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Review

Temporality in chronic diseases and adherence to long-term therapies: From philosophy to science and back☆

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ABSTRACT

This narrative review exhibits the construction and validation of a hypothesis to explain how treatment non-adherence in people with chronic disease, a major issue in contemporary medicine, occurs. I propose that non-adherence to long-term therapies is at least in part due to failure to prioritize the future, which is caused by a condition I dub disruption in time projection. This article gives the rationale for this hypothesis, which is largely grounded on philosophical arguments. Then, it demonstrates the plausibility of the hypothesis: on the one hand, it is consistent with certain epidemiological data found in the literature. On the other, it is possible to predict the underlying mechanisms of this lack of prioritization from recent achievements of neuro-economics and neuroscience. Next, it reviews empirical data that provide an experimental verification for this explanatory hypothesis. Finally, a general evolutionary and philosophical meaning for adherence is proposed, considering the advantages of its preconditions, namely, patience and foresight.

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"It is through wonder that men now begin and originally began to philosophize."
Aristotle, Metaphysics, A2, 982 b

"What an explanation of a phenomenon does is to supply a proposition which, if it had been known to be true before the phenomenon presented itself, would have rendered that phenomenon predictable, if not with certainty, at least as something very likely to occur."
Charles S. Peirce, Collected Papers, 7.192

Introduction

During those very years (1970–1980) when Roger Assan together with Pierre Lefèbvre and Roger Unger were achieving the description of the pathophysiological role of glucagon [1], Georges Tchobroutsky was proposing multiple daily insulin injections for people with type 1 diabetes [2], Anthony Cerami and his colleagues were discovering the relationship between HbA_{1c} and diabetes control [3], Jean Pirart was demonstrating the effects of this control on diabetes complications [4], Peter Sönksen was opening the way to self-monitoring for blood glucose [5] and John Pickup was describing subcutaneous insulin infusion [6], during that time when all the ingredients of modern diabetes care were being invented, in 1979 to be precise, Bryan Haynes and David Sackett defined adherence to therapy, under the name of compliance: the concordance between a patient's behaviour, such as taking a medicine or following a diet, and a prescribed therapy [7].

There was a growing concern at the time due to the mounting evidence that patients were often not following medical prescriptions, which jeopardised the benefits of the medical progress that had been achieved and, surprisingly, seeming to act against their best interest. The WHO, 25 years after this definition, published a 211-page report emphasising the paramount importance of this issue for contemporary medicine [8], in which Bryan Haynes [9] was quoted: "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments."

☆ This review follows the Prix Roger Assan that was given at the last SFD meeting held in Nantes on March 21, 2018.

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Unfortunately, recent meta-analyses have concluded that, so far, the success of these interventions is in general limited [10], suggesting that non-adherence to long-term therapies may stem from deep causal mechanisms that would be difficult to overcome.

This narrative review, first publicly presented in March 2018 as the Roger Assan Lecture to the Société francophone du diabète, describes one such mechanism. I make the point that patients' non-adherence to long-term therapies is due at least in part to a failure to prioritise the future, due to what I call disruption in time projection. First, I give the rationale for this hypothesis, which is largely grounded on philosophical arguments. Second, I show that the hypothesis is plausible: on the one hand, it is consistent with certain epidemiological data found in the literature, and on the other, its underlying mechanisms can be predicted from recent developments in neuro-economics and neuroscience. Third, I review empirical data that provide an experimental verification for this explanatory hypothesis. Finally, I propose a general evolutionary and philosophical meaning for adherence, conceived as an expression of patience and foresight, two characteristics of the human mind.

From a surprising medical issue to an explanatory hypothesis

Patient non-adherence to long-term therapies surprises by its frequency, which may be difficult to believe at first. For example, one study of different chronic diseases indicated that 27%, 35% and 63% of individual with hypertension, type 2 diabetes and gout, respectively, exhibited a medication possession ratio (ratio of total supply of medication that was dispensed, measured in days, divided by the number of days in the evaluation period, MPR) lower than 80%, a threshold which defines non-adherence [11]. The decrease in MPR generally occurs rapidly after medication initiation: within 6 months of that point, it is lower than 80%, no matter what the medication [12]. When MPR is below 80% for oral glucose-lowering therapies, the expected decrease in HbA_{1c} is lower than would be expected from evidence-based medicine [13]. This has consequences for the appearance of complications, number of visits to the emergency room, number of hospitalizations and healthcare expenses [14], and it is associated with higher rates of mortality in type 2 diabetes [15]. The most surprising feature of non-adherence may be its association with mortality in people randomized in the placebo group of clinical trials: the mortality rate was found to be twice as high in those non-adherent to the placebo. This finding led to the development of the concept of 'healthy adherers': those who are adherent to a placebo may also be adherent to a number of other healthy behaviours, explaining their lower rate of mortality [16].

With these striking consequences of non-adherence in mind, the first reaction is surprise: how is it possible that so many patients are acting against their own interest? When confronted by a surprising phenomenon, the need for an explanatory hypothesis is felt. This logical operation was discovered by the American philosopher Charles S. Peirce (1839–1914), who described it under the name of abduction, stating that it "is the process of forming explanatory hypotheses. It is the only logical operation which introduces any new idea" [17]. Peirce described the process of abduction in the following, concise form [18]:

> The surprising fact, C, is observed.
> But if A were true, C would be a matter of course.
> Hence, there is reason to suspect that A is true.

