4 From Laboratory to Clinic and Back: Connecting Neuroeconomic and Clinical Measures of Decision-Making Dysfunctions

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Introduction

Impairments in financial and social decision-making capacities are a common symptom in a number of neurological and psychiatric disorders. Such impairments have significant impact on quality of life and overall health outcomes. The NIH estimates that nearly 40 % of the risk of early preventable death in the U.S. is caused by human behavior (Office of Behavioral and Social Sciences Research 2010). However, unlike memory and motor impairments, which are readily recognized as symptoms of more serious underlying neurological conditions, we still largely lack measures to characterize decision-making deficits in clinically meaningful ways.

In the past, the lack of clinical knowledge to tackle to complexity of behavior was compounded by the lack of scientific knowledge on the biological basis of decision-making, at both neural and molecular levels. In the past decade, however, rapid progress has been made in our understanding of neural circuits and neuromodulatory systems that underlie economic decision-making. Moreover, this collaborative effort, from researchers from neuroscience, economics, and psychology, has produced a set of experimental tools that are of great potential value for clinical use (Maia and Frank 2011; Montague 2012). There is now substantial neuroimaging and neuropsychological evidence characterizing the set of brain regions that underlie decision-making, and the computations that are carried out in these regions (Schultz et al. 1997; Hsu et al. 2005; Kable and Glimcher 2007). Second, the experimental paradigms developed have now been used successfully in a number of neuropsychiatric and focal lesion patients, albeit still largely confined to research settings (Frank et al. 2004; Denburg et al. 2007; King-Casas et al. 2008).

Moreover, these applications go beyond relatively simple forms of risk-reward tradeoffs and toward decision-making in the social and interpersonal domains (King-Casas et al. 2005; Fehr and Camerer 2007), which represent some of the most poorly measured forms of dysfunction in clinical settings. The ability to make good decisions in has potentially vast real-world implications. First, we spend much of our lives devoted to the accumulation of financial and social prosperity, and often with much success. To take just one measure, the median net worth of a 65-year-old American in 2007 is more than

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double that of a 40-year old (Bucks et al. 2009). For many, however, such wealth comes at a vulnerable time when the cognitive and neurological apparatus that made this possible is beginning to break down (Plassman et al. 2008). It is well known that the elderly are disproportionate targets of fraud across the world, and constitute a conservatively estimated 30 % of all fraud victims in the United States (Templeton and Kirkman 2007; Bucks et al. 2009).

> Impairments in financial and social decision-making capacities have significant impact on quality of life and overall health outcomes, but clinical measures of dysfunction are largely missing. Recent neuroeconomic measures promises to provide such measures, but lack direct evidence that these measures capture clinically relevant behavior, in terms of abnormalities or deficits.

Despite the aforementioned advances, major gaps must be bridged before our newly acquired scientific understanding of decision-making can be applied in clinical settings, to directly improve the care of patients. In particular, much work remains in order to map behavioral and neural measures derived from these paradigms to clinically relevant characteristics. Without this sort of convincing evidence of clinical utility, it is not apparent why neuroeconomic tasks deserve a place in the clinician's toolkit. Here we attempt to shed light on this gap and discuss current challenges in using neuroeconomic measures to: (1) map clinical descriptions of decision-making impairments to laboratory measures and (2) refine and quantify these descriptions. Next, we will focus on a largely untapped source of clinical data in medical charts, which constitute a rich source of primary data, and have been largely untapped in translational research.

The organization of the paper is as follows: Sect. "Neuroeconomic Framework" will provide a selective review of current models and evidence on neural systems underlying decision-making. We will also discuss current approaches to translation research, and the challenges that face them. In Sect. "Medical Charts and Patient Data," we discuss ways to leverage clinical information contained in medical charts, and how neuroeconomic measures can be used to organize these information, and how the two can be combined to generate novel insights that cannot be using either method alone. In Sect. "Conclusion," we conclude by discussing scientific and ethical challenges to a fuller integration of these sources of experimental and clinical data.

Neuroeconomic Framework

Neuroeconomics Is an Old Idea

The conscious application of economic models to understand the inner workings of the brain is largely a new endeavor, dating back only a decade or so (McCabe et al. 2001; Glimcher 2002). However, the study of the biological basis of economic behavior has been with us dating back to the founding of ethology by Lorenz and Tinbergen. Classic works by Tinbergen (1951, 1953), for example, studied bird behavior in the context of what an animal gains by making a decision, including foraging and prey–predator interactions. Economic decision-making, in the sense of acquiring rewards and avoiding punishments, can be clearly seen to fall under the broad umbrella of this scientific tradition.

What changed with the introduction of experimental and behavioral economics ideas into the neuroscientific study of value-based decision-making is twofold. First, experimental economics has provided a broad set of experimental paradigms that have proven to be highly amenable to neuroimaging and neuropsychological studies of behavior in humans. In contrast, previous animal behavior and ethological studies are often naturalistic and difficult to implement in humans due to logistic and ethical constraints. Second, economic theory has provided a set of rigorous and quantitative models of behavior, spanning from relatively simple individual costs-benefit decision-making (e.g., portfolio choice) to complex social and strategic interactions between multiple individuals and groups (e.g., bargaining).

