of HbA1c Sucessful metabolic control Economic Context							
Posterior cingulate Cortex	23	R	6	-46	10	-0.58	0.002
Superior Parietal Lobe	7	R	21	-61	34	-0.72	0.000048
Inferior Frontal Gyrus	44	L	-61	8	13	-0.59	0.00017
Middle Temporal Gyrus	21	L	-67	-16	-2	-0.67	0.0000
Posterior insula	13	L	-31	20	7	-0.41	0.036

Anatomical Region	BA	H	Talairach (peak voxels)			T-max	P<
D. Risk averse and risk seeking profiles within patients							
Economic investment Risk seeking>risk averse							
Thalamus,	50	R	12	-22	5	-3.28	0.00058
Hipocampus,	54	R	20	-31	-2	-2.892	0.008
parahippocampus,	36	L	-19	-29	-5	-2.75	0.006
amygdala	53	L	-14	-4	-11	-2.4	0.02
Health Investment Risk seeking>Risk averse							
Inferior parietal lobe	39	R	40	-54	17	-2.47	0.021
IPL_supramarginal Gyrus	40	R	33	-28	37	-2.96	0.006
Lateral premotor area	6	L	-19	12	59	-2.59	0.006
Middle temporal lobe	21	R	48	-38	7	-2.37	0.02
Insula	13	R	35	-26	12	-2.28	0.03
Putamen	49	R	23	-2	12	-1.26	0.02

Experimental instructions and design details

- Instructions for economic and health trust games

You will play a game with 4 mediators for 7 rounds. In each round they will appear at random way. You will recognize them through the face image or the image of a computer (once one of them is a computer) as you can see in this example [in the instruction, we showed only a silhouette of a human face to the participant]. What will happen then? On every move with a trustee, you have to answer to two questions. First question: How much money do you expect to receive? It can range from 40 to 240 euros, pressing the buttons to the left or to the right to find your final option (pressing ok, the middle button). Second question: How much do you want to invest? Here, you will be confronted with three options: O, 30 or 50 Euros. The order of the buttons corresponds to the order of the option presentation (blue, red and green). After your selection, you will be presented with the trustee return, that can be more or can be less than what you initially expected. So, the next time you play with this specific player you can decide if you want to keep your investment or change it. It is very important to pay attention to each player's return. What remains to be said? Each player has a different way of return so throughout the game you will discover the best option of investment with each one. The main goal of the game is to earn money. I can say that 0 option gives you a small and fixed return and only the 50 option can lead to a jackpot return. Do you have any doubt?[…]

Ok, I will ask you to play another game that has exactly the same structure but instead of economists you will play with doctors from a fictitious endocrinology service which has the following rule: if you decide to collaborate for a successful treatment you spend less time waiting for consultation. On every move with one of three doctors

or a computer, you must answer to the first question: How much time do you expect to wait for consultation? After that, they will ask you to choose between 1, 4 or 6 pricks that means how much do you want to collaborate for a successful treatment: a little bit (1), a little (4) or a lot (6). In exchange, they will offer more waiting time for consultation or less time, according to two reasons: your commitment option and the doctor profile. The fact that there are rules does not mean that they are followed. The main goal of this game is to wait as little time as possible for the consultation. So, play attention to your options and the doctors return to decide if you would like to change or not your commitment next time you play with this trustee. Do you have any doubt? [to participants who belonged to the healthy group, we made a short introduction to diabetes disease so that they could understand the relation between pricks and successful treatment]

- Scanning session details

In the scanning sessions, for each interaction, participants were presented with a fixation cross for 8s. The first question (the expected return) is presented in the screen for 8 s (participant time response). A fixation cross was displayed again for 8 s (inter-stimulus interval, ISI). After this period, participants were confronted with the second question (investment or collaboration) for a maximum of 8s to select their option (leading to a time jitter). After an additional ISI (with fixation cross) of 8s, the participants were shown the trustee return during 6s.