A clue that may help discover a general explanatory hypothesis for the occurrence of non-adherence may be found in the answer to the following question: why did this phenomenon become a subject of discussion in 1979 (the year of compliance definition) when it has been known since Hippocrates? Hippocrates wrote in *On Decorum*: "Keep a watch also on the faults of the patients, which often makes them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or others, they sometime die. What they have done never results in a confession, but the blame is thrown upon the physician" [19]. I propose that non-adherence became a theme in 1979 because this was when medicine began to be interested in the care of chronic diseases: for example, the end of the 1970s also saw the advent of patient education, which can be seen as medicine's necessary answer to the increasingly central role played by chronic diseases, defined by the WHO as being "of long duration and generally slow progression" [20]. In other words, their definition encompasses temporality.

This leads to propose the following explanatory hypothesis (A in Peirce's terminology):

> A: Non-adherence in chronic diseases is due to a disruption in time projection.

Philosophical background of the explanatory hypothesis

The surprising observation of the phenomenon non-adherence to long-term therapies in chronic diseases leads to the question how is non-adherence possible? Inquiring after the possibility of something is typically a philosophical question. While psychologists, for example, want to see how certain phenomena come to be, instead, philosophers are interested in the conceptual line that separates the possible from the impossible, asking how they can exist [21,22]. In the first section of this article, I will therefore give three philosophical arguments to ground explanatory hypothesis A.

First argument: Adherence, a high-level construal

The psychologists Yaacov Trope and Nira Liberman proposed that, in general, our concepts can be classified into high-level concepts, that are abstract and future, and into low-level concepts, that are concrete and immediate [23]. Thus, if I consider reading in an abstract way, I think it has the ability to enrich my mind; whereas, if I consider it in a concrete way, I think about the book I am reading. In general, adherence and non-adherence can be considered to be high-level and low-level concepts, respectively, due to the nature of their rewards, which are abstract and distant in the first case (avoiding complications) and concrete and immediate in the second (such as avoiding the side effects of a treatment or obtaining the pleasure of smoking this cigar).

However, like all human beings, patients are often more attracted by immediate rewards, which may explain non-adherence. An example from diabetes care that can justify the validity of this argument can be provided by treatment adherence in pregnant women with diabetes. Adherence to guidelines for pregnancy planning in type 1 diabetes is often poor: here, the reward is abstract and may be remote (the patient is not yet pregnant); by contrast, adherence in gestational diabetes is most often good: the reward of adherence is concrete (the foetus can be felt to moving in the womb) and near (the child will be born in a month); finally, one also understands that, in these women, subsequent adherence to the recommendations for the secondary prevention of type 2 diabetes will often not be good: here again, the reward will be abstract and distant.

Second argument: Philosophical meaning of care

The philosopher Harry Frankfurt, in an essay entitled *The importance of what we care about* [24], noted an equivalence

between the notions of importance and care: if something is important to me, this implies that I care about it, and the converse is also true. Moreover, he proposed that the idea of care implies that the future is taken into account: for example, this vanilla ice cream is not important for me, it does not imply anything for my future, and it is not a cause for worry for me; however, when I say that I care about my country, it is because I take consideration for its future.

I take care of myself, if the person who will exist and be preserved (or not) in the future is important to me. Here, this line of thought puts its finger on the importance of our relation to temporality in considerations of care from a philosophical point of view. Adherence requires effort, but effort for whose benefit? Can I imagine now the future person I want to protect, who may be very different from myself as I am today? Shane Frederick showed that younger people, especially teenagers, predict that they will be very different after 5 or 10 years [25], and the philosopher Derek Parfit, in *Reasons and Persons*, wrote: "My concern for my future may correspond to the degree of connectedness between me now and myself in the future. Since connectedness is nearly always weaker over longer periods, I can rationally care less about my further future" [26]. Surely, this philosophical statement sheds light on the medical issue of non-adherence to long-term treatment in chronic diseases.

It is appropriate for the concept of temporal horizon be introduced here, and it can be evaluated by two methods: the first is to ask people to describe events that they expect to happen to them and to indicate the age that they will be when these will happen. Then, the length of the subjects' temporal horizon can be deduced with the knowledge of their age. Another method is to present the subjects with a short story and ask them to complete it, giving the duration of the end of the story they have imagined. Using these two methods, Bryan Jones and his colleagues showed that women who smoke and people with low incomes have short temporal horizons [27].

Third argument: adherence, non-adherence and rationality

Parfit's prediction, quoted above, implies that it may be rational to be non-adherent. This philosophical point of view forces us to reverse our question, which becomes: How is adherence possible? The answer may be the reverse hypothesis A* of our explanatory hypothesis A, which can be reformulated as:

> A*: Adherence to long-term therapy in chronic diseases is possible if the patient projects him- or herself into the future.

The American philosopher Donald Davidson (1917–2003), in a seminal article published in 1963, entitled *Actions, reasons, and causes*, proposed that the reason for an action not only explains it but is also its cause [28]. To illustrate his *Causal Theory of Action*, Davidson used the following example: "In order to turn the first 'and' to 'because' in 'He exercised and he wanted to reduce and thought exercise would do it, we must, as the basic move', admit that A primary reason for an action is its cause". The reason causes the action, just as insulin causes a decrease in blood glucose: this is not only a statistical association but a real causation.

Does a good reason for an action always cause that action? Do I always do what I believe is right? Socrates asserted a point of view like this, claiming that lack of self-control does not exist: "no one, he said, when he judges acts against what he judges best: people act so only by reason of ignorance". However, Aristotle declared that this view "plainly contradicts the observed facts" [29], devoting a full book of his *Nicomachean Ethics* to the subject of the weakness of the will, or lack of strength (*akrasia*), the idea that Latin philosophers will call incontinence. Related to this phenomenon, the agent has a choice between doing A or doing B. Reason tells him or her to do A; however, he or she does action B. This is irrational. This *akrasia* can express itself in different ways, such as gluttony, lust, various addictions (to tobacco, alcohol or gambling), procrastination, endless surfing on the Internet or unprotected sex [30]. All these manifestations appear to bear a common element, and I hear my non-adherent patients saying, as it were, "I know, but it's stronger than me, I can't help myself" [31].