For example, risk taking has been a prominent area of research in neuroscience prior to the introduction of formal economic models (Miller 1992; Bechara et al. 1997). However, there was considerable ambiguity in interpreting subjective attitudes toward risk, which often do not specify the fundamental variables that underlie risk perception and risk taking. Borrowing conceptualizations of risk in economics and finance, neuroeconomic studies model the risk people face in the environment as probability distributions of rewards (Fig. 4.1a). For example, a simple binary outcome lottery is defined by the probability p of winning a larger prize x and the complement $1 - p$ of winning the alternative, smaller, prize y. The risk *preference* or *attitude* of the person is defined by whether they prefer this lottery to its expected value of $p \cdot x + (1 - p) \cdot y$. A person who prefers the lottery to its expected value is said to be risk *seeking*. In contrast, a person who prefers the expected value is said to be risk *averse*. Finally, a person who is indifferent is risk *neutral*. More importantly, the neural correlates of risk processing can now be isolated by systematically manipulating the probability and reward magnitude of the gambles (Kuhnen and Knutson 2005; Preuschoff et al. 2008; Hsu et al. 2009).

Such a quantitative framework has been applied with equal, if not more success, in social behavior. In interpersonal interactions, outcomes are often determined by joint actions of multiple individuals. Here, in addition to learning about rewards and punishments available in the environment, people also need to anticipate and respond to actions of others cooperating or competing for the same rewards. In evolutionary biology and economics, these interactions are described formally using the language of game theory (Fudenberg and Levine 1998; Hofbauer and Sigmund 1998). Specifically, in addition to representing feasible set of rewards and actions available in the environment, people need to also form and update expectations about the actions and consequences of other individuals in the social environment (Fig. 4.1a). Similarly to risk, by manipulating these actions and consequences, the neural correlates of social decision-making can be characterized by manipulating the expectation and consequences of the actions of others (King-Casas et al. 2005; Zhu et al. 2012).

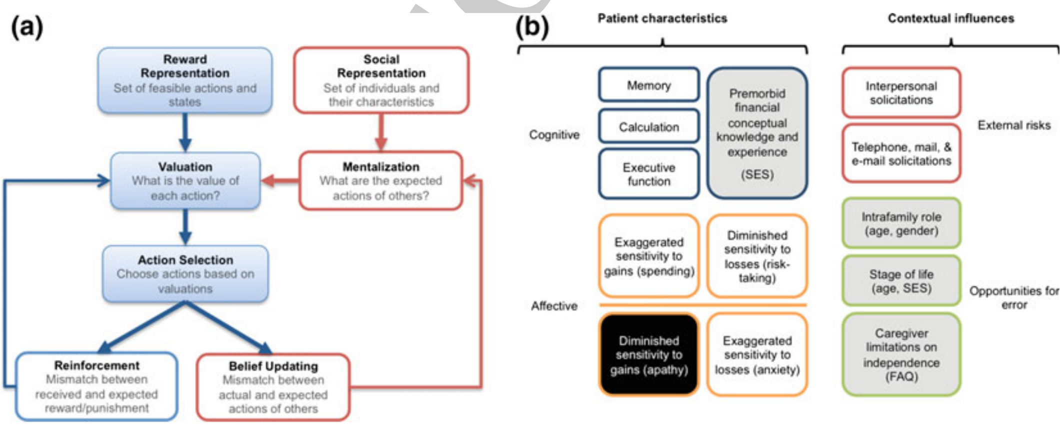

Fig. 4.1 **a** Economic decision-making in both individual and social (i.e., interpersonal) domains can be described as a series of processes that allows organisms to assign appropriate values to different actions and learning to optimize these action over the course of time. In the social domain, addition to representing feasible set of rewards and actions available in the environment, people need to also (i) represent the set of individuals and their characteristics in the social environment—e.g., whether the situation is a cooperative or competitive one, (ii) form expectation about the likely actions of these individuals, and (iii) detect and correct errors in these expectations, e.g., whether a prosocial action has been reciprocated or betrayed. **b** Applying this framework to patient settings, however, require clinicians and researchers to include a host of characteristics that go beyond this framework, including (i) patient characteristics in other cognitive factors such as memory and affect, and (ii) contextual influences such as familial circumstances and wider social influences

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Neuroeconomics in Clinical Context

Beyond isolating specific computational variables that directly influence behavior, however, applications of neuroeconomic models to clinical populations must appreciate the fact that the variation encountered in the clinical context far outstrips those in the lab, or even in typical translational studies. For example, in typical laboratory experiments, participants are screened for memory and language impairments, as well as psychotropic medication. In contrast, these experimentally excluded variables account for much of the decision-making impairments encountered in clinical settings. In the real world, furthermore, economic decision-making is a multidimensional activity that depend upon myriad cognitive and affective resources (Marson et al. 2000), and is strongly influenced by one's social milieu and life circumstances. In addition to decision-making processes themselves, clinical characterizations must also be informed by alterations in cognitive and affective function in different syndromes, as well as account for contextual influences and premorbid individual patient characteristics (Fig. 4.1b). Individual patient cognitive characteristics include disease-related impairment in domains of "fluid" intelligence such as memory, calculation, and executive function, as well as premorbidly acquired "crystallized" intelligence in the form of stored financial conceptual knowledge and experience (Agarwal et al. 2008).