♦ Economic Trust Game and payoff contingencies

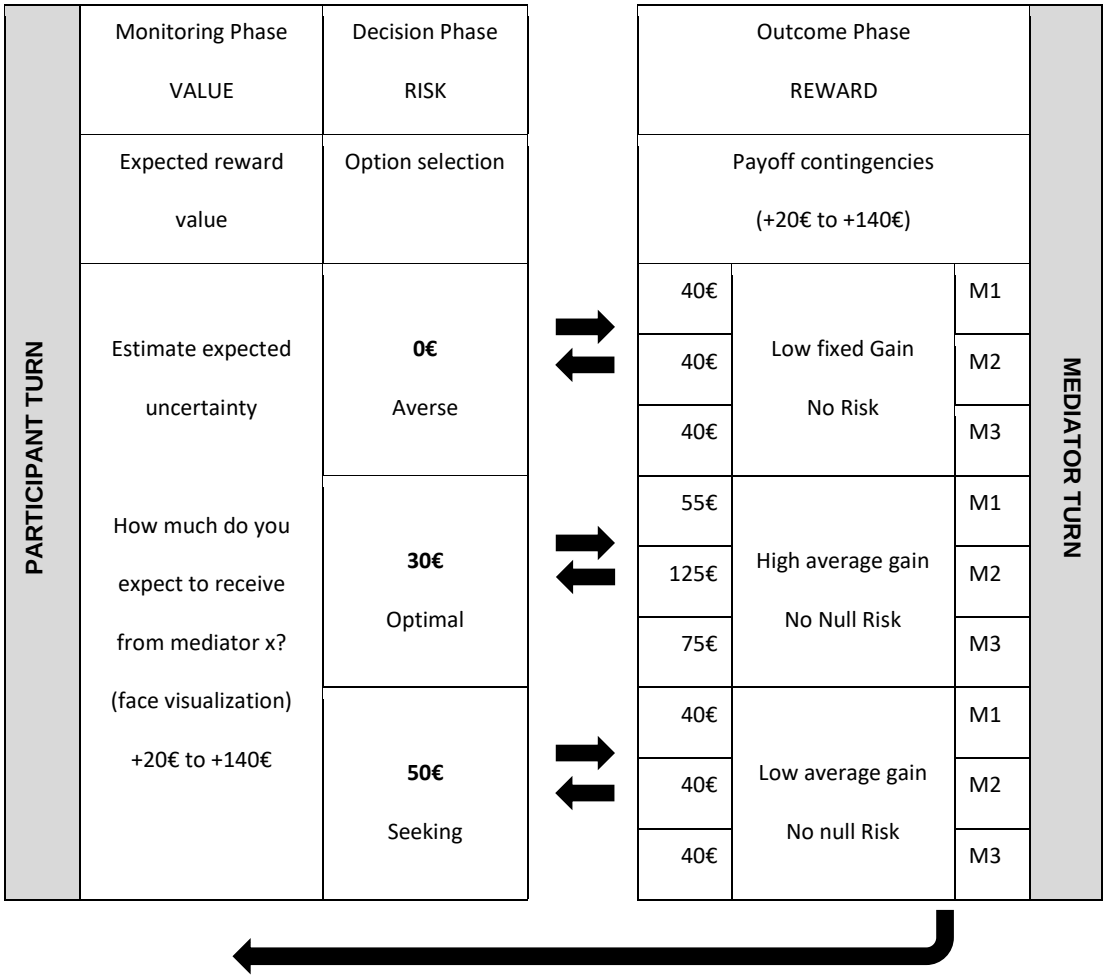

Figure 6. (A) Example of economic experimental design considering a run sequence in trust-trustee interaction. Mediator 1 has a low range for reward (trust investment is quite reciprocated, seeming a social norm violation). Mediator 2 has an extreme range, reinforcing optimal decision. Mediator 3 has a moderate range, in the middle of M1 and M2 profile (trust investment is reciprocated in a moderate way, even so seeming a social norm violation). Outcome reward also differed according to participant option (0, 30 or 50 euros) for all mediators.1. For "0" option (no risk investment) was received a known low fixed gain (40 euros;) 2. For "50 euros" option (risk investment) was offered a low average gain (same mean reward, (40 euros) that can vary from 20 to 60 euros; 3. For "30 euros" option (adjusted risk) was earned a high average gain - low, extreme and moderate reward-: Mediator 1 [35-75]; Mediator 2 [100-140]; Mediator 3 [55-95]. All of them have the same interval (40).