In *How is weakness of the will possible?* [32], his second essay devoted to the theory of action, Davidson proposed that weakness of the will results from the incapacity of the agent to conform to a principle of rationality, which he called the "principle of continence"; this principle normally enjoins the agent to act after he or she has considered everything and determined what seems best. Thus, the subject is irrational when he or she does not implement this principle, which prevents irrationality. Incidentally, there is no circularity here: Davidson discovered principles of rationality because rational people sometimes behave irrationally; in the same way, the person with diabetes is the one who does not have insulin, where insulin is the hormone that prevents her from becoming diabetic. In other words, the mechanisms of human rationality themselves carry the possibility of irrationality in germ, in the same way that the regulatory mechanisms of glycaemia lead to the possibility of the appearance of diabetes. In both cases, this is a pathophysiological reasoning: insulin was discovered because diabetes exists and had to be explained, and Davidson discovered the principle of continence because he needed to explain incontinence.

The philosopher Robert Nozick proposed a teleological vision of the principles of rationality as mental tools (he uses the word "devices") that direct our actions to our good [33]. The paradox of adherence appears at this point: in fact, if the respective rewards of adherence and non-adherence are considered and Davidson's principle of continence, which dictates to us to do what we believe best, is used, we should, rationally, in a natural way, make the choice in favour of non-adherence. According to Olav Gjelsvik [34], "Davidson's concept allows for causal/irrational deviations from what is considered best, all things considered. Theoretically, there is no reason to expect any particular pattern in these causal/irrational deviations. They might favor a long-term perspective or a short-term one". Thus, within the framework of a theory of rationality, the principle of continence leads chronic patients to non-adherence, which is an act against their long-term interest, whereas, as Nozick says, principles, from a teleological point of view, exist for our benefit. For this reason, I postulated that adherence requires the use of a second principle, which I called the "principle of foresight", that requires that the future be prioritised [35,36] and which acts as a protective device: this principle of foresight is necessary to account for if one wants to understand the possibility of both non-adherence and adherence, according to our two hypotheses: non-adherence is due to a disruption in time projection (A), and adherence to long-term therapy in chronic diseases is possible if one projects oneself into the future (A*).

Are hypotheses A and A* plausible?

Consistency with epidemiological data from the literature

If there is a causal link between temporality and adherence to medication in chronic diseases, it could be expected that non-adherence would be more frequent in younger people, who have been found to have greater difficulty in imagining the person they want to protect by adherent behaviour [25] and for whom the disease will last longer. This effect of age has been observed

consistently in adult patients with type 2 diabetes [11,37] as well as in adolescents and young adults with type 1 diabetes [38]. Adolescents have also been found to be less compliant than adults in the use of glucose sensors, which explains why the beneficial effect of continuous glucose monitoring on HbA_{1c} was only observed for adult patients in the Juvenile Diabetes Research Foundation trial [39]. Data from the transplantation literature also support this idea: adolescents who were not adherent to immunosuppressive drugs were found to be less mature than adherent patients, to focus less on long-term goals vs. short-term strategies and not to prefer delayed vs. instant gratification [40]. Finally, a causal link between temporality and adherence would also be consistent with the fact that non-adherence is more frequent in socially deprived patients, whose most immediate priorities may not include their health status [41,42].

Examination of the hypotheses in the light of neuro-economics

When asked to choose between receiving €500 today and €1500 a year from now, about two-thirds of respondents choose the immediate, smaller reward. This suggests a high rate of value discounting, leading them to think that €1500 in one year has much less value than €500 today (for example, they may consider the future larger amount to be worth only €200 today) which leads them to choose the small instant reward of €500. Time discounting is best described by a hyperbolic function, such as V = V0/(1 + kt), as indicated in Fig. 1 [43]: valuations decrease relatively rapidly for earlier delay periods and subsequently decrease more slowly.

Fig. 2 shows two curves obtained for two values of *k*: 0.01 and 0.05. The discounting rate is stronger for the high value of k, which can thus be used as a coefficient of impatience or impulsivity. A rich literature shows that this impulsivity coefficient is higher in smokers [44], in various types of addicts (review in [45]) and in obese women [46]. The same observation has been made with a fictive monetary choice proposed to adults and adolescents: adolescents were more impatient than adults and a significant positive correlation was found between the area under the curve of the value of depreciation (reflecting the level of patience, see Fig. 2) and age, with changes continuing beyond 25 years old [47]. I propose that these data are relevant to understanding the gradual onset of adherence at adulthood [11,37].

The hyperbolic nature of time discounting described above has an important consequence: when one puts the curves corresponding to a smaller-sooner reward (the dessert at the end of dinner) and a larger-later reward (becoming thin again to preserve my health) on the same figure, they intersect, implying the presence of a preference reversal (Fig. 3): it then becomes rational to choose the smaller reward, i.e. to make the choice of non-adherence [30,48,49].

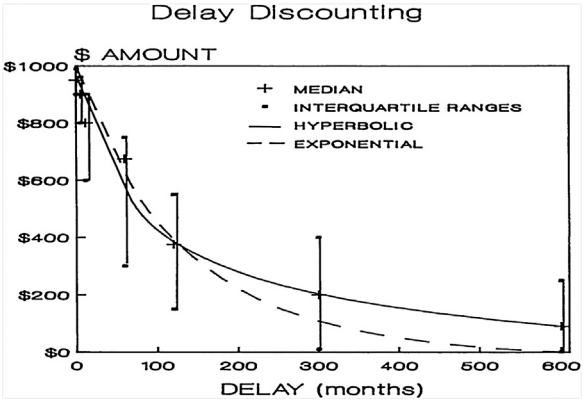

Fig. 1. Demonstration of hyperbolic time discounting. People were asked to indicate the values equivalent to $1000 given today, if received in 1, 6, 12, 60, 120, 300 or 600 months, respectively. The figure shows that a hyperbolic function fits the data (median values of distributions) better than an exponential function. From Rachlin et al. [43], copyright 1991 by the Society for the Experimental Analysis of Behavior, reproduced with permission.