Neuroeconomic research also highlights the importance of affective factors in financial decision-making (Loewenstein et al. 2001; Knutson and Greer 2008); these may have particular relevance in the clinical setting given the recognized neuropsychiatric manifestations of different neuropsychiatric syndromes (Cummings et al. 1994; Levy et al. 1996). For example, applying prospect theory, the most established empirical account of decision-making under risk (Kahneman and Tversky 1979; Tversky and Kahneman 1992), we can distinguish between the disease-related alterations in affective responses to anticipated gains and to anticipated losses. Exaggerated affective responses to gains and blunted responses to losses (or other negative consequences) would predispose patients to errors such as overspending, risky investments, and criminality; while diminished responses to gains and exaggerated responses to losses would predispose patients to conservative decisions (which may or may not be appropriate), and also to anxiety and paranoia about financial matters.

Individual patient's cognitive and affective characteristics interact with contextual influences (Fig. 4.1b). For instance, patients with dementia are less able to critically evaluate telemarketing, e-mail, and personal solicitations. At the same time, if fraud perpetrators target the cognitively impaired, then patients may be at increased risk for receiving such solicitations in the first place (Templeton and Kirkman 2007). Meanwhile, other demographic characteristics may determine whether the opportunity arises for a patient to make a certain kind of error. Some patients, such as wives in some patriarchal cultures, have never have had responsibility for investments or checking, and so would be at less risk for errors in these tasks. Other errors arise in the context of financial issues specific to a stage of life (Nielsen and Mather 2011); for instance, middle-aged patients may be more likely than elderly patients to make errors in purchasing real estate. Finally, some patients' families may act preemptively to limit patients' financial independence and diminish the likelihood of subsequent financial errors, but this depends greatly on the social and family support available to the patient.

Current Translational Approaches

The scientific benefits of a mechanistic understanding of the neural substrates underlying decision-making include: (1) understanding subtypes of decision-making deficits or (2) inferring different causes of these deficits. Most existing measures of financial management in neuropsychiatric illness are primarily designed to identify patients who no longer have the capacity to manage their financial affairs independently. Such tests, however, do not address the many patients present for evaluation at an earlier stage, when they have concerns about their financial management or have made one or two financial errors, yet still manage their finances independently. Also, if risks for different types of error in different syndromes can be established, clinicians will be better-equipped to counsel patients and families to avoid situations that place them at greatest risk (Widera et al. 2011).

In order to justify their clinical application, neuroeconomic tools need to show either diagnostic or prognostic utility. On one hand, potential *diagnostic* applications may identify specific deficits that allow clinicians to recognize the presence of a previously undiagnosed disorder. For example, if certain diseases or injuries to specific systems with the brain are associated with distinctly aberrant profiles in (e.g.,) risk tolerance or temporal discounting, identifying impaired decisions consistent with these traits may allow clinicians to make earlier clinical diagnoses, allowing for earlier treatment and behavioral interventions. On the other hand, *prognostic* applications may be helpful, particularly for patients who have been diagnosed with a disease, in predicting what decision-making errors they might be at greater risk for in the future. This could be used to improve counseling for patients to help them to avoid fraud and other financial harms, and could also be useful for risk stratification to identify high-risk patients for targeted interventions and further study.

Here, by far the most common types of translational studies are those that extend laboratory measures of behavior to clinical populations. For example, Hsu et al. (2005) was able to find behavioral differences in patients with focal lesions to different regions using predictions derived from a neuroimaging study on normal healthy young subjects. Specifically, subjects were asked to choose gambles where the probability distribution was known versus where the probability distribution was unknown. There is substantial evidence that people are averse to the latter, even when normative decision theory suggests they should be valued equivalently (Camerer and Weber 1992). Using fMRI, the authors found a set of regions, in particular the lateral orbitofrontal cortex (LOFC) that showed greater activity under ambiguity compared to risk, whereas the reverse contrast showed greater activity in the striatum (Fig. 4.2a). This result is consistent with existing notions that expected reward differences due to ambiguity aversion is reflected in the striatum, and that LOFC signals uncertainty or salience about the environment. This latter hypothesis was then tested using focal lesion patients with damage to the LOFC. Compared to the control lesion group consisted primarily of temporal pole patients, LOFC patients exhibited less sensitivity to uncertainty in the gambles per se, and were nearly risk and ambiguity neutral (Fig. 4.2b). These results thus were able to shed light on the role of OFC in processing of uncertainty in general, and advance our understanding of the complex affective and behavioral deficits found in neurological patients with damage to the OFC (Bechara et al. 2000).