♦ Health Trust Game and payoff contingencies

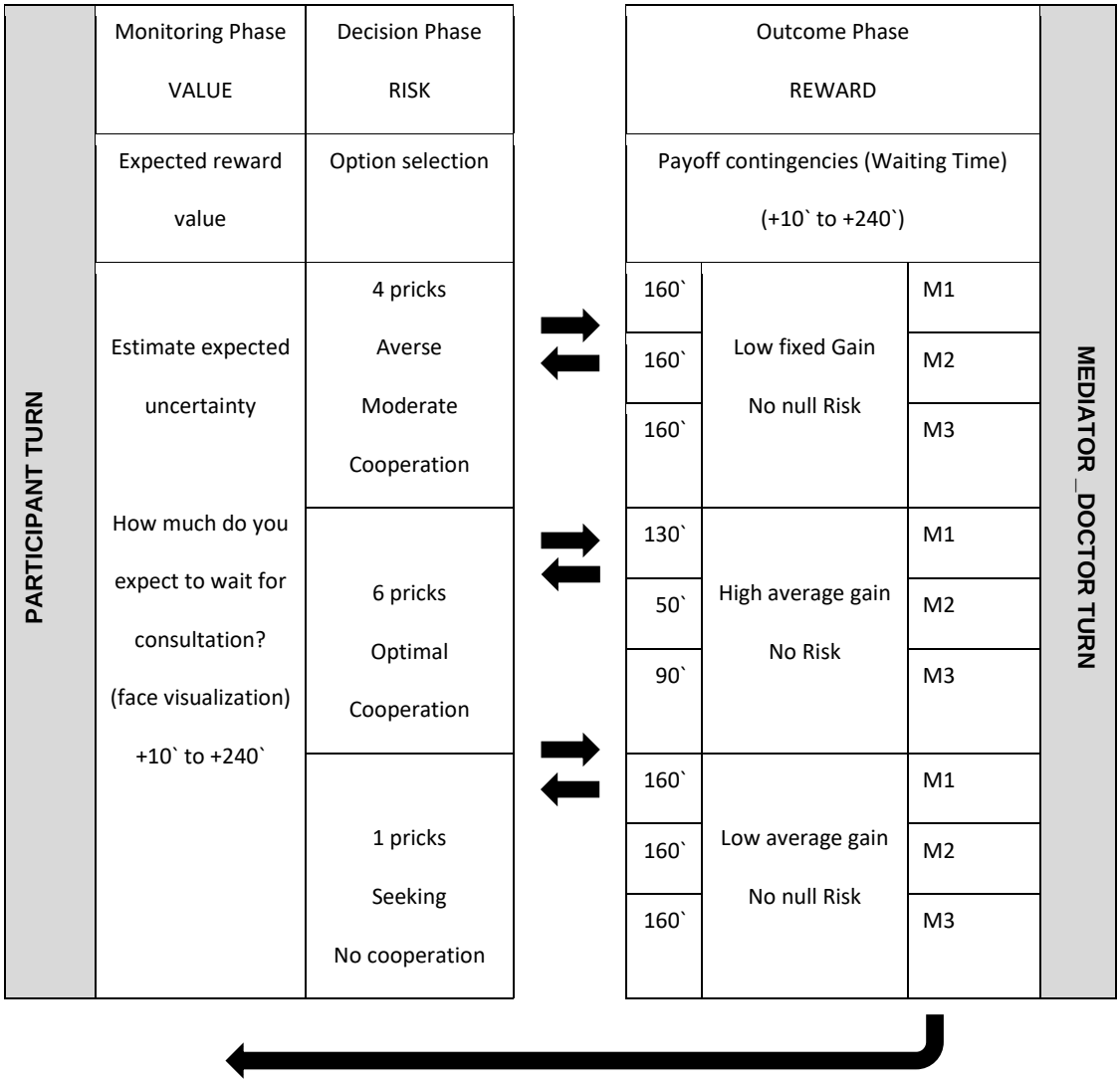

Figure 6 (B) Example of health experimental design considering a run sequence in doctor-patient interaction. Mediator 1 has a low range for reward (patient collaboration is quite reciprocated, seeming a social norm violation). Mediator 2 has an extreme range, reinforcing optimal decision fulfilling the pre-established rule. Mediator 3 has a moderate range, in the middle of M1 and M2 profile (patient collaboration is reciprocated in a moderate way, even so seeming a social norm violation). Outcome reward also differed according to participant option (1,4 or 6 pricks) for all mediators.1. For "4" option (moderate cooperation) was received a known low fixed gain (160`) 2. For "1" option (no cooperation) was offered a low average gain (same mean reward, 160`) it can vary from 120 to 160 minutes. 3. For "6" option (highest cooperation) was earned a high average gain - low, extreme, and moderate – Mediator 1 [90-170]; Mediator 2 [10-90]; Mediator 3 [50-130]. All of them have the same interval [80].

PART IV

INTEGRATIVE SYNTHESIS

Overview

This Part IV intends to summarize the thesis contributions **(the past),** discuss the novel contributions of the present thesis in the theoretical and practical framework of neuroeconomics and health, integrating all data, exploring results in line with previous research studies, interpreting outstanding results and identifying possible limitations of this study and challenges **(the present).** In face of these conclusions, new questions are addressed to guide future work **(the future).**

CHAPTER 1

THE PAST

Thesis summary

The present thesis focus on decision-making under uncertainty in self-consequent difficult choice, beyond the economic domain, namely health decision-making. T1DM disease was selected as a model of social human decision-making in the health domain because it requires iterative daily decision-making to achieve metabolic control and prevent long term complications.

In Chapter I, we reviewed fundamental work in Neuroeconomics to define the concept of decision-making under uncertainty as a basis to decipher neurocognitive and brain mechanisms, integrating contributions from economy, psychology, and neurosciences. After, we presented a Chronic Disease - Diabetes Mellitus - as a Health model of social decision-making under uncertainty considering its clinical features, therapeutic demands, psychological, and social mutual implications, as family system. Consequently, we focused on Family Health Systems Models to systematize the theoretical framework to clinical interventions on the interpersonal context of physical chronic diseases, as diabetes mellitus. Finally, we finish this section presenting the structure and aims of the thesis.

Chapter II presented the selected methodological approach, from participant`s recruitment to materials and procedures. Patients were recruited from Department of Endocrinology, Diabetes and Metabolism (EDM, Coimbra Public Hospital). Two patient groups were formed based on glycated haemoglobin values over time (biological variable). Considering the variation of HbA1c rather than the last value of HbA1c was an innovative methodology to define the group partition between metabolic

and no metabolic control. Decision-making risk profile was built through data collected from handwritten Self-report questionnaires, behavioral experimental tasks, and fMRI neuroimaging approaches. Social context was evaluated by sociodemographic data and family assessment.