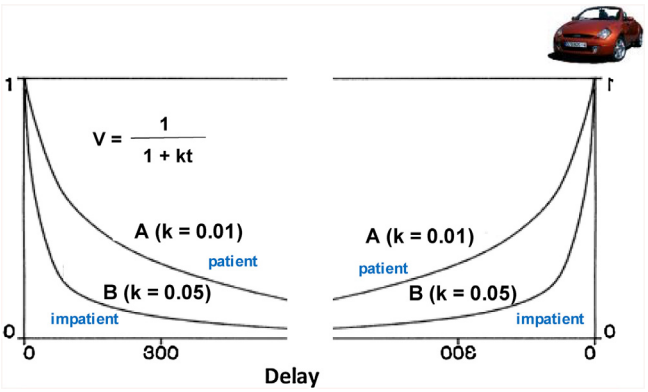

Fig. 2. Coefficient *k* of the hyperbolic function describing time discounting describes the degree of impatience. Left: hyperbolic curves showing two values of k. The higher the value, the greater the time discounting. B is more impatient than A. Right: curves constructed from the left curves by a rotation around a vertical axis. They represent the force of the desire. The figure displays desire curves for a patient (k = 0.01), and an impatient (k = 0.05) individual who booked a car, supposed to be delivered within 600 days. The night before delivery, the force of the desire will increase like an asymptote (hyperbolic function), and more abruptly in the impatient individual. Note that the area under the curve (AUC) can be used as an index of patience.

Examination of the hypotheses in the light of neuroscience

Prioritising the future, which would represent, according to our A* hypothesis, a condition of adherence, is an aspect of the so-called executive functions, which neuroscience has demonstrated are localized in the prefrontal cortex. This idea is consistent with clinical observations, such as the strange case of Phineas Gage, an engineer who worked on the railroad in the pre–Civil War United States. On September 13, 1848, an iron bar passed through his skull; however, he survived the accident. Using anatomical studies, the neurologist Antonio Damasio succeeded in demonstrating that the bar had injured Gage's orbitofrontal cortex. Damasio wrote in his book *Descartes' Error* about the clinical descriptions written by Gage's first doctor: after his accident, he became impulsive and rude, incapable of carrying out long-term projects of any sort or making appropriate decisions when playing cards and assessing the value of goods [50].

The same study [47] that examined patience in adolescents and young adults highlighted the linear evolution of the control of limbic structures by the prefrontal cortex from 10 to 35 years old. The intensity of this takeover, as determined by brain imaging, positively correlated to the degree of impulsivity in the monetary choice. Furthermore, it also seems that the limbic and executive systems do not develop in a synchronous way: a study in functional RMI showed that the activity of the nucleus accumbens in adolescents is similar to that seen in adults, while the activity of the orbitofrontal cortex remains similar to that of a child. This suggests a high ratio of nucleus accumbens to orbitofrontal cortex activity in adolescents, which could explain the risk-taking behaviours observed at that age, and possibly, non-adherence, which would represent another manifestation of risk taking (review in [51]).

In the same vein, a study in RMI showed that the activation of different brain regions during the making of a monetary choice

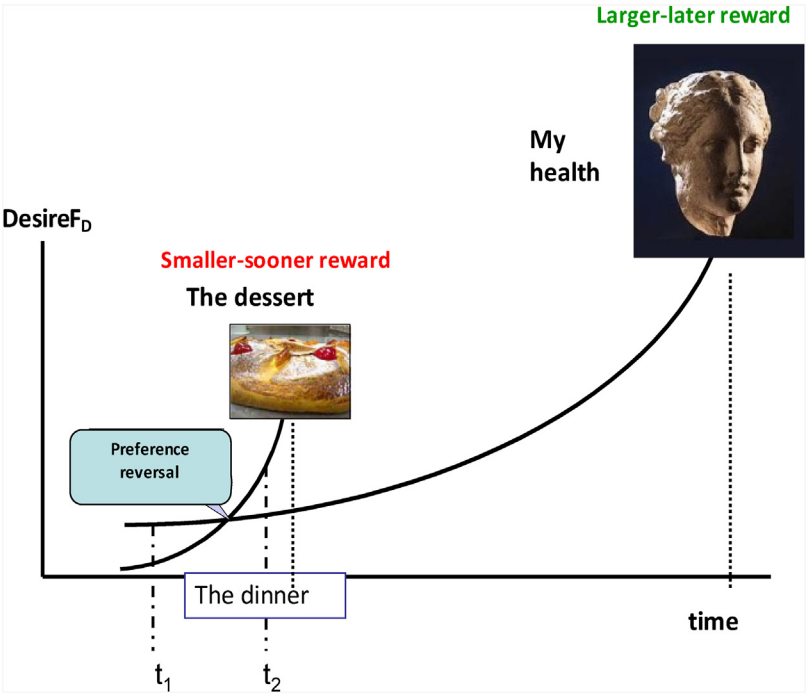

Fig. 3. Intertemporal choice. t_1: when I enter the restaurant, the value given to the preservation of my health is higher than that attributed to the dessert, and I have decided to avoid it. t_2: after preference reversal, it becomes rational to order the dessert.

depends on the genetic polymorphism of catechol-*O*-methyl transferase, an enzyme involved in the metabolism of dopamine [52]. This polymorphism has been found to be associated with brain development in children and adolescents [53]. This could have been expected, relative to the effects of the dopaminergic level on the respective control by the prefrontal cortex and the limbic system (amygdala, hippocampus) of the nucleus accumbens: for high dopaminergic levels, the prefrontal cortex is dominant; for the average dopaminergic level, the amygdala and hippocampus control the activity of the nucleus accumbens, leading to impulsivity ([54], review in [55]).