In the social domain, these paradigms have been successfully applied even in psychiatric disorders, where the etiology is much less clear and diagnostic categories remain controversial (Insel and Fernald 2004). Using an economic exchange task called the Trust game, King-Casas et al. (2008) scanned healthy and borderline personality disorder (BPD) patients during game play (Fig. 4.3a). BPD is a poorly understood mental health condition characterized by long-term patterns of unstable or turbulent emotions. These inner experiences often result in impulsive actions and chaotic relationships with other people (First and Gibbon 1997). The rules of the game are that an investor (always a healthy subject) can invest an amount x between \$0 and 20 in the trustee. The amount is tripled to $3x$ by the experimenter, and the trustee can decide to give back to the investor anywhere between \$0 and $3x$. The game is then repeated 10 times during the course of the experiment. Behaviorally, whereas the healthy-healthy pairs were able to sustain cooperation through the course of the 10 rounds, the health-BPD pairs experienced significant breakdown in trust, such that investment levels were much lower in the latter portions of the experiment. Neurally, the BPD trustees exhibited diminished responsivity in the insula to inequity signals that were present in the

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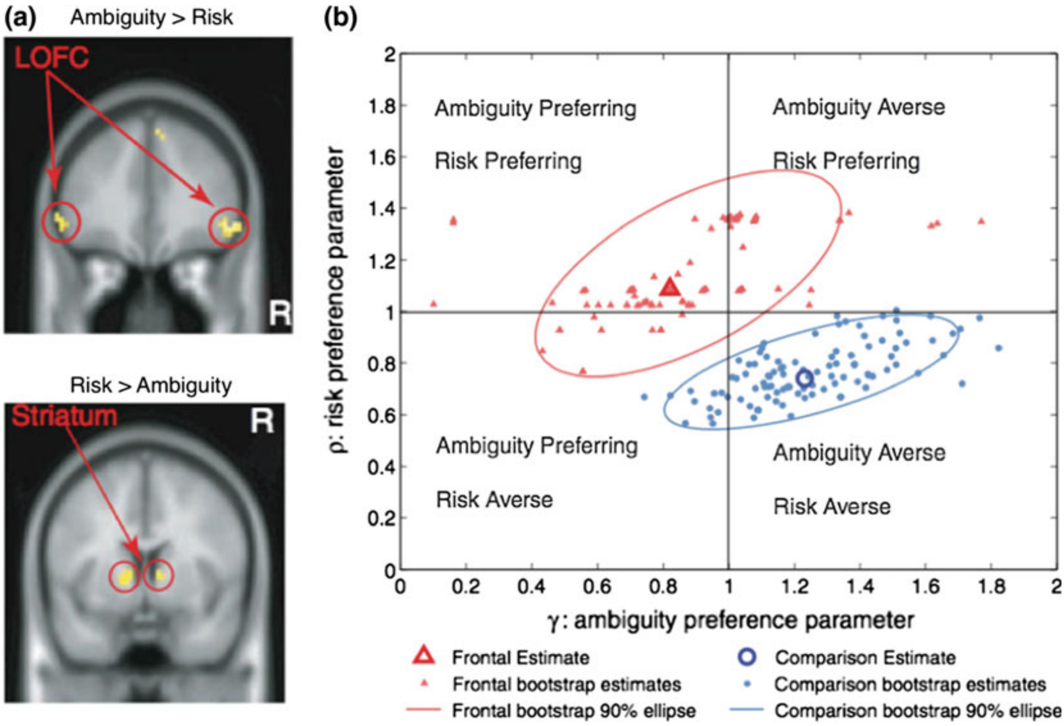

Fig. 4.2 **a** When participants did not know probability distribution of the gambles (ambiguity), areas of activation included the lateral orbitofrontal cortex (LOFC). In contrast, when the probability distribution is known (risk), the dorsal striatum was significantly activated relative to the ambiguity condition. **b** Using focal lesion patients with LOFC damage, it was found that patients with LOFC damage was significant less ambiguity and risk seeking compared to control patients with lesions in the temporal pole (adapted from Hsu et al. 2005)

investors (Fig. 4.3b). These results provide suggestive evidence that this response might serve as a possible neural marker for BPD.

Medical Charts and Patient Data

Despite these successes in applying neuroeconomic measures of behavior to clinical populations, to date there has been little direct evidence that these measures capture *clinically relevant* behavior, in terms of abnormalities or deficits. That is, does increase risk seeking behavior as assessed in an economic task, or abnormal reward-related neural response as measured in fMRI, predict increased financial risk taking in day-to-day life? One approach to evaluation would insist that such tests undergo clinical trials, in the same manner as medical diagnostic procedures and treatments (Fig. 4.4a). Such an approach may well be amenable to a select set of tools that tackle the most urgent (or particularly well-understood) problems. It goes without saying, however, that this route is inaccessible for the vast majority of basic science researchers, and puts significant barriers to researchers considering pursuing these questions.