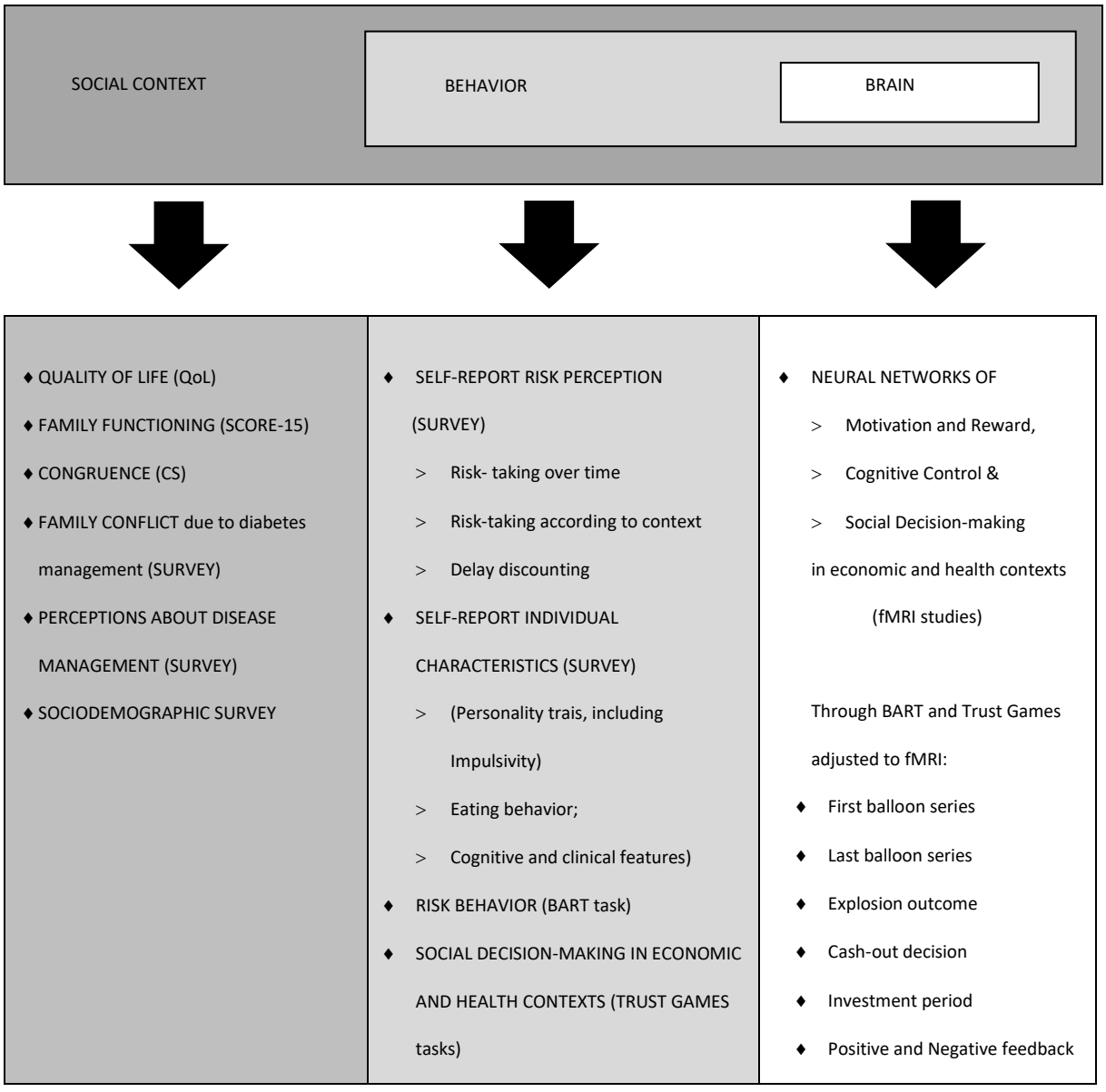

Figure 1. Schematic representation of multilevel methodology in this research and its operationalization

Results presented in Part III were arranged over five studies.

The first study (Study 1) is the house foundation of this thesis. We tested whether groups of metabolic and no metabolic control could be independently discovered through data driven cluster analysis with risk and family functioning variables. In this way, criteria for our groups' division is validated. We concluded that high rates of low adherence are related to specific risk-taking profiles associated with decision-making phenotypes. Thus, this study is also the kick-off for tracing an individual multidimensional decision-making profile.

Main results

- There is a surprising dichotomy of behavioral phenotypes predicted by the dynamics of HbA1c. A two cluster solution provided information of distinct decision profile that almost matched the biological partition based on stable or improving metabolic control (MC group) versus unstable high or deteriorating states (NoMC group);
- A multidimensional protocol revealed to be effective in detection of real-world risk taking. Groups differ in all self-reported risk-taking dimensions as well as in BART. Impulsivity, lack of planning, less health risk perception, more perceived general past and present risk-taking characterized risk profile of impaired metabolic control group. In BART game on computerized version, they performed worse in all variables studied and they did not adjust their risk decision over iterative decision-making, revealing a tendency to a risk averse profile.
- Group differences related to sociodemographic, personality, eating behavior and clinical variables for NoMC group were less household income, a smaller number of years of education, higher scores in neuroticism and lower scores in extroversion, emotional and external eating behavior, higher values of HbA1c and presence of complications. Disease onset (<18 years) was related with memory impairments and complications.

This profile was further investigate in the second study, (Study 2) **through experimental trust games in the economic and health domain**, addressing social decision-making in the context of self-consequential health issues. Beyond, iterated decision-making, this study also clarified the role of

context in decision-making under uncertainty, disentangled feedback processing from choice (calculating prediction error and understand learning and choice options in terms of investment) and highlights social decision-making, namely patient-doctor interactions. To our knowledge is the first study modelling interative trust games to the health domain.