In summary, the hypothesis of the involvement of the relationship to temporality in adherence or non-adherence to long-term therapies for chronic disease appears to be plausible because it is consistent with epidemiological data from the literature (which show poorer adherence in young people and in the socially deprived) and because a physiological substratum may exist in the form of control by the executive functions of impulsivity.

Experimental verification of the hypothesis

As noted by Sami Paavola, the process of abduction, which intends to find an explanatory hypothesis when confronted with a surprising phenomenon, follows a strategy:

> "So if I am a researcher looking for a good explanatory hypothesis for some anomalous phenomenon, I can (and must) try to constrain and guide my search by taking into account that my explanation must explain or at least be consistent with, most other clues and information that I have available concerning the subject matter. And I try to anticipate that my explanation has some chance of survival in subsequent tests and assessments" [56].

Therefore, hypothesis verification is a part of this strategy. Similarly, Claudine Tiercelin proposed that abducted hypotheses must be tested before being adopted, because they should be seen as an inference, "not to a strong explanation, or even to 'the best explanation', but only to a good explanation" [57,58]: according to Peirce, "any hypothesis may be admissible, in the absence of any special reason to the contrary, provided it be capable of experimental verification, and only in so far as it is capable of such verification" [59]. In the same line, Peter Medawar, the 1960 Nobel Laureate for Medicine and Physiology, who called for scientists not to fall in love with their hypotheses, stated the following:

> "I cannot give any scientist of any age better advice than this: the intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not. The importance of the strength of our conviction is only to provide a proportionally strong incentive to find out if the hypothesis will stand up to critical examination" [60].

The following part of this article will therefore review data from five empirical studies, performed over the last 10 years and intended to test our hypothesis prospectively.

In the first study [61], the participants were 90 outpatients with type 2 diabetes being treated at a prevention centre. Their mean age was 59 years old, their mean time since diabetes diagnosis was 12 years and their mean HbA_{1c} level was 7.6%. They were asked whether they would choose €500 today, €800 in four months or €1500 one year from now. From these options, 47, 4, and 39 patients chose €500, €800 and €1500, respectively. Nine subjects only were categorized as non-adherent according to their responses to a questionnaire investigating adherence. Not one of these subjects gave the most patient answer for the fictive monetary scenario (declaring that they would wait one year to get the €1500) ($P = 0.005$), and not one had an $HbA_{1c} < 7\%$ ($P = 0.011$). Furthermore, multivariate analysis indicated that impatience (not waiting one year) was an independent determinant for $HbA_{1c} \geq 7\%$ [RR = 5.1 (1.7–15.4), $P = 0.004$].

In the second study [62], 93 patients were recruited from diabetes departments at two hospitals. A computerized fictive

monetary choice was used to measure delay-discounting k coefficients. A positive correlation was found between delay discounting and HbA_{1c} levels ($P = 0.023$), confirming the evidence of the previous study that impatience is associated with poor metabolic control in diabetic patients. This association was partially mediated by adherence to medication.

The third study [63] had as participants 670 obese patients with type 2 diabetes and a median HbA_{1c} 7.0%. Of these patients, 60.6% gave a negative answer to the question of whether they prioritised the future, and the percentage of the negative response was higher among non-adherent patients (70.0% vs. 58.3%, $P = 0.013$). This study showed that there is a role for disobedience in the genesis of non-adherence: 32.2% of patients responded negatively to the question: do you fasten your seatbelt when you are in the back of a car, and the percentage of this negative answer was twice as great in the non-adherent patients (51.1% vs. 27.5%, $P < 0.001$). Fig. 4 shows a multiple correspondence analysis of the data: the dots distinguish two non-overlapping clusters of patients, defining adherent and non-adherent behaviour. This figure illustrates four axes, linking the Yes–No answers to questions on adherence, seatbelt behaviour (obedience), motivation and priority given to the future. It also suggests a link between adherence and trust in the doctor's recommendations.

In the fourth study [64], 1214 people with type 2 diabetes who participated in a health panel on a regular basis, whose median age was 69 years old and whose mean HbA_{1c} level was 7.15% were included. They were adherent in general, as seen in the fact that 46.2% of them gave no positive answer in response to the six-item adherence questionnaire (good adherence), 48.9% gave less than three positive answers (modest adherence) and only 4.9% gave three or more than three positive answers (poor adherence). This high adherence rate may be related to the fact that these participants were recruited from a panel of people who were being surveyed for their health. They were questioned on their patience (given a fictive monetary choice between €500 today or €1500 in one year) and temporal horizon (with the event and story method, as described above) [27]. Table 1 gives data from a multiple correspondence analysis that separated the patients into three groups: non-adherent, adherent but socially deprived and adherent and not socially deprived. This confirmed the association of patience with adherence ($P < 0.001$) and of disobedience (seatbelt not fasted in the back of a car) with non-adherence ($P < 0.001$). Adherent but socially deprived patients had no projection to the distant future (as determined using the event method), suggesting that there is an effect of social deprivation on personal temporal horizon ($P < 0.001$). This study found that non-adherent patients, who in general were socially deprived ($P < 0.001$), projected themselves well into the future using the event method ($P < 0.01$). I speculated that there is an effect of denial to explain this unexpected observation, this speculation being consistent with the fact that the story method, which evaluates someone else's temporal horizon, did not show this effect. This study demonstrated also the existence of a link between trust in one's doctor ($P < 0.001$) and adherence to medication therapy, between fidelity to habits and adherence ($P < 0.001$), and between a chance-locus of control and non-adherence ($P < 0.001$).