Here we suggest that medical charts are a unique and largely untapped data source that can provide a partial answer to this problem, and may serve as a resource to connect basic and clinical researchers. Moreover, integrating neuroeconomic measures into medical charts would allow for a low-cost and continuous inflow of clinically relevant information that can be scientifically and clinically valuable (Fig. 4.4b). Medical charts offer a focused and unparalleled collection of clinically relevant descriptions of symptoms and

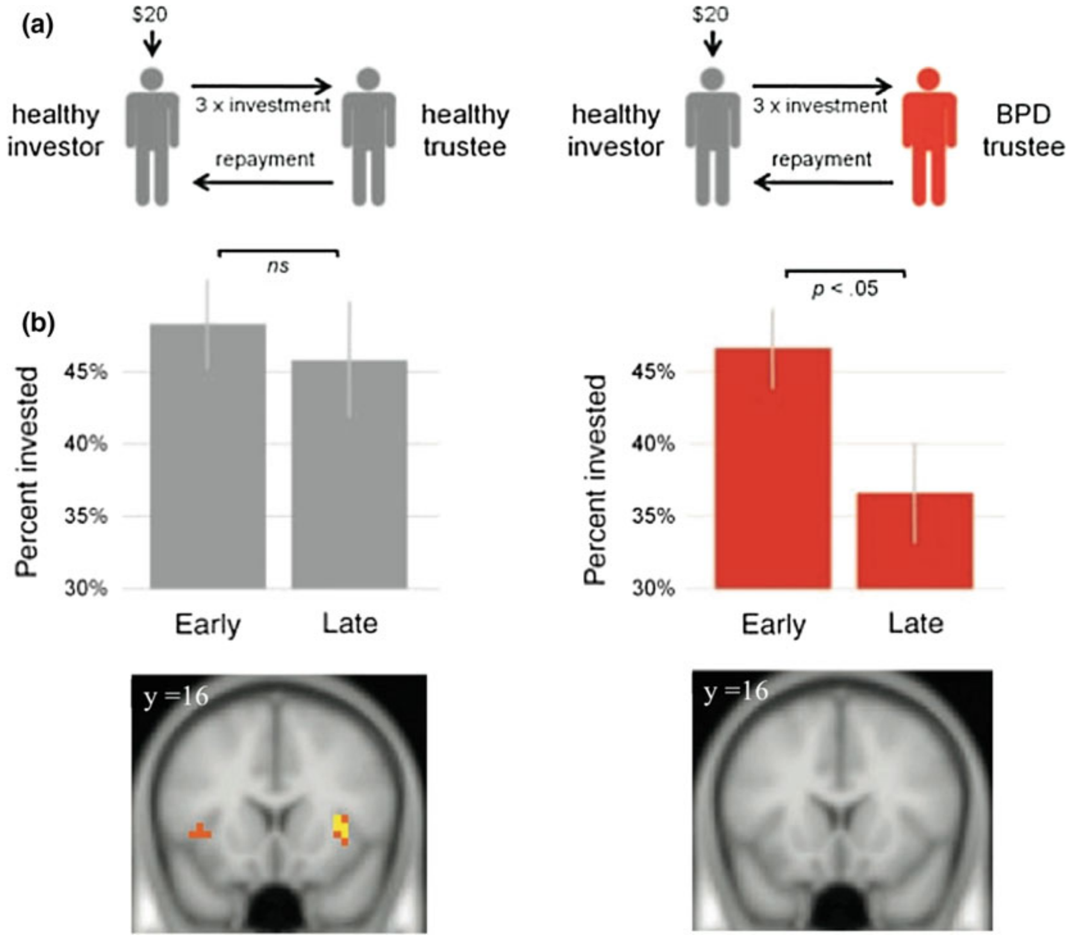

Fig. 4.3 **a** Healthy and borderline personality disorder (BPD) patients played an economic exchange task called the trust game. The rules of the game are that an investor (always a healthy subject) can invest an amount x between \$0 and 20 in the trustee. The amount is tripled to $3x$ by the experimenter, and the trustee can decide to give back to the investor anywhere between \$0 and $3x$. The game is then repeated 10 times during the course of the experiment. **b** Behaviorally, whereas the healthy-healthy pairs were able to sustain cooperation through the course of the 10 rounds, the health-BPD pairs experienced significant breakdown in trust, such that investment levels were much lower in the latter portions of the experiment. Neurally, the BPD trustees exhibited diminished responsivity in the insula to inequity signals that were present in the investors (adapted from King-Casas et al. 2008)

deficits. There is already a substantial agreement that patient's health records themselves constitute a valuable resource from a research perspective, and include "a computable collection of fine-grained longitudinal phenotypic profiles" (Jensen et al. 2012). While the data in these records have previously been scattered in paper charts across different physicians' offices (and therefore either inaccessible or only nonsystematically accessible for research), the ongoing adoption of electronic health records and shared protocols for transmitting data between medical practices is hoped to consolidate these data. These changes are expected to improve patient care, while controlling costs (Wu et al. 2006; although see Himmelstein et al. 2010) by limiting the unnecessary repetition of diagnostic tests and procedures, avoiding drug–drug interactions and other harms that may occur when providers are unaware of what other interventions have been prescribed by other providers for the same patient, and improving physicians' diagnostic