Main results

- Initial option
  - > There´s a distinct profile for both groups concerning that MC group shows a planning investment (some investment for all trustees) while in NoMc group there was no association between initial strategies and no planning.
- Sequencial learning
  - > Both groups were able to detect payoff contingencies of each mediator.
  - > However, they invested differently with relevance to health context. MC group collaborated regardless of doctor feedback while the NoMc group only opted to collaborate with the doctor that followed the initial commitment (no norm violation).

The third study (Study 3) is a systemic exercise embracing the study of the interconnections between family and diabetes management. Despite extensive knowledge about mutual interference of family functioning and chronic diseases there is a notable absence of studies that address adults with T1DM and their families. We included sociodemographic, family and eating behavior variables, because meals are intrinsically related to family dynamics. Here we focused on the study of family variables that explained the variance of no metabolic control. In turn, we reported how does diabetes management contribute to family conflict.

Main results

- There is a significant correlation between self-report measures and two solution cluster analysis based on family assessment (We introduced only general results). SCORE-15 stood out from the three administered questionnaires.
- Group NoMC scored higher on Family Difficulties and Family Communication with no statistical group differences to Family Strengths Subscale (SCORE-15). They also reported low Quality of Life (QoL), specifically on 7 of 11 total subscales such as Financial, Neighborhood, Social/Health Relationship, Job, Religion, Family/Marital and Education. Finally, considering EC subscales, they describe themselves as less connected with themselves & others (Intrapsychic/Interpersonal) and the context (Universal/Spirituality).
- Income, level of education, HbA1c, emotion eating behavior, SCORE-15 and Congruence explained the variance of impaired metabolic control.
- Group NoMC revealed more perception of family conflict and less perception of family support. Sources of conflict were mainly being annoyed by family members to follow doctor advice and food restrictions. Conflict about mealtime was related to gender (male reported more difficulties). NoMc patients showed more concerns about daily present problems whereas the MC group with future.
- Concerning marital functioning, NoMc groups obtained worse results.

The last two studies provided neuroimaging results both in terms of impulsive and social decision-making, bringing light about neural mechanisms associated to experimental task performance, addressed in study one and two. A different group of participants (patients and controls) were scanned using functional magnetic resonance while they performed the same experimental tasks (Balloon Analogue Risk Task and Trust Games in economic and health domains), which were randomized to minimize order effect. We compared patients and controls. We compared risk averse patients and risk seeking patients. We correlated brain activity with Hba1c dynamic (positive correlations related to impaired metabolic control and negative correlations related to successful metabolic control).

The Fourth study (Study 4) intended to examine the neural correlates of cognitive control or impulsivity in a sample of T1DM and healthy participants. We compared both groups during two crucial periods of the experimental task (first balloon series and last balloon series), and two crucial phases of decision-making (cash-out decision and explode outcome).

Main results

- T1DM versus Control group
  - For first balloon, under uncertainty and ambiguity, in patients-controls contrast, activated regions included a three-cluster encompassing neighboring right amygdala and ventral striatum, both known to be associated with stimulus-reward contingencies. Note higher bilateral (insula, inferior frontal gyrus and putamen), right (caudate and amygdala) and left (nucleus accumbens) activations.
  - Under conditions of complete uncertainty and ambiguity and even after iterative decision making, patients preferred low rewards and losses, related to avoidance or removal of aversive /anxious stimulus. IFG and Insula area together are related to inhibition response, which jointly with the caudate and putamen play a role in the control of action selection. This may explain the risk averse profile.

- Positive correlations with impaired metabolic control group
  - Patients with worsening metabolic control presented a distinct pattern of activations from successful metabolic control. The last group stay close from healthy participants' brain patterns of activations more parietal and posterior regions, contrasting with impaired metabolic control, frontal and anterior regions. Importantly, patients with worsening metabolic control showed increased activity in limbic and inhibitory control regions.

- Risk averse and risk seeking groups within T1DM patients
  - Patients with risk seeking profile were exposed to more tension between reward seeking and loss aversion and this behavior increased opportunities to find out task learning rules (Sokol-

Hessner, & Rutledge, 2018). Maybe why we saw dorsal striatum and error monitoring activations for cash out decisions (larger rewards), as well as inhibitory control -IFG regions (BA44, BA10). For risk averse patients, even in appraisal rewards, IFG and Insula appeared together as well as middle frontal gyrsus (BA9), reflecting hardful and maybe anxiogenous decisions.

The fifth study (Study 5) of neuroimaging is related to social decision-making in both contexts and further studied the neural correlates of self-consequent decision-making in the health domain in a clinical population, T1DM. We focused on three critical phases of decision-making: investment, positive feedback and negative feedback in both contexts, economic and health domain.

Main results

- T1DM and control group

Groups revealed a different pattern of brain activation depending on context. Emotional processing was more evident for patients in health trust games.

Investment in economic Trust Games

> Controls evoked brain activity typically involved in money tasks, namely the basal ganglia, the insula and PCC. In turn, brain activation in patients are allocated to speficic frontal regions, namely mPFC.

Investment in health Trust Games

> Patients differ from controls in subgenual (BA25) activation, limbic regions (amygdala, hippocampus and parahippocampus) and prefrontal regions [medial (BA10, BA46) and inferior (BA45, BA47)]. In contrast, controls recruited cingulate (ACC, BA24; and PCC, BA31), parietal (BA39/BA40) and PFC. Concerning subcortical structures, controls activated the caudate while patients activated the putamen.