Finally, the full verification of the hypothesis of the involvement of disruption in time projection in non-adherence to long-term medication therapies was carried out in a fifth study [65], which examined 120 hospitalized subjects with type 2 diabetes. Their mean age was 58.6 years old. As expected, these hospitalized patients had poor metabolic control (mean HbA_{1c} 9.8%) and were in general poorly adherent [14] because only 39.2% of them gave less than three positive answers to the six-item adherence questionnaire. This questionnaire addressed three psychological constructs that defined time projection: patience/impatience in a fictive monetary scenario (preferring €1500 in one year or €500 today), the magnitude of temporal horizon (greater or lesser ability to imagine future events according to the two methods described above [27]) and the perception of one's degree of physical similarity to one's current self at 1, 5 and 10 years, as described by Frederick [25]. The questionnaire evaluated also adherence to medication,

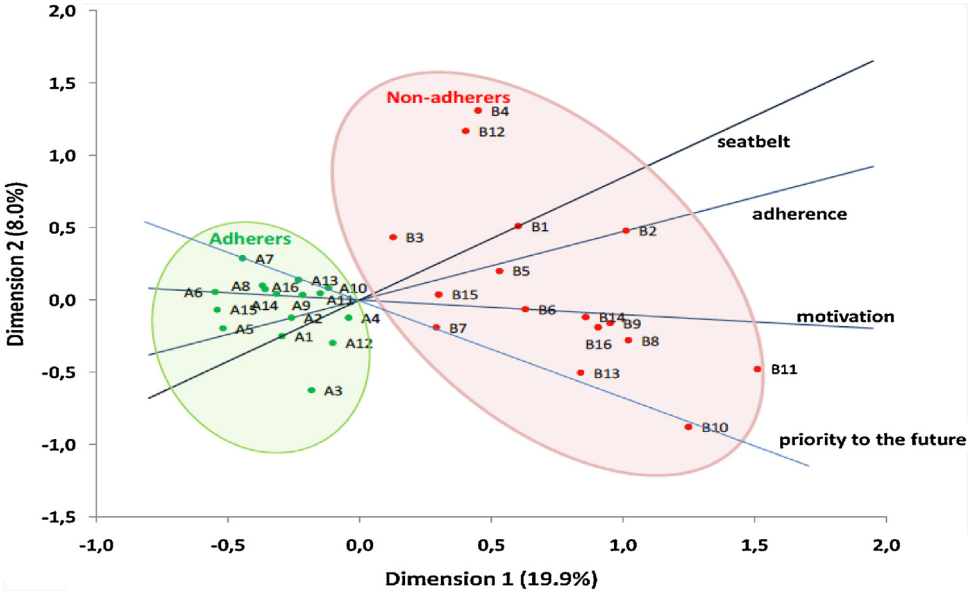

Fig. 4. Obedience, adherence, motivation and prioritisation of the future in a multiple correspondence analysis. A1: seatbelt fasteners, B1: seatbelt non-fasteners. A2: adherers, B2: non-adherers. A3: $HbA_{1c} \leq 7\%$; B3: $HbA_{1c} > 7\%$. A4: nonsmokers; B4: exsmokers/current smokers. A5: follows weight on a regular basis; B5: does not follow weight. A6: motivated; B6: not motivated. A7: priority to the future: yes; B7: priority to the future: no. A8: ready to make efforts to improve diabetes control; B8: not ready. A9: recommendations are too strict: disagree; B9: recommendations are too strict: agree. A10: not interested in changing lifestyle: disagree; B10: not interested in changing lifestyle: agree. A11: not a priority: disagree; B11: not a priority: agree. A12: have no time: disagree; B12: have no time: agree. A13: your health depends on you: agree; B13: your health depends on you: disagree. A14: your health is very important: agree; B14: your health is very important: disagree; A15: the opinion of your family is very important: agree. B15: the opinion of your family is very important: disagree. A16: following doctor's recommendations is very good: agree; B16: following doctor's recommendations is very good: disagree. From Reach [63].

Table 1
Three psychosocial groups of patients, as determined by multiple correspondence analysis.

Least adherent patients: (n = 299)	Most adherent and most socially deprived patients (n = 416)	Most adherent and least socially deprived patients (n = 499)
Disobedient (seatbelt question)[c]	Obedient (seatbelt question)[b]	Obedient (seatbelt question)[a]
High reactance[c]		
Risky behavior[b]	Cautious behavior[c]	Optimist[c]
Locus control on chance[b]		Locus control on doctors[c]
Have no trust in doctors[c]		
Do not get the flu vaccine[c]	Flu vaccine[a]	
Influenced by publicity when buying something[c]		
Break habits often[c]		Do not break habits easily[c]
	Patient[c]	Patient[c]
Project themselves in the future in events method[b] (NS for story method)	No projection in the distant future[a]	
Tendency to morbid obesity[c]	Tendency to severe obesity[b]	Tendency to normal weight[a]
Current smoker[c]	Non-smoker[c]	Previous smoker[c]
	Poor glycemic control[a]	Good glycemic control[a]
	Woman[c]	Man[c]
Employee or manual worker[c]	Rather elderly[c] and retired[c]	Rather elderly[c] and retired[c]
Socially deprived[c]	Low education level[c]	Tendency to be well educated[c]

From Reach [64].
[a] $P \leq 0.05$.
[b] $P \leq 0.01$.
[c] $P \leq 0.00$.