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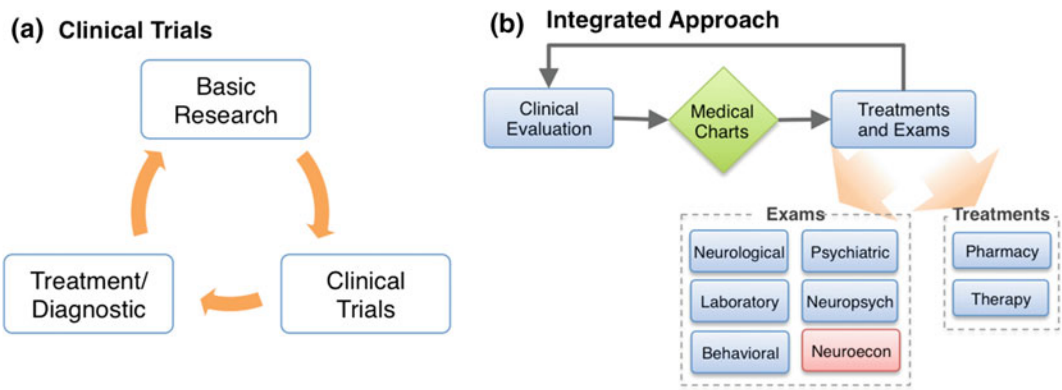

Fig. 4.4 **a** Typical translational approach using clinical trials. This is often most appropriate for novel treatment and diagnostic tools. **b** In contrast, in cases of the heterogenous set of neuroeconomic tools, it is more appropriate to incorporate measures directly in the clinician's toolkit, much as existing neuropsychological exams such as those for language and memory. These can then be refined and improved from scientific study of the relationship between test and clinical outcome

accuracy by having all relevant information readily available when the patient is seen. There is increasing interest from both the academicians and policy makers in connecting this rich domain of clinical information to scientific knowledge. This holds the promise of revolutionizing our classification, diagnosis, and prediction of diseases. Clinical texts in the form of written summaries are a cornerstone of clinical documentation. In the absence of standard behavioral or biological testing of decision-making deficits, these clinical narratives can be a key source of information regarding clinically relevant decision-making deficits.

> Medical charts offer a focused and unparalleled collection of clinically relevant descriptions of symptoms and deficits. These materials can be a unique and largely untapped data source to connect basic and clinical researchers.

Here we consider two broad approaches that could be pursued by researchers in utilizing data from these records; the choice of methods will depend in part on the nature of the records available to researchers, whether other forms of contact with patients are feasible, and on how research groups are able to manage the ethical and practical difficulties associated with research uses of clinical material. The first approach, which has been more extensively discussed in genetics and other domains of research using patient records (Jensen et al. 2012), is a "big data" approach using de-identified patient data from large groups. The second approach is a finer-grained approach correlating clinical data from identifiable patients with experimentally derived measures.

Big Data Approach

Proposed research uses of many other clinical records, as in genetics (Jensen et al. 2012) often involves a "big data" approach, where researchers gather the real-world data from community medical charts, and rely upon large numbers to compensate for the statistical noise of variations in individual physicians' documentation practices. Existing ethical and legal guidelines (discussed in greater detail in the following section) require, with some stringent exceptions, that these data be de-identified unless specific consent for use of these data is obtained. Since it would be impracticable for most research groups to obtain specific consent for such uses from (potentially) thousands of patients with whom they have no preexisting relationship, and since the validity of such "big data" approaches could be vitiated by selection effects (e.g., if the behaviors of patients who refuse to consent to the use of their data are different from those of patients who consent), a uniform approach utilizing de-identified data is most likely to succeed. After potentially identifying information is removed from patients' records, correlations could be sought between data points (such as between financial behaviors, or from financial behaviors to diagnoses).

There are limitations to this "big data" approach as applied to behavioral deficits in neurological and psychiatric diseases. Many of these hurdles reflect the complex cognitive, affective, and behavioral effects of these disorders, which are often far more difficult to quantify than those outside of the CNS. First, the vast majority of medical records are poorly suited for understanding complex behavioral deficits such as economic decision-making. For example, a typical primary care doctor's visit is 15 min, where some part is taken up by paperwork. The type of information documented, especially about behavioral issues like decision-making, will be relatively sparse—e.g. "forgetting to pay bills," and "making mistakes with money". The quantity of information, furthermore, will depend on the features that the physician views as lending support for a particular diagnosis and treatment decisions. It is likely, however, that many of the patients most likely to be of interest in research (i.e., those with behavioral disorders involving decision-making) will also have records from medical specialists in behaviorally oriented fields such as psychiatry and cognitive neurology, and that these records will be of greater potential value.