- Risk Averse and Sisk seeking
  - Comparing risk averse versus risk seeking patients during the economic investment, we found higher activity from the risk seeking individuals in economic trust game in brain areas related to the limbic system and dopaminergic midbrain region, such as Thalamus, the ventral tegmental area (VTA), hippocampus, parahippocampus and amygdala involved in motivation and reward. In health context, no contrast activation was found to compliant patients (maybe because they are indifferent to payoff contingencies as seen in study 2). Non-compliant patients (risk seeking in health setting) revealed activation in parietal and temporal regions, putamen and insula related to emotional and social attribution (they seemed to pay attention to infer intentions of others).

- Correlation between HbA1c and brain activation
  - The effect of biological worsening in investment was related with neural activity in regions related to impulsivity and emotional processing (economic context) and for error monitoring (health context).
  - In relation to negative and positive feedback, it seems that impaired metabolic control patients generate responses mainly in regions of the saliency network (in particular ACC) as well as MFG (for waiting less time to be consulted in health context). Both regions are related to emotional processing. In economic setting, successful metabolic control patients activated brain regions related to signaling aversive outcomes such as left posterior insula and inferior frontal gyrus (when receiving less money), providing future information about future action.

CHAPTER 2

THE PRESENT

Discussion

Taking all data together, our discussion will integrate results from brain, behavior and psychosocial factors around a biological variable, the dynamic evolution of HbA1c. We found out a risk-taking profile that is congruent with the biological group partition concerning personality traits, self-reported risk-taking behaviors, performance on experimental tasks, family, and social factors. We identified neural mechanisms impairments according to context and biological worsening.

The role of neuroticism, extraversion, impulsivity and eating behavior

In general, our results concur with other studies suggesting a detrimental **role of personality traits and self-report risk behaviors on health behavior** and various diseases. Neuroticism and extraversion are the main personality characteristics related to successful or impaired health outcomes (Kitayama et al., 2018; Lawson et al., 2010; Segerstrom & Smith, 2019). Rassart et al. (2020) found out an association between neuroticism and poor adaptation to refractory epilepsy. Concerning Impulsivity, it is also the personality trait reported to be associated with worse diabetes self-management (Hadj-Abo et al., 2020). Impulsivity is marked by behavior lacking sufficient reflection and foresight. Lastly, eating behavior is related with self-control. As our results, previous studies as Elfhag and Morey (2008) revealed that neuroticism is also linked to emotional eating and impulsivity for patients with obesity. They explained that neuroticism as a "tendency to experience depressive factors" and impulsivity as an "inability to resist desires", lead people to a disinhibition behavior to eat for comfort due to negative

emotions. External eating was also associated with this pattern but with a weak effect. Even though is not our main purpose, is important to notice that Eating disorders is not uncommon in diabetes disease (for detailed information, see meta-analysis of people with T1DM and disordered eating, Clery et al., 2017).

A risk averse profile under uncertainty and ambiguity

Impaired neural mechanisms in motivation and cognitive control

Linking results from behavior performance and neuronal activation on BART for impaired metabolic control, this personality pattern seems to be congruent with a risk averse profile, to avoid or eliminate the anxiogenic stimulus, namely on first play move under uncertainty and ambiguity. This is in line with top-down and bottom-up models of personality and coping, linking emotions to actions (Carver, et al., 2010). In study 1, we hypothesize that the MC group was more tolerant to ambiguity, such as in prosocial behavior people decide to trust a stranger, being more optimistic about results in social interaction. NoMC performance could also be explained by the triadic neurocognitive model (imbalance between hyperfunctioning of the impulsive system and hypo functioning of reflective/inhibition, suppressing cognitive processes to inhibit maladaptive behavior) or a model-free systematic strategy of model-free learning in decision-making (an impairment in the trade-off between incorporating new information and good use of past experiences). Neuroimaging results from BART makes light of this process with limbic, motivation and reward system activations. As OCD patients performing BART (Sohn et al., 2014) it seems that they value information of safe outcomes higher than information about risk outcomes- insula and amygdala activations might be related to anticipating negative outcomes and anxiety (Engelman at al., 2015; Singer at al., 2009; Sokol-Hessner and Rutledge, 2018). Curiously, there`s almost no differences in contrasts with outcome monitoring (cash out or explosion) which may point for our hypothesis: maybe they are focused in quickly avoiding this tension, independently of good or bad result, tending to early cash-outs.

The role of Trust based decision-making, norm violation in patient-doctor interaction and context

Linking results from behavior performance with neuronal activation in trust games, patients' differences comparing to controls for investment period but no differences for negative or positive feedback could point out that learning process is not affected, even though there was an impact on choice strategies. We had the same results in study 2 for performance according to mediators. We identify that distinct types of participants were able to estimate mediators' contingencies, but they chose differently, particularly in health context. These results provided eventually evidence that neural risk processing in this context is more affected in which concerns action selection circuitry that for brain networks related to value estimation.