social deprivation and depression. From multivariate analyses, two factors were found to be associated with adherence to medication: patience ($P < 0.001$) and long temporal horizon ($P = 0.006$). Two determinants were associated with $HbA_{1c} \geq 8\%$: non-adherence ($P = 0.003$) and reduced temporal horizon ($P = 0.011$). The data also suggested that the effects of depression and social deprivation on patient adherence are mediated by disruption in time projection. Finally, an association of non-adherence to low expected physical similarity of one's current self to one's future self, impatience, short temporal horizon, social deprivation and depression, sadness and pessimism was also shown in a multiple correspondence analysis, which separated patients into three groups: adherent patients and two groups of non-adherent patients. One of these latter groups appeared to represent a less severe form of non-adherence, differing only from the group of adherent patients by their younger age, an absence of grandchildren, a shorter temporal horizon and a higher HbA_{1c} level (Table 2).

In summary, the data of these studies appear to verify the existence of a link between what I called a disruption in time projection, with three components (impatience, short temporal horizon and low expected physical similarity of one's current to one's future self) and non-adherence to medication. In addition, impatience in a monetary choice has also been found to be associated with poor adherence to medication in asthma [66] and to the presence of obesity [46] and overweight [67,68]. It goes without saying that other factors may play a role in the genesis of adherent/non-adherent behaviour, some of which have been determined in the studies described above, such as obedience (see Fig. 4, reprinted from study 3, and Table 1 from study 4), trust in the doctor (from studies 3 and 4), fidelity to habit (from study 4), risky or cautious behaviour (from study 4), reactance (Table 1 from study 4: reactance refers to the resistance by some persons against attempts to constrain either their thoughts or their behaviors, leading them to believe that their freedom is threatened [69,70]). In particular, the importance of patient–doctor trust for the genesis of adherence cannot be overlooked [71–73]. Together with the force of habit [74], it may represent a modifiable [72] factor for improving adherence. Finally, our data suggest a role for the locus of control (Table 1 from study 4). This is consistent with the fact that an internal locus of control is associated with good adherence [75]. Locus of control may also represent a target of patient education.

A model of adherence to long-term therapies

Fig. 5 represents a tentative model of psychosocial determinants of adherence based on these empirical data. It highlights the role of time projection in the genesis of adherence to long-term therapies. It describes the complexity of the mechanisms that in fine lead people to be adherent or non-adherent to long-term therapies in chronic diseases. These mechanisms may have contradictory or synergistic effects, explaining the variance and fluctuations of the phenomenon. For instance, non-adherence may

Table 2
Three typologies of patients, demonstrating the role of disruption in time projection in non-adherence to long-term therapies.

Adherent (n = 26)	Non-adherent (1) (n = 59)	Non-adherent (2) (n = 35)
Age $\geq$ 60 years old	Age < 60 years old	
Diabetes duration > 20 years	Diabetes duration 11–20 years	
Temporal horizon > 5 years	Temporal horizon 2–5 years	Temporal horizon $\leq$ 1 year
Similarity > 50% in 10 years		Similarity in 10 years $\leq$ 50%
Patient		Impatient
Grandchildren	No grandchildren	
HbA_{1c} < 8% (64 mmol/mol)	$HbA_{1c} \geq 8\%$ (64 mmol/mol)	
Not socially deprived		Socially deprived
Not depressed		Depressed
Not sad		Sad
Not pessimistic		Pessimistic
Quit smoking	Never smoked or still smoke	

From Reach [65].

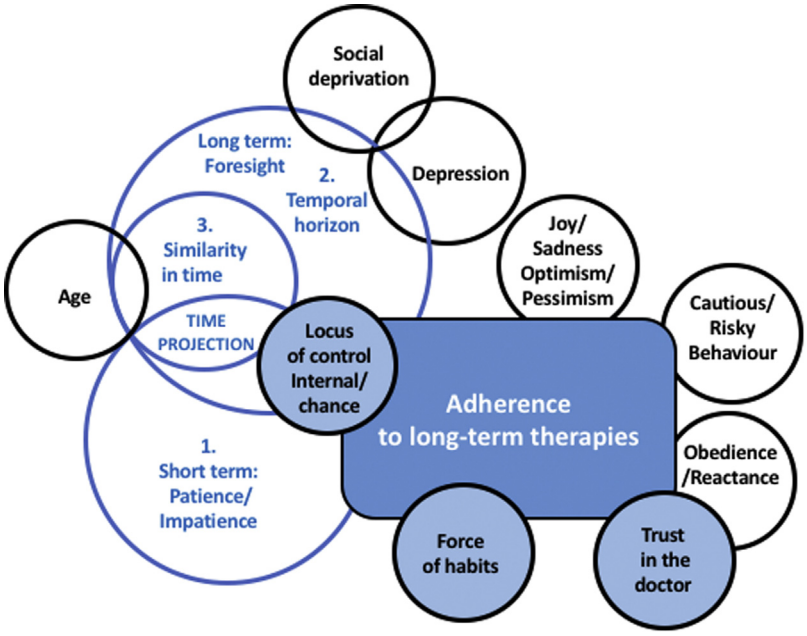

Fig. 5. A psychosocial model of adherence to long-term therapies. This tentative holistic model of adherence to long-term therapies, in which the importance of time projection is highlighted, is based on empirical data gathered in studies [61–65]. Notably, the effect of age, social deprivation and depression is mediated in this model by time projection, with its three components, that is, on the short-term, patience/impatience, and on the long-term, temporal horizon and similarity in time (the ability of self-projection in the frame of the temporal horizon), i.e. foresight. We suggest that the ability of time projection is an internal locus of control aspect. The model, also representing the intervention of other psychological determinants of adherence/non-adherence, illustrates the complexity of these mechanisms, which may have contradictory or synergistic effects. Finally, the force of habits, trust in the doctor (i.e. the quality of the patient-physician relationship), and locus of control (through patient education) may represent modifiable factors for adherence improvement.

be quite frequent in teenagers because both impatience and disobedience are expected at that age. Finally, we suggest that the ability for time projection may be involved in the internal locus of control.