Second, while correlative approaches between data points in de-identified records have proven useful in other medical domains, there may be limitations to these approaches in the context of decision-making. In domains such as genetics or pharmacology, there is a broad spectrum of potentially informative associations with variables such as allergies to medication, family medical history, or rare adverse outcomes, which may yield previously unsuspected connections. In the case of decision-making, however, many of these parts of the de-identified medical record have little to do with decision-making and are therefore likely to be of low yield. Because there will be fewer data points in each patient's chart that are directly relevant to existing hypotheses about decision-making, the potential space for revealing correlations between data points in de-identified individual charts will be reduced.

How Medical Charts Can Inform Neuroeconomic Theories and Vice Versa

In contrast, a finer-grained approach would utilize records from patients who have given specific consent for the use of their data in research. The relevant records could either be accessed from existing records, or generated in the course of research evaluations. (For instance, the research visit summaries generated by our group are often sent to a patient's physician at the patient's request, becoming a part of the medical record.) This approach would typically require the research group to have a relationship with the patient, making large numbers logistically difficult. Instead, the value of this approach would be in the opportunity to correlate clinical descriptions of decision-making impairments with other measures, including experimental measures, collected from those patients.

Despite formidable challenges, researchers are now beginning to apply a neuroeconomic framework to medical data. One path to realizing clinical value is for neuroeconomic measures to be integrated into current medical practices (Fig. 4.4b). To do so, however, requires researchers to demonstrate that medical descriptions contain the raw information needed to assess potentially subtle changes in behavior, and that these are robust to confounding factors such as prevalence of comorbidities, diverse socioeconomic status, and presence of general cognitive declines.

To this end, Chiong et al. (In Press) studied susceptibility to financial errors in dementia due to Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (FTD), and assessed whether they differed given the known neuroanatomical targets and behavioral consequences of these syndromes. The authors drew

Table 4.1 Selected patient chart documentation of financial errors (quotes are verbatim)

Alzheimer's disease	Behavioral variant frontotemporal dementia
Increasing obsessive behavior about jewelry and money, suspicious about it being money, constantly asking to see it, count it, and be assured that it is around. She often becomes quite anxious and tearful thinking it is missing or someone has taken it. She has begun hiding it	At baseline, she was quite thrifty and was a successful small business owner. In 2002, she began to be compulsively shopping and she spent a great amount of money on a motor home, two new cars, and in remodeling of the backyard area of her home
In 2006 they received a check back from New York state for $1189 in reimbursement from taxes… he could not figure out how much they owed in taxes that year and simply sent a check	He began giving money out to strangers and was lured into a bogus gambling scheme conceived by his barber. The two of them traveled to Las Vegas at considerable expense on two occasions
[The patient's wife] stated he would forget to pay bills or pay bills twice	He became more aggressive with his investment decisions, and several of his investments lost value in the range of hundreds of thousands of dollars
[S]he started putting her checks and bills in the wrong envelopes	[The patient] started investing massively in lottery tickets, wiring money abroad and falling for scams found in her junk mail or magazines. She reached the credit limit on most of her credit cards and apparently lost tens of thousands of dollars this way

upon both existing neuroeconomic knowledge on neural and cognitive components of financial decision-making and management, as well as clinical experience in evaluating financial errors made by patients with dementia (Table 4.1).

AD is characterized by early memory and executive impairments, reflecting early involvement of the medial temporal lobe and the medial and lateral parietal lobes; whereas FTD is characterized by early alterations in a social and emotional function, reflecting early involvement of the insula and the medial and orbital frontal lobes. While financial errors are observed in both diseases, the authors hypothesized that details recovered from chart data could be used to distinguish between types of financial error that are characteristic of the specific cognitive and affective profiles of each disease.

Using a retrospective chart review approach, Chiong et al. (In Press) found that financial errors are common in AD and bvFTD. 72 % of AD (N = 100) and 84 % of bvFTD (N = 50) charts included some report of financial impairment. Strikingly, in 16 % of AD cases and 30 % of bvFTD cases, the financial impairment was either the first indicator of cognitive decline or was observed concurrently with the first indicator of decline; and in 34 % of AD cases and 48 % of bvFTD cases, the financial impairment was an early indicator of disease (noted within the first 2 years of illness). While the trend toward greater impairment in FTD in these comparisons was not statistically significant, there were significant between group differences in susceptibility to specific financial errors in AD and bvFTD.

Amnestic financial errors were significantly more common in AD patients (26 %) than bvFTD patients (4 %). In contrast, bvFTD patients were more likely to spend excessively (6 % in AD vs. 34 % in bvFTD) and to otherwise exhibit diminished sensitivity to losses (0 % in AD vs. 36 % in bvFTD) . In some cases, however, the description in the chart was too sparse for more detailed analysis—e.g., one patient who "has made a number of bad decisions with respect to finances." In other cases, the nature of the errors was not recoverable because the patients' decisions had not been monitored by family members, and the patients could not explain what they had done.

In general, financial errors in AD reflected a cognitive vulnerability factor, while financial errors in bvFTD reflected a social and affective vulnerability factor. Social/affective rather than cognitive deficits conferred greater risk for financial errors. This was further supported by factor analysis showing that clinical descriptions of behavior dysfunction can be characterized by two latent factors, with Factor 1 representing social/affective vulnerability and Factor 2 representing cognitive vulnerability to errors. Errors reflecting Factor 1 were less common in AD than in bvFTD (12 % vs. 58 %, $p < 0.001$), while errors reflecting Factor 2 were more common in AD than in bvFTD (29 % vs. 6 %, $p < 0.001$).