Additionally, brain activity shows a distinct pattern for impaired metabolic control as compared with successful metabolic control highlighting the role of HbA1c in neural risk processing. Interestingly, this could explain why NoMC and MC groups differ in collaboration. While MC were indifferent to mediator contingencies and choose to cooperate, NoMC group seems to cooperate only with the mediator that did not violate previous norms ("if you cooperate, you will receive less waiting time for consultation"). In fact, NoMC showed distinct and more distributed activations in regions related to social attribution and emotional processing which could partly support our hypothesis that doctor-patient relationship is crucial for impaired metabolic control patients and they are more dependent from external reinforcement than successful metabolic control. In discussion from study 2 we hypothesize that this group might be more sensitive to norm violation in health setting.

Moreover, subcortical activation in subregions of the dorsal striatum such as putamen is relevant to explain less flexible behavior with patients. This region is related to development of habits, no sensitive to error correction learning rule. In this case, larger activation of the hippocampus and parahippocampus maybe related to autobiographic memories because patients are processing aversive stimulus, pricks and waiting time. As corroborated by behavioral results concerning clinical

expected value, expecting to receive more waiting time than in fact they received, apporting their own experience in public hospitals. In opposite, controls had activations in caudate related to goal-directed behavior and sensitive to encode association action-outcome, supporting the hypothesis of adjusted and flexible behavior.

Integrating neural results of experimental tasks, both economic investment in BART and economic investment in Trust games are convergent with evidence from other functional neuroimaging studies with monetary reward suggesting the involvement of all components of cortico-striatum-thalamic-cortico loops. Risk seeking groups showed activation in Thalamus, the striatum (particularly the caudate), the frontal cortex (middle and inferior) including the anterior cingulate cortex.

The circle of family functioning and the management of a chronic disease

Finally, psychosocial factors as Family Functioning has been associated with poor metabolic control as in previous studies with T1DM mainly in studies with young people since studies with adults are scarce (Almeida et al., 2015; Almeida et al., 2020; Lewin, 2005, Luo et al., 2019). Subscales of SCORE-15, that evaluate family functioning, had similar results to those found during Portuguese scale validation (Vilaça et al., 2014). Family Difficulties (overburden) and Family Communication seems to be more advantageous to detect group differences than Family Resources, related to family adaptation to disease. In general, our results are in line with several studies which come to similar conclusions regarding the important role of family in diabetes management. In a review of 66 articles about the role of partners and family support in success of therapeutic interventions in diabetes, Gupta et al. (2019) reported several factors affecting treatment adherence in adults with T2DM that we also found in our study. Social factors are mainly lack of family, peer, and community support; limited spouse support/divorce; uncomfortable facing social gatherings and social stigma; appropriate health beliefs, cultural and religious as we obtained by Quality of Life, Congruence and Marital Functional scales.

Economic factors, as financial constraints, psychological factors, as frustration and negative emotions, anxiety and depressions, memory/cognitive impairment, and disease related factors, as duration of disease or quality of life, was also reported. They concluded that spousal and family support are crucial to overcome negative behaviors and to improve behaviors in diabetes control. From our study we can add that family support can be perceived by patients as annoying, overprotection and control behavior, turning a supportive behavior into an unpleasant help or becoming a cause of family conflict. Mutual perceptions of caregivers and patients should be considered. As reported in discussion from study 3, our findings got relevant evidence about the recursive interplay of family and diabetes, integrating the illness, the family, the patient, and health-care system as recommended by Family System-Illness Model of John Rolland (1987, 1994, 2012).

Limitations of the study

- Psychological evaluation of depression and anxiety and coping strategies were not made even though patients were referee by their clinicians
- Cognitive flexibility was not measured by neuropsychological assessment through Wisconsin Card Sorting Test
- Circular questioning techniques and dyadic interaction measures were not selected. We only collected data from patient points of view.
- Self-report and behavioral results from BART and Trust games from patients and controls who were scanned were statistically analysis in the sample of studies 1 and 2.
- BART in computerized version outside the scanner was not paid while in scan version there was a payment. However, in our research we obtained similar risk patterns.
- Non-human mediator was not present in Health Trust Games in the behavioral computerized version outside the scanner. However, in fMRI version, both games had already the same number of mediators (four mediators for each trust game)

Study contributions

Our conclusions provide several aspects with relevance to theoretical framework and clinical practice. The outputs of the project will contribute to the following impacts:

1. To provide a broad and deep resource for future understanding of T1DM patient adherence. To identify the sub-groups of the population with similar causes of non-adherent behavior such that solutions can be tailored to population needs and applied in a cost-effective manner to multiple treatment conditions.
2. To propose an innovative methodology to define metabolic and no metabolic control in research studies considering the variation of HbA1c rather than the last value of HbA1c. This criteria for groups` division was validated by cluster analysis.
3. To model iterative Trust Games to health domain. Beyond experimental task validation, we were able to differentiate different stages of the decision process to better understand how players estimate uncertainty, disentangling players intentions and learning impairments.
4. To guide future neuroimaging studies and going forward in the study of the role of HbA1c in neural risk processing.
5. To stress the relevance of family and social factors in disease control. Family conflict due to disease monitoring as well as an association between impaired metabolic control and difficulties in marital functioning made evidence that family members should be involved since diagnosis is made. Additionally, family support could be perceived by patients as annoyed or controlled behaviors. On the other side, predictors as low economic power, eating behavior and quality of life results should be a serious advertise to imperative needs of equitable policies to allow the access to health well-being for achieving a balance diet, psychological services, and workplace inclusion for all patients. This study helps to compile and understand psychosocial factors affecting patient non-adherence to treatment regimens and the relative weighting of these factors.