This model could be useful in creating a paradigm for future studies, addressing questions such as the following: What are the cerebral substrata of foresight and patience, of obedience, disobedience and reactance, of sadness and pessimism, of risky or cautious behaviour, and of locus of control (including chance or trust in the doctor)? Are such character traits innate or acquired? Are they linked? Are they genetically determined [76]? Are they modifiable by the quality of the patient–physician relationship? What is the mechanism of action of habit [74]? Would it be possible to predict patients' health and disease status from phenotypical features shown on Fig. 5? Would it be possible to demonstrate a beneficial effect of presenting the short-term advantages of adherence to "impatient patients"? How can medical students be taught the concept of disruption in time projection (they could, for example, be instructed to incorporate questions on their projects in patient interview, in addition to the classical elements concerning their history)? Finally, if non-adherence in chronic diseases is the consequence of impulsivity, which would act as a cognitive bias [77], or of a patient's cold decision to prioritise the present, how can ethical interventions aimed at improving adherence be justified [78]? Would it be, for instance, ethical to propose a pharmacological intervention that decreases impulsivity to "impatient patients" with severe forms of non-adherence, if it proved to improve adherence?

Back to philosophy: a general meaning of adherence

Time projection is presented in Fig. 5 as having three components: the two first constructs, patience/impatience and temporal horizon, represent short- and long-term aspects, respectively, of time projection. The third, referred to as similarity in time, is the specific ability to foresee oneself physically in the frame of a more or less remote temporal horizon, and belongs, therefore, also to the long-term component of time projection.

As indicated above, most of the time, the neuronal realization of patience, i.e. the control of impulsivity, appears late in the course of cerebral maturation, perhaps marking the end of adolescence [47,51]. However, this ability to gratification delay, referred to here as patience, may appear very early in some children, as shown in the well-known marshmallow test [79], implemented by Walter Mischel, who gave four-year-old children a marshmallow, telling them that he would be absent for 20 minutes and that if, when he returned, the child had not eaten the first marshmallow, he or she would receive two. Some children were able to wait and received a second marshmallow. The experiment included interviews with the children who had managed to wait, inquiring into how they had resisted temptation: many children had spent the time imagining the marshmallow was a cloud. In other words, they had already developed the ability for abstraction that allowed them to delay gratification: they already had high-level concepts, as they were termed by Trope and Liberman [23]. Mischel followed the children in this experiment for 14 years and found that those who had been able to wait and could abstract had in later life received more schooling, had a more positive attitude about life and were better able to manage difficulties and implement long-term projects. This longitudinal study provides the evidence that patience, i.e. the ability to controlling impulsivity, grants an advantage to those people who have it.

I proposed that adherence to long-term therapies is linked to the existence of a philosophical principle, that I called "principle of foresight", that requires us to give priority to the future, forming with patience what is herein called "time projection". I suggest that, like patience, abiding by such a principle is beneficial on the long-term, consistently with Nozick's teleological posit that philosophical principles are devices developed for our good [33]. From an evolutionary point of view, time projection may represent the

culmination of a long process of hominization, which ultimately gave our ancestors a decisive advantage. Gratification delay exists also in pigeons and rats [80,81], but at a considerably lesser level than in human beings. Therefore, a high ability of gratification delay (patience) and foresight may represent specific human traits.

The conception of adherence described herein points a beneficial effect of time projection that is proposed to be one of its determinants. It may explain why healthy adherers, adherent even to a placebo, are found to live longer in randomized clinical trials [16]; on the contrary, non-adherence, being caused by a disruption in time projection, would reflect the absence of an eminently protective mechanism.

Conclusion

The investigation described herein exploited alternately philosophical (mental) and scientific (pathophysiological) approaches, as these two schemes represent two different ways, that is mind and body-centred, respectively, of describing the same entity [82]. What is described under time projection could actually encompass several philosophical and psychological descriptions of the cerebral executive functions that consciously guide behaviour in a reflective manner to give up short-term outcomes for beneficial long-term aftermaths. This can be achieved by inhibiting undesired automatic reactions and resisting visceral pangs, and prioritising the "high-level construals" described by Trope and Liberman [23,83]. Different avatars of the same concept include Mischel's "cool system" which makes delayed gratification possible [79], Alan Strathman's "consideration of future consequences" [84], Alfred Mele's "self-control" [85] (of note, Mele used the lack of self-control as an explanation of the weakness of will), Roy Baumeister's "willpower" [86], Richard Holton's "strength of will" [87], George Loewenstein's "rational self-interest" [88], and finally Harry Frankfurt's "self-love" [89,90].

Indeed, one might wish to assimilate the "principle of foresight", which I serendipitously discovered in the course of my enquiry on the cause of non-adherence, to Freud's life-sustaining *Eros* instinct that thwarts and combats *Thanatos*, the death instinct [91,92]: physicians who have patients under their care who exhibit severe forms of non-adherence often have the feeling that their patients' actions constitute nothing but a suicide in disguise. Next, leaving Sadness for Joy, one may also see this principle of foresight as the way which nature took to invent a mechanism to give human beings the unique possibility of reinforcing, through the development of the prefrontal brain and for their best interest, the Spinozian *Conatus*, thanks to whom "each thing, as far as it can by its own power, strives to persevere in its being" [93].

Disclosure of interest

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