Although preliminary, this study presents the first direct evidence to our knowledge that medical charts of dementia patients contain sufficient details about decision-making impairments for a retrospective review (Table 4.1). Due to the inherent limitations of retrospective chart reviews, however, it is impossible to determine whether alterations in neuroeconomic measures precede other cognitive and affective symptoms, whether it correlates with disease progression, nor how they change as a function of treatments. However, these questions can in principle be addressed using the approach we outlined, likely in collaboration with clinical researchers (Fig. 4.4b).

Ethical/Privacy Concerns

Ethical concerns over appropriate respect for patient privacy will be front and center in every discussion of incorporating EHRs in research (Bakalar 2013; Jaret 2013). As observed by one commentator, “In the past, health information privacy has been protected mainly by chaos” (Rothstein 2009). Traditionally, patients’ health information has been scattered across paper charts located in dozens of doctors’ offices and hospitals, with no centralized resource for sharing or aggregating the information. Thus, the privacy of patients’ medical information was protected not only by norms of confidentiality, but also by the practical obscurity conferred by its distribution across multiple incomplete sources. As we have discussed, the comprehensiveness and organization provided by electronic health records opens new possibilities for research; however, because patients are unaccustomed to the prospect of having their records available for these new purposes, they may also raise concerns.

Existing U.S. regulations, most notably the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, limit access to patients’ confidential health records. An exemption is allowed for research on materials from which potentially identifying information is removed; one way of satisfying this standard requires expert statistical/scientific consultation to ensure that the risk of reidentification is very small, and another is to remove all data from a list of 18 potential identifiers including names, date of birth, social security and license numbers, and biometric parameters. Some authors have questioned whether de-identification is sufficient to justify the use of health records in the absence of specific consent (Rothstein 2010); among other things, these authors point out that the process of de-identification (and who, if this is done manually, would have access to the raw data in order to perform de-identification) is underspecified, and that patients may have non-privacy interests in asserting control over the use of their records (including religious or ethical objections to the research, or claims to any commercial benefits that ensue). A general problem for all research using de-identified health records is to develop protocols that are flexible enough to address a range of potential individual concerns, and to focus their use on applications in which the potential societal benefit can provide a reasonable rationale for pursuing research given these barriers and questions. These considerations may favor the second, more fine-grained approach described above.

Whether identified records are used with specific consent, or de-identified records are used in the absence of consent, the sensitive nature of psychiatric illnesses and cognitive disorders like dementia also demands special care. The use of these methods to identify people making impaired decisions will specifically identify patients at risk for fraud and exploitation, so data security will be much more important in order to avoid breaches of data by bad actors who might have an interest in identifying targets for

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criminal activity. More generally, these disorders remain highly stigmatized and have many potential ramifications for employability and insurability. Patients therefore will be especially reluctant to have this information shared without very high confidence in investigators' good faith and commitment to confidentiality.

Conclusion

We now have a reasonable understanding of neural circuits that mediate economic behavior. The behavioral paradigms used in this field have been successfully applied to a variety of clinical populations. Neuroeconomics, therefore, would appear to be well-placed to provide clinical insights into decision-making deficits. However, to extend this scientific success to practical clinical use, there needs to be a sustained effort to ensconce neuroeconomic paradigms in the standard battery of clinical toolkit of cognitive and behavioral functioning, alongside tests of memory, executive function, language, etc.

> We present preliminary evidence that medical charts of dementia patients contain sufficient details about decision-making impairments for a retrospective review. Comparing financial errors in AD and bvFTD patients, we found that errors in AD reflected a cognitive vulnerability factor, while financial errors in bvFTD reflected a social and affective vulnerability factor. This account of real-world financial impairment is largely consistent with current neuroeconomic characterization of behavioral deficits in AD and bvFTD patients.

As an initial step to establishing the diagnostic and prognostic usefulness of neuroeconomic measures, research groups can use existing knowledge of what brain systems are involved in different value-based decisions, as well as of what brain systems are impaired in different diseases, to identify behavioral neuroeconomic tasks suited to identify these impairments. This project can further be advanced by the use of information from medical records to systematically assess real-world failures of decision-making in patients. As a later step, establishing the reliability and validity of these measures in a variety of patient groups and settings would encourage the broader adoption of these measures in clinical practice, potentially in a way analogous to existing established measures of neuropsychological domains such as language and executive function. Finally, although data security and ethical concerns are especially pressing given the sensitive nature of these diagnoses and behaviors, this research is also of great clinical importance given the potentially devastating consequences of disordered decision-making for patients and also for their families. Behavioral researchers therefore must be able to communicate to both clinicians and patients on applications where the potential societal benefit can provide a reasonable rationale for pursuing research despite these potential barriers, and to partner with clinical researchers when possible to refine measures that combine clinical applicability with scientific rigor.

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