CHAPTER 3

THE FUTURE

Five challenges for future work

…For Neuroeconomics research

1. Future research should therefore examine response perseverance in patients with diabetes. Is biological status a mediator between the neural mechanisms that inhibit learning (adequate adaptation of behavior) and behavioral avoidance of aversive stimulus? Or the biological worsening over time has an impact on cognitive flexibility that explains suboptimal decision-making, as continuous oscillations of HbA1c have been also related to cognitive impairments? Future neurobehavioral studies should compare impaired metabolic control patients over time with decision-making tasks.

2. Are T2DM without metabolic control patients like T1DM concerning individual risk profile? Are OCD patients like T1DM risk taking profile since they have similar results while performing BART computerized task? Future research should try to replicate this study with other diseases namely T2DM. T1DM and T2DM have in common the variation of HbA1c. These studies will be relevant to clarify the role of HbA1c impairments of neural risk processing. Future studies could compare T1DM and OCD patients. These studies will be relevant to define a more consistent hypothesis on the role of anxiety and avoidance of aversive stimulus, valuing safe outcomes in contrast with gambling disorders that value risky options.

3. Is there a different neural risk processing in economic investment performing BART or Trust economic games? How neural risk processing differ in face of different stimulus: balloon, non-human mediator, and human mediator? Future fMRI studies allowing for more direct comparisons with BART should introduce an expected value predictor prior investment and should have a temporal lag between outcome and new trial to investigate brain activity to error monitoring or performance monitoring.

…For Psychological and Chronic Disease research

4. Are impaired metabolic control patients more externally motivated and dependent than the successful metabolic control group? Future works should contemplate control locus scales in protocol, incorporate depressive and anxious scales, executive function evaluation and obtain information about clinician' points of view.
5. Longitudinal studies could be made to understand how patient disease control and their individual developmental choices are mediated by communication pattern, family support and individual perception of having a disease. Our exploratory results comparing patients with diabetes diagnosis before and after 18 years old (not mentioned because it was not the focus of this study) makes light for the negative impact of disease in memory and marital functioning and influence of civil state (more single) for patients with diabetes diagnosis in childhood or relatively young ages (disease long duration). Understand the disease impact in future choices, such as careers and closed relationships could be made through family studies focused on narratives built around growing up with diabetes from patients and caregivers. No less important would be investigate the best approaches to mobilize family members to support chronic disease management giving them skills they need to carry out these roles and evaluate how patients perceived this support.

CONCLUSION

As a single biological variable, the dynamics of HbA1c has the potential to discriminate behavioral endophenotypes for impaired metabolic control, building a foundation to develop an integrated model of decision-making profiles in self-consequential difficult choices, in health domain, namely T1DM. Beyond behavior, we integrated brain mechanisms and family context to gain a systemic interplay from micro to macro levels. Combining behavior and neuroimaging techniques, the work presented in this thesis contributes to the definition of a multidimensional risk profile that differentiates behavioral endophenotypes, considering brain, behavior, and social context to build the complex puzzle of suboptimal decision-making in health domain.

This novel and pioneering work created scientific evidence with relevance to design personalized interventions with patients with T1DM guiding adherence improvement programs:

- Impaired metabolic control is related to suboptimal decision-making. BART stood out as a relevant behavioral task to quicky screen risk taking profile in diabetes. However, a multidimensional evaluation should not be overlooked.
- Suboptimal decision-making seems not be related with learning impairments. Both groups of patients were able to learn mediators' contingencies in trust games, but they chose differently with a tendency to a risk averse profile, also in BART. Difficulty to tolerate ambiguity or maintenance of anxiogenic stimulus is the most probable cause for this risk averse pattern. MFG activation and well as Anterior Insula and Inferior Frontal Gyrus simultaneous activation are consistent with this hypothesis. Additionally, in the health context, impairment metabolic control seems to be sensitive to norm violations, making evidence to the relevance of patient-doctor relationship. fMRI data corroborates this hypothesis as revealed by distinctive patterns of brain overactivation related with impaired metabolic control patients.

- Emotional eating behavior and personality traits, as neuroticism and lack of planning are related to worse disease control. Individual characteristics and eating behavior evaluation are useful to nutritional and clinical adherence.
- Family functioning and diabetes management are interdependent. Communication patterns should be considered. SCORE-15 showed to be an appropriate instrument to measure family functioning in the context of diabetes. Family support could be a tricky measure for well-being evaluation in T1DM without additional explained reasons. Family conflict due to disease management should be appreciated in patients-family interviews.
- Neural risk processing is altered in patients with T1DM when compared with controls. The role of the dynamics of HbA1c in brain activity when performing risk taking tasks should be explored.
- Decision-making is context dependent. Considering the health domain, the brain regions that showed more activation were related to emotional processing and regions involved in autobiographic memories, namely within patients. Brain activity in economic domain trust game tasks was particularly related to neural activity in investment period (with activation in system involved in motivation, goal-directed behavior, reward, and inhibitory control).
- Trust Games have ecological validity. Both trust games can be reproduced in other studies of social decision-making. Importantly, the three-brain network related to social brain was revealed present in data analysis: motivational-reward, cognitive control, and social cognition.

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